A Conceptual Framework for Understanding the Interaction Between Smart Probiotics and the Gut-Brain Axis in Mood Regulation: An Integrative Approach

Karina Teixeira Magalhães-Guedes[1]*, Adriana Silva Borges[1] and Raquel Nunes Almeida da Silva[1]

1 Post-Graduate Program in Chemistry Engineering, Polytechnic School, Federal University of Bahia (UFBA), Federação, Salvador, 40210-630, Bahia, Brazil
*PhD in Microbiology

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Abstract: The gut-brain axis (GBA) is a bidirectional communication system connecting the gastrointestinal tract and the central nervous system through neural, endocrine, and immune pathways. Growing evidence suggests that the gut microbiota plays a central role in regulating mood and mental health. This conceptual paper proposes an integrative framework that explores how "smart probiotics"- genetically engineered or selectively enhanced microbial strains -can modulate mood via the GBA. Unlike conventional probiotics, smart probiotics are designed to detect specific environmental or physiological signals within the gut and respond with targeted actions, such as producing neurotransmitters (e.g., GABA, serotonin) or anti-inflammatory compounds. The framework outlines five core mechanisms: neurotransmitter production, immune modulation, gut barrier maintenance, vagus nerve stimulation, and responsive behaviour based on host conditions. Moreover, it highlights the use of synthetic biology and recombinant DNA technology to design microbial strains with precise therapeutic functionalities. These next-generation probiotics can act locally within the gut to alleviate inflammation, restore microbiota balance, and contribute to mood stabilization. The manuscript also emphasizes the importance of integrating nutrition science, as dietary components like prebiotics and polyphenols can enhance the efficacy of smart probiotics. Finally, the paper outlines future research directions, including the need for biomarker identification, clinical validation, and ethical considerations related to the application of genetically modified organisms in mental health interventions. This integrative approach reinforces the emerging role of smart probiotics as a promising tool in personalized psychobiotic therapies for mood regulation.

Keywords: Smart Microorganisms, Gut Microbiota Balance, Psychobiotic Microorganisms

1. Introduction

The gut-brain axis (GBA) represents a complex bidirectional communication system between the gastrointestinal tract and the central nervous system, involving neural, hormonal, and immunological pathways. Recent studies have highlighted the significant role of the gut microbiota in modulating this axis, influencing mood and cognitive functions (Liu et al., 2024). Probiotics, particularly strains from the *Lactobacillus* and *Bifidobacterium* genera, have been shown to impact mental health positively (Sabit et al., 2023; da Anunciação et al., 2024; Santos et al., 2024). The emergence of "smart probiotics," genetically engineered or selectively bred strains with targeted functional capabilities, offers new avenues for therapeutic interventions. These probiotics are designed to sense environmental cues within the gut and respond with specific beneficial actions, such as enhanced production of neurotransmitters or anti-inflammatory metabolites (Turroni et al., 2022). This manuscript proposes a conceptual framework integrating microbiology, neuroscience, and nutrition to elucidate how smart probiotics may influence mood through modulation of the GBA.

2. Background and Theoretical Foundations

2.1. Gut-Brain Axis: Structure and Function

GBA encompasses interactions among the central nervous system, the enteric nervous system, the neuroendocrine and neuroimmune systems, and the gut microbiota. Key components include the vagus nerve, which facilitates neural communication, and microbial metabolites like short-chain fatty acids (SCFAs) that influence brain function (Carabotti et al., 2015; Magalhães-Guedes, 2022) (Figure 1).

