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Review Article

Microbiota, Depression and Probiotics: A Concise Analysis

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Abstract

Introduction: The intricate interplay between gut microbiota and mood disturbances, specifically Major Depressive Disorder (MDD), is currently being updated.

Objective: To investigate the involvement of the gut-brain-microbiota axis in Major Depressive Disorder (MDD) and assess the potential of probiotics as a viable therapeutic option.

Methods: A comprehensive review of Spanish and English literature on the topic was conducted using Google Scholar, PubMed, SciELO and Web of Science databases from 2019 to 2023.

Results: The relationship between gut microbiota and Major Depressive Disorder (MDD) was explored. Bidirectional communication between gut microbiota and the brain can impact depressive symptoms. Individuals with MDD exhibited alterations in their microbiota composition, characterized by reduced beneficial bacteria and increased pro-inflammatory bacteria. Probiotics are being investigated as a complementary therapy for MDD, showing promising results, although further studies are needed.

Conclusion: This article delves into the potential use of probiotics as a complementary therapy for Major Depressive Disorder (MDD). While preclinical studies have shown encouraging outcomes concerning the benefits of probiotics in enhancing gut function and reducing inflammation, further research in this field is required.

Keywords: *Microbiome; Gut Microbiota; Gut-Brain-Microbiota Axis; Dysbiosis; Major Depressive Disorder; Depression; Probiotics*

Introduction

Major depressive disorder

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the diagnosis of Major Depressive Disorder (MDD) requires the presence of at least five of the following symptoms for at least two weeks: depressed mood for most of the day; anhedonia or lack of interest in previously enjoyed daily activities; unintended weight gain or loss; insomnia or hypersomnia almost every day; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to concentrate or make decisions; recurrent thoughts of death, suicidal ideation or suicide attempts [1]. This disorder is considered one of the leading causes of disability globally, and there is speculation of an increase in the frequency of depression within the population [2], which has economic and social consequences.

The classical theory explaining the etiology of this mood disorder was proposed by Joseph Schildkraut in the 1960s, pointing to the deficit of monoamines as the pathophysiological basis of MDD. The efficacy of imipramine (a monoamine neurotransmitter reuptake inhibitor) and iproniazid (a monoamine oxidase inhibitor) in treating depression supported his findings [3]. Subsequent research demonstrated that the depressive state has a multifactorial nature, encompassing genetic anomalies, brain network predisposition, inflammatory processes, psychological and social factors, and alterations in the gut microbiome [4,5].

Defining the gut microbiota

Although the terms "microbiota" and "microbiome" are used interchangeably, it is academically useful to highlight their distinctions. The term "microbiota" refers to the collection of diverse microorganisms inhabiting a specific niche within a living organism, and while the focus of its study is predominantly on bacteria, these microscopic populations also include archaea, fungi, viruses and parasites. On the other hand, the term "microbiome" describes the genomic compilation of various microorganisms within a defined environment [6,7].

Among the various human microbiotas, the gut microbiota is the most extensively studied due to its association with mental health. The gut microbiome is not uniform across species; intraindividual variability exists based on factors such as age, diet, gut transit time, circadian rhythm and medication exposure, especially antibiotics [8]. In this sense, the microbiome is considered a dynamic component that fluctuates over time and is heavily influenced by external factors.

The gut microbiota in major depressive disorder

Numerous studies, including meta-analyses, have demonstrated changes in microbiota composition among patients with psychiatric disorders compared to healthy individuals. These investigations concur that individuals with Major Depressive Disorder (MDD) experience a decreased population of *Coprococcus*, *Faecalibacterium* and *Bifidobacterium*, along with an abundance of pro-inflammatory genera such as *Eggerthella* and *Bacteroides*. However, there is also data suggesting potential antimicrobial effects of antidepressants; *in vitro* experiments have shown that these drugs inhibit the growth of certain bacterial strains studied [9-14].

Therefore, it is challenging to ascertain whether alterations in microbiota diversity are a direct result of depression or a side effect of antidepressant medication. Nonetheless, it is evident that intestinal dysbiosis and the prevalence of pro-inflammatory intestinal bacteria exacerbate the depressive state.

The gut-brain-intestine axis

The gut-brain-intestine axis is a bidirectional information system that regulates human behavior. It consists of a neuronal structural component (vagus nerve and enteric nerve plexuses) and a humoral component (hypothalamic-pituitary-adrenal axis and hypothalamic-sympathetic nervous system axis) [15,16].

Contemporary literature highlights three main mechanisms underpinning the gut-brain relationship. Firstly, short-chain fatty acid production -notably butyrate, acetate and propionate- by various gut microbes holds the potential to alter the blood-brain barrier permeability and influence extracellular serotonin availability. Secondly, the neurotransmitter pathway is mentioned, where gut microbes both regulate and synthesize neurotransmitters anew. For instance, it is known that *Parabacteroides*, *Eubacterium* and *Bifidobacterium* synthesize gamma-aminobutyric acid (GABA) [16,17,29].

