CRITICAL REVIEW:

EXPLORING THE COGNITIVE EFFECTS OF PSYCHOBIOTICS ON GUT MICROBIOTA

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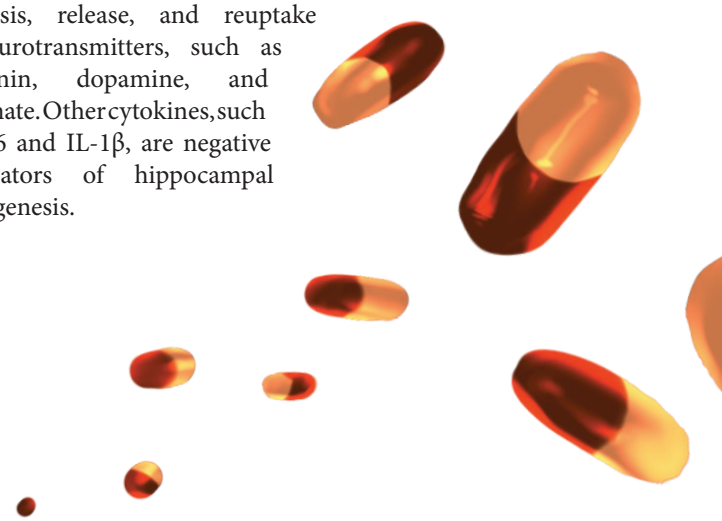
ABSTRACT

The human gastrointestinal (GI) tract houses an abundance of microorganisms which make up an environment known as the gut microbiome. Its composition is affected by a variety of factors, including the method in which an individual was born, antibiotic use, diet, and environmental exposures. Gut microbes engage in bidirectional communication with the host through the gut-brain axis, which connects the central and enteric nervous systems through neural, hormonal, and immunological signalling pathways. Therefore, the various microbes housed in the GI tract can have an effect on brain functioning and mental health through this axis of communication. Rates of mental disorders, such as depression and anxiety, have been on the rise, increasing significantly after the COVID-19 pandemic. The steady increase continues to occur despite the introduction of treatments and medications, which highlights the crucial need for novel and innovative therapies. This piece explores the relationship between the gut microbiome and various mental health disorders, as well as the potential of psychobiotics as a novel treatment strategy.

THE LINK BETWEEN GUT MICROBIOTA AND MENTAL HEALTH

The gut-brain axis is a bidirectional communication channel that links the enteric nervous system and central nervous system (CNS). Bacteria residing in the gut can affect the brain through various pathways such as traveling through the bloodstream, causing hormone release from enteroendocrine cells, inducing cytokine release from mucosal immune cells, and influencing afferent nerve pathways such as the vagus nerve. Conversely, psychological stress can affect microbial composition by altering the intestinal environment and interrupting bacterial signalling through the introduction of stress hormones, such as noradrenaline.[4] Gut microbial composition is different in patients with mental health disorders when compared to a healthy population. A majority of the human microbiome is composed of the Phyla Firmicutes and Bacteroidetes.[5] In a study done by Jiang et al., patients with major depressive disorder (MDD) were found to have increased Bacteroidetes, Proteobacteria, and decreased Firmicutes in their fecal matter compared to the general population. Focusing on genera, patients with MDD had more Enterobacteriaceae, Alistipes, and less Faecalibacterium, while those who exhibited severe depressive symptoms had a reduced quantity of Faecalibacterium in their gut microbiome.[6] Furthermore, carbohydrate malabsorption, the inability of the GI tract to absorb carbohydrates appropriately resulting in bacterial fermentation, has been associated with depressive symptoms in adult women.[7] Microbiota also modulate the release of cytokines, which have been shown to influence human behaviours. Higher levels of pro-inflammatory cytokines, such as IL-4 and INF-γ, have been demonstrated in disorders including depression.[8] These cytokines affect the synthesis, release, and reuptake of neurotransmitters, such as serotonin, dopamine, and glutamate. Other cytokines, such as IL-6 and IL-1β, are negative modulators of hippocampal neurogenesis.



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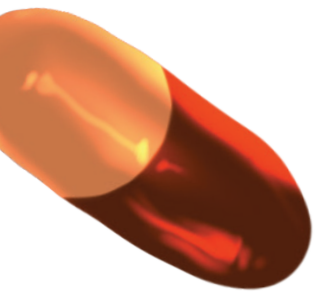
Dysregulation of hippocampal neurogenesis is associated with psychological symptoms in various disorders, such as depression, schizophrenia, and addiction.[9,10] Additionally, there is strong evidence to implicate a causal role of the gut microbiome in the mechanisms behind the development of depression. Fecal microbiota transplantation from human patients with depression to rats with depleted microbiota induced behavioural and physiological characteristics associated with depression, including anxiety-like behaviours and changes in tryptophan metabolism.[11]

