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How the Endocrine System and Microbiota Explain the Emotions Biochemistry and their Impact in Health

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Abstract

Emotional reactions stimulate neural circuits and biological pathways that produce neurotransmitters, affecting homeostasis and promoting disease. Health and emotions communicate, establishing a bidirectional cause-and-effect pathway. The composition of the microbiota also affects health and emotions, interacting through metabolites, such as short-chain fatty acids (SCFA), with the host's biochemistry. Certain genera of bacteria act in different ways on the host's homeostasis, keeping the immune system constantly vigilant and acting on the synthesis of neurotransmitters, such as serotonin and dopamine, which are responsible for well-being. When the host is in homeostasis, the synthesis of neurotransmitters is normal, which keeps the intestinal microbiota in balance. However, when the organism is out of balance, this synthesis is impaired; decreasing the concentration of the initial compounds for the production of neurotransmitters, which leads to a reduction in the concentration of neurotransmitters and exaggerated activation of the HPA axis, inducing an imbalance in the intestinal microbiota, generating dysbiosis. Due to dysbiosis, the synthesis of neurotransmitters is impaired, leading the host to develop mental disorders such as depression, anxiety and chronic stress; which contributes to the state of imbalance of the organism, harming mental and physical health. By adequately restoring the intestinal microbiota, the hyper activation of the HPA axis decreases, returning the body to homeostasis, resulting in the improvement of symptoms of depression, anxiety and chronic stress; leaving the organism healthy, both mentally and physically. Therefore, in this study we contextualize emotional research from a historical and descriptive perspective and present the main models of emotional identification. Focusing on basic emotions, we research the relationship of emotional states with the HPA axis and the microbiota, as well as how the bacteria present in the intestine affect the well-being of the host. Finally, we discuss our analysis presenting the bidirectional relationship between the endocrine system, microbiota and emotions.

Keywords: Emotions; Endocrine System; HPA Axis; Intestinal Microbiota; Mental Health

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Introduction

In the 1990s, the United States of America funded studies of neurodegenerative diseases using Magnetic Resonance Imaging (MRI) in humans [1], promoting advances in the knowledge of the brain. In this period, discoveries about the behavior of the human brain generated new fields of study [2,3], among them emotions [4,5]. Currently, there are several explorations about brain functions and emotional reactions [6]. Showed that molecules related to emotions act as receptors and ligands, activating the brain and the body simultaneously [7]. Explains if there is no homeostasis in the organism, certain emotional molecules are not produced, such as oxytocin and vasopressin, leaving the organism out of balance. With advances in studies, from the 2000s onwards it was possible to observe that the microbiota has a vital role in emotions [8], where these microorganisms help in the immune system, modulation of cytokines and in the production of short-chain fatty acids [9], which act in the conversion of tryptophan into serotonin [10], and tyrosine into dopamine [11]. This review provides a perspective on emotions, starting with their history to biochemistry and microbiota-host interactions. In this way, the reader will obtain a general understanding of the different aspects that permeate human emotions and how biochemistry and microbiota influence emotions.

Historic

Studies of human emotions and their relationship to health began many centuries ago. Figure 1 presents a Western overview of the development of emotion theory in a timeline.

Figure 1 Humours: substances that make up the human body. References: [1] Luneski et al. (2010), [2] Campos et al. (2010), [3] Andrea (2018), [4] Smith (2006), [5] Darwin (2015), [6] James (1948), [7] Gilbert (2003), [8] Jaim and Com (2016), [9] Gray (1950), [10] Wechsler (1943), [11] Seyle (1965), [12] Benedek (2011), [13] Pert (1997), [14] Amkraut and Solomon (1974), [15] Besedovsky et al. (1975), [16] Woyciekoski and Hutz (2009), [17] Besedovsky et al. (1986), [18] Salovey and Mayer (1990), [19] Goleman (2012), [20] Picard (1997), [21] Bushko (2002), [22] Damasio et al. (2003), [23] Blackburn et al. (2006), [24] Ornish et al. (2008), [25] Desbonnet et al. (2010), [26] Reigstad et al. (2015), [27] Dinan and Cryan (2017), [28] Dicks (2022).

