GUT DYSBIOSIS AND GENERALIZED ANXIETY DISORDER: A SYSTEMATIC REVIEW

https://doi.org/10.56238/sevened2024.037-038

Charline Aline Senft[1], Jamili Gonçalves[2] and Marina Werner[3]

ABSTRACT

Generalized Anxiety Disorder (GAD) is manifested by symptoms such as tension, fatigue, and negative thoughts, and can be influenced by diet. Diets high in fat and low in vitamins B2, B6 and B9 can alter the gut microbiota, causing dysbiosis, which affects the gut-brain axis, a communication pathway between gut and brain. This dysbiosis increases intestinal permeability and inflammation, impacting mood and anxiety. Therefore, the objective of this study was to search the most recent literature for studies that correlate the gut microbiota with mental health. This is a descriptive and exploratory study, carried out through a systematic review with articles published between 2014 and 2024, found in databases such as PubMed, BVS, and Google Scholar. The research used the PICO strategy, using descriptors such as "Gut microbiota", "Dysbiosis" and "Anxiety", combined by Boolean operators. The studies highlight the complex relationship between gut microbiota and mental health, showing that probiotics can reduce symptoms of anxiety and depression, although the results are more consistent for anxiety. Probiotics modulate inflammation and regulate serotonin, which is essential for emotional well-being. Dysbiosis, associated with poor diet or stress, reduces serotonin and increases inflammatory cytokines, aggravating mental symptoms. The connection between microbiota, the immune system, and mental health offers new therapeutic approaches, but more research is needed to advance this field.

Keywords: Intestinal dysbiosis. Generalized Anxiety Disorder. Gut microbiota. Mental health.

[1] Student in the Nutrition course
University of Western Santa Catarina UNOESC- Campus Videira SC
[2] Student in the Nutrition course
University of Western Santa Catarina UNOESC- Campus Videira SC
[3] Professor in the Nutrition course and Master's student in Development and Society
University of Western Santa Catarina UNOESC- Campus Videira SC

INTRODUCTION

Generalized Anxiety Disorder (GAD) is characterized by persistent anxiety symptoms, affecting behaviors in everyday life. It manifests itself through symptoms such as motor tension, headache, fatigue, hyperactivity, mood swings, as well as symptoms involving negative thoughts of the future. This disorder can begin in childhood or adolescence, however, it is very common to start after the age of 20 [1].

The diet that people adopt in their lifestyle induces changes in the intestinal microbiota, stimulating mechanisms linked to the limbic system. This system, through stimuli to release hormones, is responsible for regulating mood. A diet with a high intake of fat and a deficiency of vitamins such as B2, B6, and B9 is interconnected with stress and anxiety symptoms [2].

According to Saraiva et al. (2019) and Christofoletti et al. (2022), the high consumption of processed foods and exposure to toxins that cannot be digested by the body can lead to a disorder in intestinal function, composition, and diversity of the gut microbiota, triggering dysbiosis. Therefore, intestinal dysbiosis is characterized by changes in the activity and distribution site of the intestinal microbiota, in which pathogenic bacteria predominate over beneficial ones. This balance reflects in the increase of intestinal permeability and with this, leads to a decrease in selectivity in the absorption of toxins, bacteria, proteins or peptides, contributing to local and systemic inflammation [3,4].

The gut-brain axis is a two-way communication system between the gut and the brain, involving neural, hormonal, and immune signals. The gut microbiome, which consists of trillions of microorganisms that inhabit our gastrointestinal tract, plays a key role in this communication [5].

Studies have shown that the composition of the microbiota can influence brain function and behavior, including aspects related to anxiety, mood, and stress. Certain gut bacteria can produce neurotransmitters or substances that directly affect the brain, while others are involved in regulating the immune system, which in turn can impact brain function [6].

Deeper understanding of the interaction between the gut microbiota and GAD could lead to innovative approaches in treatment, such as gut-targeted therapies, microbiome modulation, and dietary interventions. However, it is important to note that this field of research is still evolving, and more studies are needed to fully elucidate these complex interactions [7].

