



Review Article

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The Maneuver of Psychobiotics in the Medical Aid of Clinical Depression

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ABSTRACT

The field of psychology has advanced over the years in treating psychiatric disorders such as major depressive disorder (MDD), Schizophrenia, and Alzheimer's disease (AD). Depression or clinical depression is a major mental health issue characterized by chronic sadness, hopelessness, and emptiness, which diminishes the patient's quality of life. According to WHO, an estimated 3.8% of the world's population experience depression, in which 15% of depressed patients eventually die by suicide. Recent studies in treating depressive patients have progressed with the usage of psychobiotics. Psychobiotics contain both probiotics and prebiotics, meaning psychobiotics possess the ability to introduce beneficial bacteria in the gut as well as support the growth of existing bacteria in the human gut. The gut-brain axis, which mediates the mechanism of action of psychobiotics in treating clinical depression, has been cleverly studied, and it provides promising results in the improvement of a patient's mental health status. Psychobiotics have proven their worth not only in upgrading the patient's mental health in psychological disorders but also in the enhancement of overall patient health by improving one's gut health.

Key words: *Clinical depression, Gut-brain axis, Major depressive disorder (MDD), Psychobiotics*

INTRODUCTION

Depression is a major mental health issue characterized by chronic sadness, hopelessness, and emptiness, which diminishes the patient's quality of life [1]. It is also known as Major Depressive Disorder (MDD) or clinical depression. It is a mood disorder presented with at least 2 weeks of alterations involving changes in affect, cognition, and neuro-vegetative functions like decreased appetite and energy [2]. Approximately 280 million people in the world have depression, among which 1.9 million children aged 3 to 17 have been diagnosed with depression. Patients with depression experience the feeling of anhedonia in daily activities and report physical, behavioral symptoms such as loss of energy or fatigue and low self-esteem sometimes associated with suicidal thoughts. Depression can be diagnosed using 2 different methods: the Patient Health Questionnaire (PHQ-9) score and patient-reported symptoms, which are assessed by the physician [3]. Current treatment patterns for clinical depression include antidepressants like Selective serotonin reuptake inhibitors (SSRIs) such as escitalopram, fluoxetine, and sertraline; Serotonin and norepinephrine reuptake inhibitors (SNRIs) like duloxetine, venlafaxine; Tricyclic antidepressants (TCAs) like Imipramine, Nortriptyline etc., these medications given alone woefully have a high failure probability, which leads to serious clinical challenges [4]. Psychotherapy such as cognitive behavioral therapy or interpersonal therapy helps in providing additional benefits in treating clinical depression and is most popularly used by depressive patients. Nowadays, a widely employed medication in treating depression includes a new class called psychobiotics.

Psychobiotics refer to the beneficial live bacteria that present favorable health aid to patients suffering from mental health illnesses when ingested upon interaction with the gut microbiota [5]. The terms "psycho" and "biotics" refer to mental health and living organisms, respectively, which together coined the term "psychobiotics" by Dinnan and colleagues in the year 2013 as a novel class of probiotics involved in the therapeutics of psychiatric illnesses [6, 7]. Psychobiotics contain both probiotics and prebiotics, meaning psychobiotics possess the ability to introduce beneficial bacteria in the gut as well as support the growth of existing bacteria in the human gut. The mechanism of action of psychobiotics is a topic of interest that has been widely researched in recent studies. However, theoretical knowledge suggests that its action influences the gut-brain axis of the human body, which is a bidirectional communication network between the brain and the intestine. Understanding the mechanism in the gut-brain axis helps us decipher the potential assistance provided by psychobiotics in treating clinical depression in patients.

MATERIALS AND METHODS

The focus of this review is on attaining maximum knowledge regarding the optimization of psychobiotics in the aid of treating clinical depression. The screening of articles selected was particularly focused on the relevant articles and keywords such as "clinical depression," "psychobiotics," etc. Full-text articles were then thoroughly read by the authors and assessed for eligibility, which concluded the assistance of psychobiotics in treating clinical depression, along with additional knowledge such as the indications and adverse effects, if any. Articles that explore the practical application of psychobiotics in various psychiatric conditions were considered when constructing this review. Individual articles stating the benefits of probiotics and prebiotics were also taken into account when forming the review. The authors thoroughly read the articles to sort out the relevant data, and in support of our current review, the data extraction was performed after a keen review by understanding all the selected articles. The collected data was then reviewed and written based on similar findings in various research studies and review articles, presented in a definite manner in the form of an understanding of psychobiotics and the mechanism of psychobiotics in treating clinical depression and other psychiatric illnesses. The content in this review article is supported by various research trials conducted on psychobiotics and their application in major depressive states, along with the articles that deduce indistinguishable outcomes.