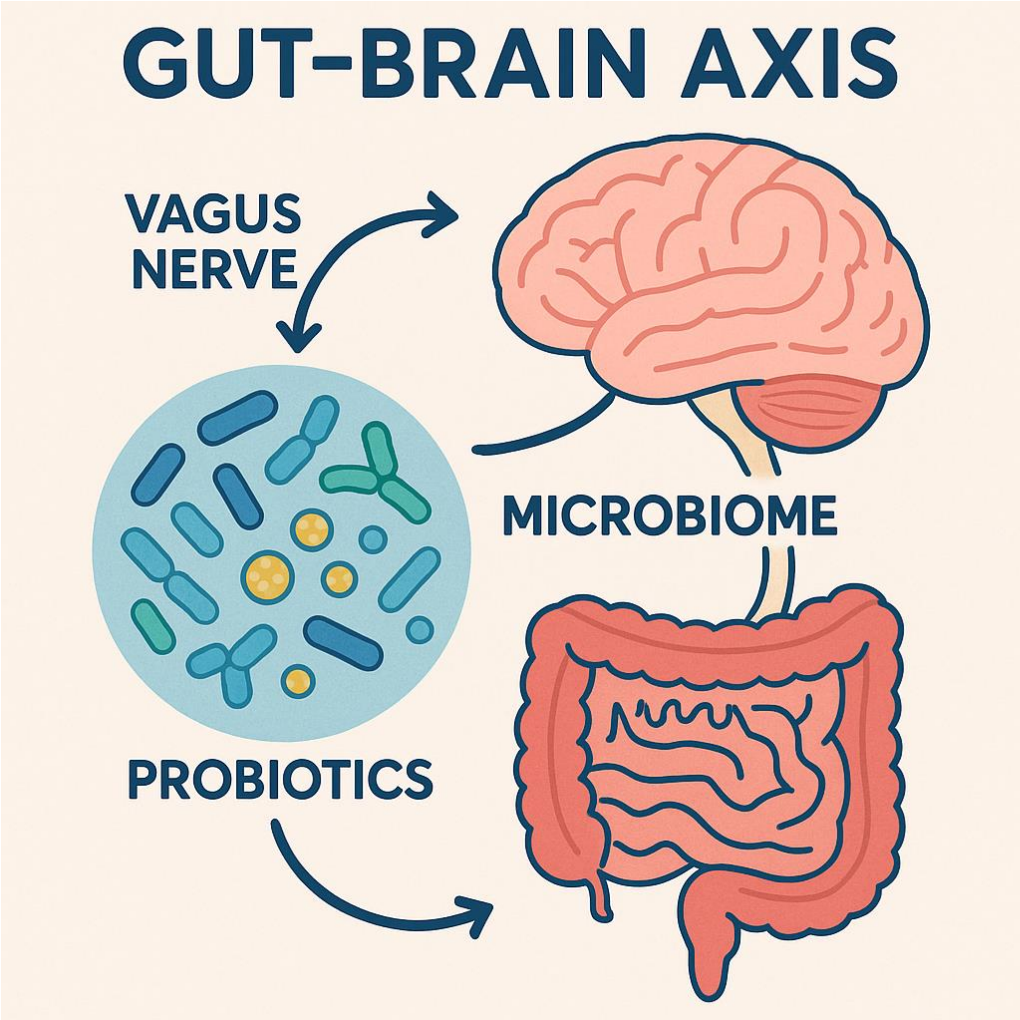

Figure 1: Gut-Brain Axis

2.2. Mood Regulation and Neurobiological Mechanisms

Mood disorders, such as depression and anxiety, are associated with dysregulation of neurotransmitters (e.g., serotonin, dopamine, GABA), neuroinflammation, and stress-related hormonal pathways like the hypothalamic-pituitary-adrenal (HPA) axis. Alterations in gut microbiota composition can impact these systems, thereby affecting mood (Foster & Neufeld, 2013).

