**ZAJKOWSKA, Izabela, NICZYPORUK, Patrycja, GIBA, Aleksandra, IŁENDO, Kamila, KRÓLIKIEWICZ, Wiktor, MARECKI, Rafał and KICMAN, Aleksandra. Synergistic modulation of gut microbiota and mindfulness-based interventions in schizophrenia: Integrating neurotransmitter regulation and multimodal therapeutic strategies. Quality in Sport. 2025;41:59834. eISSN 2450-3118.**
**https://doi.org/10.12775/QS.2025.41.59834**
**https://apcz.umk.pl/QS/article/view/59834**

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). 
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 28.03.2025. Revised: 30.04.2025. Accepted: 12.05.2025. Published: 12.05.2025.

# SYNERGISTIC MODULATION OF GUT MICROBIOTA AND MINDFULNESS-BASED INTERVENTIONS IN SCHIZOPHRENIA: INTEGRATING NEUROTRANSMITTER REGULATION AND MULTIMODAL THERAPEUTIC STRATEGIES

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## Abstract

This review explores an innovative, integrative therapeutic approach that combines probiotics, prebiotics, and mindfulness-based interventions (MBIs) to target the dysregulation of the gut–brain axis in schizophrenia. The rationale for this combined strategy is rooted in the overlapping mechanisms by which both biological and psychosocial interventions influence neurophysiological processes. Probiotics and prebiotics are shown to rebalance the gut microbiota, thereby enhancing the synthesis of key neurotransmitters—such as serotonin, gamma-aminobutyric acid (GABA), and dopamine—and reducing systemic inflammation and oxidative stress. In parallel, MBIs, including Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT), promote improvements in emotional regulation, cognitive function, and neuroplasticity through the modulation of neurophysiological pathways, notably by attenuating amygdala reactivity and heightening prefrontal cortex engagement.

Viewing these interventions through the unifying lens of the gut–brain axis presents a promising paradigm: both modalities may exert synergistic effects to support the management of persistent symptoms of schizophrenia and complement existing therapeutic approaches. By converging on shared biological and psychosocial pathways, this integrative model could offer a more comprehensive strategy for addressing the multifaceted challenges of schizophrenia. While preliminary evidence is encouraging, further controlled clinical studies are essential to determine optimal treatment protocols and to elucidate the precise mechanisms by which these therapies interact to enhance patient outcomes.

## Keywords

**schizophrenia, brain-gut axis, microbiota, probiotics, prebiotics, mindfulness, neurotransmitters, inflammation, cognitive functions, psychotherapy**

## Introduction

Schizophrenia remains one of the most formidable psychiatric disorders, characterized by a complex interplay of positive, negative, and cognitive symptoms that profoundly compromise an individual's quality of life (1). Despite decades of research, conventional pharmacological treatments—primarily targeting dopaminergic pathways—often fail to address the myriad clinical challenges, as many patients continue to experience persistent symptoms and functional impairments (2). This therapeutic gap has spurred the exploration of novel biological and psychosocial strategies that may more comprehensively target the multifaceted pathology of schizophrenia.

One promising avenue of investigation is the gut–brain axis, a bidirectional communication network that links the gut microbiota with central nervous system (CNS) function (3). Over the past decade, accumulating evidence has revealed that the composition and integrity of the gut microbiota are intricately linked to brain function and behavior. In this context, probiotics—live microorganisms that confer health benefits by optimizing the microbial balance in the gut—and prebiotics—non-digestible dietary components that promote the growth or activity of beneficial bacteria—have emerged as potential modulators of this axis (4). By fostering a favorable microbial environment, these agents can influence the synthesis of key neurotransmitters, including serotonin, gamma-aminobutyric acid (GABA), and dopamine, which are critically involved in the neurobiological dysregulations observed in schizophrenia (5). Furthermore, a well-balanced gut microbiota may attenuate systemic inflammation and oxidative stress—pathophysiological processes implicated in the progression of psychiatric symptoms (6).

