REVIEW ARTICLE

Microbiome Dysbiosis in Depression: A Narrative Review

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ABSTRACT

The comprehensive exploration of the microbial composition of the gut and its role in depression underscores a complex interplay involving alterations in gut microbiome, immune pathways, and inflammatory control. Studies reveal potential biomarkers and therapeutic targets linked to depression, with particular bacterial genera correlated with the severity of depressive symptoms. The dysregulation extends to disruptions in metabolic pathways and functions of bacterial proteins within the gut, contributing to intestinal barrier dysfunction and increased gut permeability. Notably, alterations in microbial composition are observed in various depressive conditions, including major depressive disorder (MDD), post-stroke depression (PSD), and depression during neoadjuvant cancer treatment. The influence of the gut microbiome on the central nervous system and the bidirectional relationship between depression and microbial changes are highlighted. Regulatory interventions, including antidepressants and probiotics, show promise in modulating the gut microbiome and alleviating depressive symptoms. The combination of probiotics with antidepressants emerges as a potential strategy for inducing a balanced microbiome. However, a lack of consensus exists regarding specific bacterial taxa associated with depression, emphasizing the need for further research to refine the therapeutic approaches for managing depression and related mood disorders. This review aims to explore the relationship between microbiome dysbiosis and depression, highlighting the role of dysbiosis as a potential contributing factor to depressive symptoms.

Keywords
Depression, Microbiome, Gut-brain axis, Probiotic

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Received: 24th March 2022; Accepted: 5th May 2024

Doi: https://doi.org/10.31436/imjm.v23i03

INTRODUCTION

Depression is a severe mental illness that has affected more than 264 million individuals worldwide.[1] Mental health problems occur due to various factors that trigger inner conflicts-the more exposure to the risk factors, the more prominent would be the impact on the mental health status. Craving for more prominent self-governance, strain to adjust with peers and overuse of technology are factors that lead to mental health issues.[2] Recently, there has been a significant interest in the connection between depression and the gut-brain axis, which acts as a means of communication between the enteric and central nervous systems.[3]

The human microbiome comprises microorganisms that reside on or within humans, including the skin, oral cavity, gut, upper respiratory tract, and lower genitourinary tract. The role of the gut microbiome in promoting an individual's health is so important, that it led to the development of the Human Microbiome Project (HMP), which utilises 16S rRNA gene sequencing, metagenomic sequencing, and taxonomic profiling.[4] Microbiome dysbiosis has been suggested to be involved in depression. The emergence of advanced molecular and metagenomic techniques can provide clear evidence of the association between mental disorders and the dysbiosis of the gut microbiome.[5]

Major depression pathophysiology has been associated with the dysfunction of the brain, immune system, hypothalamus-pituitary-adrenal axis (HPA), and gut-brain axis (GBA). A prior investigation led by Alvarez-Mon and colleagues revealed an elevation in bacterial translocation across the gut mucosa in individuals experiencing depression.[6] In addition, stress has also been reported to cause alteration of total bacterial numbers that may mount to dysbiosis.[7] The alteration may potentially affect the mood of an individual via the HPA axis. The HPA system includes the brain's limbic system, adrenal glands, and vagus nerve, which features the amygdala, which rules the "fight or flight" response.[8] Previous studies also reported that stress could raise the released amount of cortisone through the HPA axis. The increased cortisone level can in turn lead to anxiety and altered bowel movement, affecting the intestinal microbiome.[9]

The current treatments for depression are chemical-based such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and norepinephrine and dopamine reuptake inhibitors (NDRIs). Given this predominant reliance on medication, further studies need to be conducted to explore the potential involvement of dysbiosis in depression. Therefore, this review was undertaken to summarize all available evidence regarding the correlation between microbiome dysbiosis and depression, aiming to provide insights into alternative therapeutic approaches.

Microbial composition and their role in depression

In a comprehensive exploration of the link between gut microbiota, immune pathways, and inflammatory control in major depressive disorder (MDD), a previous study by Caso and colleagues (2021) observed higher levels of inducible nitric oxide synthase, oxidative stress, and lipopolysaccharide (a bacterial translocation marker) in individuals with active MDD compared to healthy controls. This indicated a potential dysregulation in the immune pathway in MDD, characterised by increased inflammation. Differential alterations in bacterial genera were identified, with elevated *Bilophila* and *Alistipes* levels and reduced *Anaerostipes* and *Dialister* levels in MDD patients, particularly those with active MDD. These findings suggest a potential connection between gut microbiota, immune pathways, and the severity of depression.[10]

