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RESEARCH ARTICLE

MICROBIAL MATTERS: EXPLORING THE ROLE OF THE MICROBIOTA IN DEPRESSION

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ABSTRACT

Depression, a pervasive mental health disorder, presents a multifaceted etiology prompting extensive investigation. Recent studies implicate the gut microbiota in mood regulation, emphasizing the gut-brain axis as a potential mediator of depressive symptoms. This review aims to comprehensively explore the role of the microbiota in depression, focusing on neural function, neurotransmitter synthesis, and immune modulation. Through a meticulous literature review, we synthesized current research findings to elucidate the bidirectional communication pathways of the gut-brain axis and the microbiota's contribution to depression development and manifestation. Dysbiosis, characterized by alterations in microbial composition, consistently correlates with depressive symptoms, with environmental factors such as diet, stress, and medications influencing gut microbiota and mental health outcomes. Key observations regarding the relationship between gut microbiota and depression are highlighted, including its impact on depressive symptoms, alterations in gut microbiota composition in patients with major depressive disorder, and the role of the vagus nerve in the gut-brain axis. Specific bacteria, particularly Lactobacillus, demonstrate significant roles in mental health, exerting anti-inflammatory effects and resilience to stress. Therapeutic interventions such as fecal microbiota transplantation (FMT) and probiotics show promise in alleviating depressive symptoms by restoring gut microbiota equilibrium. Additionally, dietary interventions rich in prebiotic fiber and fermented foods exhibit beneficial effects on gut microbiota and mental health. The review also discusses markers of depression and neuroimaging assessments, along with epigenetic mechanisms modulated by probiotic bacteria. Future research directions should focus on elucidating the complex interactions within the gut-brain axis and exploring novel microbiota-based interventions to improve mental health outcomes. In conclusion, this review underscores the significant role of the gut microbiota in depression and highlights the potential for microbiota-targeted interventions in mental health care. Understanding microbial influences on mood regulation is crucial for developing personalized therapeutic strategies for individuals with depression.

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INTRODUCTION

Depression is a pervasive mental health disorder with complex etiology, prompting ongoing investigation by researchers and practitioners worldwide. Recent studies have implicated the gut microbiota in mood regulation, introducing the concept of the gut-brain axis as a potential mediator of depressive symptoms. This review aims to explore the role of the microbiota in depression, investigating its influence on neural function, neurotransmitter synthesis, and immune system modulation.

Purpose: The purpose of this review is to examine the bidirectional communication pathways of the gut-brain axis and elucidate how the gut microbiota contributes to the development and manifestation of depression. By synthesizing current research findings, we aim to provide insights into the mechanisms underlying microbial influences on mood regulation and explore potential therapeutic interventions targeting the microbiota to alleviate depressive symptoms.

METHODS

A comprehensive literature review was conducted to gather relevant studies exploring the relationship between the gut microbiota and depression. Electronic databases including PubMed, PsycINFO, and Web of Science were searched using predefined keywords related to depression, gut microbiota, and microbial interventions. Studies were selected based on their relevance to the topic and quality of evidence.

Observations/findings: The review revealed a growing body of evidence supporting the involvement of the gut microbiota in depression. Mechanisms such as neurotransmitter production, immune system modulation, and gut barrier integrity were identified as key pathways through which the microbiota influences mood regulation. Dysbiosis, characterized by alterations in microbial composition, was consistently associated with depressive symptoms.

Furthermore, environmental factors including diet, stress, and medications were found to impact the gut microbiota and subsequently affect mental health outcomes. Microbiota-targeted interventions such as probiotics, prebiotics, and fecal microbiota transplantation showed promise in alleviating depressive symptoms. Based on the provided information, several key observations can be made regarding the relationship between gut microbiota and depression:

Impact of Gut Microbiota on Depressive Symptoms: Gut microbiota have been thought to influence the host's mental health and vice versa through the microbiota-gut-brain-axis. Intestinal dysbiosis has been correlated to the severity of depression and this in turn produces gastrointestinal symptoms such as irritable bowel syndrome (IBS) forming a positive feedback loop . Experimental rats receiving faecal microbiota from depressed patients exhibited depressive symptoms; indicating that changes in gut flora can affect behaviour . The concept of utilizing faecal microbiota transplantation (FMT) as a potential treatment alternative for patients suffering from depression and other mental health conditions; suggests a direct link between gut microbiota and brain chemistry . The idea of administering oral capsules has also been proposed as a better choice over transplantation since it eliminates risks associated with the procedure.