In parallel with advances in microbiota research, mindfulness-based interventions (MBIs) such as mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) have gained increased recognition as complementary therapeutic modalities. MBIs, which are founded on practices that cultivate self-regulated attention and a non-judgmental, present-moment awareness, facilitate enhanced emotional regulation and cognitive flexibility (7). Neuroimaging investigations have further illustrated that mindfulness practices can attenuate hyperactivity in the amygdala while augmenting the engagement of the prefrontal cortex—an activation pattern conducive to improved emotional and behavioral control. Emerging evidence suggests that the benefits of MBIs may extend beyond psychological well-being, potentially modulating physiological processes along the gut–brain axis and thereby hinting at a convergence between these two intervention strategies (8).

The convergence between gut microbiota modulation and mindfulness-based practices presents a novel and integrative perspective on schizophrenia treatment. Each approach addresses distinct yet interconnected aspects of the disorder—the biological underpinnings via microbial balance and the psychological facets through enhanced emotional regulation. Preliminary data indicate that the combined application of these interventions may yield synergistic benefits (9). Therefore, the objective of this review is to synthesize data from clinical trials, meta-analyses, and mechanistic studies to construct a comprehensive framework that bridges neurotransmitter imbalances, systemic inflammation, and cognitive dysfunction. By highlighting the potential interventional overlap between optimized gut health and advanced mindfulness practices, this review underscores the possibility that such integrated strategies might collectively contribute to more robust improvements in patient outcomes.

## The purpose of research

The primary objective of this review is to examine the pathways through which gut microbiota modulation via probiotics and prebiotics influences neurotransmitter synthesis and inflammatory markers in schizophrenia. Additionally, it aims to explore the complementary role of mindfulness-based interventions in improving cognitive function and emotional regulation. By integrating findings from both areas, the review highlights the potential of these approaches to deepen our understanding of schizophrenia's complex etiology and their relevance in shaping future research directions.

## Research materials and methods

On March 10, 2025, a systematic literature search was conducted using PubMed with a custom Python scraping script. Keywords included "schizophrenia," "gut–brain axis," "microbiota," "probiotics," "prebiotics," "mindfulness," and "neurotransmitters." The inclusion criteria were English-language publications without date restrictions, focusing on studies that investigated the role of gut microbiota in neurotransmitter regulation, the

effectiveness of microbiota-targeted therapies, and the impact of MBIs on cognitive and emotional outcomes in schizophrenia. Data were extracted following PRISMA guidelines and synthesized to provide a comprehensive overview of current insights and potential therapeutic implications.

**Probiotics and Prebiotics in Schizophrenia: Potential Therapeutic Tools**

Probiotics, defined as live microorganisms that provide health benefits to the host, and prebiotics, which are non-digestible dietary components that promote the growth of beneficial bacteria, have gained increasing attention as potential adjunctive therapies for schizophrenia (10) . These microbiota-modulating agents work by influencing the gut microbiota's composition and function, which in turn affects the gut–brain axis (11) . The gut–brain axis is a bidirectional communication network linking the gastrointestinal tract and the central nervous system (CNS), playing a crucial role in maintaining mental and emotional well-being. Dysbiosis—an imbalance in gut microbiota—has been implicated in the pathogenesis of schizophrenia, as it influences both neurotransmitter synthesis and immune system activation (12) .

Probiotics and prebiotics are particularly effective in enriching the gut microbiota with genera such as *Bifidobacterium* (e.g., *B. longum*, *B. adolescentis*) and *Lactobacillus* (e.g., *L. rhamnosus*, *L. helveticus*). These bacteria enhance the production of short-chain fatty acids (SCFAs), notably butyrate, which strengthens the integrity of the intestinal barrier. This is critical in reducing the translocation of lipopolysaccharides (LPS)—pro-inflammatory components of gram-negative bacteria—into systemic circulation (13) . By mitigating LPS translocation, probiotics decrease Toll-like receptor 4 (TLR4) activation in the CNS, reducing neurogenic inflammation and oxidative stress, both of which are key contributors to the neurodegeneration observed in schizophrenia (14) .