Another study done by Zhang et al. (2021) delved into the composition of the gut microbiome and its association with sleep quality in MDD patients. Significant differences in 48 microbiota targets were discovered between MDD patients and healthy controls, with specific targets linked to depression severity, sleep quality, and insomnia severity. Notably, the genera *Dorea* and *Intestinibacter* were negatively correlated to both depression and sleep quality, while *Coprococcus* and *Intestinibacter* were positively correlated to sleep quality independently of depression severity. These results propose that alterations in gut microbiota could serve as potential biomarkers or treatment targets for enhancing sleep quality in individuals with MDD.[11]

In the investigation of major depressive disorder (MDD) and selective serotonin reuptake inhibitor (SSRI) use, researchers studied older adolescents and younger adults. While no significant differences in bacterial richness or diversity were observed between the groups, and no specific bacterial taxa were associated with MDD or SSRI use, the study suggests that the relationship between gut bacteria and MDD or SSRI use in this age group may be complex and necessitate further exploration.[12]

A pilot study by Lai et al. (2021) explored the correlation between gut microbial abundances and depressive symptoms during neoadjuvant chemotherapy and radiation therapy for rectal cancer. Depressive symptoms were found to be significantly higher at the end of the treatment, with certain gut microbial taxa positively or negatively correlated with these symptoms. This suggests a potential link between gut microbiota and depressive symptoms in rectal cancer patients undergoing treatment.[13]

Additionally, gut microbiome diversity, both within and between individuals, was identified as a predictor of depressive symptom levels across different ethnic groups, potentially contributing to ethnic disparities in depression.[14] Specific differential genera in the gut microbiome were suggested to be associated with the severity of MDD, with these genera categorised into

different phyla for moderate and severe MDD. A covarying network from the Actinobacteriota phylum was identified in moderate MDD.[15]

Multi-omics analysis highlighted marked differences in gut microbiome composition, plasma cytokines, metabolism, and brain structure in MDD patients. Specific bacteria displayed extensive correlations with clinical symptoms and various biological factors.[16] Another study suggested that gut microbiome, specifically functional genera like *Streptococcus* and *Faecalibacterium*, may play a crucial role in the pathogenesis of depression in school-aged children, potentially serving as non-invasive biomarkers for distinguishing children with depression from healthy ones.[17]

Gut microbiomes and intestinal barriers dysfunction

The abundance of *Lachnospiraceae*, a bacterial family involved in the breakdown of carbohydrates into short-chain fatty acids (SCFAs), is observed to decrease in individuals with Major Depressive Disorder (MDD).[18] Analysing Clusters of Orthologous Groups (COGs) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways reveals disruptions in the metabolic pathways and functions of bacterial proteins in individuals with MDD, aligning with prior research indicating disturbances in carbohydrate and amino acid metabolism in faecal microbiomes and the metabolic phenotype of depressed mice.[19]

Furthermore, the decreased levels of fermentative bacteria, including *Blautia*, *Lachnospiraceae incertae sedis*, and *Roseburia*, result in decreased production of SCFAs, contributing to intestinal barrier dysfunction. Notably, individuals with A-MDD exhibit an overpopulation of *Proteobacteria*, particularly in the *Gammaproteobacteria* class, potentially linked to increased gut wall permeability. This heightened permeability allows invasive Gram-negative bacteria to enter mesenteric lymph nodes and circulate in the bloodstream.[20]

Research suggests a connection between the reduction of *Faecalibacterium* and MDD,[21] consistent with the anti-inflammatory effects of *Faecalibacterium*.[20] The study also associates depression with *Enterobacteriaceae*, possibly explained by elevated gastrointestinal tract permeability facilitating the dispersion of lipopolysaccharides.[22] Gram-negative bacteria, including *Enterobacteriaceae*, induce inflammation in the intestinal tract by secreting lipopolysaccharides. Increased intestinal permeability allows lipopolysaccharides to enter the bloodstream. This triggers the immune system to produce more immunoglobulins (Ig) to neutralise the lipopolysaccharides, leading to elevated plasma Ig levels.[23] The gut microbiome's influence extends to the central nervous system, where dysbiosis can disrupt the function of the HPA, impacting neurotransmission activities.[24] Increased numbers of *Alistipes spp*, when observed, may affect tryptophan activity, leading to an imbalance in the intestinal serotonergic system associated with abdominal pain, irritable bowel syndrome, and gut inflammation.[25] In summary, alterations in the host's intestinal microhabitat in MDD contribute to microbiome dysbiosis, characterised by an imbalanced microbiome.