Gut dysbiosis is a problem that frequently affects these patients, and because there is an increase in the incidence of anxiety with few studies, this review searches the most recent literature for studies that correlate the gut microbiota with mental health.

METHODS

This is a descriptive, exploratory study elaborated through an exploratory research through a systematic review using scientific articles between 2014 and 2024, found in databases: *Google Scholar, Virtual Health Library (VHL) and* PubMed.

The elaboration of the research question was based on the PICO strategy (Santos; Galvão, 2014), with "P" referring to the study population (individuals diagnosed with generalized anxiety disorder); "I" to the intervention studied or variable of interest (treatments focused on restoring the gut microbiota to treat gut dysbiosis); "C" in comparison with another variable (standard pharmacological therapies for anxiety); and "O" referring to the outcome of interest (evaluation of the efficacy of microbiota restoration in relieving anxiety symptoms). Thus, the guiding question for the construction of the research was outlined: "What is the effectiveness of the treatment of intestinal dysbiosis in relieving the symptoms of generalized anxiety disorder?"

Data collection took place from July to September 2024, in the database of Medical Publications (PubMed), Virtual Health Library (VHL) and *Google Scholar.* For the search, the following Health Sciences Descriptors (DeCS) were used: "Gut microbiota", "dysbiosis", "Anxiety" and "Treatment", combining the Boolean operators "AND" and "OR", as shown in table 1.

Table 1: Articles found according to the search strategies in the selected databases

Database/Database	Intersection
PubMed (96)	("Dysbiosis"[MeSH] OR "Dysbiosis"[Text Word]) AND ("Anxiety"[MeSH] OR "Anxiety Disorders"[MeSH] OR "Anxiety"[Text Word]) AND ("Intestinal Microbiota"[MeSH] OR "Gut Microbiota"[Text Word]) AND ("Therapeutics"[MeSH] OR "Treatment"[Text Word] OR "Intervention"[Text Word])
Google Scholar (178)	(Disbiose OR "Dysbiosis") AND (Ansiedade OR "Anxiety Disorders" OR "Transtornos de Ansiedade") AND ("Microbiota Intestinal" OR "Intestinal Microbiota") AND (Tratamento OR Terapêutica OR Intervenção)

VHL **Portuguese (19):**	(Disbiose OR "Dysbiosis") AND (Ansiedade OR "Anxiety Disorders" OR "Transtornos de Ansiedade") AND ("Microbiota Intestinal" OR "Intestinal Microbiota") AND (Tratamento OR Terapêutica OR Intervenção)
English (29)	(Dysbiosis OR "Dysbiosis") AND (Anxiety OR "Anxiety Disorders" OR "Anxiety Disorders") AND ("Gut Microbiota" OR "Intestinal Microbiota") AND (Treatment OR Therapeutics OR Intervention) Spanish
Spanish (01)	(Dysbiosis or "dysbiosis") and (anxiety or "anxiety disorders" or "anxiety disorders") and ("gut microbiota" or "gut microbiota") and (treatment or therapy or intervention).

Source: the authors (2024).

Also, to compose and optimize the selected studies, the inclusion criteria considered were: articles published between 2014 and 2024, in Portuguese, English, and Spanish, available in full for free access and that address the topic related to the research. Course completion papers, monographs, theses, dissertations, book chapters, books, editorials, articles written with children, adolescents or the elderly, bibliographic, systematic or scope review articles, articles that have been published before 2014 were excluded.

The procedures carried out for the search and selection of articles in the database were: 1) association of the three descriptors; 2) selection and application of inclusion and exclusion filters; 3) reading of titles and abstracts, discarding duplicates, those that did not fit the research theme and the inclusion and exclusion criteria; 4) categorical and critical reading of the articles in full by two authors selecting 06 articles congruent with the theme for the elaboration of this review, represented by the PRISMA (2020) flowchart (Figure 1).