2.3. Probiotics and Psychobiotics: From Classic to Smart Strains

Traditional probiotics have demonstrated psychotropic effects, including reduced anxiety and depressive symptoms. Psychobiotics are defined as live organisms that, when ingested in adequate amounts, confer mental health benefits (Magalhães-Guedes, 2022). Smart probiotics represent an advanced concept, encompassing strains engineered or selectively bred for enhanced metabolic activity, targeted neurotransmitter production, or improved gut colonization (Cryan & Dinan, 2012). Furthermore, smart probiotics can be programmed to deliver therapeutic molecules, adapt to host physiology, and interact dynamically with the native microbiota (Olle, 2013). Recent innovations have also explored the use of synthetic biology to design probiotic chassis that can sense inflammation markers and release anti-inflammatory peptides accordingly (Isabella et al., 2018).

The development of smart probiotics for the diagnosis and treatment of inflammatory bowel diseases (IBD) involves the application of recombinant DNA technology. This process utilizes molecular biology tools to insert a foreign DNA fragment into a plasmid vector—such as the pGEM-T vector system I (PROMEGA) - creating a recombinant plasmid (Virolle et al., 2020; Ma et al., 2022). The engineered plasmid is subsequently introduced into highly competent bacterial strains, such as *Escherichia coli* JM109, through transformation techniques like electroporation. These inserted DNA fragments carry specific genes responsible for the synthesis of recombinant proteins of therapeutic interest. Figure 2 demonstrates the three steps (Genetic Design, Transformation and Screening) for the genetic transformation process to form a microorganism with Smart Probiotic characteristics (Virolle et al., 2020; Ma et al., 2022):