Faecal microbiome transplantation (FMT) has proven effective in alleviating anxiety and depression behaviours in patients with irritable bowel syndrome (IBS), emphasising a potential connection between gut microbiomes and mental health. Notably, *Bifidobacterium* and *Escherichia* play significant roles in IBS formation and recovery.[26] Another study investigating the correlation between depression and gut microbiota in ulcerative colitis (UC) patients reveals higher disease severity and alterations in microbial abundance. Specifically, there are lower *Clostridiales*, *Firmicutes,* and Clostridia but higher *Bacilli* and *Gammaproteobacteria* in UC patients with depression compared to those without. These findings indicate a specific association between depression and changes in the gut microbiota in UC patients.[27]

Regulation of the gut microbiomes: Antidepressant and probiotics in depressed subjects

A previous study delved into modifications in the intestinal microbiome of individuals with depression undergoing antidepressant treatment. Thirty patients diagnosed with major depressive disorder (MDD) were administered escitalopram, an antidepressant with selective serotonin reuptake inhibitory activity (SSRI), revealing a significant difference in the Firmicutes/

Bacteroidetes ratio among the treated group, healthy controls, and a follow-up group. Interestingly, the follow-up group exhibited a notably lower ratio, suggesting that under escitalopram treatment, the intestinal flora of depressed patients tends to normalize.

The activation of pattern recognition receptors and increased production of short-chain fatty acids (SCFAs) by the gut microbiome can impact the host's immunity.[28] Patients taking the probiotic blend Bifico consisting of *Lactobacillus acidophilus*, *Enterococcus faecalis,* and *Bifidobacterium longum,* and those receiving Duloxetine showed improvements in symptoms of irritable bowel syndrome (IBS) and depression, with percentages of 87.5% and 100%, respectively. These improvements are believed to occur through the regulation of peripheral inflammation, which modulates the gut microbiome and fecal SCFA levels.[28] Surprisingly, no correlation has been identified between the severity of abdominal symptoms and SCFA levels in faeces. Bifico in combination with Duloxetine, a serotonin-noradrenaline reuptake inhibitor, has the potential to alleviate abdominal symptoms by reducing the expression of pro-inflammatory cytokines like MCP-1 and IL-1β.[28] This approach is particularly relevant considering the association between gut microbiome alterations and heightened inflammatory responses, leading to increased inflammatory biomarkers like TNF-α, IL-1β, and IL-6 in individuals with depression.[29]

The relationship between plasma cytokine levels and gut bacteria has been explored, revealing mostly negative correlations. Notable exceptions include *Roseburia* and IFN-γ, Clostridium XIVb and IL-1β, *Bifidobacterium*, and *Catenibacterium*, as well as MIP-1α and *Gemmiger*, *Catenibacterium*, and *Parasutterella*. These findings suggest a potential bidirectional relationship between gut bacteria and plasma cytokine levels, with certain microorganisms exhibiting positive correlations with specific cytokines. Previous studies propose that these gastrointestinal microorganisms could potentially influence human behaviour and psychology.[30]

Another study focused on the impact of the probiotic NVP-1704 intake (containing *Lactobacillus reuteri* NK33 and *Bifidobacterium adolescentis* NK98) on mental health and sleep quality in healthy adults with subclinical depression, anxiety, and insomnia.[31] Over an eight-week intake period, NVP-1704 significantly reduced depressive and anxiety symptoms, improved sleep quality, and lowered inflammation markers. Additionally, the probiotic treatment influenced the composition of the gut microbiome, promoting beneficial bacteria such as Bifidobacteriaceae and Lactobacillaceae while reducing harmful Enterobacteriaceae. These findings suggest the potential benefits of NVP-1704 for individuals with subclinical symptoms of depression, anxiety, and insomnia.

In contrast, a study investigating the effects of *Bifidobacterium longum* 1714 on stress, cognitive performance, mood, and sleep in healthy human volunteers during a prolonged stress period (university exam period) showed that, although *B. longum* 1714 improved sleep quality and duration compared to the placebo group, it did not alleviate symptoms of chronic stress, depression, or cognitive measures.[32] While the probiotic shows promise in improving sleep, further research is needed to understand its ability to modulate sleep during prolonged stress.

