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Beyond the Gut Feeling: Exploring the Role of "Psychomicrobiotic" and Biomeme Hypothesis.

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Abstract

Introduction: Recent studies have highlighted the significant impact of the human gut microbiota on the nervous system, correlating with various psychological and behavioral phenotypes, such as mood, cognition, sleep, and personality. This intricate bidirectional communication, known as the "Microbiota-Gut-Brain Axis" (MGBA), plays a crucial role in both the development and function of the brain in health and disease states. Dysbiosis of the gut microbiota, characterized by perturbations and alterations, has been associated with anxiety, depression, and a spectrum of neuropsychiatric disorders. This review synthesizes the clinical application of the MGBA in managing major psychiatric illnesses in adults, termed "Psychomicrobiotic." Materials and method: A scoping review was conducted through comprehensive searches of Scopus, Web of Science, and PubMed databases from inception to December 2019, yielding 12 relevant systematic reviews and meta-analyses. Herewith, the titles, abstracts, and full-text articles were screened for the selection of relevant papers. Results: The findings reveal promising effects of interventions targeting gut microbiota on anxiety and depression symptoms, albeit with limitations such as variability in study populations, methodologies, and intervention durations. Mechanistically, dysbiosis influences psychiatric pathology through neuro-immuno-endocrine pathways and epigenetic regulation. While evidence supports the efficacy of probiotics in alleviating symptoms of anxiety and depression, further research is warranted, particularly in schizophrenia and bipolar disorder. Overall, this review underscores the imperative for high-quality research to elucidate the association between psychiatric illness and the human gut microbiome, offering potential avenues for novel therapeutic strategies.

Keywords

Microbiome-Gut-Brain Axis, Gut-Brain Communication, Psychobiotics, Dysbiosis, Probiotics.

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Introduction

There are relevant and robust bidirectional communication between the brain and the gastrointestinal tract known as the gut-brain axis (GBA), which creates growing awareness among scientific and medical societies[1]. This bidirectional link, which are regulated by the neural, hormonal, and immunological systems, is essential for preserving the homeostasis while perturbation of these systems affects the stress-response and overall behaviour of human being[2]. Therefore, there is a need to explore the potential therapeutic strategies by targeting microbiota dysbiosis in major psychiatric disorders which is term as ‘‘psychomicrobiotic’’[3].

Moreover, current research of this area also helps us to conceptualize the physical and social concomitants of mental disturbance; hence, further supporting the notion of mental health is not narrowly placed in the head but is integrated by the human body and interaction with the environment[4]. However, the understanding into wider environmental factors that shape differences in human microbial communities, particularly in social conditions, is still limited[5]. Another complex phenomenon that cannot be understood within a specific frame as either biologically and environmentally is behaviour, which is very diverse, and many have their origin in religion[6]. Interestingly, some hypothesize that certain aspects of religious behaviour in the society could be influenced by microbial host control, and the transmission of some religious rituals occurs concurrently with both ideas (memes) and parasitic organisms[7]. This hypothesis was named as Biomeme hypothesis. Nevertheless, there are hundreds of other explanations for people looking for common spiritual practices which are conventionally studied by psychological and sociological field rather than microbiology[8]. Whether adherence to a particular religious practice offers benefit to human societies or not is still debatable[7]. Based on our knowledge, there is a lack of published materials to exhibit the role of the gut-brain axis in the treatment of major psychiatric illnesses in adults. Therefore, this review intends to provide a review of the clinical application of GBA in managing major psychiatric illness in adult (Psychomicrobiotic).

While the existing literature has provided valuable insights into the association between gut microbiota and psychological and behavioral phenotypes, there remains a need for further exploration and understanding. This review aims to delve deeper into the clinical implications of the MGBA, specifically focusing on its role in managing major psychiatric illnesses in adults, a concept termed "Psychomicrobiotic." By synthesizing current evidence from systematic reviews and meta-analyses, this review seeks to elucidate the therapeutic potential of targeting the MGBA in the context of psychiatric disorders. Through a comprehensive examination of the literature, this review endeavors to contribute to a more nuanced understanding of the intricate interplay between gut microbiota and mental health, ultimately paving the way for novel therapeutic strategies and interventions.