Clinical studies underscore the promise of these interventions in schizophrenia management. For example, Jamilian et al. demonstrated that a 12-week regimen of probiotic supplementation combined with selenium significantly improved Positive and Negative Syndrome Scale (PANSS) scores in patients with chronic schizophrenia. Additionally, this combination enhanced metabolic health, as evidenced by improved blood glucose levels, insulin sensitivity, and reductions in markers of oxidative stress and inflammation (15) . These findings emphasize the interconnectedness of metabolic dysfunction and psychiatric symptoms in schizophrenia, suggesting that targeting the gut–brain axis could provide comprehensive health benefits.

Further evidence linking gut health to psychiatric symptoms comes from Severance et al., who investigated the effect of probiotics on fungal species such as *Candida albicans* and *Saccharomyces cerevisiae*, which are markers of gut dysbiosis. Their study revealed that probiotic supplementation significantly reduced *C. albicans* antibody levels in men, correlating with a reduction in the severity of positive psychiatric symptoms. This research highlights the role of gut dysfunction in schizophrenia and underscores the potential for probiotics to modulate these symptoms (16) .

The therapeutic potential of combining probiotics with other interventions has also been explored. Ghaderi et al. examined the effects of a 12-week supplementation with probiotics and vitamin D. This regimen resulted in improved antioxidant capacity, reduced inflammation (e.g., C-reactive protein and malondialdehyde), better glycemic control, and lower lipid profiles. The anti-inflammatory effects of vitamin D, which inhibits pro-inflammatory cytokines such as TNF-α and IL-6, further support the role of combined interventions in schizophrenia management (17,18) .

Moreover, Mohammadi et al. demonstrated cognitive benefits in patients with schizophrenia who received probiotics containing *Lactobacillus* and *Bifidobacterium* in combination with vitamin D. While significant cognitive improvements were observed, reductions in PANSS scores did not reach statistical significance. However, the intervention lowered CRP levels, further indicating anti-inflammatory effects mediated through gut–brain axis modulation (19) .

Prebiotics such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS) also contribute to gut–brain communication by promoting the growth of beneficial gut bacteria. These prebiotics indirectly increase serotonin synthesis by modulating tryptophan metabolism, a key precursor of this neurotransmitter. When administered with probiotics as symbiotics, they enhance bacterial metabolite production, which activates neuronal GPCR receptors (e.g., GPR41 and GPR43), potentially improving neuroplasticity and cognitive function (20) .

Butyrate, a critical SCFA produced by gut bacteria, plays a central role in maintaining gut barrier function and has potent anti-inflammatory properties. Studies have shown that schizophrenia patients often exhibit reduced levels of butyrate-producing bacteria. Notably, Buchanan et al. found that supplementation with oligofructose-enriched prebiotics elevated butyrate levels, leading to improved gut-blood barrier integrity and reduced systemic inflammation (21,22) . Furthermore, butyric acid's neuroprotective effects—mediated through its role in dopamine modulation and immune system regulation—highlight its potential relevance in schizophrenia treatment (23) .

Taken together, these findings suggest that probiotics and prebiotics represent promising tools in the management of schizophrenia. By modulating the gut microbiota, reducing oxidative stress, mitigating neuroinflammation, and enhancing neurotransmitter regulation, these interventions have the potential to complement existing pharmacological treatments. Future research should focus on elucidating the precise mechanisms underlying these effects and integrating them into personalized therapeutic strategies for schizophrenia.