The first studies on emotions date back to Ancient Greece with Hippocrates [12]. Emotions only became the focus of studies again in the 19th century with Charles Darwin in 1872, after the publication of the book the expression of the emotions in man and animals [13]. In 1884, William James and Carl Lange developed the James-Lange theory, which defines emotions as physiological responses to multiple stimuli [14]. In 1915, [15] described the fight or flight reaction as a result of atomic inhibition and the activation of the endocrine response (activation of the hypothalamic-pituitary-adrenal axis). In 1965, Seyle (1965) showed that stress increases the secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland [16]. In 1974, discovered the communication between the HPA axis and the immune system, linking emotions with diseases. The following year, [17], demonstrated that corticosteroids suppress the immune system. At the end of the 20th century and beginning of the 21st century, the relationship between the brain and the biochemistry of emotions is the focus of studies; creating the term molecules of emotions [6]. Furthermore, studies have shown that there is a relationship between emotions and neurodegenerative diseases [18], as well as that stress can affect telomerase [19]. From the 2010s onwards, the study of emotions began to be related to the intestinal microbiota, with [8], showing the importance of bacteria in emotions. Furthermore [9], showed that the microbiota helps the immune system, modulate cytokines and produce short-chain fatty acids, which play an important role in the conversion of tryptophan into serotonin [10], and tyrosine into dopamine [11], both neurotransmitters vital for emotions.

Emotions and Emotional Models

Many papers and reviews seek to provide an overview concerning emotion categorization models [20-25]. As depicted in the Figure 2, there are three general approaches to modeling and classifying emotions: discrete, dimensional, and evaluative. In Figure 2, we also present a relationship between primary emotions and the neurotransmitters produced during an emotional reaction.

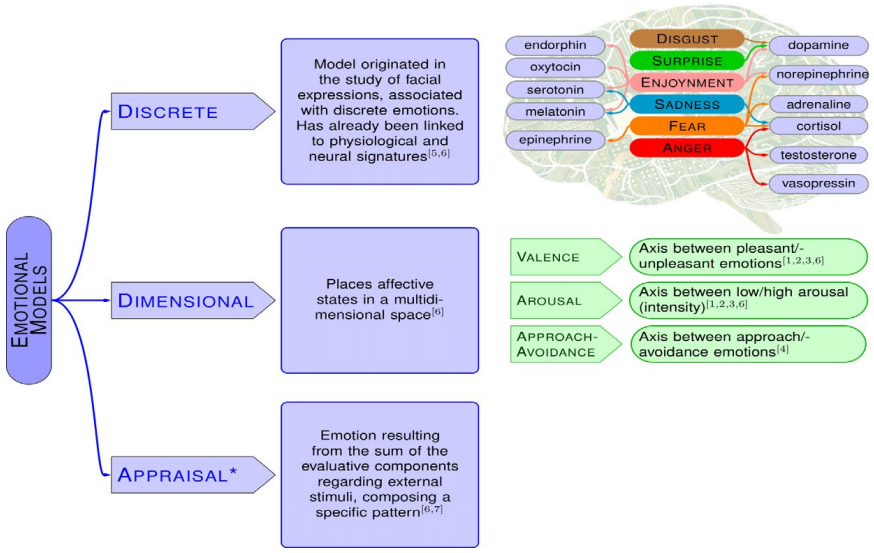

Figure 2 Summary of the main emotional models: discrete, dimensional and appraisal (Relationship between the appraisal and discrete models). Map of the physiology of emotions, associated with the discrete model, representing the relationship between basic emotions and neurotransmitters. References: [1] Bradley and Lang (1999), [2] Bradley and Lang (2007), [3] Harmon-Jones et al. (2017), [4] Hütter and Genschow (2020), [5] Ekman (1992b), [6] Lange et al. (2020), [7] Brosch and Sander (2013).

Table 1: Main discrete models used in basic emotion classification.