Method

This review adopts a scoping review approach to comprehensively explore the literature surrounding the Microbiota-Gut-Brain Axis (MGBA) and its implications for psychiatric disorders. The scoping review methodology was chosen to provide a broad overview of the existing literature, encompassing a range of study designs and methodologies to capture the diversity of research in this field[9]. Three electronic databases (Web of Science, Scopus, and PubMed) were searched for either relevant published full papers or dissertations written in English literature from the inception of databases to December 2019. The search strings applied were: ("Meta-analysis" OR "systematic review”) AND (“gut microbiome" OR "gut-brain" OR dysbiosis) AND (psychiatric OR psychiatry OR mental OR mind OR psychology OR psychological OR behaviour OR behavioural). For the different databases, the research strategy was adapted according to respected databases.

The search results were limited to the systematic review and meta-analysis studies that only involved human participants, which focused on the effects of any intervention toward mental health in adults in relation to the GBA. Other articles such as editorials, commentaries, correspondences, non-systematic review, and abstracts alone were excluded.

Then, the duplicates were removed after reviewing the search results. The titles, abstracts, and full-text articles were screened and excluded if they did not meet the criteria by two reviewers. If there were disagreements, reviewers would discuss with each other and reached the agreement through the discussion. The selection process of these studies is represented in Fig 1. The information of the studies such as publication details, method of the studies, the total number of the studies, illness, intervention, result, funding, and limitation of each study was extracted and organized into a review table (Table 1). There was no prior registration or protocol published which regard for this review.