In order to reduce possible biases in the evaluation of the studies, such as analysis and design errors, two researchers participated in all stages of the research flowchart, reading the articles and filling in the instruments (tables with the data of the studies present in this review) using the double-blind method for subsequent comparison. Also, in cases where non-conformities occurred, a new reading and completion of the instruments was carried out by a third author.

In addition, the included studies were compiled and analyzed, and represented in the form of a table with the following data: author, year, title of the journal, number of participants, objective, duration of the study, and main results and intervention strategies.

The categorization of the results was carried out in a structured manner based on previously established criteria. Initially, the selected studies were analyzed for their methodological, thematic and contextual characteristics. The extracted data were organized

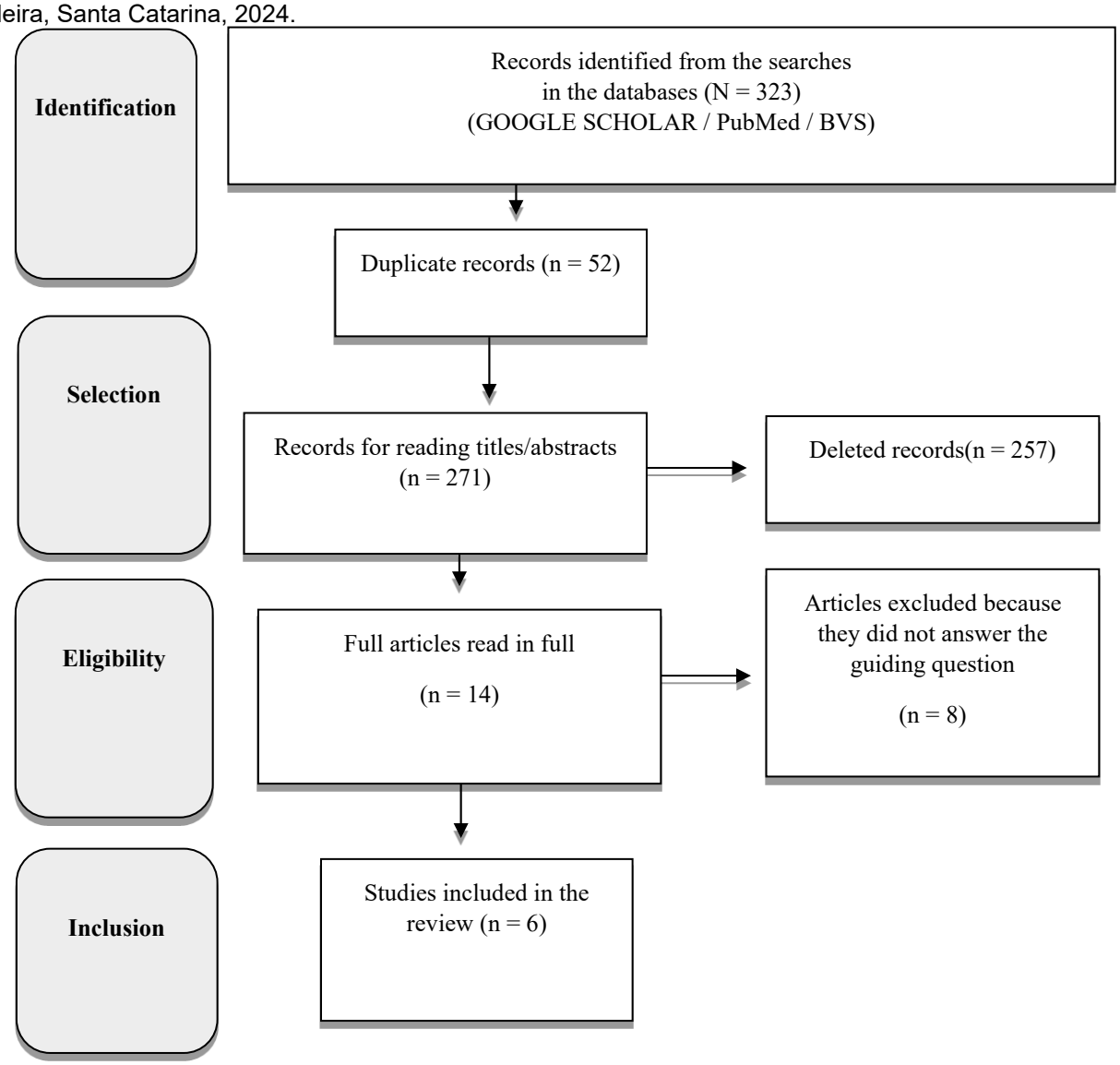
into categories according to their relevance to the study objectives, grouping the findings into main themes and subthemes, when necessary. Categorization will follow criteria such as type of intervention, target population, outcomes evaluated, and methodology employed. To ensure consistency, the categorization was validated by consensus among the researchers involved, ensuring the clarity and coherence of the groupings carried out.

