MEDDOCS Open Access Publisher

MedDocs Microbiology

Open Access | Review Article

Microbial Influences on Neurotransmitters: Exploring the Gut-Brain Axis and Psychobiotic Therapies

***Neethu Asokan*[1]*; *Pushpendra Kumar*[2]**

[1]*Department of Lifesciences, Sri Satya Sai University for Human Excellence, Kalaburagi, Karnataka, India.*

[2]*Faculty of Pharmacy and Pharmaceutics, Maharaja Agrasen Himalayan Garhwal University, Pokhra, Uttarakhand, India.*

***Corresponding Author(s): Neethu Asokan**

Department of Lifesciences, Sri Satya Sai University for Human Excellence, Kalaburagi, Karnataka, India.

Email: neethusasokan@gmail.com

Received: Dec 17, 2024

Accepted: Jan 21, 2025

Published Online: Jan 28, 2025

Journal: MedDocs Microbiology

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Psychobiotics; Gut-brain axis; Neurotransmitters; Therapy; Psychotic disorders.

Abstract

Advanced research has focused its influence on neurotransmitter production, affecting the general aspects of both mental and emotional health. This chapeter explores intricate interaction between the gut microbiota and neurotransmitters like dopamine, GABA and acetylocholine. Microbial metabolism in the gut releases a myriad of metabolites that can influence neurotransmitter synthesis and functions. The gut microbes exerts regulatory effects on the immune system through interactions with intestinal immune cells and the production of such immunodulatory molecules. The gut-mind bidirectional communication termed as gut-brain axis highlights the role of gut microbiota in immune system modulation, brain functions, mental health, potential implications for neuro inflammatory conditions and mental health disorders. Moreover the neural pathways that connects the gut and the brain including the vagus nerve and other enteric nervous system serve as conduits for microbial signals to influence central nervous system functions. Psychobiotics modulates neurotransmitter levels and thereby improve mental health through mechanisms like enhancing serotonin production or reducing neuroinflammation. Identification of novel and potent microbes with psychobiotic potential could open a way for targeted therapeutic treatments in psychotic disorders. There are however few challenges that remain in harnessing the therapeutic potential of the psychobiotics. The chapter will enlighten the insights into the role of gut microbiota in brain health and their potential therapeutic strategies.

Introduction

The gastrointestinal region and large intestine consists of humongous microorganisms that are essential for human health and physiology. Numerous studies have discussed the capability of gut microbes to metabolize dietary substrates to generate bioactive compounds with neuroactive properties. Certain bacteria have been known and found to ferment dietary substances producing dhort chain fatty acids like acetate, propionate and butyrate [1]. Prebiotics and probiotics have been known to be the source of such healthy microbes that can produce neuroactive bioactive compounds. Probiotics are live microorganisms that has many health benefits when administered in adequate amounts whereas Prebiotics uphold the growth of probiotics and also has potential in modulating neurotransmitter levels thereby improving mental health. The indepth study on the role

Cite this article: Asokan N, Kumar P. Microbial Influences on Neurotransmitters: Exploring the Gut-Brain Axis and Psychobiotic Therapies. MedDocs Microbiol. 2025; 4(1): 1003.

of these microbes in neurotransmitter synthesis and functions could give a scope for novel therapies.

Microbial Metabolism and Neurotransmitter Production

The mechanisms and complex relationships of microbial metabolism and neurotransmitter production involve several interactions with gut microbiota, dietary substrates and host physiology. Previous studies have mentioned the pivotal roles of specific microbial species and the pathways in these processes. Several microbial enzymes like tryptophan decarboxylase and aromatic amino acid decarboxylase are significant enzymes that help in the production of neurotransmitters from dietary substances or precursors [2]. These can traverse the blood – brain barrier thereby interacting with the host neuro system and pathwasys influencing mood, cognitions, emotions and behavior.

The dynamic interplay of gut-microbes with dietary intake and neurotransmitter regulation has a pivotal part in the bidirectional communication of gut-brain axis [3]. Dysregualtion of these pathways could be a trigger in the mental health and well being as they are associated with psychiatric disorders like depression, anxiety, steess and other neurodegenerative disorders. Consequently, it can be seen that probiotics and prebiotics along with diet rich in fiber could restore the balance of neurotransmitters thus improving the mental well being.

Bacteroides, Firmicutes, and *Actinobacteria* are currently known for their involvement in synthesis of SCFAs like acetate, propionate and butyrate. These have a vital role on neural functions, modulate neurotransmitter synthesis and immune regulations. They also involved in the release, regulation of neuroinflammation and maintenance of blood-brain barrier integrity [4]. The gut microbes are known to synthesis or produce Serotonin from tryptophan and other neurotransmitter similarly are produced like GABA and dopamine from respective precursors [5]. GABA is an inhibitory neurotransmitter while dopamine is involved in cognitive functions responsible for reward oriented behaviours and controls other neural activities [6].

The neurotransmitters namely Gamma-Aminobutyric Acid (GABA), noradrenaline, serotonin, dopamine and acetylocholine were found from gut microbiomes and influenced brain activity directly [7]. Bacterial metabolites like long and short chain fatty acids also exhibit neuroactive properties. This ability of gut microbes to synthesize and release neurotransmitters and neuromodulators suggests a novel approach for treating neuropsychiatric disorders [7]. Further research in this domain is advancing opening a door to therapeutic purposes.

The synthesis of neurotransmitter synthesis by gut microbes involves intricate biochemical pathways. GABA, Serotonin, Dopamine and other neurotransmitters are produced by certain microbes through several enzymatic processes using several precursors from diet. Current studies have shown that the elevated levels of GABA in the human gut is from the intestinal microbiota like *Bacteroides, Bifidobacteria,* and certain *LAB* (*Lactobacilli*) [8,9,2].

Advanced technologies like sequencing and computational approaches have caused a deeper understanding of microbiota and their metabolic pathways that help in neurotransmitter synthesis. Metagenomic and metatranscriptic analyses have enabled a better understanding on gut Microbiome, their function, metabolism and impact on mental health [10].

Serotonin

One of the neurotransmitter synthesized by the brain is Serotonin. It is associated with appetite, mood control, digestion, memory, sexual desire. Social behavior and sleep wake cycle. It is a part of several physiological functions and is found in GIT, blood platelets and the central nervous system. In the brain, serotonin transmits signals between nerve cells (neurons). Serotonin is synthesized from the amino acid tryptophan and is primarily found in the serotonergic neurons of the CNS [5]. It functions by binding to and activating serotonin receptors located on the surface of target cells, influencing their activity. However quite a few researches have mentioned the contribution of gut Microbiome in Serotonin synthesis [5].

Serotonin synthesis by gut Microbiome ever since has become an emerging area of research highlighting its association with the gut microbiota and the Central Nervous System (CNS). While serotonin is known as a neurotransmitter in the brain, a significant portion of serotonin in the body is actually produced in the gastrointestinal tract. Serotonin is synthesized from the amino acid, tryptophan which is obtained through the diet and is absorbed in the intestines.