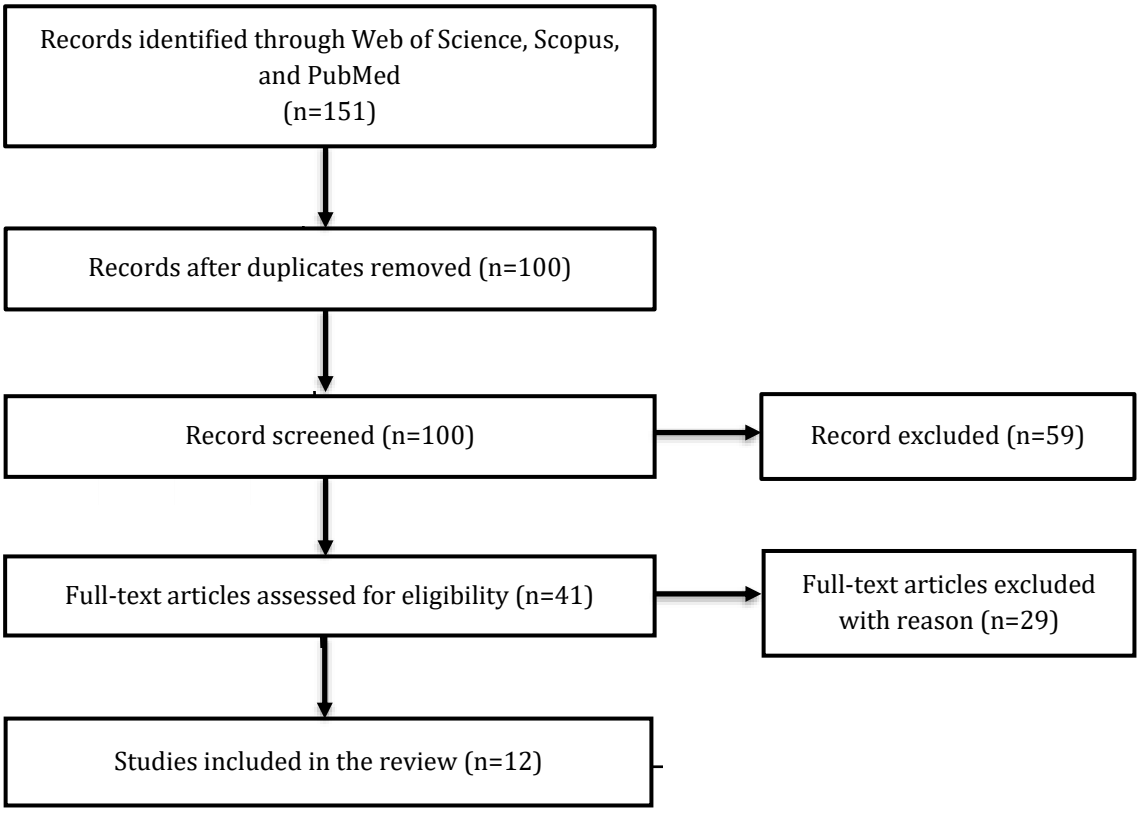

Figure 1: Flow diagram for paper screening result

Result

The initial electronic searches retrieved a total of 151 articles. After removing duplicates, 100 articles were screened by titles, abstracts, and full-texts, only 12 reviews met the criteria. These systematic review and meta-analysis were published since 2015 with total 169 studies. The discussion focused on the effect of

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non-probiotic, prebiotic, and probiotic toward mental illness such as anxiety disorder, depression, and schizophrenia. Overall, there are five meta-analyses and seven systematic reviews exploring the effect of probiotic and non-probiotic toward mental health and psychiatric illness. One systematic review studies the impact of probiotic supplementation on schizophrenia symptoms with only three studies included in the report. Two systematic reviews examine the study of both depressive and anxiety symptoms. Moreover, three reviews explore the study on anxiety symptoms only while another five on depression, which is the most common subject for systematic reviews. There is only one systematic review examine the broad range of mental illness or disturbance (stress, mood, anxiety, schizophrenia, psychoticism, somatization, interpersonal sensitivity, obsessive-compulsive behaviour, coping skill, and externalizing behaviours in ASD) to support the theory of psychobiotics.

Overall, the support of antidepressant and anxiolytic for psychomicrobiotic exist. However, there is a need for further study on effect of psychomicrobiotic in schizophrenia patients as well as bipolar disorder and other major psychiatric illness. There are a lot of limitations in conducting probiotic studies such as variability of a population, method, sample size, duration of the intervention period, bacterial strains used, and placebo product used.

Discussion

In the human GI tract, the commensal bacteria took advantage from a nutritionally rich and protected habitat while they, in turn, help the host by making indigestible nutrients available to the body, producing energy, vitamins, and other metabolites as well as to protect against pathogenic microbes by building a protective biofilm to the gut tissue [22]. Meanwhile, dysbiosis is a condition where the composition and functions of the microbiome are shifted from their normal beneficial state to other states that is detrimental to the host's health as it may negatively affect CNS functioning through various intertwined pathways that collectively form the GBA[3]. The mechanisms underlying these bidirectional communications involve neuro-immuno-endocrine mediators, which comprise of the enteric nervous system (ENS), the central nervous system (CNS), the autonomic nervous system (ANS), and the hypothalamic-pituitary adrenal (HPA) axis[23].

The bidirectional communication between the various systems in the GBA also has been driven by the vagus nerve[24]. The vagus significantly plays a role in the transmission of immune information from the gut to the brain as well as maintaining the homeostasis associated with the immune system[25]. There are also certain vagal with afferent signals from the gut to the brain that can initiate an anti-inflammatory reaction, which activates an efferent response and release the mediators together with acetylcholine that diminishes inflammation through interaction with immune cells[23].

Apart from that, inflammation has become a candidate pathway for explaining psychiatric pathology as repeated abnormal profiles of proinflammatory and anti-inflammatory cytokines are observed in depression, bipolar disorder (BD), schizophrenia, obsessive-compulsive disorder (OCD), posttraumatic stress disorder and anxiety disorders[26]. This can be explained by the lipopolysaccharide (LPS) molecules of the microbiomes that can activate the Toll-like receptors (TLR), mainly TLR4, that will further regulate the expressions of many inflammatory mediators and cytokines through the activation of the NF-κB pathway. Chronic activation of the immune system resulted from the dysbiosis will affect the brain functions, which finally lead to mental disorders like anxiety disorder[12].

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Table 1: the studies included in this review.