**Mindfulness**

In recent years, mindfulness-based interventions (MBIs) such as mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) have garnered increasing attention as promising therapeutic approaches. Mindfulness is characterized by two core components: self-regulated attention and a focus on the present moment with openness, curiosity, and acceptance (24) . Beyond reducing stress, MBIs may influence biological processes by engaging the gut–microbiota–brain axis—a bidirectional signaling pathway that connects the gut with the central nervous system. This connection is increasingly recognized as playing a significant role in mental health and, more specifically, in neuropsychiatric disorders like schizophrenia.

An intriguing study by Khine et al. sought to demonstrate this connection by investigating the impact of cognitive function on the gut microbiome. They enrolled older adults (aged 60–85) with mild cognitive impairment (MCI) alongside individuals with normal cognition, implementing a 9-month mindfulness program that focused on sensory training, body scanning, and visual-motor tasks. After the intervention, distinct microbiota profiles emerged in patients with MCI—including alterations in Ruminococcus, Coprococcus, Parabacteroides, Fusobacterium, Enterobacteriaceae, Ruminococcaceae, and Phascolarctobacterium (25) . Considering that cognitive dysfunction affects about 98% of schizophrenia patients—even among those not undergoing antipsychotic treatment (26) -these findings raise the possibility that MBIs might offer similar benefits for cognitive processes in individuals with schizophrenia.

Beyond their influence on the gut microbiota, the relationship between mindfulness, psychological flexibility, and symptom severity in schizophrenia spectrum disorders (SSD) has also been explored. For instance, Böge et al. found that individuals with SSD exhibited lower levels of mindfulness and psychological flexibility compared to healthy controls. These diminished levels were associated with higher depression scores and reduced emotional adaptability, suggesting that MBIs could mitigate negative affect and improve overall functioning (27) . In a similar vein, Bergmann et al. demonstrated that higher mindfulness levels were correlated with better physical health, improved psychological well-being, and enhanced environmental comfort—with reduced depression mediating these associations (28) . Such findings indicate that mindfulness practices might contribute to reversing or at least attenuating some of the detrimental emotional and cognitive effects seen in schizophrenia.

Meta-analytical evidence further supports these observations. Yu-Chen Liu et al. reported that mindfulness therapy resulted in a sustained reduction of negative symptoms in schizophrenia, particularly noting significant improvements in nurse-led intervention groups (29) . Similarly, Keke Qin et al. found enhancements in psychosocial functioning, increased self-awareness, and elevated mindfulness among patients, concluding that MBIs could serve as an effective adjunct to primary therapy in schizophrenia (30) . These aggregated data not only reinforce the potential for MBIs to improve clinical outcomes, but they also underscore the need for further research into how such practices may be tailored to individual patient profiles.

Qualitative insights enrich this picture further. Angie Ho Yan Lam et al. investigated the subjective experiences of mindfulness practice among individuals with SSD and found that many participants reported positive emotional shifts after mindfulness training, enabling them to better manage negative emotions (31) . In a systematic review, Sabé and colleagues highlighted the benefits of MBIs, including reductions in negative symptoms, enhancements in overall mental status, and even fewer hospitalizations, despite variations in program structures (MBSR versus MBCT) (32) . Such qualitative and aggregate findings indicate that the experiential

components of mindfulness—like increased self-awareness and emotional regulation—can foster significant improvements in day-to-day functioning for patients.

Clinical studies have provided further support with direct symptomatic benefits. For instance, Sheng et al. reported that for patients with severe schizophrenia, eight sessions of MBIs combined with regular meditation over an eight-month period significantly reduced both hallucinations and delusions (33). In another study, Shen et al. found that six weeks of MBIs led to marked reductions in negative symptoms and overall psychopathology, while also enhancing cognitive performance and short-term memory in patients with chronic schizophrenia (34). Moreover, Zierhut et al. evaluated mindfulness-based group therapy (MBGT) in combination with oxytocin. They reported that although MBGT alone reduced stress, improved mood, and boosted attention, when paired with oxytocin, the intervention produced faster and more pronounced alleviation of symptoms, including reductions in apathy and emotional indifference (35).