Research has revealed that serotonin synthesis can be influenced by gut microbiota through several mechanisms. Commensal bacteria within the gastrointestinal tract have been identified as capable of synthesizing serotonin directly from luminal tryptophan found in the colon. Additionally, certain spore-forming bacteria promote serotonin biosynthesis in Enterochromaffin Cells (ECs) located in the colon. Certain bacteria in the gut, particularly species belonging to the phyla Firmicutes and Bacteroidetes, have been found to possess the enzymes, tryptophan decarboxylase, necessary to convert tryptophan into serotonin [5]. The serotonin produced by gut microbes influence intestinal motility, secretion of fluids, affecting gut-brain communication via the enteric nervous system. The gut microbiome enhances the production of enteric serotonin (5-HT) through the production of Short-Chain Fatty Acids (SCFAs), phenolic compounds, and indolic compounds derived from microbial metabolism. These microbial-derived metabolites play a role in promoting serotonin production within the gut, influencing gastrointestinal functions. By affecting the metabolism of luminal tryptophan in the gut, microbiota alters the availability of peripheral tryptophan, which in turn affects central tryptophan levels and thereby central serotonin levels [11]. This interaction of gut Microbiome with the brain modulates both peripheral and central serotonin levels, potentially influencing mood, behavior, and overall health through the gut-brain axis [11].

Kynurenine pathway is a metabolic pathway found in the gut bacteria that metabolize about 90 percent of the essential amino acid tryptophan [12]. It is enzymatically converted to kynurenine which his metabolized into several metabolites like kynurenic acid, quinolinic acid and picolinic acid. These compounds play a vital role in immune modulation, neuroprotection and influencing neurotransmitter systems [12].

Have [13] demonstrated that tryptophan concentration in plasma of male germ-free animals was elevated due to possible influence of gut microbes on CNS serotonergic neurotransmission through humoral route [13]. This study however have supported the existence of complex relationship between gut-brain axis.

Dopamine

Dopamine is one of Catecholamine neurotransmitter among norepinephrine and epinephrine. They are known as biogenic amines as they are derived from the amino acid tyrosine. They are associated with functions like motor control, learning, memory formation, motivation, reward, mood regulation, cognitive processes and in stress response. They also regulate carbohydrates and lipid metabolism therby affecting cardiovascular health [14]. Dysfunctions in the dopamine system are associated with conditions such as depression, addiction, and schizophrenia [15], highlighting its critical role in regulating mood, reward processing, and cognitive functions. Dopamine is integral to the brain's reward system, motivation, pleasure, and motor control [16], playing crucial roles in regulating behaviors such as reward anticipation, motivation to act, and movement coordination. A decreased dopamine levels in specific brain regions, a characteristic in depression patients, may contribute to symptoms such as anhedonia (loss of pleasure) [17]. Meanwhile, a heightened dopamine activity within distinct brain circuits is linked to positive symptoms such as hallucinations and delusions that are the common symptoms in Schizophrenia patients [18].

Dopamine is synthesized from the amino acid tyrosine in neurons located primarily in the substantia nigra and the ventral tegmental area of the brain. Furthermore, gut microbes have been identified as a critical source of luminal Norepinephrine (NE). Bacteria residing in the gut lumen possess uptake systems that function as a net sink for biogenic amines and neuroactive substances [19]. DA is the main catecholamine neurotransmitter in mammalian CNS, being relevant for processes such as affection, emotions, working memory, attention, motivation, reward, locomotor activity, neuroendocrine regulation, and ingestion of water and food [20,21]. Changes in dopaminergic transmission have been associated in severe CNS disorders, including anxiety [22,23], ADHD [24], Parkinson's disease [25], compulsive food intake [26], and numerous others. These conditions highlight the critical role of dopamine in regulating various aspects of neurological function and behavior, underscoring its significance in both health and disease contexts.

Have [6] reported in their studies that sunthesis of neurotransmitter by gut Microbiome is indeed an indirect process. They have stated that Dopamine synthesis by gut microbe involve several enzymatic pathways converting several metabolites to finally produce Dopamine [6]. While specific mechanisms are still not investigated it has been proved that certain bacterial species are involved in the production of Dopamine from tyrosine [6]. The synthesis has been known to begin with L-DOPA (L-3,4-dihydroxyphenylalanine), a tyrosine derivative sourced from diet or sometimes synthesized within the body. The gut microbes influence this by metabolizing dietary compounds and modulating gut-brain signaling pathways. This limelights the significance of gut microbiome to affect neurological pathways and processes through dopamine regulation thereby contributing to gut-brain axis.

Catecholamine Biosynthesis pathway is the dopamine biosynthesis pathway that involves several enzymatic reactions starting with tyrosine conversion to L-DOPA by the enzyme tyrosine hydroxylase [14]. L-DOPA is finally converted to the neurotransmitter Dopamine by aromatic L-amino acid decarboxylase enzyme. While dopamine synthesis primarily occurs in the Central Nervous System (CNS) and certain peripheral tissues, there are several studies that mention the influence of gut microbiota modulating dopamine levels and its metabolism. Gut microbes can metabolize several dietary components to produce metabolites that may act as precursor for dopamine synthesis [27].

Some microorganisms in the intestine and gut were reported to produce neurotransmitters either by the utilization of dietary substrates or as a result of their metabolic pathways in small quantites [28]. The compounds produced like L-DOPA influence the function and expression of several receptors thus affecting the signaling pathways and impact dopamine metabolism indirectly.

Gamma-Amino butyric Acid (GABA)

Gamma-Aminobutyric Acid (GABA) is one of the major neurotransmitter in the central nervous system that has a decisive role in regulating neuron excitability. It usually acts by binding to specific receptors located on membranes of neurons. On binding they inhibit the neuron activity and reduce the ability to generate an action potential and transmit signals to other neurons. GABA maintains the balance between excitation and inhibition, influence functions like anxiety regulation, sleep induce and motor control [29].

GABA synthesis has been studied extensively and the role of certain gut microbes in GABA synthesis were reported [2]. Glutamate decarboxylase pathway or GAD pathway is found in certain microbes [30]. Those gut microbes were found to possess enzymatic machinery to convert glutamate to GABA in the lumen of GIT influenced by various factors like diet and microbe [30] .The enzyme is glutamate decarboxylase that can catalyze decarboxylation of glutamate to produce GABA [30]. Lactic acid bacteria were reported to be potent synthesizers of GABA, strains like *Lactobacillus paracasei PF6, Lactobacillus delbrueckii subsp. bulgaricus PR1, Lactococcus lactis PU1*, and *Lactobacillus brevis PM17* during the fermentation of re-formed skimmed milk [14]. Reported [31] the GABA production abilities from traditional dairy products like raw milk. The strains like *Lactococcus lactis* subsp. lactis and *Streptococcus thermophilus* synthesized more than 1 mM of GABA. Previous studies have reported to possess GAD genes that produce isozyme GADs especially *Lactococcus lactis* subsp. lactis and *Streptococcus thermophiles* [32]. GABA were also reported to be biosynthesized by several LAB strains belonging to the genera of *Lactobacillus, Lactococcus, Lactiplantibacillus, Streptococcus, Weissella, Pediococcus, Leuconostoc, Enterococcus, Lacticaseibacillus, Levilactobacillus* and *Secundilactobacillus* [32]. GABA can also be synthesized through deamination and decarboxylation reactions of putrescine, spermine, spermidine, ornithine, and L-glutamine [32].

