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The Psychobiotics in Depression and Anxiety: Efficacy, Mechanisms, and the Underestimated Risk of Antibiotic Resistance

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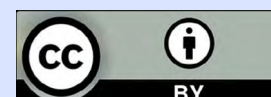
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ABSTRAKT

Background. Depression and anxiety are highly prevalent, and up to one-third of depressed patients fail to achieve remission despite standard pharmacotherapy. This gap has prompted interest in the gut microbiome, via the gut - brain axis, as an adjunctive target. Psychobiotics - probiotics, prebiotics, synbiotics, and postbiotics with documented mental health effects - are promising, though their microbiological safety remains underexplored.

Aim. To synthesize evidence on psychobiotic efficacy in depression and anxiety, outline gut-brain mechanisms, and highlight safety concerns regarding antimicrobial resistance transfer from bacterial formulations.

Material and methods. This narrative review was based on a literature search of PubMed and Google Scholar, identifying clinical trials, meta-analyses, and studies on gut-brain communication, microbiota composition in depression/anxiety, psychobiotic efficacy, and antibiotic resistance in probiotic strains.

Results. Four gut-brain pathways were identified: vagal, HPA-axis, immune, and tryptophan/serotonin routes. Depression and anxiety are linked to dysbiosis with reduced butyrate-producing and increased pro-inflammatory taxa; causality is supported by fecal transplantation studies. Probiotics show the strongest evidence for antidepressant and anxiolytic effects, especially as pharmacotherapy adjuncts. Evidence for other forms remains limited. Many probiotic strains carry mobile antibiotic resistance genes, and their use during antibiotic therapy has been linked to expansion of the gut resistome, raising safety concerns.

Conclusions. Probiotics offer the most robust evidence for adjunctive treatment; other forms need further research. Strain selection should weigh both efficacy and resistance safety.

KEYWORDS

probiotics, prebiotics, depressive disorder, anxiety disorder, antibiotic resistance

Introduction and Purpose

Depression and anxiety disorders are among the most common psychiatric disorders globally and present a therapeutic challenge. According to a 2025 World Health Organization report, based on Global Burden of Disease estimates, the global prevalence of depressive disorders affects approximately 4% of the population, which corresponds to over 330 million individuals worldwide, whereas, according to a 2021 report, approximately 359 million people suffer from anxiety disorders. Despite the implementation of appropriate and evidence-based therapeutic regimens, it is estimated that approximately 30–33% of patients with depression fail to achieve full remission of depressive symptoms. Furthermore, there are specific patient populations, such as pregnant women, for whom pharmacotherapy options for both depression and anxiety disorders remain limited. For these reasons, there is an ongoing search for adjunctive treatment strategies. Among these approaches, the role of the gut microbiome as a potential therapeutic target has gained interest in recent years. It is estimated that the human gastrointestinal tract is inhabited by approximately 100 trillion micro-organisms (most of them bacteria, but also viruses, fungi, and protozoa) forming an ecosystem known as the gut microbiome. Certain microorganisms within this ecosystem can positively influence mental health through the gut-brain axis, forming the basis for the concept of psychobiotics.

According to the World Health Organization's definition, probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Prebiotics are defined as substrates that are selectively fermented by the gut microbiome, thereby exerting a positive effect on host health. Synbiotics, on the other hand, represent „a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host”. Postbiotics, meanwhile, consist of non-viable microorganisms or their components that provide physiological benefits to the host. Psychobiotics thus constitute a functional subgroup of probiotics, prebiotics, synbiotics, and postbiotics that demonstrate a potential impact on mental health mediated through the gut-brain axis.

This narrative review aims to synthesize current evidence on the efficacy of psychobiotics in treating depression and anxiety, outline their underlying mechanisms of action, and highlight critical safety concerns – particularly the risk of antimicrobial resistance transmission associated with bacterial formulations.