Quantity	Emotions	Articles
Four	Happy, sad, fear/surprise, disgust/anger	(Jack et al., 2014)
Six	Anger, surprise, disgust, enjoyment, fear, sadness	(Ekman, 1992a)
Seven	Happiness, sadness, anger, fear, surprise, disgust, interest	(Ekman and Friesen, 1971)
Eight	Joy, sadness, anger, fear, trust, disgust, surprise, anticipation	(Plutchik, 1982)
Nine	Sringara (erotic), Hasya (comic), Karuna (pathetic), Raudra (furious), Veera (heroic), Bhayanaka (terrible), Bibhatsa (odious), Adbhuta (marvelous), Santa (peace)	(Tripathi et al., 2018)

Discrete model

The discrete model, also called "Affect-program theories" [24], has its origins in work focused on facial expressions [26] and are linked to evolutionary stimuli and triggers. As depicted in Table 1, several sets of basic emotions have already been theorized and associated, traditionally, with the result of subjective analyses. Recently, these emotions have been related to physical and physiological manifestations, giving rise to the investigation of psychophysiology [27].

Dimensional model

The dimensional model is called of Constructionist theory [24]. In this model, emotion is understood as a cultural process, learned and expressed differently in each culture. In this theory, infinite affective states are in a multidimensional space [24]. The valence-arousal [20] and the approach-avoidance axis are among the dimensional models.

Evaluation model

There are also a third approach, the Appraisal Models, or Appraisal theories [24]. In this approach, every external stimulus triggers a specific emotion. Each external stimulus is evaluated by the individual generating an evaluative component. The sum of these components generates a particular pattern linked to an emotion. The discrete model's evaluative pattern is often associated with a feeling. The evaluative components are also associated with physiological processes related to emotions. The main goal of this theory is to study how a stimulus triggers emotional components and physiological processes [24,28].

Hybrid models

Additionally, some hybrid models unite features of the discrete and dimensional models. One of the best-known models is Plutchik Wheel of emotions [29]. Although it emerged before the categorization of emotion models, the wheel of emotions features eight primary emotions (joy, anticipation, anger, disgust, sadness, surprise, fear, and acceptance) differentiated by intensity levels.

Emotions and Health

Relationship between the biochemistry of emotions and health

The theory of [6] presents the concept of emotion molecules

as groupings of atoms consisting of receptors and ligands, being classified in three groups: the neurotransmitters (such as acetylcholine, norepinephrine, dopamine, histamine, glycine, GABA, and serotonin), the steroids (such as testosterone, progesterone, and estrogen), and the peptides, which make up about 95% of the ligands. The Table **S1**, available in the supplementary material, shows the molecules produced by the basic emotions. Neuropeptides act to produce emotional states or moods and the person experiences them as emotions or feelings. This mechanism simultaneously activates a specific neuronal circuit throughout the brain and body [6]. Chemical imbalance in the body can trigger the onset of disease. Therefore, rebalancing is essential for reestablishing homeostasis and maintaining physical and mental health. This rebalancing can, according to psychopathology, be restored by stimuli that facilitate the release of substances that regain homeostasis. The molecules of emotions constitute some of these substances. In diseases such as anxiety and depression, for example, the inhibition or release of oxytocin and vasopressin can restore chemical and emotional balance [7]. The substances that make up the "molecules of emotions" are produced by the endocrine system: Hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-gonadal (HPG), hypothalamic-pituitary-thyroid growth hormone/ factor growth like insulin-1 and hypothalamic-posterior pituitary axis, as well as other sources of hormones, such as the endocrine pancreas and endocrine adipose tissue [30]. As depicted in the Figure 3, we will explore, in greater depth, the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-gonadal (HPG) axes, and the pineal gland.

HPA axis-Hypothalamic-Pituitary-Adrenal

The HPA axis directs the neuroendocrinological response to stress, mediated by the release of corticotropin factor (CRF), adrenocorticotrophic hormone (ACTH), and corticosteroids [31]. The daily rhythm of the HPA axis is regulated by the suprachiasmatic Nucleus [32], that is, the brain's biological clock [33]. Its hormonal end product, cortisol, acts as a messenger between this central clock and the peripheral tissues [32] and as one of the most potent endogenous feedback compounds in the pro-inflammatory signal transduction machinery [33]. The HPA axis is also responsible for the production of Vasopressin (AVP), Oxytocin (OT), Beta-endorphin (BE), adrenaline, noradrenaline (NE), and dopamine (DA). These molecules have vital organic functions, acting as anti-inflammatory, antioxidant, vasoconstrictor, diuretic, and blood pressure regulation, among others [34-39]. Table **S3** shows the relationship between the emotion molecules produced by the HPA axis and health.