Previous studies have demonstrated that GABA receptors are present in gut Microbiome. It was also noted that glutamic acid decarboxylase genes are distributed among several microorganisms namely, *Lactobacillus plantarum, Lactobacillus brevis, Bifidobacterium adolescentis, Bifidobacterium angulatum, Bifidobacterium dentium,* and other gut-derived bacterial species, indicating their potential for GABA synthesis [33]. Have reported that the GABA-producing pathways are actively expressed by *Bacteroides* through a transcriptome analysis of human stool samples from healthy individuals.

According to [8], *Bacteroides* is a common genus in human guts that synthesis GABA from glutamate [8]. It is also an inhibitory neurotransmitter in the CNS. There are several researches in *L. plantarum* since it can produce GABA through GAD sys-

tem [8,14]. The GAD system had genes and GAD operon that encodes glutamic acid decarboxylase enzymes (gadA or gadB genes) and the Glu/GABA antiporter gadC. Together they facilitated glutamate decarboxylation and GABA secretion in bacteria [34]. GABA production requires proton consumption and maintains cytosolic pH hemostasis. Disorders like epilepsy, anxiety, tension, depression, schizophrenia, and Autism Spectrum Disorders (ASD) are due to GABAergic neurotransmission and impaired GABA receptor function [35].

Acetylcholine

Acetocholine is a neurotransmitter that is essential for several cognitive functions like learning, memory, arousal and attention as well as regulating muscle contraction [36]. Studies have shown that Ach is synthesiszed in nerve terminals and gut microbes play a vital role in their synthesis. Choline obtained through diet like eggs, liver, soybeans or as gut microbe metabolite is the precursor for Acetocholine synthesis [37].

Escherichia, Enterobacter, and *Klebsiella* are involve in choline conversion to Acetocholine. Firstly, choline is converted to Trimethylamine (TMA) via choline TMA-lyase activity [38]. The metabolites synthesized by gut microbiota are involved in several functions like inflammation, oxidative stress and lipid metabolism; thereby indirectly impacting neurotransmitter synthesis [39].

"The Cholinergic Pathway" or "Cholinergic Neurotransmission" is reported to be the pathway of Acetocholine synthesis by gut microbiome [40]. The trimethylamine is metabolized by the host liver into trimethylamine N-oxide (TMAO) [38]. Impairement of the cholinergic pathway is associated with irregularity in cognitive functions like in dementia or Alzheimer disease. Reduction in acetylcholine levels can affect attention, memory and decision making in humans [41]. Based on these reports many therapies have developed to curb acetylcholinesterase inhibitors [42].

Immune System Modulation

The gut microbes consists of bacteria, fungi and viruses that play a central role in immune system and functions [43]. These microbes contribute to immune tolerance preventing unnecessary immune responses [44]. The immune response has been detected to begin from infancy; where infants are initially exposed to microbes during birth and through breast feeding thus establishing gut microbes [45,46]. It has been proved through research that exposure to diverse microbes are essential for developing tolerance to antigens and allergies. However, once the early microbial colonization is disrupted may lead to long term implications [47].

Psychobiotics hold promise in restoring the function of the gut barrier and reducing the levels of pro-inflammatory cytokines and glucocorticoids. They enhance anti-inflammatory cytokines thereby strengthening the blood-brain barrier and gut barrier, collectively alleviating inflammations in the body. They also modulate the gut Microbiome composition and regulate their responses by altering cytokine production, enhance gut barrier function, interact with gut associated lymphoid tissue and minimize immune mediated disorders [48].

Gut Microbiome decrease pro inflammatory cytokines such as TNF-alpha, IL-6 and increase anti-inflammatory cytokines like IL-10 promoting a more balanced immune response [49]. Some gut microbe strains of *Lactobacillus* and *Bifidobacterium*, are reported to reduce systemic inflammation by modulating immune cells activity and cytokine production. Psychobiotics are also known to support optimal immune responses and contribute to gut health and gut barrier integrity that can prevent harmful microbes and toxins flowing into the systemic circulation [50]. Hence they are considered promising therapeutic agents for treating conditions by restoring immune balance, treat mental disorders and supporting mental well-being simultaneously [50].

The significant gap worth addressing is the risk of false positives and negatives in research that require further scrutiny. Moreover, further investigation is vital to understand theoretical and methodological gaps in knowledge of research in gut-brain axis. The most general queries include the role of gut hormones, their mechanisms of action and the impact of factors such as diet, sex, and age on the psychobiotics mechanism. Filling these research gaps with quality investigation could bring major milestones in gut-brain axis research [14].

Neural Pathways and the Vagus Nerve

The vagus nerve is considered as the longest cranial nerve and has sensory fibers that transmit signals to the brain from organs such as the heart, lungs, pancreas, liver, stomach, and intestines [14]. It is comprised of both sensory and motor neurons. The vagal afferent terminals located beneath the gut epithelium where the signals are received either directly or indirectly. These signals influence various host behaviors and others like depression, anxiety, and loss of appetite [39]. The bidirectional communication between gut and brain is made possible by vagus nerve and hence it forms a part of gut-brain axis. This facilitates interactions that impact not only mental health but also immune responses and overall physiological homeostasis [51,39].

These nerves are found connected to the gut microbiota; they receive the signals send by these microbes and it directly or indirectly influence the physiological responses and mental health. Several researches indicates that gut microbe derived signals impact mood-related behaviors like lethargy, depression, anxiety, and appetite regulation [51,39]. The process of detecting signals of gut microbes take place through indirect pathways including bacterial compounds, metabolites and even intermediary cells within the gut epithelium that can convey luminal signals. There are also other reports on the utilization of vagus nerves by gut microbes to influence the mental health and physiological responses [51,39]. They also provide a defensive function to the intestinal epithelial barrier. It has been reported that the low vagal activity makes the intestine more permeable promoting systemic inflammation and chronic disease [14].

Studies on mice have shown that neurochemical and behavioral effects were found absent in mice that have undergone vagotomy, showing that the vagus nerve is the primary pathway enabling bidirectional communication between the microbiota and the brain [52]. The gut microbiota are hence known to influence neural pathways and brain function through various mechanisms like neurotransmitter synthesis, Short chain fatty acid production, Immune system modulation, Vagus nerve communication and its impact on Blood-brain barrier all collectively represent gut-brain axis [4,53].