Description of the State of Knowledge

The Gut-Brain Axis – Four Pathways of Communication

According to scientific reports, there are four primary communication pathways through which the gut microbiota interacts with the central nervous system.

The microbiota and the brain communicate with each other via several distinct routes, including the immune system, tryptophan metabolism, the vagus nerve, and the enteric nervous system, with the involvement of bacterial metabolites such as short-chain fatty acids (SCFAs) and branched-chain amino acids.

The first of these pathways is the vagus nerve. Among other mechanisms, short-chain fatty acids produced by gut bacteria activate receptors on the terminals of the vagus nerve, which mediates the transmission of signals from the gut to the brain. Robust evidence supporting this hypothesis was presented in a 2011 study by Bravo et al. The authors demonstrated that the administration of the *Lactobacillus rhamnosus* JB-1 strain to mice reduced anxiety- and depression-related behavior and altered the expression of GABA receptors in the brain. However, these effects were completely absent in vagotomized mice, which indicates that the vagus nerve is a major route for transmitting signals from gut bacteria to the brain.

The second pathway is the hypothalamic-pituitary-adrenal (HPA) axis – the stress response system, which can be modulated by signals originating from the gut microbiota. The third pathway is the immune system – the gut microbiome is involved in neuro-inflammatory processes via its impact on innate and adaptive immunity.

The fourth pathway is the metabolic route associated with tryptophan metabolism. Bacteria or their metabolites participate in the production of serotonin by the enterochromaffin cells of the gut. Since peripheral serotonin is unable to penetrate the blood-brain barrier, it influences the central nervous system (CNS) indirectly. This indirect modulation is theorized to rely on vagal afferents and inflammatory responses within the gut, though the precise mechanisms require further investigation.

Dysbiosis in Depression and Anxiety Disorders

A growing body of evidence indicates that patients diagnosed with Major Depressive Disorder (MDD)

exhibit a characteristic pattern of gut dysbiosis that differs from the microbiome composition of healthy control groups, although the results of individual studies show considerable methodological heterogeneity. A publication by Sanada et al. – comprising 16 studies with 1,003 participants – demonstrated that the Prevotellaceae family and the Coprococcus and Faecalibacterium genera are significantly reduced in patients with MDD compared to healthy controls.

A larger 2023 meta-analysis conducted by Gao et al., which included 44 studies with 2,091 patients and 2,792 control subjects, revealed that participants with depression harbor fewer butyrate-producing bacteria, while bacteria with pro-inflammatory properties are elevated. It is worth noting, however, that the same meta-analysis did not show significant differences in α -diversity (a measure of the species richness of gut bacteria within a given individual, expressed by the Shannon or Chao1 index).

Crucial data are also provided by a 2019 study by Valles-Colomer et al. conducted on a cohort of 1,054 participants, with validation in independent datasets comprising 1,070 individuals. The authors demonstrated that butyrate-producing bacteria – Faecalibacterium and Coprococcus – were associated with higher quality of life indicators, whereas Coprococcus spp. and Dialister spp. were significantly depleted in individuals with depression, even after adjusting for the confounding effects of antidepressants.

Key evidence for a causal – rather than merely correlational – relationship between the microbiome and depression is provided by fecal microbiota transplantation (FMT) experiments. Zheng et al. (2016) provided compelling evidence for the role of the microbiome in depression by demonstrating that germ-free mice colonized with fecal microbiota from MDD patients exhibited depression-like behaviors, in contrast to those receiving microbiota from healthy controls. This constitutes evidence for the role of the gut microbiota in the pathophysiology of depression. These results, however, require further research and the validation of this relationship in humans.

The literature shows inconsistent data regarding microbial α - and β -diversity in anxiety and depression; nevertheless, both disorders share a common functional shift. This is characterized by a dysbiotic state in which the abundance of pro-inflammatory bacteria is elevated, while the population of anti-inflammatory, SCFA-producing microbes is significantly reduced.