Etiopathogenesis: From cause to disease

Lack of proper understanding about mental health concerns can lead to complications in understanding the disease manifestations and can hinder employment of required care plan [8]. There are various listed factors involved in the etiology of depression. The brain-gut-microbiota axis represents a highly intricate system where neural, immune, and chemical signals interact, and it seems that all of these interconnected networks play a role in the development of depression [9]. Be it a result of biological factors such as alterations in the brain's chemistry or hormonal imbalances or a result of psychological factors such as personality traits (low self-esteem, pessimism) or psychological stressors such as losing a loved one or career failures, depression is presented in an individual in different grades rating from mild to severe presenting various symptoms. Other causes of depression result from social isolation, traumatic life events, substance abuse, and basic lifestyle practices. When noted in terms of causing depression, a pattern such as a traditional Western diet containing higher fats and sugary products contributed to a higher risk of depression, whereas Mediterranean diet patterns are inversely related to the incidence of depression [10, 11]. Owing to the extensive use of antibiotics in patients suffering from common flu and various bacterial diseases, circumstantial evidence provides that they result in reduced diversity of the gut microbiota, which further results in an increased risk of mental disorders. An expanding body of research investigates how exercise affects the gut microbiota and the gut-brain axis. Particularly, it has been discovered that lack of exercise has negative impacts on immunity, stress, and energy homeostasis [12]. A disrupted serotonergic system is one of the main causes of depression [13]. Additionally, it has been suggested that stress exposure is the primary cause of depression, leading to a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis, which in turn alters the release of cortisol and corticotrophin-releasing hormone (CRH). Depression is speculated to have endocrine system malfunction as one probable contributing factor, as an increase in noradrenaline and other hormones has been noted [14].

The explanation of pathogenesis involved in the MDD occurrence due to dysbiosis of gut microbiota has been vague so far. Numerous studies demonstrate the connection between the microbiota-gut-brain axis and the pathogenesis of depression [15]. Imbalance in the gut microbiota results in an increase in the pro-inflammatory

bacteria, such as a rise in bacteroidetes/firmicutes ratio and depletion of anti-inflammatory bacterial genera *Blautia*, *Faecalibacterium*, and *Coprococcus*. Many significant mediators that play a role in the interactions between the gut microbiota and the host, including microbial metabolites, are produced by the bacteria themselves; bacterially modified host molecules like bile acids (BAs) result IN dysbiosis in the microbial metabolome, causing inflammatory response in the gut epithelium of the host. The manifestation of clinical depression is also associated with disrupted intestinal barrier functions [16]. The damaged intestinal barrier (leaky gut), because of depleted microbiota [17], sensitizes systemic inflammatory responses and results in increased regulatory T cell (Th17), interleukin [IL]-6, IL-1 β and d tumor necrosis factor-alpha (TNF- α) which confer to the pathogenesis of depression [18].

The gut-brain interplay: Its role in clinical depression

A majority of antidepressant medications on the market now aim to change the activity of neurotransmitters in the brain, but they have a slow beginning of action and may cause unpleasant side effects like headaches, nausea, agitation, drowsiness, and sexual dysfunction [19, 20]. They do not generally reduce the ubiquity of mental illness, therefore leading further studies and implementing adjunct therapies. These regularly used antidepressants cause treatment-resistant major depressive disorder (TRD), wherein patients have become easily prone to future cases of relapse, chronicity, persistent mental impairments, and suicide [21]. These antidepressants mainly focus on brain abnormalities while ignoring other organ dysfunctions, perhaps also focusing on studies involving other organs manifesting depression symptoms, providing a wide view of understanding the pathogenesis of depression and finding its cure. Nutritional interventions involving healthy dietary options are essentially involved in the manipulation of mental health problems by lowering such incidences. A growing area of psychiatry called nutritional psychiatry investigates the link between dietary habits and the likelihood of developing mental health issues. The solid data gathered and presented in this review suggests that probiotic therapy may reduce levels of inflammatory markers and/or increase serotonin availability to alleviate symptoms related to MDD. By lowering the stigma, delay, and side effects connected to conventional antidepressants, the possibility for probiotics to be employed as a novel treatment for clinical depression could have a significant effect on patients seeking antidepressant treatment [22].