Generalised anxiety disorder is another common mental illness that displays microbial dissimilarities. Compared with a healthy population, patients had a lower prevalence of Faecalibacterium, *Eubacterium rectale*, Lachnospira, Butryicicoccus, and Sutterella in their gut microbiome.[6] These genera are involved in the production of short-chain fatty acid (SCFA) compounds that, when insufficiently produced can compromise immune responses and further contribute to brain abnormalities.[12-14] Furthermore, stress and the microbiome have a two-way connection.[3] Certain gut bacteria are capable of reducing symptoms of stress and anxiety. In particular, Lactobacilli increases γ-Aminobutyric acid (GABA) levels in the CNS, a neurochemical essential for inhibitory responses and controlling feelings of stress and fear, by activating GABA signalling pathways in the vagus nerve.[15] A study conducted by Crumeyrolle-Arias et al. on germ free (GF) mice demonstrated an amplified hormonal stress response system known as the hypothalamic–pituitary–adrenal (HPA) axis. GF mice had a higher expression of the corticotropin-releasing hormone gene compared to healthy mice, which caused a hypersecretion of stress-related hormones, such as adrenocorticotropic hormone and corticosterone. Anxiety-like behaviours associated with novel challenges, such as social interaction or exposure to an open environment, increased in GF mice as they were observed to defecate more and spend more time hiding in corners. The reintroduction of gut microbiota into the mice that were genetically prone to anxiety was shown to reduce their stress- and anxiety-related behaviours, suggesting a link between the HPA axis and gut microbes.[16] GF mice also exhibit increased tryptophan metabolites, such as kynurenic acid, due to the absence of the bacterial metabolism of tryptophan. Kynurenic acid inhibits excitatory amino acid receptors, which is also observed in psychiatric illnesses like schizophrenia.[13]



Inversely, stress responses can lead to an imbalance in one's microbiome composition, a condition known as dysbiosis. If left untreated, dysbiosis leads to the development of chronic gastrointestinal illnesses, such as irritable bowel syndrome.[3] Stress exhibited by the host organism changes the habitat of gut bacteria by reducing the quality of the gut epithelium and interfering with gene expression and signalling due to the presence of the stress hormone noradrenaline.[3,17] Studies with adult mice exposed to stress demonstrate decreased Bacteroides and increased Clostridium compared to controls, which cause the intestinal barrier to become more permeable, facilitating circulation of bacterial components.[18] Further, studies in humans found bacterial translocation in other parts of the body in stress-related psychiatric disorders. Specifically, the translocation of bacterial components, such as lipopolysaccharides, can trigger inflammatory responses and induce depressive behaviours.[19]

PSYCHOBIOTICS: A POSSIBLE TREATMENT SOLUTION

Psychobiotics, encompassing probiotics and prebiotics, are live organisms that can improve mental health by promoting a favourable balance of gut bacteria when consumed in sufficient amounts.[17] The most commonly known psychobiotics are *Lactobacillus* and *Bifidobacterium*,[17] which have demonstrated utility in alleviating symptoms of CNS disorders, such as depression, anxiety, and schizophrenia.[18]

In 2020, Tian et al. conducted a study inducing chronically stressed male mice with *Bifidobacterium breve* CCFM1025 five weeks prior to behavioural testing.[19] Neurological changes in the brain, levels of corticosterone in the serum, cytokine levels, composition of fecal microbes, and the content of SCFA were assessed.[19]

The effect of SCFA on 5-hydroxytryptophan (5-HTP), a precursor of serotonin, was measured using an in vitro model of enterochromaffin cell.[19] The *B. breve* CCFM1025 treatment showed a considerable decrease in chronic stress through the increased production of beneficial metabolites and modification of neurotransmission in the brain.[19] Under conditions of prolonged stress, CCFM1025 was shown to modify the gut microbial composition, thereby decreasing the heightened levels of hyperfunction and inflammation in the HPA axis.[19] The in vitro treatment observed a positive correlation between CCFM1025 and 5-HTP.20 In contrast, *Bifidobacterium pseudolongum*, a Bifidobacteria in the intestine with an unknown physiological function had a negative correlation to 5-HTP.[21] Brain-derived neurotrophic factor (BDNF), a factor that stimulates and controls the growth of new neurons, experienced an increase in response to CCFM1025, while c-Fos, a marker for neuronal activity, was decreased.[22,23]

Although positive results were observed, all of the data generated from the Tian et al. study used male mice, despite depression in humans being more prevalent among females.[19] Future studies should assess antidepressant-like effects of CCFM1025 in female mice before delving into clinical studies. The study also did not specify which metabolites produced by CCFM1025 contributed to the observed antidepressant-like effects. To address this gap, a metabolomics-based analysis of CCFM1025 should be conducted.[19]