The analysis revealed that the microbiome profile in depression is characterized by an increased relative abundance of the Actinobacteria and Proteobacteria phyla, as well as the Rikenellaceae, Porphyromonada-

ceae, and Bifidobacteriaceae families, with a concomitant decrease in the abundance of the Firmicutes phylum and the Prevotellaceae and Ruminococcaceae families. In contrast, in individuals with anxiety disorders, a higher proportion of the Bacteroidetes phylum, the Enterobacteriaceae family, and the Fusobacterium genus was observed, alongside a reduction in the Firmicutes phylum and genera such as Lachnospira, Faecalibacterium, Sutterella, and Butyrivibrio.

When analyzing reports on specific taxonomic differences within the microbiome, however, caution must be exercised, as study findings can be contradictory due to the presence of significant confounding factors, such as diet and pharmacotherapy.

Efficacy of Probiotics in the Treatment of Depression and Anxiety Disorders

Among the available evidence regarding the efficacy of probiotic interventions in depression and anxiety disorders, meta-analyses published in recent years play a significant role. In 2025, Asad et al. published a meta-analysis covering data from selected databases up to May 2023. The analysis confirmed a statistically significant effect of probiotic therapy on the reduction of depressive symptoms and its moderate efficacy in alleviating anxiety. However, it is worth noting that the results of individual studies were highly heterogeneous; detailed verification revealed that these discrepancies were influenced by factors such as the duration of treatment and the specific composition of the preparations used. It was observed that in the treatment of anxiety disorders, probiotics containing a single specific strain demonstrated greater efficacy compared to alternative multi-strain products. Furthermore, the analysis suggests that a shorter duration of probiotic supplementation (<8 weeks) correlates with a greater reduction in depressive symptoms. This may be influenced, among other factors, by higher patient adherence in short-term studies compared to longer, 90-day trials, which was observed in some of the analyzed groups. Reduced compliance may limit the final clinical efficacy of probiotic therapy. No significant therapeutic effect for prebiotics in the context of depression and anxiety was noted in this study.

Jusiak et al. came to similar conclusions in their recent review (2026), which synthesized randomized controlled trials and meta-analyses from 2016-2024 regarding probiotic interventions for depression. Their analysis confirmed that probiotics containing Lactobacillus and Bifidobacterium considerably lower depressive symptom severity. Additionally, while prebiotics showed inconsistent efficacy, synbiotics appe-

ared to enhance the therapeutic response. The authors concluded that probiotics and synbiotics serve as safe adjuncts worthy of further investigation alongside conventional depression therapies .

In 2023, Nikolova et al. provided further significant insights into the use of probiotics for depression and anxiety disorders. In this pilot randomized clinical trial, the efficacy of an 8-week supplementation with a multi-strain preparation was evaluated as an adjunctive therapy in patients with Major Depressive Disorder (MDD) who were continuing standard pharmacotherapy. The analysis included 49 participants, 24 of whom were assigned to the probiotic group and 25 to the placebo group. Compared with the control group, the group receiving the probiotic demonstrated a significantly greater reduction in the severity of both depressive and anxiety symptoms. This study also demonstrated that an 8-week course of adjunctive treatment with a multi-strain probiotic is well-tolerated by adults with MDD. The authors of this pilot study suggest that these results regarding the use of probiotics as adjunctive therapy in MDD are promising and warrant further large-scale research .

Significant observations were also made by Tian et al. in a randomized controlled trial published in 2022. The 4-week study involved 45 patients, of whom 25 received a placebo and 20 received a probiotic containing *Bifidobacterium breve* CCFM1025. It was observed that patients receiving CCFM1025 achieved a greater antidepressant effect than those receiving the placebo (based on assessment using the HDRS-24 and MADRS scales). The authors suggest that the modulation of the serotonergic system may underlie the emotional disturbances and gastrointestinal issues of these patients, as the bacterial strain used in the study was observed to significantly reduce serum serotonin turnover compared to placebo. The authors hypothesize that this process may be the result of gut microbiome remodeling and alterations in tryptophan metabolism .