Hormonal Pathways and the HPA Axis

Psychobiotics form a bidirectional relationship with hor-

monal pathways, and the HPA (Hypothalamic-Pituitary-Adrenal) axis. The gut microbes produce several compounds like the Short-Chain Fatty Acids (SCFAs) through the fermentation of dietary fibers. The gut microbes are also reported to modulate peptide hormones like GLP-1 and PYY, affecting appetite regulation and energy metabolism. Activation of the HPA axis, in response to tension or stress via CRH release from the hypothalamus and subsequent cortisol release, can in turn influence gut microbiota composition and activity. He HPA axis functions as the principal neuroendocrine system responding to physiological and physical stress in humans. This axis involves intricate interactions among the hypothalamus, pituitary gland, and adrenal cortex, orchestrating the release of hormones such as cortisol (or corticosterone in rats) in response to stressors [54]. These hormones help regulate numerous physiological processes, ensuring adaptation and homeostasis under challenging conditions. Cortisol is known for its immunosuppressant properties, crucial for regulating inflammation in the body. During chronic stress, cortisol production increases. Paradoxically, this heightened cortisol level fails to exert its anti-inflammatory effects, disrupting its usual negative feedback on the HPA axis and leading to hypercortisolemia [54]. This excess of glucocorticoids inhibits immune function, heightens sensitivity to threats, induces negative moods, impairs memory, and compromises cognitive functions [55].

Early-life gut microbial colonization significantly impacts brain function and behavior, including stress response modulation. Research indicates bidirectional influences where HPA axis activity affects gut microbiota composition and increases gastrointestinal permeability [56]. These changes in gut permeability and immune responses may contribute to disruptions in neuroendocrine function, highlighting the complex interplay between gut microbes and physiological pathways.

A disparity in gut microbiota has been linked to dysregulation of the HPA axis, a pivotal system in the body's response to stress. Restoring microbial balance has demonstrated promising effects in reducing HPA axis activity. Previously [57] conducted a study using a probiotic formulation containing *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175, which when tested clinically was found to impact HPA axis on chronic stress [57,14]. Similarly, [58] explored the impact of *Lactobacillus plantarum* 299v on the HPA axis in humans exposed to school-related chronic stress. In their placebo-controlled study, participants who received the bacterial culture had lower salivary cortisol intensities compared to the other set of participants. This proved the potential of gut microbiota to alleviate chronic stress by modulating HPA axis.

Additionally few preclinical studies have explicated mechanism of gut microbes influencing and reducing chronic stress. In [46] his studies have demonstrated that germ free mice showed heightened HPA axis response to stress compared to other mice. This suggested that microbes could influence and impact in shaping the development and regulation of stress response system. Additionally, a recent research by [59] stated the role of SCFAs in moderating HPA axis activity and stress resilience. These findings highlight the intricate relationship of gut microbes and its metabolites with neuroendocrine pathways. This could pave way for the therapeutic potential to diminishing stress and alleviating HPA axis Dysregulation. Therefore, the re-establishing of gut microbes through probiotic and prebiotic interventions and modulation of microbial metabolites could be a promising approach to mitigate HPA axis hyperactivity induced by chronic stress.

Psychobiotics and Neurotransmitter Modulation

Gut microbes can stimulate the synthesis of neurotransmitters in the gut and these gut microbes are collectively called as psychobiotics like *Lactobacillus* and *Bifidobacterium* [50]. The synthesized neurotransmitter plays an important role in emotional stability, stress response and motivation. The gut microbes involved in the bidirectional communication affect the brain function and behavior and can be efficiently used to cure several psychoiatric disorders. These microbes can ultimately cross the gut brain barrier and modulate neurotransmitter receptor expression and function [60]. These interactions describes the potential of psychobiotics to directly and indirectly regulate the neurotransmitter activity through complex gut brain signaling pathways [60].

Adjustment of neurotransmitter level and their activity within the brain influence neuronal signaling and communication. These serve as crucial chemical messengers that transmit signals between neurons, supporting the complex communication throughout the nervous system. Effective neurotransmitter modulation is fundamental in regulating essential physiological functions like the mood regulation, cognition, and the response to stress [50].

Selective Serotonin Reuptake Inhibitors (SSRIs) are a class of antidepressants that inhibit the reuptake of serotonin causing an increase in serotonin levels in the synaptic cleft. The signaling increases contributing to therapeutic effects of these drugs against depression, anxiety and stress [61]. It has also been reported that medications targeting glutamate receptors, such as NMDA receptor antagonists or modulators will be more effective against such disorders [62].

GABA, as discussed earlier regulate neuronal excitation and improves mood, diminish anxiety and stress [63]. Medications and drugs that enhance GABAergic signaling are used to calm brainactivity. It has been reported that dysfunctions in such signaling of GABA and dopamine can be linked to Parkinson's disease and schizophrenia. Hence drugs to regulate these signaling can be a good therapeutic agent [64].

Glutamate serves as primary neurotransmitter in the CNS, influencing synaptic transmission and neuronal plasticity essential for brain function and cognition. The modulations of its signaling are known to maintain synaptic homeostasis. However its Dysregulation is associated with various neurological and psychiatric disorders like epilepsy, Alzheimer's disease, schizophrenia, and mood disorders [65]. Several pharmacological research targeting glutamatergic signaling is an area well studied for therapeutic development. There are reports stating the effects of ketamine on depression that were treatment resistant [66].

Cholinesterase inhibitors are other notable compounds that are widely used as medications. These drugs prevent the breakdown of Acetylcholine in the synaptic cleft, enhancing cholinergic transmission. These compounds are widely used for the treatment of Alzheimer's disease to improve cognitive function and alleviate symptoms associated with memory loss and cognitive decline [42]. Additionally, acetylcholine is reported to influence nervous system nd regulate functions like heart rate, digestion, and glandular secretion. Drugs that may selectively target muscarinic acetylcholine receptors are utilized to modulate autonomic functions, particularly in conditions like overactive bladder or certain gastrointestinal disorders [67].

The complex mechanism involved in Neurotransmitter modulation can be categorized into four namely synthesis, release, reuptake, and degradation. These processes are targeted clinically to influence neurotransmitter activity and eliminate several disorders [68].

Synthesis: This process involves several enzymatic reactions that convert the respective neurotransmitters' precursors into neurotransmitters such as serotonin, dopamine, and GABA. Clinical studies can influence this step by enhancing enzymatic activity to increase neurotransmitters production.

Release: When an action potential reaches the synaptic terminal, it triggers the release of neurotransmitters into the synaptic cleft. The release of the neurotransmitters are modulated by various factors including calcium influx into the presynaptic terminal. There are possible drugs that may alter neurotransmitter release.

Reuptake: After the release they are removed from synapse by reuptake transported located in presynaptic membrane. For example, Serotonin and dopamine uptakers respectively abbreviated as SERTs and DATs are responsible for retrieving serotonin and dopamine back into the presynaptic neuron. There are also several drugs that may inhibit these transported thereby prolonging the presence of neurotransmitters in the synapse and enhance their signaling.