HPG axis-Hypothalamus-Pituitary-Gonadal

The HPG axis refers to the ovaries in women and testes in men [40]. It is responsible for the production of hormones essential to the regulation of reproduction and fertility [41], ovarian folliculogenesis and steroidogenesis (Vila and Fleseriu, 2020), and for maintaining the homeostasis of the organism [42]. Control of the HPG axis occurs at all levels, including the brain and pituitary gland, and allows for the promotion or inhibition of gonadal sex steroid secretion and function [41]. The steroids produced by it are responsible for the different responses to physical or psychological threats between the sexes [43]. In addition, this axis can modulate and be modulated by stress hormone signaling, including corticosterone [41]. The hormones produced by the HPG axis have metabolic functions, act in the composition of body fat and muscle mass, and reduce insulin sensitivity, among other [44].

Table **S5** shows the relationship between the emotion molecules produced by the HPG axis and health.

HPA and HPG axes

Some mechanisms relate to the HPA and HPG axes. Through

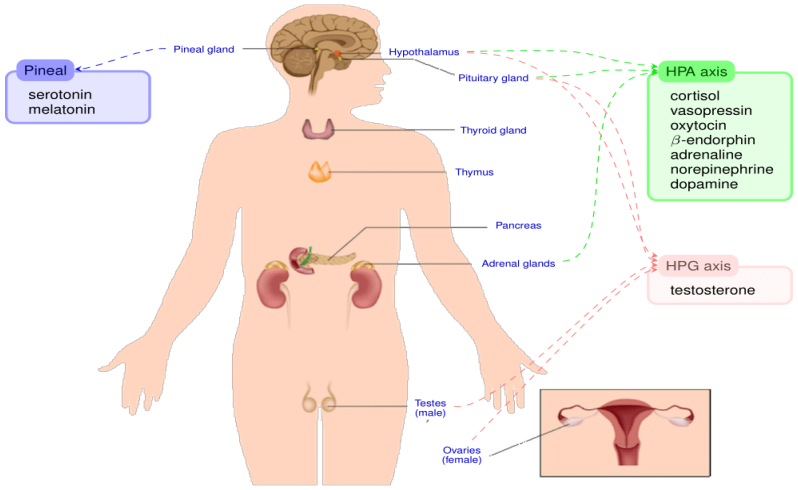

Figure 3 Schematic of the endocrine system and its participation in the HPA, HPG and pineal axes and their respective neurotransmitters and hormones. This is a cutout of the axes of the endocrine system with emphasis on the molecules that have special participation in the mechanisms related to emotions.

them, gonadal hormones can influence the development of the HPA axis. Hypothalamic neurons expressing gonadal steroid receptors are crucial for adequately regulating the HPA and HPG axes. Dysregulation of one or both can result in stress-associated emotional responses [42]. The HPA and HPG ax work together to increase survival and reproductive success. They adjust to each other, integrating environmental, psychological, reproductive, and genetic factors [42].

Pineal Gland

The pineal gland is an unpaired neuroendocrine organ in the brain's midline. Its principal function is to transduce light and dark information to the body by releasing the hormone melatonin [45], during the night. It is related to how our body prepares for sleep. Bright light controls melatonin levels varying in 24-hour cycles, generally increasing between 9 pm and 10 pm and decreasing in the morning [46]. This gland is connected to the central rhythm generator in the hypothalamus's suprachiasmatic nucleus (SCN) via a multi-synaptic pathway [47]. It receives adrenergic innervation, which activates a cascade of circadian events to produce melatonin from serotonin [45]. Melatonin and serotonin have essential functions in mood regulation and the body's rhythm with the circadian cycle. These molecules act: as regulators of homeostatic balance, anti-inflammatory, antioxidants, neuromodulators in learning, sleep regulation, skin protection, and against the effects of stress, among others [48-55].

Table **S7** shows the relationship between the emotion molecules produced by the HPA axis and health.