The "gut-brain axis" or "microbiota gut-brain axis" (MGBA) is the main site of action of the psychobiotics and their role in curing clinical depression [23, 24]. Recent advances in understanding the role of psychobiotics on the gut-brain axis to cure depression have unlocked knowledge of an already existing connection between bacteria and humans [25]. It is a direct biochemical signaling between the gastrointestinal (GI) tract and the central nervous system that has been discovered by neuro-gastronomy research in the last ten years. The human "second brain" is referred to as the gut microbiota because of their crucial function in the control of the central nervous system [26]. Numerous neurological, immunologic, and humoral routes are used by the billions of bacteria that live in the human gut to mediate the bidirectional communication between the gut and the brain. The enteric nervous system (ENS), which is specific to the gut, is permanently and directly connected to the brain by the nerves. The microorganism system present in the gastrointestinal system of a human is essential in maintaining the host's immunity. There are about 100 trillion microorganisms in an adult gastrointestinal tract GIT [27]. Through their interactions with one another and the host, these microbes have a significant impact on human health [28]. Studies have been performed to evaluate the effect of gut microbiota on neurodevelopment and neuropsychiatric disorders, proving their importance [29]. It is important to emphasize that the mucous cell layer, which separates the ENS from the intestinal microbiota, prevents intestinal microorganisms from directly accessing this local neural system [30].

The development of theoretical knowledge and its dynamic fusion with empirical application laid the groundwork for revolutionary medicine. One such idea is the possibility of bidirectional communication within the microbiome-gut-brain axis (MGBA), which could represent a significant advance in current medical practice. Researchers and physicians are very interested in the enormous potential of probiotics, notably for treating mental problems. Probiotics are live bacteria that, when taken, have positive benefits on one's mental and physical health. They can be found in nutritional supplements and meals like fermented dairy goods and vegetables. According to a growing body of research, probiotics may operate as potential accompaniment in treatment along with the anxiolytic and antidepressant agents when consumed as part of a balanced diet. The Greek word "bios" (which means "for life") and the Latin word "pro" (which means "for life") merge to form the etymological hybrid word "probiotic." In recent years, it has been found that microbes may regulate how serotonin is generated in the gut. For instance, it has been discovered that certain gut strains can influence the gut's enterochromaffin cells' ability

to synthesize serotonin. Daily probiotic supplementation markedly enhanced anhedonia and mood, decreased anxiety, and enhanced sleep. Furthermore, the probiotic's lack of side effects and adverse occurrences suggests that it was well-tolerated and safe to use in this population. Therefore, these probiotics deserve study to explain the manner in which they might function as Psychobiotics. In comparison to prebiotics, probiotics have illustrated the upper hand in the reduction of clinical depression [31]. Most commonly used bacteria in probiotics are Lactobacillus, Bifidobacterium, Bacillus, Streptococcus, Enterococcus, and Escherichia.

The mode of action of psychobiotics is strain-specific, and each strain varies in its mechanism of action. Three possible mechanisms have been proposed for the gut microbiota's interaction with the GBA: inducing the intestinal epithelium to release neuroactive chemicals, influencing serum cytokine levels, and directly activating the vagus nerve [32]. These strains, when used either as a single or combination strain, can reduce depression in humans. Other than the regulation of the HPA-axis and sympatho-adrenal medullary (SAM)-axis and the inflammatory reflex, psychobiotics are also involved in cognitive functions of the brain, such as learning, memory, and behaviour [33], which is influenced by changes in the glial cells [34]. Psychobiotics administration achieves MGBA homeostasis, which is threatened by factors such as stress and anxiety; depressive symptoms are well managed when homeostasis is maintained [35]. It also proves that C-reactive protein (CRP) levels showing baseline readings are important in the improvement of depression. An anti-inflammatory mechanism is one of the many potential methods through which probiotics may lessen depressed symptoms. Many preclinical studies suggest the benefits conferred by using probiotics alone in the case of depression. However, it is proven advantageous when probiotics are used along with antidepressants [36]. The anti-depressive impact of the probiotic intervention was demonstrated using depression scores based on validated clinical scales and several depression-related biomarkers, such as cortisol, pro-inflammatory cytokines, and brain-derived neurotrophic factor (BDNF) levels. According to Bravo *et al.* (2011), the combination of probiotics with antidepressant effects is linked to increased GABA receptor expression and levels of BDNF, noradrenaline, and serotonin that have been restored [17].