These findings are complemented by a study published in 2022 by Schaub et al. In this article, patients experiencing a depressive episode received either a multi-strain probiotic or a placebo as an adjunct to standard treatment for 31 days. Evaluation was conducted pre-intervention, immediately post-intervention, and after a 4-week follow-up period, using the Hamilton Depression Rating Scale (HAM-D), microbiome profiling, and neuroimaging methods. Results showed that this adjunctive therapy reduced depressive symptoms, improved microbiological parameters (maintenance of enterotype structure, increase in species richness and pro-health bacterial taxa), and,

at the central level, reduced negative biases and modified emotional valence. These findings confirm the vital role of the microbiota-gut-brain axis in the pathophysiology of MDD and point to probiotic therapy as a readily available method to increase the effectiveness of conventional depression treatment .

In the context of the anxiety component, significant data are provided by the publication of Walden et al. (2023). In their study on the use of a multi-strain probiotic in 70 patients, the authors documented a simultaneous, parallel improvement in both anxiety severity and mood, which correlated with an increase in plasma serotonin. This provides strong evidence for the hypothesis of a shared, gut-brain axis-dependent pathophysiological basis for both conditions .

In a pilot, randomized, double-blind study published by Browne et al. in 2021, the impact of probiotic supplementation was assessed in 40 low-risk pregnant women exhibiting elevated anxiety or depression scores. The analysis showed no significant differences in the reduction of these symptoms between the group receiving the probiotic and the placebo group. However, the authors proved that the intervention was feasible and well-accepted by the patients. As the main limitations of this project, the researchers identified the small sample size and the late initiation of supplementation, suggesting that in future studies, it would be optimal to start therapy in the first trimester. Given the negative impact of depression and anxiety during pregnancy on the well-being of the mother and neonate, as well as the more limited pharmacological options compared to non-pregnant individuals, future research with fewer limitations could provide valuable, practical data on this topic .

A distinct yet closely related area is the influence of probiotics on cognitive function. In 2025, Guo et al. published a meta-analysis demonstrating that probiotic supplementation significantly improves cognitive function, processing speed, memory, and spatial abilities in the elderly. These results open an interesting clinical perspective: probiotics possess potential not only as an antidepressant and anxiolytic intervention but also in the context of cognitive deficits that may accompany depression .

In conclusion, the presented reports confirm the high clinical potential of probiotic therapy as a versatile intervention supporting the treatment of affective and anxiety disorders, as well as improving neurocognitive function. However, the final efficacy of these strategies remains strictly dependent on the precise selection of bacterial strains, the duration of treatment, and the level of patient therapeutic adherence, which identifies key directions for future research.

Table 1. Summary of studies on probiotics in depression and anxiety disorders

Study (Year)	Intervention	N / Duration	Key Outcome
Nikolova et al. (2023)	Multi-strain probiotic	N=49; 8 wks	↓ depressive & anxiety symptoms vs. placebo
Tian et al. (2022)	Bifidobacterium breve CCFM1025	N=45; 4 wks	↓ depressive symptoms; ↓ serum serotonin turnover
Schaub et al. (2022)	Multi-strain probiotic	N=47; 31 d + 4-wk FU	↓ depressive symptoms; improved microbiome & neuroimaging markers
Walden et al. (2023)	Multi-strain probiotic	N=70; 6 wks + 3-wk FU	↓ anxiety; improved mood; ↑ plasma serotonin
Browne et al. (2021)	Probiotics	N=40 (pregnant); wk 26-30 - delivery + 8-wk FU	Intervention feasible & well-tolerated; no significant difference in depressive and anxiety symptoms vs. placebo
Asad et al. (2025)	Meta-analysis (probiotics, prebiotics)	Databases to May 2023	Probiotics: ↓ depression; moderate ↓ anxiety; no significant difference for prebiotics
Guo et al. (2025)	Meta-analysis (probiotics)	Databases to December 2023	↑ cognitive functions, processing speed, memory, spatial abilities in older adults
Jusiak et al. (2026)	Narrative review	Databases between 2016–2024	Probiotics and synbiotics ↓ depressive symptoms; prebiotics inconsistent

Abbreviations: FU – follow-up.

