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MICROBIOTA AND DEPRESSIVE DISORDERS – A REVIEW

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ABSTRACT

Introduction: Depression, affecting 1 in 8 individuals with a 27.6% rise during COVID-19, prompts an exploration of the gut-brain-microbiota axis's role in mental health, focusing on depression.

State of Knowledge: The gut microbiota regulates the brain-gut axis, impacting neurotransmitter production. Dysbiosis correlates with depressive behaviors. Factors like short-chain fatty acids and neurotrophins play roles in gut-brain communication.

Materials and method: A literature review was conducted using the "PubMed" and "Google Scholar" databases with the keywords "Gut microbiota", "Fecal microbiota", "Depression and microbiota", "Depression", „Probiotics role", „Mental health and priobiotics", „Probiotics and prebiotics", „Prebiotics and brain".

Summary: Altered gut microbiota links to psychiatric disorders, disrupting composition stability by age three through antibiotic use. Imbalances impact neurotransmitters and inflammation, crucial in depression pathophysiology.

Treatment and Impact on Gut Microbiota: Antidepressants affect gut microbiota diversity bidirectionally, offering potential tailored therapies. The Mediterranean diet correlates with lower depression risk. Excessive sugar intake triggers neuroinflammation.

Fecal Microbiota Transplantation: FMT emerges as a promising depression treatment, reshaping gut microbiota and modulating the gut-brain axis. Lactobacillus and Bifidobacterium spp. show potential in mitigating depression symptoms. FOS and GOS positively influence gut microbiota.

Conclusion: This review underscores the intricate gut-brain-microbiota axis in depression, suggesting personalized therapeutic approaches for effective management.

Keywords
Gut Microbiome, fecal microbiota, depression treatment, Depression, Probiotics

INTRODUCTION

1 in 8 people suffer from a mental disorder characterised by impaired cognitive, behavioural or emotional dysfunction, which impairs a person's functioning in many important areas. One of the most significant psychiatric disorders that impair life is depressive disorder. The COVID-19 pandemic and the present restrictions have led to a 27.6% increase in cases of depression. [1] The latest data report that around 800,000 people with depression commit suicide every year. [2]

The gut microflora is crucial and regulates the brain-gut axis; bacteria regulate the production of neurotransmitters and their precursors (e.g. serotonin, GABA, tryptophan) and can secrete and increase levels of essential proteins and metabolites involved in the the release of neuropeptides and gut hormones - such as short-chain fatty acids and brain-derived neurotrophic factor. [3] During over-activation of stress reactions, the immune system also plays an important role immune system, adversely affecting the integrity of the intestinal barrier and the intestinal microflora. [4]

The mechanisms underlying the pathophysiology of depression are still unknown. New leads targeting the brain-gut-microflora axis may remind us of a fundamental truth about depression and thus contribute to the development of new antidepressants or other solutions to affect this disease and indirectly other psychiatric disorders. Animal models of depression have shown that abnormal composition of the gut microbiota is associated with depression-like behaviour. [5]

In this article, we conduct an analysis of scientific information indicating that the brain-gut microflora axis influences mental health disorders, particularly depression.

MICROBIOTA

The intestinal microbiota is a collection of fungi, viruses and numerous bacteria, unique to a particular organism, while conditioning the entire body. The digestive tract is referred to as the 'second brain'. The nervous system and the gastrointestinal tract, despite

their separateness, arise from the same germinal layer - the ectoderm, [6] and therefore it is not surprising that recent research suggests an increasing association between the gut microbiota and psychiatric disorders. [5]

The human intestinal microflora is composed of two main genera, namely *Bacteroidetes* and *Firmicutes*, the next two best known genera being *Actinobacteria* and *Verrucomicrobia*. The composition of the microflora stabilises by the age of three. From then on, it resembles the microbiome of an adult, although it may change under the influence of various factors. The healthy
large intestine also hosts primary pathogens such as *Campylobacter jejuni*, *Salmonella enterica*, *Vibrio cholerae* and *Escherichia coli*, but in very limited numbers. [7]

However, no definite cause-and-effect correlation has been proven on intestinal dysbiosis and depressive disorders, though there is increasing circumstantial evidence of an increased risk of serious psychiatric disorders (e.g. depression, anxiety and psychosis) following antibiotic use, even five to 10 years after use, which is related to the fact that antibiotics and other drugs consumed in large quantities affect the diversity of the intestinal flora. [8,9]

Thus far, it is not clear whether the change in the microbiota is due to depression or whether depression is due to changes in the microbiota combined with the excessive use of medication. A collective finding from the research is that during psychiatric disorders there is an increase in bacteria and pro-inflammatory cytokines and this is simultaneously related to systemic infection of the body. Patients with depression have an increase in the amount of *Bacteroides* and a decrease of the amount of *Blautia*, *Faecalibacterium* and *Coprococcus* [11-13] and the intestinal microflora becomes more pathogenic. [14,15] Interestingly - among people who are overweight, the ratio of *Bacteroides* to *Firmicutes* is disturbed in favour of *Firmicutes*, while in lean people there is an increase in *Bacteroides*. Furthermore, fungal dysbiosis plays an important role and its disturbed structure has a significant impact on the occurrence of depression. [16]