All ethical precepts were respected by the researchers at all stages of the research, citing and referencing all the works included in the study.

RESULTS AND DISCUSSION

A total of 323 articles were found and, after analyzing the title, abstract, and applying the inclusion and exclusion criteria, 06 articles were included to be used in the final sample of this review. The search and selection of articles followed the recommendations of the PRISMA 2020 group (MOHER *et al.*, 2019) and can be seen in the following flowchart (Figure 1).

Figure 1 – Representation of the Flowchart of the articles included in the study according to PRISMA (2020). Videira, Santa Catarina, 2024.



Source: adapted from PRISMA 2020 (MOHER et al, 2009).

The six articles that made up the final sample were published between 2016 and 2024, in English, Portuguese, and Spanish. The types of articles were bibliographic reviews, systematic review and integrative search in the literature.

Table 2 presents the characterization of the articles that were used for the final sample, considering objective, year of publication, journals, country, duration of the study, and methodological quality of the study. These articles used in the final sample were published between 2017 and 2024 in English and Portuguese.

Table 2: Characterization of the studies included in the final sample. Videira, Santa Catarina, 2024.

Author Year	Newspaper	Country	No. of participants	Objective	Duration of the study	Main results
Lopes, et al, 2024 [1]	Contemporary Magazine	Brazil	05	The study aimed to investigate the effect of the gut microbiota on mental health, using integrative literature review as a method for this investigation.	-	The article highlights that the microbiota-gut-brain axis modulates the central nervous system (CNS) through the production of cytokines and changes in intestinal permeability, directly impacting mental health. In addition, patients with neuropsychiatric disorders, such as depression, anxiety, and schizophrenia, often have an imbalance of the microbiota.
Torres, et al, 2024 [9]	RBONE	Brazil	06	To analyze the efficacy of the Low FODMAP diet on anxiety, depression and quality of life in Irritable Bowel Syndrome by Rome IV criteria.	2 months	The literature search found 2,311 articles in the databases, after the inclusion and exclusion criteria, four (n=4) clinical trials involving 99 patients were included in the integrative review.
Zhu, et al, 2024 [11]	Journal homepage.	China	10	To report how stress in early life and anxiety-like behaviors are related to the gut microbiota.	-	Early stress reduced levels of amino acid transporters in the gut of mice, causing a drop in blood glutamine (Gln) levels and synaptic dysfunction in the medial prefrontal cortex (mPFC). Dysbiosis reduced the

						presence of **Lactobacillus reuteri**, limiting the replacement of glutamate (Glu) and GABA in the brain. The Supplementation with **L. reuteri** restored amino acid transport in the gut and corrected behavioral abnormalities, showing that manipulation can reverse the negative effects of stress.
Souzedo, Bizarro and Perreira, 2020 [5]	J Bras Psychiatr	Brazil	03	Objective of analyzing the gut-brain axis and depressive symptoms: a systematic review of randomized clinical trials with probiotics.	4 to 12 weeks.	A total of 587 articles were found, eight articles were included in the final sample. All randomized controlled trials, double-blind or triple-blind, were conducted in different geographic regions. The aim of these studies was to investigate the impact of probiotic consumption on symptoms of depression. allocated to the placebo or experimental group and received the intervention for periods ranging from four to twelve weeks
Minayo, Miranda and Telhado, 2021 [8]	Science and Collective Health	Brazil	03	To conduct a systematic review on the effects of probiotics on depression and anxiety as an	4 to 12 weeks	Of 107 articles found, only 9 articles met the selection criteria established in the methodology. In the analyses of studies on