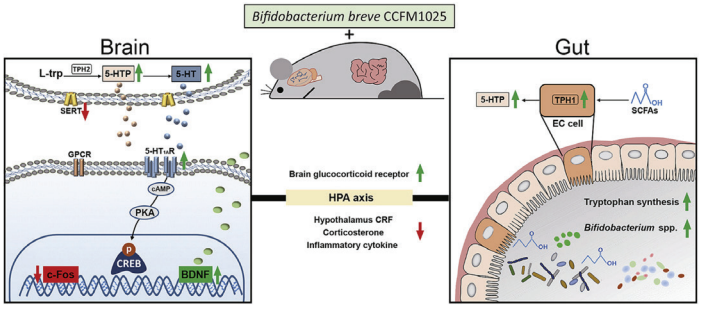


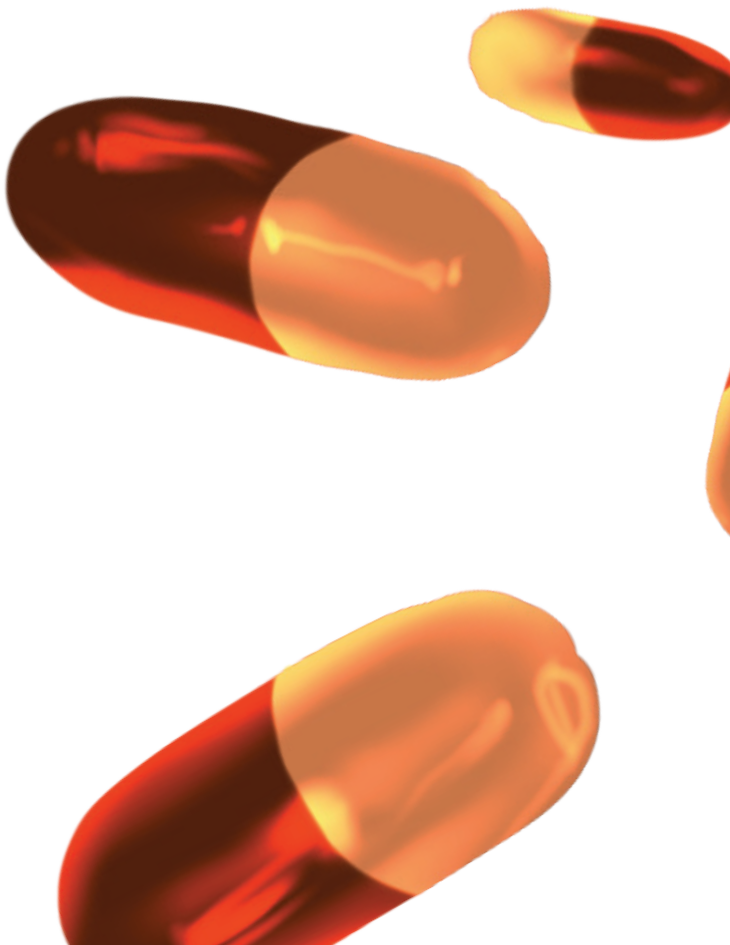
Figure 1. Metabolic pathways of *B.breve* CCFM1025 inducing antidepressant-like effects via reshaping gut microbial composition and increasing the production of beneficial metabolites, reducing inflammation in the HPA axis, upregulating BDNF expression and downregulating c-Fos in the brain.[19]

The results of Tian et al.'s study are confirmed by a randomized controlled trial, which compared the effectiveness of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 to a prebiotic supplement in individuals diagnosed with MDD and taking antidepressant medication.[24] Using the Beck's Depression Inventory (BDI), a significant decrease in BDI scores was seen eight weeks later in participants on the probiotic formula compared to the placebo group.[24] In contrast to probiotics, the study noted that supplementation with prebiotics, non-digestible nutrients that nourish gut bacteria, did not yield any significant effects.[24,25] A decrease in the kynurenine to tryptophan ratio for the group taking the probiotics suggests that probiotics may improve depressive symptoms.[24]

However, limitations in the analysis of the fecal microbiome do not provide sufficient confidence in these results as the human gut microbiota is highly variable and may have directly impacted the response of the participants consuming the probiotic formula.[24] Furthermore, the intervention was conducted at different times throughout the year.[24] Therefore, seasonal changes in lifestyle and diet may have altered the effect of the probiotic.

CONCLUSION

The gut-brain axis has prompted new areas of research to find safer and more effective alternatives to current antidepressants, which carry safety concerns and many side effects. Further human studies are required to identify the mechanism of action of psychobiotics in relation to mental health, specific bacterial strains yielding maximum benefit, and the implications of using psychobiotics as a clinical therapy for CNS disorders. Despite the limitations of current studies, existing data demonstrates that psychobiotics are unlikely to produce adverse events and are safe for long-term use. Further research on the effect of specific strains of bacteria on the CNS in humans may provide better insight on the use of diet and supplements as a treatment option for the management of CNS disorders, such as depression and anxiety.



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Dr. Miranda Green is a recent PhD graduate from the Foster lab. Her research focuses on the relationship between the microbiome, immune system and brain. Her work has been published in renowned journals such as the International Journal of Molecular Sciences and Frontiers in Bioengineering and Biotechnology.

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