A deficiency of acetate, butyrate and propionate has been linked to psychiatric disorders particularly depression, [17,18] and their administration produced antidepressant effects, [19] furthermore gut-produced neurotransmitters such as serotonin or gamma-aminobutyric acid affect emotional behaviour and regulate the function of many organs. [20] The effect of trimethylamine N

oxide also appeared to be significant. [21] The microflora is additionally impacted by lipopolysaccharides, lactate and group B vitamins. [22-24]

Neurotransmitters and metabolites present in the intestines affect brain function. [25] Altering the microbiome disrupts the intestinal environment, damaging the intestinal barrier and triggering inflammatory responses. [26,27] A change in the composition of the intestinal microbiota results in dysfunction of the intestinal barrier and the development of an inflammatory response, metabolite translocation occurs and thus exacerbates inflammation - which plays a large role in the pathogenesis of depression. [28,29] The subsequent step of this reaction is an abnormal activity of the intestinal nervous system. [30]

The phrenic nerve, which transmits information from the gut to the brain, is also significant, and its anterograde vagotomy inhibits depression-like symptoms in rat studies. [31,32] An
important reinforcement of gut-brain axis communication is the vagus nerve, [33] which has also been used and validated in clinical trials for the treatment of treatment-resistant depression. [34] Inflammatory signals reaching the brain cross the blood-brain barrier and lead to inflammation of the nervous system, [35] while also affecting the activation of neuropathological processes in the brain - demyelination, non-functional neurogenesis or synaptic defects [36-39] at the same time contributing to the pathogenesis of depression. It also increases cortisol levels (via HPA activation) affecting intestinal pathology and leading to an intestinal mucosal malfunction. [40]

TREATMENT OF DEPRESSION AND IMPACT ON INTESTINAL MICROFLORA

The cornerstone of depression treatment is pharmacotherapy and psychotherapy. The drugs - SSRIs, SNRIs, TLPDs - affect the intestinal microflora, its diversity and composition. An interaction between treatment and metabolism, drug efficacy and activity has been shown. Studies also indicate antimicrobial effects of antidepressants, particularly on Gram-positive bacteria. [41] A correlation has been found between depression and changes in the numbers of the *Bacteroidaceae* family, while increases among the *Lachnospiraceae*, *Prevotellaceae* and *Ruminococcaceae* families mainly contribute to bipolar disorder. Pharmacological treatment also contributes to changes in the microflora - SSRI treatment increases the number of *Eubacterium ramulus*, while TPPDs increase the abundance of *Clostridium leptum*. Duloxetine also significantly increases the quantity of *Eubacterium rectale*, by more than

100-fold in the compared to the group not taking the drug. [43] During bacterial metabolism, butyrate is produced, which inhibits inflammatory reactions and therefore has an adjunctive effect on antidepressant treatment/therapy. [44] The intestinal microflora alters and influences the bioavailability, efficacy and activity of antidepressants. [45] *Streptococcus salivarius*, *B. uniformis, B. thetaiotaomicron* and *E. coli IAI1* increase the bioaccumulation of duloxetine, which reduces efficacy by affecting its bioavailability. [43] The treatment resistance that occurs is related to the composition of the microflora - an increase in the amount of bacteria belonging to the Proteobacteria type. [46] Ketamine has a long-lasting antidepressant effect and may be effective in treatment-resistant patients, with the microflora being a modulator of the antidepressant effect of ketamine, [47] while the presence of *Phylum Actinobacteria*, class *Coriobacteriia* and *Butyricimonas* and *Turicibacter*, may contribute to the potent antidepressant effect of ketamine. [48,49] Furthermore, ketamine may reduce the likelihood of inflammation by affecting tryptophan metabolism, and it has been shown that ketamine can restore bacterial populations that produce inflammatory compounds and short-chain fatty acids. Altering the
intestinal microbiota through the use of probiotics may have the effect of reducing side effects that may occur (e.g.: diabetes, obesity, cardiovascular disease) due to the use of antidepressants. [50] **Prospects for gut microflora applications**

The effect of probiotics, prebiotics, diet, microorganisms modulates the composition of the gut microbiota, and this affects the appropriate balance in the gut, which can be used for providing proper treatment for depression.

DIET

The association between diet, gut microflora and depression is increasingly being studied. A Mediterranean diet, rich in fibre or polyphenols, which have anti-inflammatory effects, is claimed to be beneficial for health. The excessive sugar consumption has a pro-inflammatory effect on the nervous system, linked to a disruption of insulin signalling, which is very important for brain function, and this simultaneously affects and disrupts serotonin synthesis and exacerbates mood disorders.