				alternative treatment.		depression disorder, it was not possible to reach a conclusion that the administration of one or several probiotic strains is effective for the improvement of symptoms. However, for symptoms of anxiety and stress, they showed a significant improvement, because they do not have deteriorated mental conditions.
Timothy G Dinan e John F. Cryan, 2017 [12]	Neuropsychopharmacolo g	Ireland	02	Explore the mechanism s of interaction between the brain-gut-microbiota axis and how this affects behavior and the immune system.	-	The gut microbiota plays an essential role in regulating the immune system by influencing the production of lymphocytes and cytokines that modulate inflammatory responses. The microbiota's relationship to immunity also affects the intestinal barrier, helping to protect against pathogens while facilitating nutrient absorption. Evidence shows that the gut microbiota directly affects behavior through the microbiota-gut-brain axis. Animal studies indicate that changes in the microbiota can

						influence mood, anxiety, and exploratory behavior. In humans, the impact of the microbiota is explored in psychiatric disorders, such as depression and schizophrenia.

Source: the authors (2024).

DISCUSSION

The present study carried out by Souzedo, Bizarro and Pereira (2020), analyzed the impact of probiotic consumption on depression symptoms through eight randomized, double-blind or triple-blind trials in different regions. Of the eight articles used for the research, depressed people who did not use antidepressants, only had depressive symptoms, and had a combination of bacteria species as material for use. In all studies, subjects were divided into a placebo or experimental group and interventions ranged from four to twelve weeks. However, some studies found that probiotic supplementation was helpful in treating depressive symptoms, but others reported no significant difference. Taking into account the methodological difference between the studies, they may have contributed to the different results obtained [5].

Minayo et al. (2021), classified for analysis nine studies that evaluated the effects of probiotics administered daily to individuals with depression, anxiety, and psychological stress, and to qualify and quantify changes in individuals' symptoms, they used questionnaires with scientifically validated scales. In the analyses of studies that evaluated the effects on depression, it was not possible to reach a conclusion that the administration of one or several probiotic strains is effective for the improvement of the symptoms of the disorder. Three of the studies showed an improvement in symptoms, where a total of 150 adults were evaluated, but it was not specified which parameters showed an improvement to determine the scope of the intervention. However, studies have shown positive changes in mood improvement [8].

After conducting research by Dinan and Cryan (2016), suggest that the use of probiotics and nutritional interventions may be beneficial for the treatment of stress-related disorders, where they indicate that the absorption of dietary amino acids by gut epithelial cells plays an important role in the regulation and concentration of amino acids in the blood and brain, contributing to the normal functioning of brain function. On the other hand, the

imbalance of excitatory and inhibitory neurotransmitters in the brain and the activation of signaling cascades can be significant factors in stress-induced neurobehavioral abnormalities [11].

It can be said that in the literature analyzed in the study by Minayo et al. (2021), they described the fact of a hypothesis that probiotics act effectively on mental health through the regulation of inflammatory markers and serotonin neurotransmitters, and that it may be possible to say that these mechanisms work together to produce the effects of the administered probiotics, when it is taken into account that the immune system, the central nervous system, and the enteric nervous system are connected to each other. Another class of probiotics are psychobiotics, which are capable of producing substances such as GABA and serotonin involved in cognitive and mood regulation, acting directly on the brain-gut axis, which has already proven benefits in the inflammatory profile and emotional processes when administered [8].

There is evidence from studies reported by Dinan and Cryan (2016), which state that certain bacteria existing within the human gut are able to play a key role in immune development and have the ability to produce molecules with neuroactive properties that can impact the physiology and behavior of the brain. The gut microbiota plays an essential role in regulating the immune system by influencing the production of lymphocytes and cytokines that modulate inflammatory responses. The microbiota's relationship to immunity also affects the intestinal barrier, helping to protect against pathogens while facilitating nutrient absorption. Evidence shows that the gut microbiota directly affects behavior through the microbiota-gut-brain axis [10,12].