The supplementary material adds more details about the relationship between the HPA, HPG axes, and the pineal gland, and emotions. In addition, Table **S2**, Table **S4** and Table **S6** describe the function, actions, therapeutics, and more pathogenesis associated with the hormones and steroids produced by the HPA and HPG axis, and the pineal gland is also available in the supplementary material.

The Bidirectional Relationship between HPA Axis, Microbiota and Emotional Disorders

The HPA axis is a crucial component of the brain-gut-microbiota (BGM) axis, providing biological responses to stressful stimuli. In turn, the gut microbiota assists in regulating the hormones of the hypothalamic-pituitary-adrenal (HPA) axis [56].

Figure 4 illustrates the bidirectional relationship that exists between emotional disorders, the HPA axis, and the microbiota, commencing with the gut-brain axis signaling.

The Brain-Gut-Microbiome Axis in Health and Disease

The brain-gut-microbiome axis can be considered a two-way pathway where intestinal bacteria actively communicate with the brain, and in return, the brain interacts with these bacteria. While the study of brain-gut communication has been explored over the years, in-depth research into gut microbes began at the beginning of the 21st century [8]. Currently, it is well-established that the intestinal microbiota plays a pivotal role in neurotransmitter synthesis, the production of short-chain fatty acids (SCFAs), and immune system modulation through cytokine release [9].

The intestinal microbiota is intricately involved in the synthesis of neurotransmitters, including gamma-aminobutyric acid (GABA), noradrenaline, serotonin, dopamine, and acetylcholine. Furthermore, it has the capacity to produce short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. These SCFAs are vital metabolites for the host, synthesized exclusively by intestinal bacteria. SCFAs play a significant role in regulating host epigenetic activity, particularly in histone deacetylase function [9].

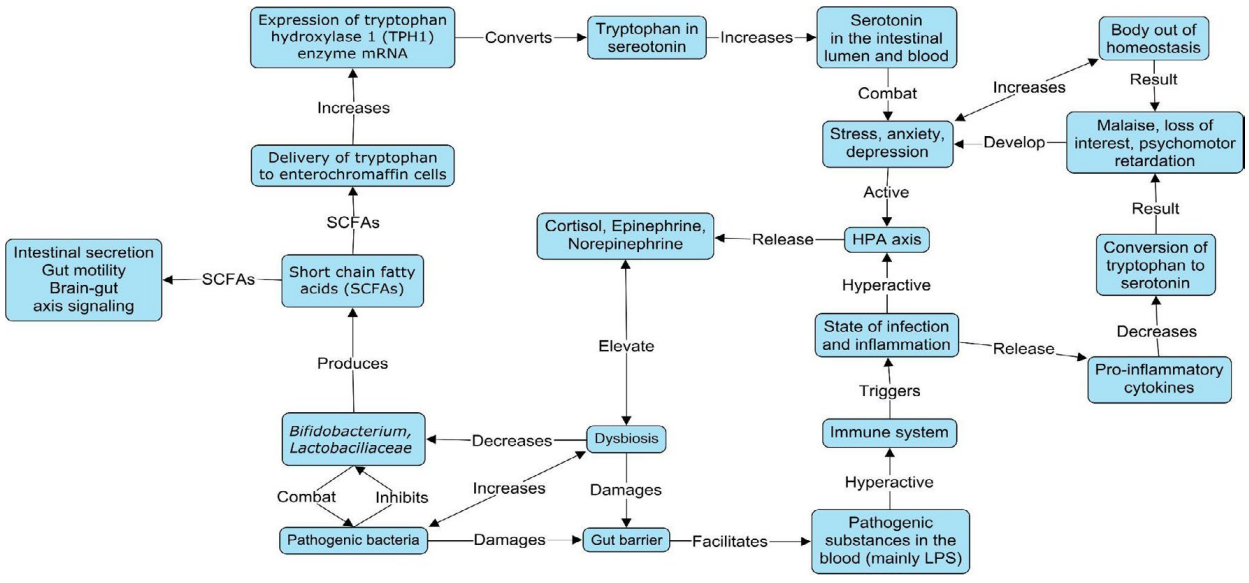

Figure 3 Schematic of the interaction between the microbiota, HPA axis and emotions. This figure describes both the benefits of probiotic bacteria and the harm of pathogenic bacteria, as well as the beneficial and harmful effects on the host's body.