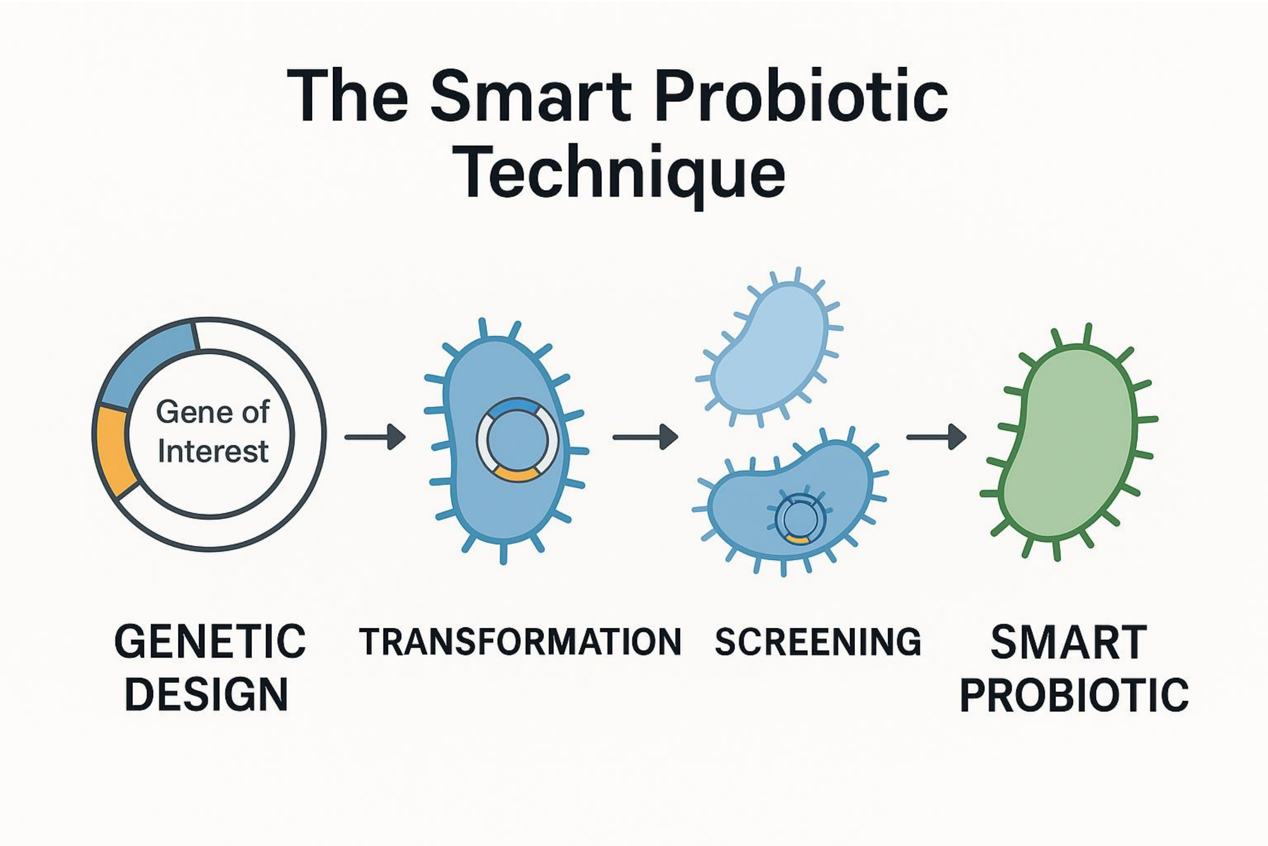

Figure 2 The Smart Probiotic Technique

Genetic Design: A gene of interest is selected based on the desired function (e.g., production of serotonin, anti-inflammatory peptides, or sensing molecules). This gene is inserted into a plasmid or synthetic DNA construct.

Transformation: The recombinant DNA is introduced into the probiotic strain (commonly *Lactobacillus* or *Escherichia coli*) using methods such as electroporation or heat shock.

Screening: Transformed strains are screened for the expression and stability of the desired function. Only strains showing appropriate response and function are selected. The selected smart probiotic is tested under simulated gastrointestinal conditions or in vitro models to confirm efficacy, safety, and responsiveness to environmental cues. The validated smart probiotic is integrated into food products, supplements, or therapeutic interventions aimed at modulating specific health outcomes, such as mood regulation.

Advancements in molecular biology and genetic engineering have made it possible to design next-generation probiotic strains—termed smart probiotics—with tailored functionalities (Virolle et al., 2020; Ma et al., 2022). These engineered microbes are designed to target sites of intestinal inflammation and deliver bioactive compounds directly in situ, offering targeted support in IBD management. Through genetic modification, probiotic microorganisms can be programmed to synthesize diagnostic or therapeutic molecules. This is achieved by manipulating their metabolic pathways (Figure 3), often by introducing or silencing specific genes that encode enzymes involved in key biochemical reactions. Once administered orally, these engineered probiotics colonize the gut. Upon detecting host-derived physiological signals, these signals interact with the transcriptional machinery of the smart probiotic, activating gene expression responsible for producing the desired therapeutic compound. The secreted molecule then acts locally, alleviating inflammation and mitigating IBD-related symptoms (Virolle et al., 2020; Ma et al., 2022).