	Title	Total no. of study	Illness	Intervention	Result	Funding Source	Limitation	References
1.	Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials.	34	Depression and anxiety	Prebiotic and probiotic	Generally, there is support for effects of antidepressant and anxiolytic for probiotics. Prebiotics did not differ from placebo for depression (d=−.08, p=.51) or anxiety (d=.12, p=.11). Probiotics yielded small but significant effects for depression (d=−.24, p < .01) and anxiety (d=−.10, p=.03). Sample type was a moderator for probiotics and depression, with a larger effect observed for clinical/medical samples (d=−.45, p < .001) than community ones. This effect increased to medium-to-large in a preliminary analysis restricted to psychiatric samples (d=−.73, p < .001).	Non-profit	Could not evaluate to what extent potential psychotropic effects of these regimens persist after cessation of treatment None of the trials included adolescent samples The prebiotic findings are preliminary	[10]
2.	Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials.	10	Anxiety and depression symptoms	Probiotic	A total of 10 randomized controlled trials (4 in clinically diagnosed and 6 in non-clinical samples) that provided limited support for the use of some probiotics in reducing human anxiety and depression.	No funding	Small sample sizes of the study Only 3 trials included a formal assessment of the food intake or supplementation adherence. Differences in probiotic formulations, dosage, and the duration of	[11]

							supplementation in all studies.	
3.	Effects of regulating intestinal microbiota on anxiety symptoms: A systematic review.	21	Anxiety	Probiotic and Non probiotic	Overall, 11 studies showed a positive effect on anxiety symptoms by regulating intestinal microbiota, which indicated 52% of the 21 studies were effective, and there were five studies that used probiotic supplements as interventions and six used non-probiotic interventions. In addition, it should be noted that six of seven studies showed that regulation of intestinal microbiota could treat anxiety symptoms, the rate of efficacy was 86%.	Non-profit	Differences in the research design types, subjects, interventions and anxiety assessment scales of the articles included The overall heterogeneity was too large	[12]
4.	Efficacy of probiotics on anxiety A meta-analysis of randomized controlled trials	12	Anxiety	Probiotic	The 12 studies involved 871 subjects in the probiotics group and 680 subjects in the control group. Due to the relatively high heterogeneity among the included studies ($I2$ = 51%; P = 0.02 for 2 test), a random effect model was selected for quantitative synthesis. Overall, the meta-analysis revealed no significant difference between the probiotics and placebo groups in alleviating anxiety (SMD = –0.12, 95% confidence interval [CI] –0.28 to –0.04, P = 0.14).	Non-profit	Relatively high heterogeneity between the included studies. Limited information of other key variables that may exert influence on the results such as the age, sex of the sample, specific stain of flora, drug form, and dosage of probiotics. The anxiety assessment scales significantly varied across the included studies	[13]

5.	Can psychobiotics "mood" ify gut? An update systematic review of randomized controlled trials in healthy and clinical subjects, on anti-depressant effects of probiotics, prebiotics, and synbiotics.	32	Depression	Probiotic Prebiotic Synbiotic	The results of studies on prebiotics and synbiotics are not conclusive and current evidence is not sufficient to either support or decline anti-depressant effects of probiotics due to the strain-specific manner effect of probiotics on depression. Only seven studies from 32 articles reported significant anti-depressant effects of psychobiotics. Some probiotic strains showed beneficial effects on depressive symptoms. However, the results were inconsistent. Few studies investigated the effects of prebiotics or synbiotics on depression, and did not come up with much promising results	No funding	There is inconsistency of the results among the studies, unclear overall risk of bias, and use of multistrain formulations in the majority of these clinical trials. Most of the studies did not assess baseline gut microbiota composition or its changes after the treatments	14
6.	Goh 2019 Effect of probiotics on depressive symptoms: A meta-analysis of human studies	19	Depressive	Probiotic	The overall effect of probiotics on depressive symptoms was statistically significant (SMD = −0.31; 95% CI, −0.56 to −0.07; *P*=0.01). Probiotics were effective in reducing depressive symptoms in the clinical population (SMD = −0.40; 95% CI, −0.74to −0.06; *P*=0.02),	Non-profit	Lack of uniformity in the sample size and population distribution among the included studies. The study design varied among the included studies. Selective publication bias of the studies The sample size of patients with MDD was small.	15