Other Forms of Psychobiotics: Prebiotics, Synbiotics, FMT, and Postbiotics

Over recent years, the majority of scientific research has focused on analyzing the impact of probiotics on depression and anxiety disorders. However, a growing body of evidence indicates that psychobiotics can also take other forms worthy of attention. These include prebiotics, synbiotics, fecal microbiota transplantation (FMT), and postbiotics.

Prebiotics are defined as substrates that are selectively utilized by host microorganisms, conferring a health benefit on the host. This group primarily includes fructooligosaccharides (FOS), galactooligosaccharides (GOS), and inulin. The most commonly available prebiotic substances serve as a nutritional substrate for bacteria of the genera *Bifidobacterium* and *Lactobacillus*. These microorganisms utilize them, which stimulates their proliferation. However, prebiotics do not support the growth of pathogenic bacteria, including certain strains of the genus *Clostridium*.

In a psychiatric context, particularly interesting observations were made in a study by Schmidt et al. This study evaluated the effects of a three-week supplementation of fructooligosaccharides (FOS) and galactooligosaccharides (GOS) on the cortisol secretion profile in humans. The authors demonstrated that individuals receiving GOS experienced a statistically significant

decrease in the salivary cortisol awakening response (CAR) compared to the control group receiving a placebo. These findings suggest that selected prebiotics exhibit potential in reducing physiological indicators of stress.

Promising data regarding the anxiolytic potential of galactooligosaccharides (GOS) are also provided by a study by Johnstone et al. (2021). The authors evaluated the impact of a four-week supplementation of this prebiotic in young women, analyzing the participants in terms of anxiety levels, mood, and depressive traits using psychological self-assessment questionnaires. The results showed that GOS administration led to a noticeable downward trend in subjectively perceived stress; however, this effect was apparent almost exclusively in women characterized by high baseline anxiety. Notably, the study also observed changes in the composition of the gut microbiota – patients receiving GOS showed a significant increase in the abundance of bacteria of the genus *Bifidobacterium* compared to the control group. These findings provide further evidence supporting the hypothesis that the proportion of *Bifidobacterium* species in the gut microbiome may be a determining factor in improving psychological well-being.

Synbiotics represent another, more advanced form of psychobiotic intervention. They are formulations that combine live probiotic microorganisms with a sub-

strate (or substrates) selectively utilized by host microorganisms that confers a health benefit on the host.

In 2018, Ghorbani et al. conducted a study on 40 outpatients with moderate depression. All patients initially received fluoxetine (20 mg/d) for 4 weeks, and subsequently, for 6 weeks, received either a synbiotic capsule (containing bacteria from the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, as well as fructooligosaccharides) alongside fluoxetine, or a placebo alongside fluoxetine. The study demonstrated a significantly greater reduction in depressive symptoms in patients who received the adjunctive synbiotic compared to those who received the placebo with fluoxetine.

In 2023, Zhang et al. published a meta-analysis that included 13 randomized controlled trials involving 786 participants with mild to moderate depression. This study showed that patients who received a prebiotic, probiotic, or synbiotic achieved a reduction in depressive symptoms compared to those who received only a placebo; however, a significant antidepressant effect was observed exclusively in participants receiving probiotics. The authors also highlighted that high-quality evidence regarding the use of these formulations in the treatment of depression is lacking, and this issue requires further detailed investigation.