Unlocking the gut-brain connection with psychobiotics

Psychobiotics have been shown to prove their positive influence on the improvement of the mental health of patients suffering from depression [37]. It was discovered that probiotics appear to be beneficial in lowering depressive symptoms when taken in conjunction with antidepressants in a 2021 meta-analysis of 7 randomized clinical trials (RCTs) including 404 patients. In the research that followed, anxious and depressive symptoms—which were linked to both brain and intestinal inflammation—were induced in mice by chronic immobilization stress (IS). When given Lactobacillus reuteri, Bifidobacterium adolescentis, Lactobacillus mucosae, or Bifidobacterium longum, mice performed better in the forced swimming, light/dark transition, elevated plus maze, and light/dark test. Furthermore, brain-derived neurotrophic factor (BDNF) levels were increased, whereas nuclear factor B (NF-B) activation and microglial cell infiltration were decreased in the hippocampus. Additionally, Lactobacillus mucosae administration was demonstrated to ameliorate cognitive decline, anxiety, and depressive symptoms, as well as intestinal homeostasis during Escherichia coli-induced mouse colitis. Furthermore, by reestablishing gut and brain equilibrium, the usage of probiotic cocktails containing Lactobacillus and Bifidobacterium strains was able to lessen depressive behaviors [38]. Hence, bifidobacterium and Lactobacillus probiotic supplements are currently used often to treat the symptoms of depression [39], and they have a remarkable influence on the patient's mood. A four-week study conducted by Tillisch *et al.* 2013 on healthy female volunteers who consumed a fermented milk product containing a combination of probiotics, including Bifidobacterium animalis subsp. lactis, Streptococcus thermophilus, Lactobacillus bulgaricus, and Lactococcus lactococcus subsp. lactis revealed that probiotic consumption affected healthy people's brain activity in emotional centers. Healthy individuals who drank a milk beverage containing Lactobacillus casei Shirota for three weeks reported happier moods.

A single-center study created the hospital anxiety and depression scale (HADS) score, including seven questions to gauge anxiety and seven to gauge depression. Answers to each question range from 0 to 3. Each component score, which ranges from 0 to 21, is used to produce the combined values for the depression and anxiety components. An indication of potential depression or anxiety is indicated by a depression/anxiety component score of 8 or above. Then, individuals with a component score of 8 or higher received an invitation to take part in the study. No psychiatric medications were given to the study participants. After utilizing the multispecies probiotics for a month, the HADS score (both the total score and the component scores) and the EQ-5D-5L score greatly improved, and the improvements persisted after a second month. It has been demonstrated that

administering probiotics can increase and restore the levels of the neurotransmitters of interest, including 5-hydroxytryptamine (5-HT), norepinephrine (NE), and Gamma-aminobutyric acid (GABA), which have been linked to the development of depression. The mode of action of this specific probiotic characteristic is akin to the way some antidepressants work in terms of effectiveness.

Another study conducted by Steenbergen was conducted in patients administered with lyophilized probiotics powder containing bifidobacteria. Prior to and after the intervention, participants' mental state was assessed using the revised Leiden Depression Sensitivity Scale (LEIDS-r), Becker Depression Scale II (BDI-II), and Becker Anxiety Scale (BAI). The findings indicated that the consumption of probiotics over a 4-week period led to a significant reduction in overall cognitive responses related to depression, particularly in terms of aggressive and reflective thought patterns. This study provided initial evidence that a 4-week regimen of multispecies probiotics had a positive influence on the cognitive responses associated with natural mood fluctuations in mentally healthy individuals [40].