7.	Nikolova 2019 Gut feeling: randomized controlled trials of probiotics for the treatment of clinical depression: Systematic review and meta-analysis.	3	Depression	Probiotic Probiotic with antidepressant	There is limited evidence for the efficacy of probiotics in depression at present, although there may be a beneficial effect of probiotics on depressive symptoms when administered in addition to antidepressants. Only three studies met inclusion criteria (229 individuals randomized), two of which administered probiotics as a supplementary treatment to antidepressants and one as a standalone treatment. Upon removal of the latter study from the meta-analysis due to clinical heterogeneity, there was an overall positive effect of probiotics on depressive symptoms (standardized mean difference = 1.371, 95% confidence interval 0.130–2.613).	Non-profit	Limited number of published RCTs. Heterogeneity exist between the studies, including: the type of intervention either add-on *or* standalone, the content of intervention such as strain combinations and dosing, the population either confirmed diagnosis of MDD *or* self-report, depression severity either mild or moderate for inclusion, and AE reporting (one study did not report AE rates). Different exploratory analyses performed in each trial	[16]
8.	A meta-analysis of the use of probiotics to alleviate depressive symptoms.	10	Depression	Probiotic	Probiotic supplementation has an overall insignificant effect on mood. 10 clinical trials with a total of 1349 patients were reviewed, comparing the use of probiotics to placebo controls. There was no significant difference in mood between the treatment and placebo group post-intervention as the SMD was -0.128 (95% CI -0.261 to 0.00463, P=0.059). A	No funding	Inter-study discrepancies with respect to probiotic dosing, bacterial strains and strain combinations	[17]

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					separate subgroup analysis of studies conducted in healthy versus depressed individuals found significant improvements in the moods of individuals with mild to moderate depressive symptoms (SMD -0.684, 95% CI -1.296 to -0.0712, P=0.029) and nonsignificant effects in healthy individuals (SMD -0.0999, 95% CI -0.235 to 0.0348, P=0.146).		Majority of studies were conducted in healthy individuals	
9.	The effects of probiotics on depressive symptoms in humans: a systematic review. Ann Gen Psychiatry.	10	Depressive symptoms	Probiotic	There is evidence for probiotics alleviating depressive symptoms as the majority of the studies found positive results on all measures of depressive symptoms. However, further double-blind randomized control trials are needed. Ten studies met criteria and were analysed for effects on mood (five studies), anxiety (seven studies), and cognition (3 studies).	Industry	Widely varies duration of intervention, quantity and strains of the probiotics	[18]
10.	Effect of probiotics on depression: A systematic review and meta-analysis of randomized controlled trials	5	Depression	Probiotic	Probiotics were associated with a significant reduction in depression. The meta-analysis showed that probiotics significantly decreased the depression scale score (MD (depressive disorder) = - 0.30, 95% CI (-0.51–-0.09), p = 0.005) in the subjects. Probiotics had an effect on both the healthy population (MD = -0.25, 95% CI (-0.47–-0.03), p = 0.03) and patients with major depressive disorder (MDD) (MD = -0.73, 95% CI (-1.37–-0.09), p = 0.03). Probiotics had an effect on the population aged under 60 (MD = -0.43, 95% CI (-0.72–-0.13), p = 0.005), while it had no effect	Non-profit	Inconsistency of probiotics selected in the reference documents, the dose and treatment Interferences such as diet and medication The RCTs are from the different countries. Thus, people with different genetic constitutions or	[19]

					on people aged over 65 (MD = -0.18, 95% CI (-0.47–0.11), p = 0.22).		microbial exposure may have a different response to identical probiotics. Different in the depression rating scales chosen by the research projects. Small sample size some of the study	
11.	A Systematic Review of the Effect of Probiotic Supplementation on Schizophrenia Symptoms	3	Schizophrenia	Probiotic	There was no significant difference in schizophrenia symptoms between the group that received probiotic supplementation and the placebo group post-intervention as the standardized mean difference was –0.0884 (95% CI –0.380 to 0.204, *p* = 0.551).	No funding	Only 3 trials included	[20]
12.	Systematic review of evidence to support the theory of psychobiotics	10	Stress, mood, anxiety,and externalizing behaviors in ASD. Schizophrenia psychoticism, somatization, interperso	Probiotic	Overall, ten trials that met the inclusion criteria showed limited evidence for the effectiveness of probiotic interventions in psychological outcomes. However, the trials is incomplete and lacks applicability.	Industry	Variability in population, method, sample size, duration of intervention period, bacterial strains used, and placebo product use.	[21]