Degradation: Once back in presynaptic neuron these neurotransmitters undergo degradation by enzymes like monoamine oxidase. These enzymes break down neurotransmitters into inactive metabolites. Several drugs that inhibit these enzymes may increase the level of neurotransmitters in the brain and prolong their effects.

The neurotransmitter modulation can also be achieved through several other means which typically involve lifestyle changes, diet changes, therapies and means that doent invove administration of drugs. It has been reported that physical activity and exercises have influence on neurotransmitter levels in the brain. Aerobic exercise has been proved to increase serotonin levels thereby increasing mood regulating effects [69].

Diet modulation is another important aspect having direct influence on neurotransmitter synthesis. Certain nutrient like tyrosine has a great impact on neurotransmitter synthesis and function [70]. Another important essential nutrient is Omega-3 fatty acids having beneficial effects on mental well-being. Omega 3 fatty acids are abundant in fatty fish like Salmon and Mackerel and have the ability to increase serotonin levels levels in the brain, potentially alleviating symptoms of depression [71].

Adequate sleep is another important factor that play a major role in balancing and regulating neurotransmitter balance. Sleep deprivation can disrupt serotonin and dopamine levels leading to mood disturbances and cognitive effects. It was noted that individuals who are late sleepers and those who sleep less had depression, suicidal thoughts, stress and anxiety [72].

Practicing mindfulness, yoga and meditation were found to have a positive impact on neurotransmitter release. They reduced stress hormone levels, reduced depression and calmed the nerves.

Several reports have mentioned the impact of sunlight and outdoor exposure influencing the neurotransmitter levels in body. It has been known to regulate serotonin levels, thereby having a direct effect on mood and even sleep patterns [73]. Supplementing with micronutrients such as folate, vitamin B12 and vitamin D has been found to modify neurotransmitter activity and enhance mood in individuals with depression [74].

Gut microbes can communicate bidirectionally with CNS through various pathways including the activation of vagus nerve, stimulation of endocrine cells, immune signaling and gut microbe metabolite transportation to CNS via circulation. This is the gut brain axis which the Microbiome uses to influence the brain activity and functions [39]. Psychobiotics like enteric pathogens and probiotics activate vagal nerves and modify the neurological activity, change Brain Derived Neurotropic Factor (BDNF), Gamma-Aminobutyric Acid (GABA) and oxytocin signaling within the brain [75].

Enterochromaffin cells (EC cells)

The cells present specifically in the epithelial lining of the gastrointestinal tract are enterochromaffin cells or EC cells. These cells are pivotal for the regulation of neurotransmitter modulation and gastrointestinal functions mainly due to its ability to produce and release signaling molecules like serotonin. A subset of bacteria, notably spore-forming types such as *Clostridia spp*., has recently been identified as capable of significantly promoting serotonin biosynthesis from enterochromaffin cells. In vivo studies have demonstrated that a combination of metabolites produced by these bacteria, including α-tocopherol, butyrate, cholate, deoxycholate, p-aminobenzoate, propionate, and tyramine, were found to exhibit serotonin-inducing activity in vitro [5]. Enterochromaffin cells producing serotonin may transmit signals beyond the gut to the brain, potentially intersecting with established pathways of gut-brain signaling in both developmental and acute contexts [5]. Immune-mediated signaling facilitated by the gut microbiota help in maturation of the neuroimmune system. Disruption of these microbial cues during development can lead to persistent dysfunction of this system throughout life [28].

Microbial metabolites

Microbial metabolites in the stomach enter the systemic circulation and influence several physiological functions. One significant group is polyphenolic metabolites that not usually not detectable in urine or blood. They reach the circulation at a biological active levels and has an influence on body functions [76,77]. These have been reported as inflammation mitigators and neuroprotection enhancers thereby protecting the brain and neurons. Several studies have shown that these metabolites can cross the blood brain barrier in experimental models protecting the neurons [78,79]. It has already reported by experimenting on animal models that oral polyphenol administration can reduce neurotoxic aggregation and enhances neuroplasticity [80,81].

In spite of the well-established networks between the gut and brain, the lack of mechanistic understanding of how bacterial molecules exert their effects through these pathways is a limitation. Unraveling these mechanisms holds promise for developing novel drug discovery approaches, especially in targeting gastrointestinal sites to effectively influence brain health [39,82]. Advanced current research aims to elucidate the brain cells that are directly influence microbial metabolites of gut. Studying on how these chemical messengers work on neuronal development may contribute to understanding the gut-brain axis research [83,28].

Potential New Psychobiotic Strains

The identification of potential new psychobiotic strains holds promise for advancing our understanding of the gut-brain axis and developing novel therapeutic interventions for mental health disorders [14]. Psychobiotics are live microorganisms that, when ingested in adequate amounts, confer mental health benefits through interactions with the gut microbiota and the central nervous system [84]. Many researches are focused on screening potent microbial strains with probiotic and prebiotic capabilities to modulate the neurotransmitter levels, inflammations and stress response pathways so that they can be used for creating breakthrough treatment strategies.

Some of the potential new strains include Lactobacillus rhamnosus, that has established beneficial effects on mood, anxiety, depression and stress-related behaviors in preclinical and clinical studies [85]; *Bifidobacterium longum*, another probiotic strain that has shown potential as a psychobiotic having ability to attenuate stress induced neuroendocrine and behavioural responses [86].

Lactobacillus plantarum have a strong immunomodulatory activity, while Bifidobacterium breve influence the levels of serotonin and dopamine thereby alleviating stress, anxiety and [87]. Another organism Akkermansia muciniphila though not a probiotic has been reported to improve mood and congnition increasing mental wellbeing [88].

Challenges and Considerations in Psychobiotic Therapy

Psychobiotics has evolved to be an intriguing and rapidly evolving field of study especially for therapy of psychiatric disorders [48]. They can improve mental health, reduce stress, anxiety and depression [50]. Despite the promising potential of psychobiotic therapy there are several challenges and limitations. The future scope of psychobiotic research need comprehensive clinical trial, elucidation of mechanism of action and personalized medicine approaches. The potential considerations were reported to modulation of neurotransmitters, production of metabolites and influence of HPA axis [27].

The primary challenge in gut-brain research is developing novel therapies for psychiatric disorders. The involvement of CNS, enteric system and immune system makes it more complicated [89]. Better understanding of this complexity may enable development of novel therapies and identification of potential strains.

The variability in individual gut microbiomes is another challenge in gut-brain research. The genetics, diet, lifestyle and environment are some factors that could impact the mental health posing the need for personalized medicine approach [90]. The variability of gut microbiota can affect how the individuals respond to medicines and therapies. Some reports have been published on tailoring psychobiotics to understand their role in mental health. One major challenge among the other factors is that the traditional treatment may not fit every individual and may not be efficient [91]. Another limitation is that the measurement of these psychological and behavioural outcomes is hard and difficult. Thus there is a need for advanced experimental strategies that can apprehends the mode of action of psychobiotics [84].