A study on atypical antipsychotic treatment in paediatric inpatients concluded that longitudinal changes in the gut microbiome occurred during the treatment period. Specific bacteria, namely *Romboutsia* and *Klebsiella*, showed significant increases after three months of atypical antipsychotic treatment. The intriguing finding was that the initial makeup of the gut microbiome was linked to the likelihood of gaining weight while undergoing atypical antipsychotic treatment.[33]

Taxonomic distribution of the microbiome in depressed subjects

Our review of current studies on human depression and dysbiosis uncovered a lack of consensus regarding the specific bacterial taxa most correlated to depression. The published correlation studies are concordant primarily at the phylum level. This observation aligns with the findings of a prior study,[34] which attributed this lack of consensus at more specific taxa levels to differences in

study designs. Consequently, further research is imperative to identify the specific bacterial taxa most crucial in the development of depression.

Furthermore, a study done by Chen et al. (2017) aimed to identify potential biomarkers for diagnosing major depressive disorder (MDD) through the analysis of serum metabolites and faecal microbial communities.[35] They recruited MDD patients and healthy controls, identifying 24 differential serum metabolites, with 10 of them related to inflammation. They identified 17 differential genera of gut microbiota, 14 belonging to the Firmicutes phylum and associated with inflammation. Five inflammation-related metabolites were recognized as potential biomarkers, showing significant correlations with Firmicutes genera. These biomarkers effectively distinguished MDD patients from healthy controls, suggesting that disturbances in Firmicutes may play a role in the onset of depression by regulating inflammatory responses.

In another study on individuals with MDD,[13] researchers analysed the gut microbiome and the microbial tryptophan biosynthesis and metabolism pathway (MiTBamp) in comparison to healthy controls. The study found that MDD patients had reduced levels of *Bacteroidetes* and increased levels of *Actinobacteria* compared to healthy controls. Moreover, specific KEGG orthologues in the MiTBamp were significantly lower in the MDD group, with increased levels of *Bifidobacterium*. The study suggests that gut microbiota alterations, particularly in the MiTBamp, could serve as potential biomarkers to distinguish MDD patients from healthy controls.

An observational study by Lee et al. (2021) reported the relationship between alterations in gut microbiota and their metabolites in patients undergoing treatment for depression. The research involved 33 patients categorised as non-responders, responders, and stable remitters based on their treatment outcomes. The study found that non-responders exhibited lower alpha diversity in the Phylogenetic Diversity index compared to responders during the treatment course. Additionally, non-responders showed increased estimated glutamate synthesis functions by the microbiota compared to responders and stable remitters. However, no specific microbiome or metabolome differences were identified among the three groups.[36] A bidirectional Mendelian randomization study suggested a protective effect of *Actinobacteria*, *Bifidobacterium*, and *Ruminococcus*, and a potentially anti-protective effect of Streptococcaceae on major depressive disorder.[37] Another study concluded that microbiological changes in both unipolar and bipolar depression are sex-specific. The gender-specific biomarker panel exhibits better diagnostic performance, providing valuable insights for future clinical differentiation and microbial intervention in depression based on gender-specific patterns.[38] Additionally, a study revealed age-related differences in the composition and diversity of gut microbiota in patients with major depressive disorder. Specific microbial taxa may also be associated with gastrointestinal symptoms in late-life depression.[39]

Suggested therapies to improve microbiome in depression subjects

Given the significant role of the gut microbiota in mental health, microbiota-targeted interventions, such as probiotics, prebiotics, and synbiotics, hold promise as novel therapeutic approaches for managing depression and related mood disorders.[40] Interventions such as prebiotic fibre supplementation, specifically inulin, have shown positive effects on gut microbiota and social behaviour, especially in individuals undergoing alcohol withdrawal.[41]

Meanwhile, traditional Chinese medicine, exercise, and specific probiotic strains, such as *Lactobacillus*, have shown positive effects on mental health, sleep, and depressive behaviours in both animal models and humans.[42] Additionally, interventions that reduce stress-induced inflammation in the gut and the brain, such as synbiotics and specific herbal remedies like Wenyang Jieyu decoction, may alleviate depressive symptoms.[43]

Psychobiotics are probiotics that may be beneficial to mental health. They can affect the microbiota-gut-brain axis through immunological, humoral, neurological, and metabolic pathways. These microorganisms are becoming more and more popular as innovative therapeutic options

for the successful management of mental illnesses.[44]

Probiotics potentially reduce the effect of inflammatory bowel syndrome (IBS) by modulating the gut microbiome composition.[28] The combination of probiotics with an antidepressant such as Duloxetine could be used to reduce depression and abdominal symptoms among IBS-D patients.[28] It is also supported by another study that suggested a combination of probiotics including *L. acidophilus*, *L. casei*, and *B. bifidum* for eight weeks can reduce depression in patients without IBS.[45]

Moreover, increased stress levels trigger complex physiological responses in the body, including changes in cortisol secretion through the HPA axis.[46] This alteration in cortisol levels can compromise the immune system, rendering individuals more vulnerable to infections. Notably, probiotics have shown promise in mitigating the impact of stress-induced immune suppression. Additionally, immunosuppression, often associated with chronic stress, leads to increased oxidative stress and inflammatory cytokine levels. These factors can disrupt normal neuronal function, potentially manifesting in various physiological alterations[47].