Finally, cytokines and chemokines synthesized by specific bacteria can regulate crucial brain centers, such as the hypothalamus, via the vagus nerve. This can activate the hypothalamic-pituitary-adrenal axis and orchestrate pro-inflammatory states that can be potentially harmful [16].

The role of gut microbiota in depression pathophysiology

Several studies suggest that neuroinflammation mediated by microbial cytokines and chemokines plays a substantial role in the development of some psychiatric disorders. Meta-analytic evidence indicates that blood levels of the pro-inflammatory cytokine IL-6 are elevated in patients with psychosis, bipolar disorder and MDD [17-19]. These inflammatory mediators, produced by intestinal dysbiosis, can travel through the peripheral blood to the brain through any of the three proposed pathways: humoral, cellular or neuronal. Once in the brain, they can stimulate glial cells, especially microglia, to release more inflammatory cytokines with a neurodegenerative effect, especially in hippocampal areas, thus producing alterations in mood [18,19].

Furthermore, psychological stress also has a direct effect on brain immune cells. It was observed that mice subjected to isolation stress showed an increase in the branching of hippocampal microglia [20]. Likewise, another study demonstrated that chronic stress induces the migration of bone marrow monocytes to the rat hippocampus, inducing depressive behaviors [21]. Prolonged stress can alter the intestinal microbial ecosystem due to the hyperactivity of the hypothalamus-pituitary-adrenal axis [18].

Other inflammatory components associated with depression include tumor necrosis factor (TNF)-alpha, IL-1 and highly potent microbial antigens, such as lipopolysaccharides (LPS) [22].

TNF-alpha and IL-1 can increase the production of adhesion molecules in the endothelium, facilitating the migration of leukocytes to the brain [23]. It was demonstrated that the level of TNF-α negatively correlated with various cognitive functions such as attention, verbal memory, executive function, sustained attention, and psychomotor speed [24]. On the other hand, an immunometabolic analysis showed that *Eggerthella spp.* significantly increases IL-1α [25]. It was also discovered that species of *Bacteroides* produce a functionally distinct form of LPS that can stimulate microglia to increase the expression and synthesis of inflammatory mediators like TNF-alpha and IL-1 [26,27]. All the aforementioned molecules could be used as biomarkers for monitoring individuals with MDD [28].

Probiotics as adjunct therapy in MDD

The potential of probiotics as a therapeutic option in mood disorders, such as depression, is being widely investigated due to encouraging results obtained in preclinical trials [30-32]. According to systematic reviews, probiotics can improve the function of the intestinal barrier, decrease levels of serum zonulin (a protein that regulates the permeability of tight junctions between intestinal lining cells), bacterial endotoxins, LPS and pro-inflammatory factors such as C-Reactive Protein (CRP), IL-6 and TNF-alpha, while increasing the population of *Bifidobacterium* and *Lactobacillus* [33].

A recent meta-analysis that included 16 randomized clinical trials demonstrated that probiotics are significantly more effective in treating anxiety and depression compared to placebo, as measured by the Beck Depression Index and the State-Trait Anxiety Inventory [34]. Other authors have identified that, while probiotics offer improvements in the clinical condition of individuals with mood-related depression, they appear to be more effective when administered alongside antidepressants rather than as independent treatment [35].

Researchers agree that conducting more high-level clinical studies is necessary to obtain robust results and provide accurate recommendations for medical practice [36].

Conclusion

Major Depressive Disorder (MDD) is a common and debilitating mental illness considered one of the leading causes of disability worldwide. The intestinal microbiota plays a significant role in its development, and it has been discovered that patients with MDD exhibit imbalances in their composition, with a decrease in beneficial bacteria and an increase in inflammatory bacteria.

The communication between the intestinal microbiota and the brain is bidirectional, and evidence has been found that imbalances in the microbiota can trigger inflammatory responses in the brain, contributing to the development of depression. Additionally, the inflammatory mediators produced by intestinal dysbiosis can affect the permeability of the blood-brain barrier and the availability of neurotransmitters such as serotonin, which are also implicated in depression.

Probiotics have been studied as complementary therapy for MDD, and the results from preclinical studies are promising. It has been observed that probiotics can improve the function of the intestinal barrier, reduce inflammation and increase the population of beneficial bacteria in the gut. Furthermore, recent meta-analyses have proven probiotics to be more effective in treating anxiety and depression when administered alongside antidepressants.

Considerations from the Authors

Given the intrinsic dynamics of the human microbiota and the extensive heterogeneity of the conducted studies, the presence of significant biases must be considered. A deeper understanding of the complex interaction between the intestinal microbiota and mood is required before implementing probiotic therapies in clinical practice.

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