Another obstacle is the regulatory and standardization process. Psychobiotics are currently marketed as dietary supplements or nutraceuticals rather than pharmaceuticals or drugs [92]. This has caused a reduction in stringency in regulation affecting the quality and efficiency of psychobiotics. Hence establishing demanding standards like strain specific labeling, dosage recommendations and manufacturing practices must be encouraged for safety and effectiveness of the psychobiotics. Evolution of regulatory framework that can align with the current scientific advancements is essential to facilitate the approval of psychobiotics in market [93]. The storage conditions must also be improved so that the psychobiotics remain viable and efficient.

Immunocompromised patients or individuals may find it challenging even though normal people could consume them with safety [94]. Adverse side effects could be a challenge under such conditions. These limitations must be considered to prevent unwanted consequences [95].

Scope of psychobiotics research is multidimentional and interdisciplinary. Depression, anxiety, dementia, autism and other neurodegenerative disorders are all linked to modifications in gut microbiome [59]. Further studies on the gut-brain axis modulation could relatively help develop novel treatments. A recent study has mentioned the use of certain microbes to develop better treatment for psychiatric disorders [96].

The variability in individual responses to psychobiotic therapy, approaches in personalized method taking into consideration the individual's microbiome profile, genetic makeup, and lifestyle factors could help develop a better treatment [97]. Advances in microbiome sequencing and bioinformatics can facilitate the development of such personalized treatments. Incorporation of artificial intelligence and machine learning algorithms to predict individual responses and need could bring a vast development and novelty in therapies.

Unveiling the complex mechanism as discussed above can be another significant limitations or challenge in gut-brain axis research. Advanced techniques in genomics, metabolomics and imaging techniques may help unravel the complexities in mechanism of action. This can provide insights into the fundamental biology of mental health.

Another major consideration is the ethical regulation which must be addressed in every psychobiotic advances. Issues related to piracy, patent, privacy and consent should all be taken into consideration [94].

Conclusion

Gut-brain axis research is a exponentially advancing research in medicine. The collaboration of various fields like Microbiology, Biotechnology, Psychiatry and Psychology, Bioinformatics, Artificial Intelligence and Immunology could promise a progressive result. Besides several challenges in the psychobiotics research, integrating knowledge from various fields could lead to a better understanding of the mechanisms and therapies bringing about standardization which is essential in developing novel therapies. In conclusion, the therapy using psychobiotics has immense potential for improving mental health by modulating the gut brain axis. The scope of psychobiotic research is promising with opportunities to explore their effects on psychiatric disorders, elucidate mechanisms of action, and integrate personalized medicine approaches. The ultimate motive is to ensure an accessible and affordable therapy for all individuals without any health complications.

References

1. Canfora E E, et al. Gut microbial metabolites in obesity, NAFLD and T2DM. Nature Reviews Endocrinology. 2015; 15(5): 261-273.

2. Barrett E, Ross R P, O'Toole P W, Fitzgerald G F, Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine. Journal of applied microbiology. 2012; 113(2): 411-417.

3. Nadeem M S, Kumar V, Al-Abbasi F A, Kamal M A, Anwar F. Risk of colorectal cancer in inflammatory bowel diseases. In Seminars in cancer biology. Academic Press. 2020; 64: 51-60.

4. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. Nature reviews Gastroenterology & hepatology. 2019; 16(8): 461-478.

5. Yano J M, Yu K, Donaldson G P, Shastri G G, Ann P, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015; 161(2): 264-276.

6. Lyte M. Microbial endocrinology: Host-microbiota neuroendocrine interactions influencing brain and behavior. Gut Microbes. 2014; 5(3): 381-389.

7. Wall R, Cryan J F, Ross R P, Fitzgerald G F, Dinan T G, et al. Bacterial neuroactive compounds produced by psychobiotics. Microbial endocrinology: The microbiota-gut-brain axis in health and disease. 2014; 221-239.

8. Otaru N, Ye K, Mujezinovic D, Berchtold L, Constancias F, et al. GABA production by human intestinal Bacteroides spp: Prevalence, regulation, and role in acid stress tolerance. Frontiers in Microbiology. 2021; 12: 656895.

9. Duranti S, Ruiz L, Lugli G A, Tames H, Milani C, et al. Bifidobacterium adolescentis as a key member of the human gut microbiota in the production of GABA. Scientific reports. 2020; 10(1): 14112.

10. Heintz-Buschart A, Wilmes P. Human gut microbiome: Function matters. Trends in Microbiology. 2018; 26(7): 563-574.

11. Gao K, Mu C L, Farzi A, Zhu W Y. Tryptophan metabolism: A link between the gut microbiota and brain. Advances in Nutrition. 2020; 11(3): 709-723.

12. Hayaishi O. My life with tryptophan-never a dull moment. Protein Science. 1993; 2(3): 472-475.

13. Clarke G, Grenham S, Scully P, Fitzgerald P, Moloney R D, et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Molecular Psychiatry. 2012; 18(6): 666-673.

14. Del Toro-Barbosa M, Hurtado-Romero A, Garcia-Amezquita L E, García-Cayuela T. Psychobiotics: mechanisms of action, evaluation methods and effectiveness in applications with food products. Nutrients. 2020; 12(12): 3896.

15. Grace A A. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nature Reviews Neuroscience. 2016; 17(8): 524-532.

16. Klein M O, Battagello D S, Cardoso A R, Hauser D N, Bittencourt J C, et al. Dopamine: Functions, signaling, and association with neurological diseases. Cellular and Molecular Neurobiology. 2019; 39(1): 31-59.

17. Belujon P, Grace A A. Dopamine system dysregulation in major depressive disorders. International Journal of Neuropsychopharmacology. 2017; 20(12): 1036-1046.

18. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: Version III-the final common pathway. Schizophrenia Bulletin. 2009; 35(3): 549-562.

19. Sudo N. Role of gut microbiota in brain function and stress-related pathology. Bioscience of microbiota, food and health. 2019; 38(3): 75-80.

20. Baik J H. Dopamine signaling in reward-related behaviors. Frontiers in neural circuits. 2013; 7: 152.

21. Nieoullon A. Dopamine and the regulation of cognition and attention. Progress in Neurobiology. 2002; 67(1): 53-83.

22. Zarrindast MR, Khakpai F. The modulatory role of dopamine in anxiety-like behavior. Archives of Iranian Medicine. 2015; 18(9): 591-603.

23. Zweifel L S, Fadok J P, Argilli E, Garelick M G, Jones G L, et al. Activation of dopamine neurons is critical for aversive conditioning and prevention of generalized anxiety. Nature Neuroscience. 2011; 14(5): 620-626.

24. Faraone S V. The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. Neuroscience & Biobehavioral Reviews. 2018; 87: 255-270.

25. Charvin D, Roze E, Perrin V, Deyts C, Betuing S, et al. Haloperidol protects striatal neurons from dysfunction induced by mutated huntingtin in vivo. Neurobiology of disease. 2008; 29(1): 22-29.

26. Coccurello R, Maccarrone M. Hedonic eating and the delicious circle: From lipid-derived mediators to brain dopamine and back. Frontiers in neuroscience. 2018; 12: 271.