Gut microbiota have also been shown to affect the release of neurotransmitters. In depressive disorders where exists a deficiency of 5-HT in the brain, the gut microbiota produce tryptophan that crosses the impaired blood brain barrier (BBB) giving rise to precursors of 5-HT in order to make up for its deficiency (2). Certain bacteria such as Lactobacillus plantarum and Bifidobacterium adolescentis were reported to be producers of gamma-aminobutyric acid (GABA) and displayed a similar efficacy as Fluoxetine on experimental rodents (2). Bifidobacterium infantis was found to restore noradrenaline (NE) levels back to normal in depressed mice models (2). Colonization by certain Bacteroides species was found to aggravate depression by depleting levels of serotonin (2). Moreover, gut microbiota were found to regulate neuroinflammation, behaving as neuroprotective agents. Certain harmful bacteria disrupt the blood brain barrier (BBB) causing neuroinflammation which resulted in redirection of tryptophan metabolism towards kynurenine pathway giving rise to neurotoxic quinolinic acid, affecting astrocyte function and producing depressive symptoms (2). Metabolites produced by the gut microbiota play a role in the hypothalamic-pituitary-adrenal axis (HPA axis). Cytokines released due to gut dysbiosis, and inflammation affect the HPA axis, activating the innate immune system, modulating steroidogenesis and ultimately resulting in depression (2).

Changes in Gut Microbiota Composition: A number of factors have been known to modulate the composition of the human gut microbiota, with disease occurring when their balance is extremely disturbed. Several experiments were conducted on both humans as well as rodent models in order to explore the composition of the gut microbiota. Gut dysbiosis is associated with mental health disorders such as depression; with studies showing a reduction in the number of anti-inflammatory bacteria and increase in the pro-inflammatory ones . Bacteroidetes and Firmicutes are the two dominant phyla that colonize the gastrointestinal system of humans; and have been documented to be the most affected in patients suffering from depression.

Patients with Major Depressive Disorder (MDD) were found to possess a greater number of Enterobacteriaceae and Alistipes and fewer butyrate producers such as Faecalibacterium, Coprococcus, and Dialister when compared to their healthy counterparts of the same age, gender and Body Mass Index (BMI) . In addition, metabolites of tryptophan such as indole and its derivatives, produced by organisms like Escherichia coli have been found to play a role in causing depression, anxiety and other mood disorders . Overall, these changes in the composition of the gut microbiota disrupt the intestinal epithelium resulting in gut microbial translocation producing inflammatory response which in turn contributes to the pathogenesis of depression.

Antidepressants are reported to exert anti-microbial effects on the GIT, thus resulting in restoration of the gut microbiota equilibrium. Treatment with antidepressants produces variation in the diversity of stool microbiota, where remission was associated with greater diversity . Moreover, individuals with a lower microbial diversity preceding antidepressant therapy were found to have a poorer prognosis in the long term, thus failing to achieve remission .

Role of Vagus Nerve in Gut-Brain Axis: SSRIs have been found to increase the vagal activity in control groups, which suggests that there's a potential mechanism for their antidepressant effects. The enteric nervous system communicates with the GM and there is a transmission of signals to the CVS. Antidepressant effect of probiotics relies on the integrity of vagus nerve. One study divided the sub-diaphragmatic portion of the vagus nerve in depressed rodents which resulted in decrease of depression symptoms and also affected the composition of the GM. Some bacteria, such as L. rhamnosus, also exert anxiolytic effects through the vagus nerve.