Complementing these findings, Dai et al. assessed a mixed mindfulness-based cognitive therapy (M-MBCT) that combined face-to-face sessions with self-guided exercises. This integrative approach significantly increased psychological resilience and self-esteem, while also reducing stigma. These psychosocial improvements are particularly valuable given the social challenges that many patients with schizophrenia encounter (36). Additionally, Böge et al. later demonstrated that MBGT led to moderate to large improvements in attention, positive and negative symptoms, psychological resilience, quality of life, and social functioning, further affirming the multifaceted benefits of mindfulness-based approaches (37).

Adding a neurobiological perspective, Abram et al. observed that higher mindfulness levels were associated with a "younger" brain age, as determined by high-resolution neuroimaging—a marker correlated with better emotional well-being. Participants with elevated mindfulness levels exhibited brain activity patterns like healthy individuals, suggesting neuroprotective effects that might mitigate the accelerated brain aging sometimes observed in schizophrenia (38). Moreover, another study by Angie Ho Yan Lam and colleagues found that specific facets of mindfulness—such as non-judgment and heightened self-awareness—were linked to reduced rumination and negative emotions, as well as decreases in psychotic symptoms like hallucinations (39).

Research by Madani et al. offers additional insights into attention modulation strategies for managing auditory hallucinations. Their study compared three approaches—avoidance, focusing, and attending to attention—and found that patients using a focused attentional strategy reported significantly less discomfort and fewer hallucinated words. These findings suggest that targeted attentional training may effectively reduce both the frequency and distress associated with auditory hallucinations (40). Complementing these results, Hochheiser et al. investigated the interplay of metacognition, attention, cognitive insight, and self-compassion. They determined that increased mindfulness and enhanced awareness of one's internal states were associated with higher levels of self-compassion, whereas excessive cognitive insight correlated with heightened self-criticism (41). Together, these studies highlight the potential of mindfulness practices not only to reshape attentional control but also to recalibrate internal self-assessment and emotional responses in schizophrenia.

Expanding on the impact of mindfulness at the neurophysiological level, Creswell et al. observed that individuals with higher mindfulness exhibited lower amygdala activity and increased prefrontal cortex engagement during emotional tasks, thereby promoting more adaptive emotional regulation (42). In support of the clinical relevance of these findings, a meta-analysis conducted by Hodann-Caudevilla et al. revealed that the incorporation of MBIs alongside standard treatments led to significant improvements in both positive and negative symptom domains, as well as overall functioning and illness insight among patients with schizophrenia (43).

Moreover, regular mindfulness practice appears to offer multidimensional benefits. In addition to enhancing emotional regulation and reducing stress, MBIs have been found to diminish negative symptoms such as apathy and emotional indifference, thereby improving overall psychosocial functioning and quality of life. Intriguingly, emerging research suggests that mindfulness may also influence the gut–brain axis. (44) By potentially reducing gut dysbiosis—commonly observed in schizophrenia—mindfulness practices could help shift the balance of the gut microbiota toward an increased prevalence of beneficial bacteria like *Lactobacillus* and *Bifidobacterium*, while reducing pro-inflammatory bacteria such as certain Firmicutes and Proteobacteria (6). This rebalancing may contribute to decreased systemic inflammation and improved neurotransmitter balance, further enhancing mental health outcomes when combined with conventional pharmacotherapy.

In summary, the multifaceted body of evidence—from refined attentional control and neurophysiological changes to enhanced psychosocial functioning and beneficial shifts in gut microbiota—supports the promise of

mindfulness-based interventions as a valuable adjunctive strategy in schizophrenia management. MBIs not only foster improved emotional regulation and cognitive self-awareness but may also help rebalance the gut–brain axis, offering an integrative pathway to address the complex, multi-layered symptomatology associated with this challenging disorder. Continued research into these interrelated mechanisms is crucial for developing innovative, personalized therapeutic approaches that can ultimately improve clinical outcomes and quality of life for patients with schizophrenia.