Similar conclusions were drawn in a 2025 study by Zhang et al. However, it additionally demonstrated that prebiotics, probiotics, and synbiotics, as adjunctive treatments, exhibit efficacy in alleviating symptoms of not only depression but also anxiety and sleep disorders.

However, it should be noted that the number of randomized clinical trials evaluating synbiotics exclusively – as opposed to probiotics alone – remains very limited, which complicates the formulation of definitive conclusions and recommendations regarding the optimal composition and dosage of these formulations in the therapy of depressive and anxiety disorders.

A distinct category of intervention is fecal microbiota transplantation (FMT), which involves transferring stool from a healthy donor to a recipient. While FMT has gained clinical acceptance for the treatment of recurrent *Clostridioides difficile* infection, its application in psychiatry remains in the early stages of research. In 2022, Doll et al. published a case report involving two patients who received FMT as an adjunctive treatment for major depressive disorder (MDD). In both patients, depressive symptoms decreased in severity four weeks after the fecal microbiota transplant. However, studies of this kind are currently very scarce and characterized by small sample sizes, making it difficult to draw binding clinical conclusions. Furthermore, the FMT method still raises safety concerns. While fecal microbiota transplantation, as an adjunct to standard treatment,

has the potential to reduce depressive symptoms, evidence regarding its efficacy and safety is highly limited, and its application requires further detailed research.

Another direction attracting growing interest is postbiotics, defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) as preparations of inanimate microorganisms and/or their components that confer a health benefit on the host. From a practical perspective, postbiotics possess several advantageous characteristics that set them apart. They exhibit longer stability under storage and transport conditions than probiotics, which significantly facilitates their use and distribution. Furthermore, they are considered safer than probiotics due to the absence of risk for inducing bacteremia or fungemia. However, it is important to note that postbiotics may pose risks in other aspects; for instance, lipopolysaccharides (LPS) released from dead Gram-negative bacteria can trigger sepsis or toxic shock. For this reason, every postbiotic requires an individual safety profile assessment before being introduced to the market.

Clinical data regarding the impact of postbiotics on depressive and anxiety disorders remain at a preliminary stage – available studies primarily focus on mood and stress in healthy adults rather than clinically diagnosed psychiatric disorders. In a 2023 study, Mutoh et al. demonstrated that heat-inactivated *Lactobacillus helveticus* MCC1848 significantly improves positive mood indices (measured via the PANAS questionnaire) compared to placebo.

Meanwhile, Watanabe et al., in a 2025 study, confirmed that heat-inactivated *Lactiplantibacillus plantarum* SNK12 significantly reduces salivary cortisol concentrations. Although the evidence is not yet sufficient to formulate clinical recommendations for MDD and anxiety disorders, it confirms the biological activity of postbiotics and justifies further research – especially in high-risk patients for whom the use of other types of psychobiotics may be contraindicated.

Safety: Antibiotic Resistance as an Underestimated Problem

Currently, psychobiotics are attracting increasing interest, and the number of studies concerning them is constantly growing. In many cases, however, insufficient attention is paid to the safety of their use – this issue is sometimes neglected and overlooked. One of the most significant problems associated with their use is the presence of antibiotic resistance genes (ARGs) in the genomes of probiotic bacteria found in widely available preparations, as well as the possibility of their transfer to the gut microbiome. This issue is currently of particular importance due to the

Table 2. Summary of studies on other psychobiotic forms (prebiotics, synbiotics, fecal microbiota transplantation, and postbiotics) in depression and anxiety disorders