SOV (sub diaphragmatic vagotomy) has been shown to block the development of depression-like phenotypes which occur-due to certain bacteria. Bravo et al. (2011) reported that Lactobacillus rhamnosus attenuated stress-induced depression-like behaviours in mice compared with controls, and that vagotomy blocked the effects of Lactobacillus rhamnosus in brain. We previously reported that sub-diaphragmatic vagotomy (DV) attenuated depression-like behaviours, higher levels of pro-inflammatory cytokines (i.e., interleukin-6 (IL-6) and tumor necrosis factor (TNFa)), decreased expression of synaptic proteins and abnormal composition of the out microbiota in mice after administration or LPs (shang et al. 2020)

Role of Specific Bacteria, Particularly Lactobacillus, in Mental Health: Some strains of Lactobacillus display anti-inflammatory effects and increase serotonin release which is similar to the mechanism of action of SSRIs. The usage of specific lactobacillus strains negatively affects the activation of inflammatory markers involved in depression. Lactobacillus spp and Bifidobacterium spp. are the most widely studied probiotics in depression . These bacteria can produce lactic acid as their primary metabolic end-product and are able to survive the various Physiological stressors down the gastrointestinal tract, thus qualifying them as preferred probiotics.

Lactobacillus and Bifidobacterium probiotics displayed drastic effects on the augmentation of BDNF levels in patients

suffering from depression. L.helveticus R0052 and B. longum R0175 are the most commonly studied probiotics associated with such an effect on the BDNF levels in depression

Resilience to Stress: Resilience to chronic social defeat stress (CSDS) in rodents is associated with higher levels of specific bacteria, such as Bifidobacterium, suggesting a potential role of gut microbiota in resilience. Furthermore, oral administration of Bifidobacterium significantly increased the number of resilient mice suggesting that Bifidobacterium confers resilience. It has also been reported that betaine supplementation contributes has anti-inflammatory effects that promote resilience to anhedonia. Moreover, the genera Lactobacillus, Clostridium cluster III, and Anaerofustis were relatively higher in LH susceptible whereas acetic acid and propionic acid were lower in the faeces of LH susceptible rats. These findings support the role of brain–gut–microbiota axis in susceptibility and resilience to stress .

Therapeutic Interventions: Faecal microbiota transplantation (FMT) and probiotics have shown promise in improving depressive symptoms, possibly by restoring abnormalities in gut microbiota composition. Various case reports, meta-analyses, and systematic reviews have also shown improvement in depressive symptoms in patients treated with FMT. Nonetheless, definitive conclusions cannot be concluded from FMT clinical trials of patients with depression due to limited studies enlisting short-term and long-term adverse events (4). Dietary interventions, such as fruits and vegetables rich in prebiotic fiber, fermented foods, whole grains, and legumes are constituents of a psychobiotic diet that have been proven to ameliorate depressive symptoms. Several studies demonstrated profound changes in microbial diversity, increased abundance of Lactobacillus and Bifidobacterium, and reduced inflammatory markers .

Probiotics have also been demonstrated to possess comparable effectiveness to antidepressants with similar mechanism as SSRIs resulting in serotonin synthesis, having favourable side-effect profiles and no associated stigma barriers. Lactobacillus spp. and Bifidobacterium spp. are the most widely studied probiotics in depression. These catalase-negative bacteria produce lactic acid as their primary metabolic end-product of carbohydrate fermentation and confer abilities to survive the various physiological stressors down the gastrointestinal tract, key features qualifying them as preferred probiotic candidates. They also have the most significant effect on the augmentation of BDNF (brain-derived neurotrophic factor) levels in patients with depression . Administration of specific lactobacillus strains have also shown to inhibit activation of TNF alpha and NF-B which are involved in pathogenesis of depression . The most recent studies have further concluded that combined strains have better health outcomes than single strains of probiotics. Cumulatively, combined probiotic strains of Lactobacillus and Bifidobacterium spp. remain an ideal option for their significant anti-depressive potential . Certain studies demonstrated distinct stress-alleviating effects of probiotics including improved mood and overall psychological well-being assessed through a self-reported measures such as hospital anxiety and depression scale (HADS) as well as reduced free urinary cortisol levels indicating their usefulness as a preventive intervention in MDD.