## Conclusions

In summary, converging evidence from preclinical, mechanistic, and clinical studies strongly supports the notion that targeting both the gut–brain axis and incorporating mindfulness-based interventions (MBIs) offers promising complementary strategies in the management of schizophrenia. Probiotic and prebiotic supplementation can rebalance the gut microbiota, leading to an enhanced production of critical metabolites such as butyrate, improved intestinal barrier integrity, and a reduction in systemic inflammation. These physiological improvements are pivotal for stabilizing the synthesis and regulation of key neurotransmitters—particularly serotonin, gamma-aminobutyric acid (GABA), and dopamine—which play crucial roles in the neurobiological underpinnings of schizophrenia.

Simultaneously, MBIs have been shown to improve emotional regulation and cognitive function through well-documented neurophysiological mechanisms, including decreased amygdala activity and increased engagement of the prefrontal cortex. These changes not only alleviate stress and anxiety but also contribute to enhanced neuroplasticity and overall psychosocial well-being. Consequently, integrating gut-modulating therapies with mindfulness practices may simultaneously address both the biological and psychological dimensions of schizophrenia, targeting core symptoms as well as associated metabolic and inflammatory dysfunctions.

The potential synergy between these interventions is particularly noteworthy, as it offers a novel pathway for alleviating residual symptoms that often remain unresponsive to conventional dopaminergic treatments. On one side, gut-modulating strategies reduce systemic inflammation and oxidative stress; on the other, mindfulness-driven approaches promote adaptive emotional and cognitive responses. Together, these modalities may help correct the underlying imbalances that contribute to the complex clinical presentation of schizophrenia.

Nevertheless, despite these promising insights, several research gaps remain unresolved. Critical questions regarding the optimal dosages, treatment durations, and specific conditions under which these interventions yield maximal benefits continue to persist. Future controlled clinical trials with rigorous methodologies are essential to validate the efficacy and safety of combined gut-modulating and mindfulness-based approaches. Moreover, these studies should aim to elucidate the mechanistic pathways involved and identify reliable biomarkers of treatment response, thereby paving the way for personalized therapeutic protocols.

Ultimately, the integration of these emerging interventions could signify a paradigm shift in the management of schizophrenia. By addressing both neurobiological impairments and psychosocial deficits, a multimodal strategy has the potential to substantially improve patient outcomes. This integrative approach not only broadens the current therapeutic repertoire but also offers renewed hope for patients who continue to experience the debilitating effects of schizophrenia despite conventional treatment options.

## Disclosure

### Author's contribution

Conceptualization: Rafał Marecki, Patrycja Niczyporuk; Methodology: Patrycja Niczyporuk; Software: Aleksandra Giba, Izabela Zajkowska; Check: Izabela Zajkowska; Formal analysis: Ada Ejsmont; Investigation: Patrycja Niczyporuk; Resources: Kamila Iłendo, Patrycja Niczyporuk; Data curation: Kamila Iłendo, Izabela Zajkowska; Writing-rough preparation: Aleksandra Giba; Writing-review and editing: Ada Ejsmont, Rafał Marecki, Aleksandra Kicman; Visualization: Aleksandra Giba; Supervision: Rafał Marecki, Aleksandra Kicman; Project administration: Rafał Marecki, Aleksandra Kicman.

### Funding Statement

This research did not receive any external funding and was supported solely by the Medical University of Bialystok.

**Institutional Review Board Statement**
Not Applicable.

**Informed Consent Statement**
Not Applicable.

**Data Availability**
Statement Not Applicable.

**Acknowledgements**
This research has not received any administrative or technical support.

**Conflict Of Interest**
The authors declare no conflict of interest.

**All authors have read and agreed with the published version of the manuscript.**

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