27. Strandwitz P. Neurotransmitter modulation by the gut microbiota. Brain Research. 2018; 1693(Pt B): 128-133.

28. Sampson T R, Debelius J W, Thron T, Janssen S, Shastri G G, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell. 2016; 167(6): 1469-1480. e12.

29. Rudolph U, Knoflach F. Beyond classical benzodiazepines: Novel therapeutic potential of GABAA receptor subtypes. Nature Reviews Drug Discovery. 2011; 10(9): 685-697.

30. Azcarate-Peril M A, Ritter A J, Savaiano D, Monteagudo-Mera A, Anderson C, et al. Impact of short-chain galactooligosaccharides on the gut microbiome of lactose-intolerant individuals. Proceedings of the National Academy of Sciences. 2017; 114(3): E367-E375.

31. Valenzuela J A, Flórez A B, Vázquez L, Vasek O M, Mayo B. Production of γ-aminobutyric acid (GABA) by lactic acid bacteria strains isolated from traditional, starter-free dairy products made of raw milk. Beneficial microbes. 2019; 10(5): 579-587.

32. Iorizzo M, Paventi G, Di Martino C. Biosynthesis of Gamma-Aminobutyric Acid (GABA) by Lactiplantibacillus plantarum in fermented food production. Current Issues in Molecular Biology. 2023; 46(1): 200-220.

33. Cataldo P, Dinardo F R, De Nisco M, Marotta F. Distribution of glutamic acid decarboxylase genes in gut microbiota suggests their potential for gamma-aminobutyric acid production. Nutrients. 2020; 12(9): 2603. https://doi.org/10.3390/nu12092603.

34. Wu Q, Shah N P. High γ-aminobutyric acid production from lactic acid bacteria: emphasis on Lactobacillus brevis as a functional dairy starter. Critical Reviews in Food Science and Nutrition. 2017; 57(17): 3661-3672.

35. Fatemi S H, Stary J M, Earle J A, Araghi-Niknam M, Eagan E. GABAergic dysfunction in schizophrenia and mood disorders as reflected by decreased levels of glutamic acid decarboxylase 65 and 67 kDa and Reelin proteins in cerebellum. Schizophrenia

research. 2005; 72(2-3): 109-122.

36. Ruivo L M T G, Baker K L, Conway M W, Kinsley P J, Gilmour G, et al. Coordinated acetylcholine release in prefrontal cortex and hippocampus is associated with arousal and reward on distinct timescales. Cell reports. 2017; 18(4): 905-917.

37. Koeth R A, et al. Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature Medicine. 2013; 19(5): 576-585.

38. Zeisel S H. Choline, other methyl-donors and epigenetics. Nutrients. 2017; 9(5): 445.

39. Cryan J F, Dinan T G. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nature Reviews Neuroscience. 2012; 13(10): 701-712.

40. Xie Z, Du J, Gan M, Zhou C, Li M, et al. Short-term dietary choline supplementation alters the gut microbiota and liver metabolism of finishing pigs. Frontiers in Microbiology. 2023; 14: 1266042.

41. Fisher A. Cholinergic modulation of amyloid precursor protein processing with emphasis on M1 muscarinic receptor: perspectives and challenges in treatment of Alzheimer's disease. Journal of neurochemistry. 2012; 120: 22-33.

42. Birks J S. Cochrane Dementia and Cognitive Improvement Group. Cholinesterase inhibitors for Alzheimer's disease. Cochrane database of systematic reviews. 1996; 2016(3).

43. Wanyi Z, Jiao Y, Wen H, Bin X, Xuefei W, et al. Bidirectional communication of the gut-brain axis: New findings in Parkinson's disease and inflammatory bowel disease. Frontiers in Neurology. 2004; 15: 1407241.

44. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014; 157(1): 121-141.

45. Round J L, et al. The gut microbiota shapes intestinal immune responses during health and disease. Nature Reviews Immunology. 2009; 9(5): 313-323.

46. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. Journal of Physiology. 2004; 558(1): 263-275.

47. Stefka A T, et al. Commensal bacteria protect against food allergen sensitization. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111(36): 13145-13150.

48. Dinan T G, Cryan J F. Brain-gut-microbiota axis and mental health. Psychosomatic medicine. 2017; 79(8): 920-926.

49. Plaza-Díaz J, Solís-Urra P, Rodríguez-Rodríguez F, Olivares-Arancibia J, Navarro-Oliveros M, et al. The gut barrier, intestinal microbiota, and liver disease: molecular mechanisms and strategies to manage. International journal of molecular sciences. 2020; 21(21): 8351.

50. Sarkar A, Lehto S M, Harty S, Dinan T G, Cryan J F, et al. Psychobiotics and the manipulation of bacteria-gut-brain signals. Trends in Neurosciences. 2016; 39(11): 763-781.

51. Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. Frontiers in neuroscience. 2018; 12: 336468.

52. De la Fuente-Nunez C, Meneguetti B T, Franco O L, Lu T K. Neuromicrobiology: how microbes influence the brain. ACS chemical neuroscience. 2018; 9(2): 141-150.

53. Rooks M G, Garrett WS. Gut microbiota, metabolites and host immunity. Nature Reviews Immunology. 2016; 16(6): 341-352.

54. McEwen B S. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiological Reviews. 2007; 87(3): 873-904.

55. Sapolsky R M. Stress and the brain: Individual variability and the inverted-U. Nature Neuroscience. 2015; 18(10): 1344-1346.

56. Grenham S, Clarke G, Cryan J F, Dinan T G. Brain-gut-microbe communication in health and disease. Frontiers in physiology. 2011; 2: 16175.

57. Ait-Belgnaoui A, Durand H, Cartier C, Chaumaz G, Eutamene H, et al. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. Psychoneuroendocrinology. 2012; 37(11): 1885-1895.

58. Andersson H, Tullberg C, Ahrné S, Hamberg K, Lazou Ahrén I, et al. Oral administration of Lactobacillus plantarum 299v reduces cortisol levels in human saliva during examination induced stress: A randomized, double-blind controlled trial. International journal of microbiology. 2016; 2016(1): 8469018.

59. Foster J A, Rinaman L, Cryan J F. Stress & the gut-brain axis: Regulation by the microbiome. Neurobiology of Stress. 2017; 7: 124-136.

60. Fung T C, Olson C A, Hsiao E Y. Interactions between the microbiota, immune and nervous systems in health and disease. Nature Neuroscience. 2017; 20(2): 145-155.

61. Stahl S M. Mood disorders and antidepressants. Cambridge University Press. 2013a.

62. Krystal J H, Mathew S J, D'Souza D C, Garakani A, Gunduz-Bruce H, et al. Potential psychiatric applications of metabotropic glutamate receptor agonists and antagonists. CNS drugs. 2010; 24: 669-693.

63. Sieghart W. Allosteric modulation of GABAA receptors via multiple drug-binding sites. Advances in Pharmacology. 2015; 72: 53-96.