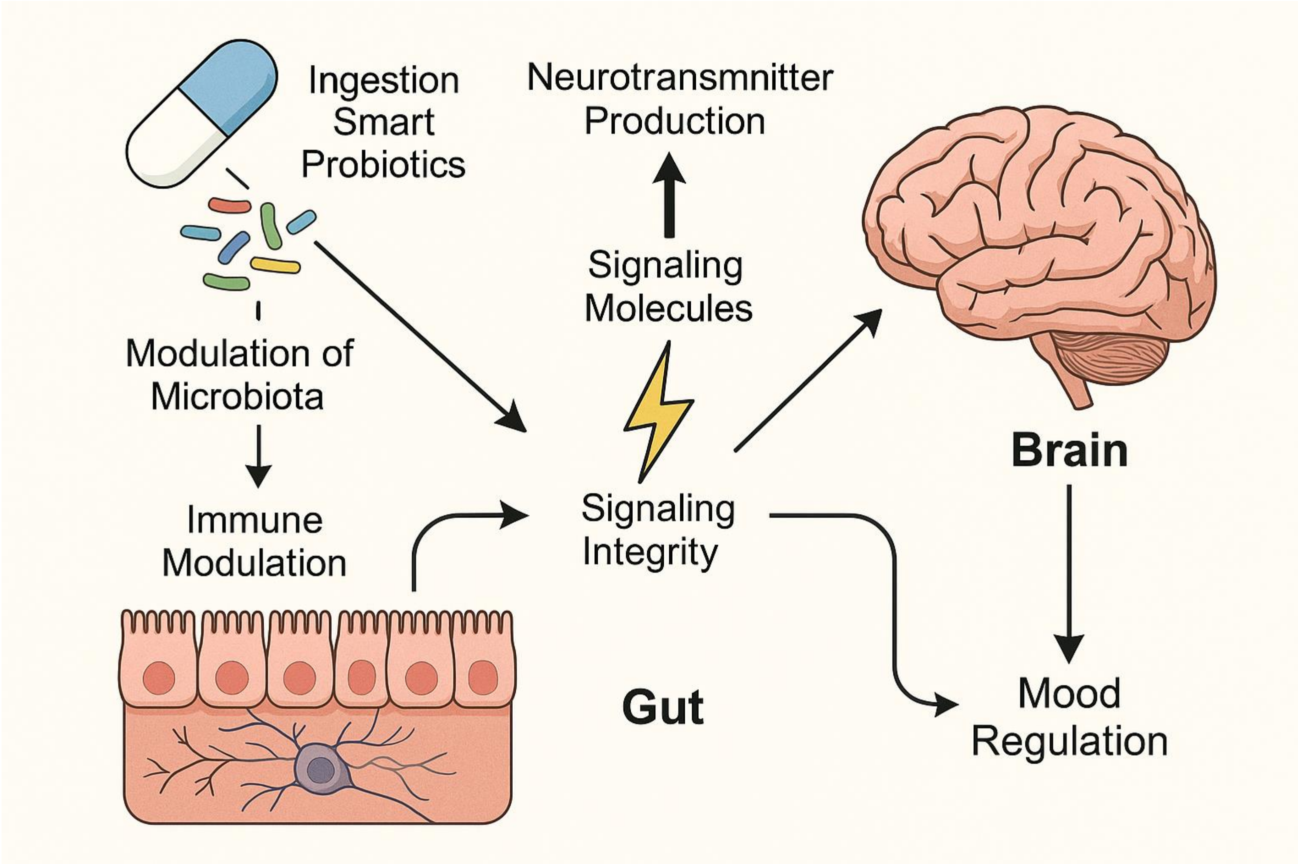

Figure 3 Smart probiotic metabolic pathways

3. Proposed Conceptual Framework

This framework posits that smart probiotic influence mood via several interconnected pathways within the GBA:

Neurotransmitter Production: Smart probiotics can be designed to produce or stimulate the production of neuroactive compounds such as GABA and serotonin (Liu et al., 2024).

Immune Modulation: They modulate immune responses and reduce systemic inflammation, which is closely linked to depressive symptoms (Sabit et al., 2023; Magalhães-Guedes, 2022).

Gut Barrier Integrity: Enhanced probiotic strains may improve intestinal permeability, reducing the passage of endotoxins that can trigger neuroinflammation (Cryan & Dinan, 2012).

Neural Pathway Stimulation: Interaction with the vagus nerve enables direct communication between the gut and brain (Bravo et al., 2011).

Responsive Behavior: Smart probiotics can dynamically adjust their function based on environmental signals in the host’s gut, enabling real-time modulation of gut-brain interactions (Turroni et al., 2022).