Furthermore, this alteration in brain function is intricately linked to mental health conditions like anxiety and depression. Decreased levels of essential neurotransmitter precursors, such as tryptophan and tyrosine, alongside elevated inflammatory cytokines, have been observed in individuals with anxiety and depression. Serotonin and dopamine, crucial neurochemicals in preventing depression, are synthesized at reduced levels when precursor amino acids, tyrosine, and tryptophan, are depleted. [48]

During stress or inflammation, enzymes like indoleamine 2,3-dioxygenase (IDO) may be upregulated. IDO catalyses the breakdown of tryptophan into kynurenine as part of the immune response. This can lead to reduced availability of tryptophan for serotonin synthesis, contributing to decreased serotonin levels.[49] Thus, combining probiotics with antidepressants presents a potential strategy to restore microbial balance in individuals with depression, thereby modulating neurotransmitter production and potentially alleviating depressive symptoms.

Probiotics can also synthesise vitamins and other necessary nutrients that may affect general health, including brain function. It was found that participants receiving probiotic supplementation felt less distracted by ruminative thoughts.[50] The study involved 27 individuals with euthymic bipolar disorder who received probiotic treatment for three months. The participants showed a significant reduction in cognitive reactivity to sad mood.

Numerous potential psychobiotic bacterial strains have been found recently through microbiome studies; among these, bacteria that produce short-chain fatty acids (SCFAs) have drawn particular interest from neurobiologists. Bacteria capable of producing short-chain fatty acids (SCFAs), such as *Clostridium*, *Bifidobacterium,* and *Lactobacillus* play a distinctive role in a range of psychiatric diseases. This implies that these bacteria could serve as promising candidates for novel psychobiotics, given that SCFAs are potential mediators of the microbiota-gut-brain axis.[48] Figure 1 summarises the potential role of probiotics (psychobiotics) in promoting a balanced gut microbiome for the prevention and treatment of depression.

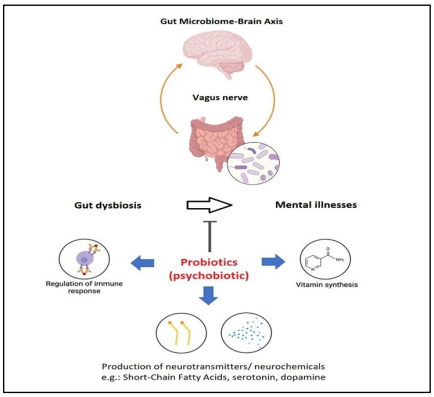

Figure 1: The potential role of probiotics in the prevention and treatment of depression

CONCLUSION

In summary, the extensive research on the relationship between microbial composition and depression reveals a complex interplay involving alterations in gut microbiome, immune pathways, and inflammatory control. Many studies highlighted potential biomarkers

and treatment targets for depression, showing age-related differences, sex-specific biomarkers, and various associations with gastrointestinal symptoms, thus contributing to the intricate landscape of microbial dysbiosis and neuroimmune regulation in individuals with depression. Dysregulation extends to disruptions in metabolic pathways and functions of bacterial products, leading to intestinal barrier dysfunction and increased gut permeability. Regulatory interventions, including antidepressant treatments and probiotics, show promise in modulating the gut microbiome and alleviating depressive symptoms. The combination of probiotics with antidepressants emerges as a potential strategy for inducing a balanced microbiome, especially in patients with comorbid conditions like irritable bowel syndrome. Overall, targeting the gut microbiome holds therapeutic potential in managing depression, but continuing research is crucial to further understand and refine these interventions for enhanced mental well-being.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENT

The authors acknowledged the Ministry of Higher Education, Malaysia [FRGS/1/2022/SKK11/UIAM/02/2] for the funding. The authors also acknowledge Nurul Alia Risma Rismayuddin and Wan Nur Fatihah Wan Mohd Kamaluddin for their assistance.

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