Through the modification of neuroendocrine and direct neuronal transmission, probiotics can stabilize the HPA axis; it is supported by the documented evidence of a decrease in 5-hydroxy-indole acetic acid (5-HIAA) levels in patients treated with SSRIs, and the same effects were noted in mice treated with *Lactobacillus plantarum*. After the administration of psychobiotics in the patients, no signs of any side effects or adverse events were noted, hence proving the safety and well-tolerance of these new category drugs in treating clinical depression [41].

Learning the psychobiotic potential: Enhanced benefits for psychiatric disorders

Psychobiotics may be used as an addition to antidepressants to treat depressive symptoms. Probiotics that produce GABA, for instance, have been linked to reduced sleeplessness; major depressive disorder, bipolar disorder, and Schizophrenia are only a few of the most severe and incapacitating mental diseases that have been the subject of research on the gut microbiome and microbial manipulation with probiotics. Probiotics' action in proving their significance in helping anxiety has also been proven, and they show activity by reducing oxidative stress, altering pain hormones, or reducing the circulating cytokines. When the host is under physical or physiological stress, his gut microbiota is extremely responsive. Stress dramatically lowers levels of the Firmicutes phylum, particularly in *Bifidobacterium* and bacteria from the Lactobacillaceae family, and simultaneously affects the composition and percentage of the intestinal microbiota. Long-term psychosocial stress results in an ongoing state of elevated HPA-axis activity, increased corticosteroid production, and dysfunction of the sympathetic nervous system, which is typically accompanied by deficits in prefrontal cortex (PFC) activity, immunological function, and behavior [42].

Lactobacillus helveticus (*L. helveticus*) and *Bifidobacterium longum* (*B. longum*) are synbiotics used in people who are under stress to reduce gastrointestinal discomfort, as stress plays an important role in gastrointestinal functions. Certain studies also suggest the benefits of using probiotics in autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) patients [43]. The symptoms and physiological mechanisms associated with the main neurological illnesses, such as depression, AD, and PD, are significantly impacted by gut microbiome modification. In the realm of depression research, there's a growing focus on examining the structure of the microbiota in individuals affected by this disorder. Many studies have pointed out that people with depression exhibit disruptions in both the composition and quantity of strains present in their gut microbiome [44].

CONCLUSION

In this review, we aimed to prove the influence of psychobiotics in treating clinical depression and improving overall human health. Psychobiotics are a recently introduced class of drugs that has proven its worth not only in treating depression but also various other psychiatric disorders. The mechanism of action of psychobiotics is mediated through the microbiota gut-brain axis, which is a bidirectional connection between the gut and the brain. It exerts its effects in various ways, such as: 1) Neurotransmitter production- Neurotransmitters, including serotonin, dopamine, and gamma-aminobutyric acid (GABA), can be produced by certain bacteria in the stomach. These neurotransmitters are essential for controlling emotions, including anxiety and mood; 2) Inflammation regulation- The anti-inflammatory characteristics of psychobiotics are thought to help lessen systemic inflammation in the body, including the brain. They may have a good effect on mood and mental health because of this anti-inflammatory function; 3) Hormones regulation- Cortisol, one of the hormones that control mood and stress reactions, is produced and regulated in part by gut flora. Psychobiotics may assist in controlling these

hormone levels, resulting in a more stable emotional state; and 4) Immune system modulation- Gut bacterial imbalance can result in immune system malfunction, which has been linked to several psychiatric diseases. The immunological response may be modulated by psychobiotics, potentially lowering the risk of mental health problems. Its overall assistance in treating clinical depression is commendable. Further studies to understand psychobiotic's mechanism in curing depression at a deeper level and their potential advantages in other psychiatric disorders are required for thorough knowledge. Based on the available data, it is safe to say that psychobiotics can be used in combination with antidepressants as supplementary drugs in treating mental disorders.

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ETHICS STATEMENT : This literature review was approved by the ethics review committee and listed under the IEC number: CMRCP/IEC/2022-23/09. The study was performed by conducting thorough literature review and data extraction and concluded after complete understanding of analysed data.

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