The work in question by Souzedo, Bizarro and Pereira (2020), described that the intestinal microbiota has an influence on our brain, taking into account that the composition of the microbiota, where it is has microorganisms capable of stimulating the afferent neurons of the ENS, thus triggering inflammation that leads to the production of cytokines that cross the blood-brain barrier acting directly on the brain, causing a disturbance. When a microbiota of a healthy individual is compared with that of a depressed patient, a significant decrease in intestinal permeability is found [1].

However, the authors Dinan and Cryan (2016) described that the gut microbiota has come to be recognized as a critical brain function and regulator of behaviors, where its composition can be influenced by several factors, such as: diet, antibiotic use, and stress. Studies conducted with mice show a growing body of evidence indicating that stress early in life can cause lasting changes in the gut microbiota, thus contributing to the development of possible neuropsychiatric disorders throughout life [11].

With this, Souzedo, Bizarro and Pereira (2020), reported that dysbiosis occurred by the ingestion of low-quality food, and immunological adversity are responsible for the decrease in the availability of serotonin in the body, since about 95% of all serotonin in the body is synthesized by intestinal enterochromaffin cells. Another precursor of serotonin is the tryptophan metabolites, which are also generated in the microbiota. As a result, dysbiosis influences brain concentrations, which positively impacts the development of mental illnesses [1].

As presented in the work of Dinan and Cryan (2016). Depression is considered a pro-inflammatory state that is associated with the presence of biomarkers of inflammation. With the impairment of intestinal barrier functions and a significant increase in intestinal permeability, intestinal bacteria translocate through the intestinal wall to mesenteric lymphoid tissue, where the exposure of mucosal immune cells increases, which can activate an immune response and the release of inflammatory cytokines with stimuli from the vagus nerve and spinal afferent neurons. In addition, there is an increase in intestinal permeability, which can also increase the translocation of metabolic products produced by bacteria and cause centrally altered activity [10].

However, the present study by Minayo et al. (2021) commented that the symptoms of anxiety and stress showed a significant improvement when compared to those of depression, due to the fact that depressive conditions include deteriorated mental states, thus being a challenging disorder for treatment. People with high stress on a daily basis have changes in the intestinal barrier, resulting in the production of inflammatory cytokines, all of which indicates that these people may present symptoms of depression and anxiety, since patients with such symptoms have an increased profile of pro-inflammatory cytokines and positive acute phase proteins, therefore, the relationship between the intestine, inflammatory profile and neuroendocrine responses are intrinsic [8].

Research carried out by Dinan and Cryan (2016) points out that the main function of intestinal barriers is to regulate the absorption of nutrients, electrolytes and water for absorption and thus prevent the entry of pathogens and toxins. Microglia are a type of resident brain cell, similar to macrophages, key immune cells that detect environmental changes in the brain and regulate neuroinflammatory processes. A growing body of evidence points to a connection between microglia and the microbiota-gut-brain axis, which has implications for several neurodegenerative disorders and stress-associated conditions [10].

In addition, the studies presented by Torres et al. (2024), point to an association between IBS, anxiety, and depression, mediated by the peripheral central mechanism and

genetic factors, this brain-gut microbiota interaction may explain altered bowel habits, abdominal pain, and psychiatric comorbidities associated with IBS. These predictive models are associated with the quality of life of individuals, found an association between gastrointestinal symptoms and psychological factors with reduced quality of life in patients with irritable bowel syndrome [9].

Torres et al. (2024), analyzed the effects of the *low* FODMAP diet on anxiety, depression, and quality of life, using the Rome IV criterion in patients with irritable bowel syndrome (IBS), where they were able to observe that patients with anxiety, depression, and distress have severe gastrointestinal symptoms, in addition to fatigue and worsening quality of life. The acceptability of the low-FODMAP diet is very important for the management of IBS patients, but it requires significant dietary restrictions and the elimination of some common foods in everyday life. Therefore, it can be stated that IBS is directly associated with anxiety, depression, and reduced quality of life, through gastrointestinal symptoms, psychological, and dietary factors [9, 10].