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			nal sensitivity, obsessive–compulsive behavior, coping					

Moreover, dysbiosis can affect epigenetic regulation (histone acetylation, DNA methylation) and gene expression of receptors and mediators (SLC6A4, BDNF, GABA, GPRs) involved in depressive disorders[27]. Besides, dysbiosis can also alter gene expression in the hippocampus and the paraventricular nucleus of the hypothalamus (PVN)[28].

Anxiety

The studies of the microbiome GBA and preclinical studies point out that dysbiosis influences anxiety and stress behaviours[29]. Evidence from germ-free animal models and probiotic studies indicate a connection between disrupted gut microbiota and anxiety[30]. Patients with generalized anxiety disorder compared to healthy controls have markedly decreased microbial richness and diversity, distinct metagenomic composition with reduced short-chain fatty acid (SCFA)-producing bacteria (associated with a healthy status) and overgrowths of bacteria, such as *Escherichia-Shigella, Fusobacterium and Ruminococcus gnavus*[31]. The abundances of *Eubacterium_coprostanoligenes_*group, *Ruminococcaceae_UCG-014*, and *Prevotella_9* correlated negatively with the anxiety severity and positively with anxiety reduction, whereas the abundances of *Bacteroides* and *Escherichia-Shigella* were positively associated with anxiety severity[32]. Moreover, more than half of the studies in one systematic review demonstrate a positive response to treat anxiety symptoms by regulation of intestinal microbiota[12]. However, the evidence for probiotics' effectiveness in alleviating anxiety is still insufficient[13].

Depression

Depression is associated with decreased gut microbiota richness and diversity as fecal microbiota transplantation of microbiota-depleted rats from depressed patients can cause behavioral-like depression (anhedonia and anxiety) and physiological features of depression such as tryptophan metabolism alteration in the recipient animals[33]. Intestinal dysbiosis in depressed patients is associated with increased levels of gut *Bacteroidetes*, *Enterobacteriaceae*, *Alistepes*, and reduced levels of *Firmicutes phylum* and *Faecalibacterium* as compared to healthy subjects which initiate a local and systemic immune response that will compromise the gut-brain communication and increased gut permeability as well as bacterial translocation[34]. The *Faecalibacterium* was negatively correlated with the severity of depressive symptoms[35]. Therefore, the GBA alteration with probiotics showed significantly greater improvement in depressive symptoms as compared to those receiving placebo[15].

Schizophrenia

Several studies have investigated the association of intestinal microbiota with schizophrenia[36]. Schizophrenia is associated with alteration in gut microbiota composition that is both correlated with symptom severity and specific to schizophrenia[37]. There is a fairly increased abundance of *Lactobacillaceae, Halothiobacillaceae, Brucellaceae*, and *Micrococcineae* and decreased *Veillonellaceae,* which was manifest in schizophrenic patients with poorer global functioning and severer negative symptoms [20]. Furthermore, for the patient with first-episode of psychosis, the gut microbial composition was associated with the severity of psychotic symptoms and global functioning during hospitalization[38]. However, limited inferences can be made concerning the current evidence for probiotics efficacious in schizophrenia[20].

Bipolar

The gut microbial community differences have been observed in bipolar disorder as there is a reduced fractional representation of *Faecalibacterium* and an unclassified member from the *Ruminococcaceae* family from the phylum *Firmicutes*. Increased *Faecalibacterium* was associated with reduced depressive symptoms, improved physical health, and better sleep among these patients[38]. Faecalibacterium negatively associates with the self-reported burden of disease measures in bipolar individuals. These suggest that therapeutically increasing *Faecalibacterium* in bipolar patients may be useful to reduce disease burden[39].