In addition to neurotransmitter synthesis and short-chain fatty acid production, the microbiota also wields influence over the immune system through cytokine release. Under balanced conditions, cytokines released in the intestine can reach the brain without the need to traverse the blood-brain barrier. However, in brain areas where the blood-brain barrier is less effective, such as the hypothalamus, cytokines can directly influence the HPA axis, leading to cortisol release. This mechanism holds the potential to trigger stress response mechanisms [9]. The HPA axis is responsible for centrally regulating the body's response to stressful situations, and consequently, it can have a substantial impact on the brain-gut-microbiome (BGM) axis. Various pathological disorders, whether of psychological or physical origin, possess the capacity to significantly dysregulate the HPA axis, with direct repercussions on the balance of the BGM axis [57].

HPA axis, microbiota and emotions: a two-way street

Alterations in the HPA axis can lead to the development of emotional disorders, such as stress [58], anxiety, and depression [10]. These disorders, in turn, disrupt the HPA axis, resulting in a condition known as intestinal dysbiosis. Intestinal dysbiosis, or microbial intestinal dysbiosis, involves a modification in the composition of the intestinal microbiota, impairing the body's equilibrium and exacerbating the symptoms of stress, anxiety, and depression, potentially leading to cognitive impairment. Dysbiosis impairs the intestinal barrier, leading to intestinal permeability and the entry of lipopolysaccharides. End toxemia is the entry of lipopolysaccharide (LPS) into the bloodstream. High circulating concentrations of LPS stimulate intestinal inflammation and neurodegeneration due to HPA axis hyperactivity. Neurodegeneration results in an overproduction of cortisol [59]. Cortisol is a hormone produced by the HPA axis and is closely linked to stress, anxiety, and depression, playing a crucial role in anti-inflammatory pathways [58]. The intestinal microbiota plays a role in regulating HPA axis hormones [58], especially cortisol, which also affects the microbiota, promoting dysbiosis [56]. Stress, whether environmental, emotional, or physiological, triggers an increase in the concentration of pro-inflammatory cytokines, stimulating the HPA axis. This stimulation activates the paraventricular nucleus of the hypothalamus, responsible for secreting corticotropin-releasing hormone (CRH). When plasma concentrations of CRH rise, they activate the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. This hormone, in turn, induces the release of glucocorticoids by the adrenal cortex, which can lead to dysbiosis [59]. Stress also stimulates the production of catecholamine's [60], which can stimulate the growth of Gram-negative bacteria, leading to increased intestinal permeability and the passage of lipopolysaccharide into the bloodstream, leaving the individual in a state of inflammation. The inflammatory mediators synthesized by this condition, such as pro-inflammatory cytokines (IL-1, IL-6, and TNF-α), contribute to the onset of depression [61]. Chronic depression and anxiety hyper activate the HPA axis through the immune system, increasing the production of reactive oxygen species, nitrogen, nucleic acids, lipids, reduced concentrations of antioxidants, and amino acids like tryptophan, a precursor of serotonin [10], and tyrosine, a precursor of dopamine [11]. Administration of lactobacilli and Bifidobacterium can restore the functionality of the HPA axis (homeostasis framework), improve memory, cognition, and reduce the symptoms of depression and anxiety. When dysbiosis is suppressed, and intestinal homeostasis is restored, symptoms of anxiety and depression improve [56].