An experiment on the effects of sweetened foods on the mental health of UK residents was conducted between 1985 and 2013 in 11 phases. The conclusion of these studies was an increased risk of depression as a result of a high sugar diet. Another study followed 49,261

Swedish women for more than 20 years and found a lower risk of depression in those who followed the diet more closely. [51] A 12-week randomised controlled trial showed that a Mediterranean diet with an effect on reducing gastrointestinal inflammation significantly alleviates depressive symptoms and improves quality of life in young men with clinical depression. [52,53]

Therefore, how to take care of the microbiota? It is advisable to eat slowly, chew food thoroughly, do not overeat, eat according to the daily rhythm, eliminate trans fats, limit sugars and introduce omega-3 fatty acids into the diet, eat fruit and vegetables, fermented products, drink sufficient fluids and do not overuse antibiotics. [6] It is recommended to combine this with antidepressant medication, psychological interventions and lifestyle changes, rather than using diet alone to treat depressive disorders.

FMT

A very promising strategy for treating depression is FMT, i.e. the transformation of the gut microflora due to the administration of faecal flora from healthy individuals. Based on preclinical studies, it has been shown that FMT can reduce depressive behaviour. In mice, microflora transplantation alleviated depressive behaviour due to alcohol consumption and suppressed nervous
system inflammation. [54] In patients with irritable bowel syndrome with predominant diarrhoea (IBS-D), FMT treatment progressively relieved depressive symptoms, regardless of remission of gastrointestinal symptoms. [55] Another study evaluated the efficacy of orally frozen FMT capsules for add-on therapy in patients with depression and found that depressive symptoms significantly decreased 4 weeks after transplantation. [56] Although there have been articles where adverse effects and complications of FMT therapy have been described, [57] the introduction of FMT treatment is gaining popularity in scientific and clinical research. [58]

PROBIOTICS AND PREBIOTICS

Probiotics are live micro-organisms that, when administered in adequate amounts, benefit the health of the host and are the best-studied therapy for depression by affecting the microflora. Several probiotic species and subspecies have been identified that can alleviate depression; that being primarily based on supplementation with *Lactobacillus spp* and

Bifidobacterium spp. [13]

It is difficult to clearly identify the position and impact on the gut microflora due to a number of factors that are involved - such as age, co-morbidities and region. The synergistic effect of probiotics may suggest the use of multi-species probiotics rather than a single species. [59] *A. muciniphila* and *C. butyricum miyairi 588* have been demonstrated to alleviate stress-induced depressive behaviour in mice. [60-62] However, there is still a discrepancy between laboratory studies and clinical application. It has also been reported that betaine supplementation contributes to resistance to anhedonia in stressed mice through an anti-inflammatory effect. [63]

Prebiotics are used by the gut microflora to produce certain beneficial bacteria. The best documented prebiotics influencing mental health and the treatment of depression are Fructooligosaccharides (FOS) and Galactooligosaccharides (GOS), alongside polyphenols, inulin and compounds from vegetables, herbs and plants. The use of FOS and GOS affects depressive behaviors in male C57BL/6J mice with normalization of the intestinal microflora, a decrease in pro inflammatory cytokines and an increase in intestinal acetate and propionate. [64]

Another study compared the effects of probiotic (*L. helveticus* and *B. longum*) and prebiotic (GOS) supplementation on remission of depression in depressed patients and found that 8 weeks of probiotic (not prebiotic) supplementation, alleviated depressive symptoms. [65] Administration of 4G-β-d-galactosaccharose for 24 weeks improved self-efficacy in depressed patients, but did not alleviate their depressive symptoms. [66]

Prebiotics do not have a direct effect on the body, but only indirectly benefit the health of the host through the growth of probiotics, so prebiotics have often been used together with probiotics in the treatment of depression.

SUMMARY AND CONCLUSIONS

This study focuses on the relationship between gut microflora and depression, looking at the impact of microbiota, diet and therapy on mental health. The authors emphasise that mental disorders, especially depression, are a social problem of increasing importance, especially in the context of the COVID-19 pandemic. They also observe that the gut microbiota may play a key role in regulating mental health by affecting the brain-gut axis.

The study presents ample evidence of a link between gut microflora and depression.

Research suggests that an abnormal composition of the gut microflora may be associated with symptoms of depression. The authors discuss the various mechanisms through which the gut microbiota affects mental health, including neurotransmitter production, effects on the intestinal barrier, and interactions with the immune system. It has been discussed that pharmacotherapy, especially antidepressants, can affect the composition of the gut microflora. Furthermore diet, probiotics, prebiotics and even FMT (faecal transplant) therapies are being considered as potential methods to help treat depression by regulating the gut microflora. Perspectives on the applications of gut microflora in the treatment of depression point to the role of probiotics, prebiotics and diet. Perspectives on the applications of gut microflora in the treatment of depression highlight the role of probiotics, prebiotics and diet. Introducing lifestyle changes, such as the Mediterranean diet, can also have a beneficial effect on mental health. It is worth continuing research on this subject for a better understanding of the mechanisms of gut microflora effect on mental health and in order to develop effective therapies supporting the treatment of depression.

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Concept and design [KK] [MD], analysis and interpretation of data [MG] [MO], intellectual content and data research [AZ] [ZM], work integrity and coherence [KK] [MM], project supervision and final revision [KK], writing of manuscript and first revision [MD] [ZM], drafting of manuscript, data research and analysis [KK] [MD], translation [IM]

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