Study (Year)	Intervention	N / Duration	Key Outcome
Schmidt et al. (2015)	FOS / GOS (prebiotic)	N=45; 3 wk	↓ salivary cortisol awakening response
Johnstone et al. (2021)	Galactooligosaccharides (prebiotic)	N=64; 4 wk	↓ stress (high-anxiety subgroup); Bifidobacterium
Ghorbani et al. (2018)	Synbiotic + fluoxetine	N=40; 6 wk	↓ depressive symptoms vs. placebo + fluoxetine
Zhang et al. (2023)	Meta-analysis (probiotics, prebiotics, synbiotics)	N=786	↓ depressive symptoms after prebiotics, probiotics, synbiotics; significant ↓ only for probiotics
Zhang et al. (2025)	Meta-analysis (prebiotics, probiotics, synbiotics)	N=6 097	Efficacy for depression, anxiety, and sleep symptoms
Doll et al. (2022)	Fecal microbiota transplantation	N=2; 4-wk FU	↓ depressive symptoms (case report; limited evidence)
Mutoh et al. (2023)	Heat-inactivated <i>L. helveticus</i> MCC1848 (postbiotic)	N=46; 4-wk FU	↑ positive mood indices
Watanabe et al. (2025)	Heat-inactivated <i>L. plantarum</i> SNK12 (postbiotic)	N=50; 4wk	↓ salivary cortisol concentration

Abbreviations: FOS – fructooligosaccharides; GOS – galactooligosaccharides; FU – follow-up.

global problem of antimicrobial resistance, which is estimated to be responsible for at least 700,000 deaths globally per year; this number is projected to increase significantly in the coming years .

There are two ways by which bacteria can acquire antimicrobial resistance. The first involves genetic mutations occurring within the microorganism itself. The second is horizontal gene transfer (HGT), which occurs primarily through conjugation (direct cell-to-cell contact involving conjugative plasmids), transformation (uptake of free DNA from the environment), or transduction (mediated by bacteriophages). In HGT, small fragments of genetic material are transferred between bacteria, and this process requires neither cell division nor phylogenetic relatedness between the donor and the recipient. A study by Toth et al. analyzed the genetic data of bacterial strains commonly used in probiotics in search of antibiotic resistance genes (ARGs). Some antibiotic resistance genes are encoded intrinsically (innate resistance), and the probability of their transfer to other microorganisms is negligible and close to zero. However, there are also acquired ARGs, termed mobile genes, which can be transferred to other bacteria, raising significant concerns. The study by Toth et al. demonstrated the presence of ARGs in the majority of the tested strains, a significant portion of which were mobile .

A review by Shahali et al. showed that the horizontal transfer of genes, such as tet and erm, from *Lactobacillus* bacteria in probiotics to pathogenic bacterial strains (including *Enterococcus faecalis*, *Enterococcus hirae*, *Lactococcus lactis*, and *Listeria monocytogenes*) can induce resistance to antibiotics such as tetracyclines and erythromycin. This observation highlights a real clinical risk and the necessity of expanding research to further investigate this problem .

Particularly crucial data are also provided by a study by Montassier et al. This study analyzed the impact of probiotic supplementation on the gut resistome, which can be defined as the collection of ARGs in an individual's microbiome. According to the authors' findings, the use of probiotics may lead to its reduction. However, this beneficial effect is possible only in the gastrointestinal tracts of individuals susceptible to colonization. Conversely, it was shown that in individuals undergoing antibiotic therapy, the same probiotic preparation promotes the proliferation of bacterial strains carrying resistance genes, including vancomycin resistance, leading to an expansion of the gut resistome – although not necessarily due to the direct transfer of ARGs from the microorganisms contained in the probiotics. These reports are of particular value because probiotics are most frequently recommended as an adjunct to or following antibiotic therapy – precisely the conditions under which their

impact on the gut microbiome may not necessarily be beneficial.

Similar conclusions were drawn in a study by Radovanovic et al. This review established that following antibiotic therapy, probiotics might exacerbate the problem of antibiotic resistance in the lower gastrointestinal tract microbiome, rather than helping to restore its balance. However, this study also emphasized that there is no conclusive evidence linking this process to the transfer of ARGs from probiotic bacteria to gut microorganisms.