4. Integrating Nutrition, Microbiology, and Neuroscience

The interaction between nutrition, microbiology, and neuroscience is a cornerstone in understanding and optimizing the gut-brain axis (GBA), particularly in the context of smart probiotic interventions. Nutritional components play a pivotal role in shaping the composition, activity, and resilience of the gut microbiota, which in turn modulates neurophysiological responses relevant to mood and cognition. Dietary substrates such as prebiotic fibers (e.g., inulin, fructooligosaccharides), polyphenols (e.g., flavonoids, catechins), and essential micronutrients (e.g., zinc, magnesium, B-vitamins) exert synergistic effects with probiotic strains, enhancing microbial viability, colonization capacity, and metabolic output (Sarkar et al., 2016; Foster & Neufeld, 2013).

These nutrients not only support the growth of beneficial microbes but also modulate the production of bioactive metabolites, including short-chain fatty acids (SCFAs), neurotransmitters (e.g., GABA, serotonin), and anti-inflammatory compounds that influence the central nervous system (Liu et al., 2024; Cryan & Dinan, 2012). Such interactions underscore the importance of dietary context in the efficacy of psychobiotic therapies (Magalhães-Guedes, 2022).

Moreover, recent advances in high-throughput *omics* technologies—such as metabolomics, transcriptomics, proteomics, and metagenomics—have enabled deeper insights into the functional dynamics of the host-microbiota interface. These tools facilitate the identification of individual microbial signatures and metabolic pathways that correlate with mental health outcomes, paving the way for precision nutrition approaches (Sarkar et al., 2016). In this framework, smart probiotics can be strategically combined with personalized dietary plans to enhance their therapeutic potential, ensuring targeted modulation of the GBA (Turroni et al., 2022; Ma et al., 2022).

By integrating nutritional science with microbial biotechnology and neurobiology, this multidisciplinary approach supports the design of tailored interventions for mood regulation and mental wellness. Future research should continue to explore these interactions in clinical settings, fostering the development of effective, safe, and sustainable strategies for microbiota-driven mental health support.

5. Future Research Directions

Future research should focus on validating the proposed framework through in vitro and in vivo studies, including randomized controlled trials. Identifying specific biomarkers for mood improvement and developing personalized interventions based on individual microbiota profiles are promising directions. Ethical considerations regarding genetic modification and long-term effects also warrant attention.

6. Conclusion

This conceptual framework provides a comprehensive and integrative perspective on the role of smart probiotics in mood regulation via the gut-brain axis (GBA). By bridging the disciplines of microbiology, neuroscience, and nutrition, the model emphasizes the complexity of host-microbe interactions and the necessity of a systems biology approach to mental health interventions. The incorporation of genetically engineered probiotic strains capable of sensing and responding to host physiological cues introduces a new paradigm in psychobiotic therapy—one that is dynamic, targeted, and personalized.

Smart probiotics offer several innovative mechanisms for modulating emotional and cognitive functions, including the production of neuroactive compounds, regulation of immune and inflammatory responses, reinforcement of gut barrier integrity, and direct signaling through the vagus nerve. These multifunctional strains hold great promise in addressing the growing burden of mood disorders such as anxiety and depression, especially in cases where conventional treatments fall short or cause adverse effects.

Furthermore, the synergy between functional nutrition and smart probiotics opens new avenues for precision mental health care, leveraging diet and microbiota-targeted therapies to optimize individual outcomes. As such, this framework lays the groundwork for future experimental studies, clinical trials, and translational applications. Continued interdisciplinary collaboration will be crucial to validate these hypotheses, identify relevant biomarkers, and ensure the safety, efficacy, and ethical use of smart probiotic technologies. Ultimately, smart probiotics represent a transformative frontier in personalized, microbiota-centered mental health strategies.