Limitations of probiotics include observable discrepancies and inconsistencies among the findings of various studies on the gut microbial profile of depressed subjects, mainly in terms of identified bacterial genus and species possibly due to varying age groups, health status, lifestyle, and receptivity of the study subjects along with technical aspects of the study . Other aspects to be considered include factors such as type of strains, dose, administration method, clinical outcome, host factors, and practical applicability and feasibility in a clinical setting .

Prebiotics like inulin and FOS (fructooligosaccharides) as well as phytochemicals like resveratrol, quercetin, chlorogenic acid etc increase the abundance of beneficial bacteria including Bifidobacterium, Lactobacillus, Faecalibacterium, and Anaerostipes. Such microbes release mood-regulating neurotransmitters like GABA, serotonin, norepinephrine, and dopamine as well as produce SCFAs (short-chain fatty acids) including butyrate, which have anti-inflammatory and neuroprotective effects. SCFAs can cross the blood-brain barrier, affecting mood and behaviour . Thus, they have been implicated in ameliorating depression-related symptoms, while disturbances in bile acid metabolism are associated with depressive symptom severity . Synbiotics, which combine probiotics and prebiotics, and postbiotics and inanimate microbial components also offer potential therapeutic benefits for depression .

Markers of Depression and Neuroimaging:

Certain microbial markers which have been found in the faeces of individuals suffering from depression, along with neuroimaging assessments, may aid in the diagnosis of depression, potentially allowing for personalized treatment approaches. The most common biomarkers include elevation of stress hormones mainly serum corticosterone levels, pro-inflammatory cytokines (TNF-alpha, IL-1β, IL-4, IL-8, and IL-10), and altered levels of neurotransmitters (including 5-hydroxytryptamine (5-HT), dopamine (DA), norepinephrine (NE), gamma-aminobutyric acid (GABA), and neurotrophin, brain-derived neurotrophic factor (BDNF)). Along with Structural and functional evaluation of the frontolimbic regions, amygdala, and hippocampus, which are done using magnetic resonance imaging (MRI) . Certain microbial markers, along with neuroimaging assessments, may aid in the diagnosis of depression, potentially allowing for personalized treatment approaches.

Epigenetic Mechanisms: depression is influenced by activation or silencing of multiple genes due to environmental factors, involving gut microbes and related metabolites; This involves three pathways: post-translational histone modifications, RNA interference, and DNA methylation. Studies showed that DNA methylation is mainly presented with a suppressive effect on gene transcription, on the other hand, histone acetylation and succinylation sites on lysine is associated with a gene induction effect in the hippocampus. In addition, probiotics like lactobacilli and E.coli, exerted a prophylactic and annuling epigenetic effects which had a potential effect on mRNA expression on DNA and histone modifiers . Probiotic bacteria can modulate host epigenetic patterns, potentially influencing depressive outcomes through DNA methylation and histone modifications.

Future Directions: Further research is needed to elucidate the complex relationship between gut microbiota and depression, including the mechanism of brain–gut–microbiota axis, the pathogenesis of depression, the effect of antidepressant and the

potential use of machine learning and metabiotics in precision psychiatry. Further research is needed to elucidate the complex relationship between gut microbiota and depression, including the potential use of machine learning and metabiotics in precision psychiatry

CONCLUSION

The findings of this review underscore the significant role of the gut microbiota in depression and highlight the potential for microbiota-targeted interventions in mental health care. Understanding the mechanisms underlying microbial influences on mood regulation is crucial for developing personalized and effective therapeutic strategies for individuals with depression. Future research should focus on elucidating the complex interactions within the gut-brain axis and exploring novel microbiota-based interventions to improve mental health outcomes.

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