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Moreover, in bipolar and schizophrenic patients, probiotic supplementation was shown to alleviate gastrointestinal complaints, reduce rehospitalization rates, an improvement in cognitive tasks, and potentially reduce the severity of the symptom[40].

Addressing gaps in understanding the gut microbiome and psychiatric disorders

The existing literature reviewed herein has shed light on the intricate relationship between the gut microbiome and psychiatric disorders, particularly anxiety, depression, and schizophrenia. However, despite the wealth of evidence presented, several gaps in understanding persist, warranting further investigation.

Firstly, there remains a need for a more comprehensive analysis of meso- and micro-structural responses within the gut-brain axis (GBA). While existing studies have provided valuable insights into the macro-level interactions between the gut microbiome and the central nervous system (CNS), a deeper understanding of the underlying mechanisms at the cellular and molecular levels is warranted. Specifically, elucidating how specific microbial species and their metabolites influence neuronal signaling, neurotransmitter production, and neuroinflammatory pathways within the CNS could provide crucial insights into the etiology and pathophysiology of psychiatric disorders.

Moreover, while the review highlights the potential therapeutic benefits of probiotics in managing psychiatric symptoms, the precise mechanisms underlying these effects remain poorly understood. Future research efforts should aim to delineate the mechanisms by which probiotics exert their therapeutic effects, including their impact on gut barrier integrity, immune function, and neuroendocrine signaling. Additionally, investigating the role of the gut microbiome in mediating the pharmacokinetics and pharmacodynamics of psychotropic medications could offer novel avenues for personalized treatment approaches in psychiatry.

Furthermore, the review underscores the need for longitudinal studies to elucidate the temporal dynamics of the gut-brain axis and its implications for psychiatric health. Longitudinal research designs would enable researchers to assess the stability and resilience of the gut microbiome over time, as well as its susceptibility to external factors such as diet, medication, and stress. Additionally, longitudinal studies could provide valuable insights into the trajectory of psychiatric symptoms in relation to changes in gut microbial composition, facilitating the development of targeted interventions for disease prevention and management.

In conclusion, while the review provides valuable insights into the role of the gut-brain axis in psychiatric disorders, several gaps in understanding persist. Addressing these gaps will require a multidisciplinary approach encompassing molecular biology, neuroscience, microbiology, and psychiatry. By elucidating the meso- and micro-structural responses underlying GBA hypotheses, researchers can advance our understanding of the pathophysiology of psychiatric disorders and pave the way for novel therapeutic interventions.

Recommendation & Conclusion

The findings from the systematic reviews, meta-analyses, and studies reviewed highlight the complex interplay between the gut microbiome and psychiatric disorders, particularly anxiety, depression, and schizophrenia. While some evidence suggests a potential role for probiotics in alleviating symptoms associated with these disorders, the overall picture remains nuanced and inconclusive. Despite the

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promising results observed in certain studies, it is evident that more research is needed to fully elucidate the direct relationship between the gut-brain axis and psychiatric disorders. The current body of evidence, while informative, is still limited in scope and depth. Moreover, the practicality and implications of the "biomeme hypothesis" remain uncertain. While it presents an intriguing concept linking microbial influences to cultural and religious behaviors, further empirical investigation is necessary to validate its validity and relevance.

Nevertheless, the review underscores the potential of probiotics to modulate behavior through microbiota perspectives. This highlights the importance of ongoing research efforts to explore the therapeutic potential of probiotics in managing psychiatric disorders. In light of the gaps and limitations identified in the existing literature, there is a clear need for high-quality research to establish a robust association between probiotics and the human gut microbiome. Such research endeavors should aim to address methodological inconsistencies, expand the breadth of investigation across various psychiatric conditions, and consider the long-term effects and mechanisms of action underlying probiotic interventions.

Ultimately, advancing our understanding of the gut-brain axis and its implications for psychiatric health holds significant promise for the development of novel therapeutic approaches and interventions. It is imperative that future research in this field prioritizes rigorous study designs, interdisciplinary collaboration, and comprehensive exploration of the microbiome's role in mental well-being.

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