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References

1. Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., Bienenstock, J., & Cryan, J. F. (2011). Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences of the United States of America*, 108(38), 16050–16055. https://doi.org/10.1073/pnas.1102999108
2. Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut–brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology*, 28(2), 203–209. [No DOI available – open access: https://www.annalsgastro.gr/index.php/annalsgastro/article/view/2188]
3. Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nature Reviews Neuroscience*, 13(10), 701–712. https://doi.org/10.1038/nrn3346
4. da Anunciação, T. A., Guedes, J. D. S., Tavares, P. P. L. G., de Melo Borges, F. E., Ferreira, D. D., Costa, J. A. V., Umsza-Guez, M. A., & Magalhães-Guedes, K. T. (2024). Biological significance of probiotic microorganisms from kefir and kombucha: A review. *Microorganisms*, 12(6), 1127. https://doi.org/10.3390/microorganisms12061127
5. Foster, J. A., & Neufeld, K. A. M. (2013). Gut–brain axis: How the microbiome influences anxiety and depression. *Trends in Neurosciences*, 36(5), 305–312. https://doi.org/10.1016/j.tins.2013.01.005
6. Isabella, V. M., Ha, B. N., Castillo, M. J., Lubkowicz, D. J., Rowe, S. E., Millet, Y. A., Anderson, C. L., Li, N., Fisher, A. B., West, K. A., et al. (2018). Development of a synthetic live bacterial therapeutic for the human metabolic disease phenylketonuria. *Nature Biotechnology*, 36(9), 857–864. https://doi.org/10.1038/nbt.4222
7. Liu, W., Yang, H., Li, T., Qiu, C., & Zhao, J. (2024). Gamma-aminobutyric acid as a potential postbiotic mediator in the gut–brain axis. *NPJ Science of Food*, 8, Article 10. https://doi.org/10.1038/s41538-024-00253-2
8. Ma, J., Lyu, Y., Liu, X., Jia, X., Cui, F., Wu, X., Deng, S., & Yue, C. (2022). Engineered probiotics. *Microbial Cell Factories*, 21, 72. https://doi.org/10.1186/s12934-022-01754-y
9. Magalhães-Guedes, K. T. (2022). Psychobiotic therapy: Method to reinforce the immune system. *Clinical Psychopharmacology and Neuroscience*, 20(1), 17–25. https://doi.org/10.9758/CPN.2022.20.1.17
10. Olle, B. (2013). Medicines from microbiota. *Nature Biotechnology*, 31(4), 309–315. https://doi.org/10.1038/nbt.2551
11. Sabit, H., Patel, H., Alwan, H., Riaz, O., & Khan, M. (2023). The effect of probiotic supplementation on the gut–brain axis in psychiatric patients. *Current Issues in Molecular Biology*, 45(5), 4080–4099. https://doi.org/10.3390/cimb45050199
12. Sarkar, A., Lehto, S. M., Harty, S., Dinan, T. G., Dunbar, R. I. M., & Cryan, J. F. (2016). Psychobiotics and the manipulation of bacteria–gut–brain signals. *Trends in Neurosciences*, 39(11), 763–781. https://doi.org/10.1016/j.tins.2016.09.002
13. Santos, E. N., Magalhães-Guedes, K. T., Borges, F. E. M., Ferreira, D. D., da Silva, D. F., Conceição, P. C. G., Lima, A. K. C., Cardoso, L. G., Umsza-Guez, M. A., & Ramos, C. L. (2024). Probiotic microorganisms in inflammatory bowel diseases: Live biotherapeutics as food. *Foods*, 13(24), 4097. https://doi.org/10.3390/foods13244097
14. Turroni, F., Ventura, M., Buttó, L. F., Duranti, S., O'Toole, P. W., Motherway, M. O. C., & van Sinderen, D. (2022). Next-generation probiotics: Promising tools to manage immune-mediated diseases. *Microorganisms*, 10(5), 975. https://doi.org/10.3390/microorganisms10050975
15. Virolle, C., Goldlust, K., Djermoun, S., Bigot, S., & Lesterlin, C. (2020). Plasmid transfer by conjugation in Gram-negative bacteria: From the cellular to the community level. *Genes*, 11(10), 1239. https://doi.org/10.3390/genes11101239