64. Nutt D J. The role of dopamine and norepinephrine in depression and antidepressant treatment. Journal of Clinical Psychiatry. 2006; 67(Suppl 6): 3-8.

65. Sanacora G, Zarate Jr C A, Krystal J H, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nature Reviews Drug Discovery. 2008; 7(5): 426-437.

66. Newport D J, Carpenter L L, McDonald WM, Potash J B, Tohen M, et al. APA Council of Research Task Force on Novel Biomarkers and Treatments. Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. American Journal of Psychiatry. 2015; 172(10): 950-966.

67. Wessler I, Kirkpatrick C J, Racké K. Non-neuronal acetylcholine, a locally acting molecule, widely distributed in biological systems: Expression and function in humans. Pharmacology & Therapeutics. 1998; 77(1): 59-79.

68. Stahl S M. Mood Disorders and Antidepressants: Stahl's Essential Psychopharmacology. Cambridge university press. 2013b.

69. Dishman R K, Berthoud H R, Booth F W, Cotman CW, Edgerton V R, et al. Neurobiology of exercise. Obesity. 2006; 14(3): 345-356.

70. Wurtman R J, Wurtman JJ, Regan M M, McDermott J M, Tsay R H, et al. Effects of normal meals rich in carbohydrates or proteins on plasma tryptophan and tyrosine ratios. The American journal of clinical nutrition. 2003; 77(1): 128-132.

71. Su K P, Matsuoka Y, Pae C U. Omega-3 polyunsaturated fatty acids in prevention of mood and anxiety disorders. Clinical Psychopharmacology and Neuroscience. 2015; 13(2): 129.

72. Banks S, Dinges D F. Behavioral and physiological consequences of sleep restriction. Journal of Clinical Sleep Medicine. 2007; 3(5): 519-528.

73. Lambert G W, Reid C, Kaye D M, Jennings G L, Esler M D. Effect of sunlight and season on serotonin turnover in the brain. The Lancet. 2002; 360(9348): 1840-1842.

74. Lewis S J, Lawlor D A, Davey Smith G, Araya R, Timpson N, et al. The thermolabile variant of MTHFR is associated with depression in the British Women's Heart and Health Study and a meta-analysis. Molecular psychiatry. 2006; 11(4): 352-360.

75. Foster J A, McVey Neufeld K A. Gut-brain axis: How the microbiome influences anxiety and depression. Trends in Neurosciences. 2013; 36(5): 305-312.

76. Selma M V, González-Sarrías A, Salas-Salvadó J, Andrés-Lacueva C, Alasalvar C, et al. The gut microbiota metabolism of pomegranate or walnut ellagitannins yields two urolithin-metabotypes that correlate with cardiometabolic risk biomarkers: Comparison between normoweight, overweight-obesity and metabolic syndrome. Clinical Nutrition. 2018; 37(3): 897-905.

77. Ozdal T, Sela D A, Xiao J, Boyacioglu D, Chen F, et al. The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. Nutrients. 2016; 8(2): 78.

78. Chen M L, Yi L, Zhang Y, Zhou X, Ran L, et al. Resveratrol attenuates trimethylamine-N-oxide (TMAO)-induced atherosclerosis by regulating TMAO synthesis and bile acid metabolism via remodeling of the gut microbiota. MBio. 2016; 7(2): 10-1128.

79. Wang L, Hu L, Yan S, Jiang T, Fang S, et al. Effects of different oligosaccharides at various dosages on the composition of gut microbiota and short-chain fatty acids in mice with constipation. Food & Function. 2017; 8(5): 1966-1978.

80. Farr S A, Niehoff M L, Ceddia M A, Herrlinger K A, Lewis B J, et al. Effect of botanical extracts containing carnosic acid or rosmarinic acid on learning and memory in SAMP8 mice. Physiology & behavior. 2016; 165: 328-338.

81. Zhang L, Xu T, Wang S, Yu L, Liu D, et al. Curcumin produces antidepressant effects via activating MAPK/ERK-dependent brain-derived neurotrophic factor expression in the amygdala of mice. Behavioural brain research. 2012; 235(1): 67-72.

82. Sharon G, Sampson T R, Geschwind D H, Mazmanian S K. The central nervous system and the gut microbiome. Cell. 2016; 167(4): 915-932.

83. Erny D, Hrabě de Angelis A L, Jaitin D, Wieghofer P, Staszewski O, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nature neuroscience. 2015; 18(7): 965-977.

84. Dinan T G, Stanton C, Cryan J F. Psychobiotics: A novel class of psychotropic. Biological psychiatry. 2013; 74(10): 720-726.

85. Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, et al. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. British Journal of Nutrition. 2011; 105(5): 755-764.

86. Bercik P, Park A J, Sinclair D, Khoshdel A, Lu J, et al. The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. Neurogastroenterology & Motility. 2011; 23(12): 1132-1139.

87. Savignac HM, Kiely B, Dinan TG, Cryan J F. Bifidobacteria exert strain-specific effects on stress-related behavior and physiology in BALB/c mice. Neurogastroenterology & Motility. 2014; 26(11): 1615-1627.

88. Reunanen J, Kainulainen V, Huuskonen L, Ottman N, Belzer C, et al. Akkermansia muciniphila adheres to enterocytes and strengthens the integrity of the epithelial cell layer. Applied and environmental microbiology. 2015; 81(11): 3655-3662.

89. Mayer E A, Knight R, Mazmanian S K, Cryan J F, Tillisch K. Gut microbes and the brain: paradigm shift in neuroscience. Journal of Neuroscience. 2014; 34(46): 15490-15496.

90. Turnbaugh P J, Ley R E, Mahowald M A, Magrini V, Mardis E R, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006; 444(7122): 1027-1031.

91. Hill C, Guarner F, Reid G, Gibson G R, Merenstein D J, et al. Activity of cecropin P1 and FA-LL-37 against urogenital microflora. Nature Reviews Gastroenterology and Hepatology. 2014; 11(8): 506.

92. Sanders M E, Guarner F, Guerrant R, Holt P R, Quigley E M, et al. An update on the use and investigation of probiotics in health and disease. Gut. 2013; 62(5): 787-796.

93. Gibson G R, Hutkins R, Sanders M E, Prescott S L, Reimer R A, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nature reviews Gastroenterology & hepatology. 2017; 14(8): 491-502.

94. Venugopal G, Manikkam R, Manigundan K, Usha Nandhini S, Saravanan T S, et al. Isolation and Identification of Probiotics Microorganisms. In Postbiotics. New York, NY: Springer US. 2023; 3-11.

95. Didari T, Solki S, Mozaffari S, Nikfar S, Abdollahi M. A systematic review of the safety of probiotics. Expert opinion on drug safety. 2014; 13(2): 227-239

96. Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linløkken A, et al. Correlation between the human fecal microbiota and depression. Neurogastroenterology & Motility. 2014; 26(8): 1155-1162.

97. O'Toole P W, Jeffery I B. Gut microbiota and aging. Science. 2015; 350(6265): 1214-1215.