Probiotics

Probiotics consist of live microorganisms that, when consumed in appropriate quantities, confer health benefits to the host [62]. In this context, numerous scientific studies have been conducted to investigate the use of probiotics in reducing stress, treating depression, and controlling the HPA axis. A study conducted by [59-61,63], revealed that germ-free mice (GF) exhibited HPA axis hyperactivity. However, the administration of *Bifidobacterium longum* subsp. *infantis* in GF mice successfully reversed this exaggerated HPA axis response. Similarly, GF mice subjected to psychological stress and administered probiotics demonstrated a reduction in the HPA axis response. Furthermore, probiotic administration had the potential to prevent abnormal brain activity in mice suffering from chronic stress. Other studies conducted by [64,65] demonstrated that supplementation with the bacterium *Bifidobacterium longum* 1714 was effective in reducing stress-related cortisol levels and daily stress levels in healthy patients. In addition to stress reduction, these studies highlight the beneficial effects of probiotics in the treatment of depression [8]. Conducted a study in which *B. longum* subsp. *infantis* was able to elevate blood tryptophan concentrations, thereby influencing central serotonin transmission. Moreover, a cocktail containing various probiotic bacterial strains revealed promising results in reducing negative thoughts and behaviors [8-61]. Demonstrated that germ-free mice (GF) mice showed hyperactivity of the HPA axis. When administered *B. longum* subsp. *infantis* in GF mice, the exacerbated HPA axis response was able to be reversed. Similarly, when GF mice that underwent psychological stress were fed with probiotics, the HPA axis response was reduced. In addition, such administration of probiotics may prevent abnormal brain activity in mice that suffer from chronic stress.

Discussion

Although it may seem like a recent topic, the relationship between emotions and health has been contemplated since the early days of medicine. From ancient Greece to the present, this connection has been built upon scientific theories and discoveries. However, it was in the 20th century that these connections were fortified. In 1920, with Cannon's groundbreaking study [66], which established a link between stress and the activation of the neuroendocrine system in mammals? Subsequently, in 1935, when Edward C. Kendall isolated the cortisol granule and in 1970 [67], with Candance Pert and Solomon Halbert Snyder [6], who delineated the biochemical mechanism of molecules responsible for generating emotional states.

These discoveries and theories paved the way for a deeper understanding of the relationship between emotions and the functioning of the human body. Specifically, the influence of the endocrine system, particularly the hypothalamic-pituitary-

adrenal (HPA) axis, in responding to emotional stimuli became a focal point of study. The HPA axis plays a pivotal role in regulating the body's responses to stress, releasing hormones such as cortisol and adrenaline in reaction to such stimuli [58].

In recent decades, research has turned its focus toward the gut-brain axis, recognizing the intestinal microbiota as a significant player in modulating emotional responses and regulating the HPA axis [63]. The microbiota, comprising billions of microorganisms residing in the gut, plays a remarkable role in synthesizing neurotransmitters and producing short-chain fatty acids, such as acetate, propionate, and butyrate. These compounds are critical for the body's equilibrium and, moreover, they impact epigenetic activity, including the function of histone deacetylases, which in turn leaves accessible regions of the DNA that are responsible for synthesizing neurotransmitters [9]. Research has identified that certain biochemical molecules, such as cortisol and serotonin, are inherently linked to basic emotions and the body's emotional responses. The balance of these molecules is crucial, with both the endocrine system and the microbiota playing a fundamental role in maintaining this equilibrium. For instance, the release of cortisol is directly associated with the stress response, making it a key component in the functioning of the HPA axis [56].

Dysfunctions in biochemical and emotional pathways cause the HPA axis to be hyper activated, releasing greater concentrations of cortisol, adrenaline and norepinephrine. Among the three hormones, cortisol is the one that causes the greatest damage to the body and microbiota, damaging the intestinal barrier and developing dysbiosis [56]. When probiotics are damaged, pathogenic bacteria alter the body's homeostasis, leading to hyper activation of the immune system and the HPA axis, which in turn releases more cortisol into the blood, which further damages the intestinal barrier [68]. Thus, understanding this intricate web of interactions among emotions, the endocrine system [69-90], the microbiota, and overall health opens new perspectives for the treatment and prevention of emotional and mental disorders. Future research in this field may provide valuable insights for more effective therapeutic approaches, offering hope for improving the quality of life for those who suffer from emotional and stress-related disorders.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

GTL, ESL and CPP designed and implemented the analysis. ASF, CRP and JNM contributed to the search and analysis. GTL, ESL and CPP wrote the original draft of the manuscript. ASF, RTR, DG, and JNM made substantial contributions, revisions and approved the final manuscript. JNM supervised the whole project. All authors contributed thoughts and advice, discussed the results, and contributed to writing the final manuscript.

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Supplemental Data

SUPPLEMENTAL FILE 1, DOCX File - Supplementary Results and Tables

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