The European Food Safety Authority (EFSA) is the primary institution responsible for assessing the safety of microorganisms used in the food and feed chain within the European Union, including probiotic strains. In response to the growing awareness of the risks associated with the use of microorganisms, EFSA developed the Qualified Presumption of Safety (QPS) system. This system involves their regular safety assessment and is not granted on a one-time, permanent basis; the list of microorganisms with this status is verified and regularly modified by EFSA, with each update encompassing a review of new scientific data. A prerequisite for obtaining and maintaining QPS status is undergoing a detailed analysis regarding antibiotic resistance. Crucial in this process is distinguishing between two categories of resistance: intrinsic resistance, which is considered acceptable, and acquired resistance, which is classified as posing a potential risk and requires in-depth analysis prior to obtaining QPS status. In the United States, meanwhile, probiotics are subject to oversight by the FDA.

A significant practical problem remains the fact that a large proportion of probiotic supplements available on the market, particularly those imported from outside the EU or purchased online, have not undergone the full verification required for QPS status, and their safety profiles remain unknown. Consequently, it is especially important to purchase probiotic preparations from verified sources, and in the case of medical professionals recommending their use, to raise patients' awareness on this subject.

A separate category comprises high-risk populations, in whom even probiotic strains possessing QPS status require special caution. High-risk groups primarily include immunosuppressed patients, neonates, premature infants, and elderly patients. In these groups, cases have been described where probiotic bacteria began to behave as opportunistic pathogens, resulting in some instances in severe pneumonia, endocarditis, or sepsis. Furthermore, there are also reports suggesting heightened caution when using probiotics in pregnant women, particularly those with

obesity, as there is scarce evidence indicating a possible increased risk of pre-eclampsia in these patients. These reports are, however, very limited, and this association requires further research. In high-risk groups, routine discontinuation of probiotics is not warranted, as they can provide benefits to some patients; however, it is recommended to exercise particular caution and use preparations of an appropriate quality and safety standard.

An open question, requiring further verification in clinical trials, remains whether prebiotics and postbiotics can serve as a safe therapeutic alternative to probiotics in situations where the use of live microorganisms is contraindicated.

Conclusions

An analysis of the available literature indicates significant differences in the strength of scientific evidence regarding the efficacy of probiotics, prebiotics, synbiotics, and postbiotics in the treatment of depressive and anxiety disorders. The strongest evidence is provided by probiotics, for which several independent meta-analyses consistently demonstrate a statistically significant antidepressant effect and – in a portion of the studies – an anxiolytic effect as well. It should be noted, however, that this same line of evidence does not unequivocally confirm the efficacy of prebiotics, synbiotics, and postbiotics; in many publications, data concerning them remained statistically insignificant or heterogeneous, which highlights the necessity of conducting further, better-designed clinical trials on these forms of intervention before binding therapeutic recommendations can be formulated.

A key aspect of this review involves evaluating the previously discussed efficacy data alongside the microbiological safety of probiotics – an area that has been underexplored in existing literature. In clinical practice, the selection of a probiotic preparation should consider not only the documented efficacy of a given strain but also its safety status – it is recommended to use exclusively preparations with a confirmed QPS (Qualified Presumption of Safety) status that have been verified for the absence of transferable antibiotic resistance genes.

The dynamic development of this field opens up significant research and clinical perspectives, including the concept of selecting a probiotic strain based on the patient's individual metagenomic profile and resistance, as well as the development of probiotics devoid of mobile genetic elements. It is also advisable to expand clinical trials evaluating the efficacy of psychobiotics

as an adjunctive therapy in combination with standard pharmacotherapy. Further clinical trials are also necessary to assess whether, in conditions where live bacterial cultures are absolutely contraindicated, prebiotics and postbiotics can serve as a safe and effective alternative.

Furthermore, this review points out significant methodological limitations of previous studies in this field. Considerable heterogeneity in the strains used, dosages, and duration of interventions is observed across individual studies, which complicates direct comparisons of results and limits the statistical power of the conducted meta-analyses.

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