CONCLUSION

It can be concluded that the studies carried out reveal the complexity of the relationship between the gut microbiota and mental health. Studies indicate that intervention with probiotic strains can have significant benefits in reducing symptoms of anxiety and depression, although depression-related outcomes are less consistent.

In addition, probiotics play an important role in modulating inflammation and regulating serotonin, which is essential for emotional well-being. Dysbiosis, often caused by poor diet or stress, leads to decreased serotonin and increased inflammatory cytokines, contributing to the development of anxious and depressive symptoms.

In addition, the interconnection between microbiota, immune system, and mental health opens up new possibilities for the treatment of emotional disorders. Continuity of research is important to broaden understanding and develop more effective therapeutic strategies.

REFERENCES

1. Lopes, W. A. D., et al. (2024). A conexão da microbiota e a saúde mental. *Revista Contemporânea*, *4*(2). https://doi.org/10.56083/rcv4n2-057

2. França, T. B. (2019, 18 de dezembro). Interação entre o eixo microbiota-intestino-cérebro, dieta e transtornos de humor: uma revisão narrativa. Recife: Universidade Federal de Pernambuco.

3. Saraiva, F. R. S., Carvalho, L. M. F., & Landim, L. A. S. R. (2020). Depressão e disbiose. *Nutr Bras*, 18(3).

4. Christofolett, G. S. F., Paiva, N. L. do C., Pinheiro, G. J., & Ferreira, T. C. (2022, 20 de fevereiro). O microbioma intestinal e a interconexão com os neurotransmissores associados à ansiedade e depressão. *Braz J Hea Rev*, *5*(1), 3385-3408.

5. Souzedo, F. B., Bizarro, L., & Pereira, A. P. A. (2020). O eixo intestino-cérebro e sintomas depressivos: uma revisão sistemática dos ensaios clínicos randomizados com probióticos. *J Bras Psiquiatr*, *69*(4), 269-276.

6. Dash, S., et al. (2015). O microbioma intestinal e a dieta em psiquiatria: foco na depressão. *Curr Opin Psychiatry*, *28*(1), 1-6. https://doi.org/10.1097/YCO.0000000000000117

7. Pereira, L. C., et al. (2024). Influência da microbiota intestinal na saúde mental: implicações clínicas. *Rev Ibero-Americana Humanidades, Ciências e Educação*, *10*(05).

8. Minayo, M. de S., Miranda, I., & Telhado, R. S. (2021). Revisão sistemática sobre os efeitos dos probióticos na depressão e ansiedade: alternativa terapêutica? *Ciênc Saúde Coletiva*, *26*(9), 4087-4099. https://doi.org/10.1590/1413-81232021269.21342020

9. Torres, D. R. S., et al. (2024). A dieta low fodmap na ansiedade, depressão e qualidade de vida na síndrome do intestino irritável pelo critério Roma IV. *Rev Bras Obesidade Nutr Emagrecimento*, *18*(114), 509-516.

10. Dinan, T. G., & Cryan, J. F. (2017, 1 de janeiro). Imunidade e comportamento de micróbios: psiconeuroimunologia encontra o microbioma. *Neuropsychopharmacology*. https://doi.org/10.1038/npp.2016.103

11. Zhu, J., et al. (2024). Gut microbiota mediate early life stress-induced social dysfunction and anxiety-like behaviors by impairing amino acid transport at the gut. *Gut Microbes*, *16*(1). https://doi.org/10.1080/19490976.2024.2401939

12. Dinan, T. G., & Cryan, J. F. (2017). Micróbios, imunidade e comportamento: a psiconeuroimunologia encontra o microbioma. *Neuropsicofarmacologia*, *42*(1), 178-192. https://doi.org/10.1038/npp.2016.103