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MICROBIOTA INTESTINAL E NEUROINFLAMAÇÃO EM ADULTOS: uma revisão Da conexão intestino-mente-corpo

GUT MICROBIOTA AND NEUROINFLAMMATION IN ADULTS: A review ofthegut-mind-body connection

MICROBIOTA INTESTINAL Y NEUROINFLAMACIÓN EN ADULTOS: Una Revisión de la conexión intestino-mente-cuerpo

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Resumo

Introdução: A microbiota intestinal desempenha papel fundamental na regulação de processos imunológicos, metabólicos e neuroendócrinos, sendo o eixointestino-cérebro um campo emergente na compreensão dos transtornos neuropsiquiátricos e inflamatórios. Alterações nesse ecossistema, caracterizadas como disbiose, têm sido associadas a desfechos clínicos relevantes, como depressão, ansiedade e inflamação sistêmica. **Objetivo:** Analisar criticamente a relação entre microbiota intestinal, manifestações neuropsiquiátricas e processos inflamatórios em adultos, bem como avaliar a efetividade de intervenções voltadas à sua modulação. **Métodos:** Trata-se de uma revisão integrativa da literatura, conduzida conforme as recomendações do protocolo PRISMA. A busca foi realizada nas bases MEDLINE, LILACS e PubMed, utilizando descritores DeCS combinados por operadores booleanos. Foram incluídos estudos publicados entre 2020 e 2024, nos idiomas português, inglês e espanhol. A avaliação da qualidade metodológica foi realizada por meio dos instrumentos do Joanna Briggs Institute (JBI), e o nível de evidência foi classificado segundo o sistema GRADE. **Resultados:** Foram incluídos 16 estudos, evidenciando associação consistente entre disbiose intestinal e alterações inflamatórias e neuroquímicas, incluindo aumento da permeabilidade intestinal, ativação do eixo hipotálamo-hipófise-adrenal e modulação de neurotransmissores. Intervenções com probióticos apresentaram evidência mais robusta, comefeitos moderados na redução de sintomas depressivos e ansiosos. O transplante de microbiota fecal demonstrou potencial terapêutico, porém com evidência limitada, enquanto intervenções dietéticas mostraram resultados promissores, porém heterogêneos. **Conclusão:** A microbiota intestinal atua como importante modulador dos processos neuropsiquiátricos e inflamatórios,embora a evidência disponível ainda seja limitada por heterogeneidade metodológica. Intervenções direcionadas à modulação da microbiota representam estratégia promissora, porém demandam maior padronização e robustez científica.

Palavras-chave: Disbiose; microbiota intestinal; sistema imunológico; eixo intestino-cérebro-microbiota; comunicação celular.

Abstract

Introduction: The gut microbiota plays a central role in regulating immunological, metabolic, and neuroendocrine processes, with the gut-brain axis emerging as a key pathway in understanding neuropsychiatric and inflammatory disorders. Dysbiosis has been associated with clinically relevant outcomes,including depression,anxiety,and systemic inflammation.**Objective:** To critically analyze the relationship between gut microbiota, neuropsychiatric manifestations, and inflammatory processes in adults, as well as to evaluate the effectiveness of microbiota-targeted interventions. **Methods:** An integrative literature review was conducted following PRISMA guidelines. Searches were performed in MEDLINE, LILACS, and PubMed databases using DeCS descriptors combined with Booleano perators. Studies published between 2020 and 2024 in Portuguese, English, and

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Spanish were included. Methodological quality was assessed using Joanna Briggs Institute (JBI) tools, and the level of evidence was classified according to the GRADE system. **Results:** Sixteen studies were included, showing a consistent association between gut dysbiosis and inflammatoryand neurochemical alterations, such as increased intestinal permeability, hypothalamic-pituitary- adrenal axis activation, and neurotransmitter modulation. Probiotic interventions demonstrated the most robust evidence, with moderate effects in reducing depressive and anxiety symptoms. Fecal microbiotatransplantationshowedpromisingbutlimitedevidence,whiledietaryinterventions yielded heterogeneous results. **Conclusion:** Gut microbiota acts as a relevant modulator of neuropsychiatric and inflammatory processes. However, current evidence is limited by methodological heterogeneity. Microbiota-targeted interventions represent a promising therapeutic approach, although further high-quality studies are required to support clinical application.

Keywords: Dysbiosis;gut microbiota;immune system; gut-brain-microbiotaaxis;cellcommunication

Resumen

Introducción: La microbiota intestinal desempeña un papel esencial en la regulación de procesos inmunológicos, metabólicos y neuroendocrinos, destacándose el eje intestino-cerebro como un campo emergente en la comprensión de los trastornos neuropsiquiátricos e inflamatorios. La disbiosis intestinal se ha asociado con alteraciones clínicas relevantes, incluyendo depresión, ansiedad e inflamación sistémica. **Objetivo:** Analizar críticamente la relación entre microbiota intestinal, manifestaciones neuropsiquiátricas y procesos inflamatorios en adultos, así como evaluar la eficacia de intervenciones dirigidas a su modulación. **Métodos:** Se realizó una revisiónintegradora de la literatura, siguiendo las recomendaciones del protocolo PRISMA. La búsqueda se llevó a cabo en las bases de datos MEDLINE, LILACS y PubMed, utilizando descriptores DeCS combinados con operadores booleanos. Se incluyeron estudios publicados entre 2020 y 2024 en portugués, inglés y español. La calidad metodológica fue evaluada mediante los instrumentos del Joanna Briggs Institute (JBI) y el nivel de evidencia fue clasificado según el sistema GRADE. **Resultados:** Seincluyeron16estudios, queevidenciaronunaasociaciónconsistenteentredisbiosis intestinal y alteracionesinflamatoriasy neuroquímicas. Lasintervencionesconprobióticosmostraron evidencia más robusta, con efectos moderados en la reducción de síntomas depresivos y ansiosos. El trasplante de microbiota fecal presentó potencial terapéutico, aunque con evidencia limitada, mientras que las intervenciones dietéticas mostraron resultados prometedores pero heterogéneos. **Conclusión:** La microbiota intestinal actúa como un modulador relevante de los procesos neuropsiquiátricos e inflamatorios. Sin embargo, la evidencia disponible presenta limitaciones metodológicas, lo que resalta la necesidad de estudios más robustos para su aplicación clínica.

Palabrasclave: Disbiosis;microbiotaintestinal;sistemainmunológico;ejeintestino-cerebro- microbiota; comunicación celular.

1. Introduction

Over the past decades, the gut-brain axis has emerged as a central focus of research in the fields of neuroscience, immunology, and psychiatry. The term “gut-brain axis” refers to the bidirectional communication between the gastrointestinal tract and the central nervous system —encompassing neural networks as well as immunological and metabolic pathways— as well as to neuroendocrine signaling and the microbial metabolic activity capable of influencing and crossing the gut-

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brain barrier. (GAO *et al.*,2023; HOMANN*etal.*, 2022)

In this context, gut dysbiosis, defined as a imbalance in the composition and diversity of the intestinal microbiota, has been implicated in the development of various neuropsychiatric conditions, including depression, anxiety, and neurodevelopmental and neurodegenerative disorders.(HOMANN *et al*., 2022)

Recent studies demonstrate that individuals with disorders such as major depression, anxiety, and Attention Deficiti Hyperactivity Disorder (ADHD) present alterations in the abundance of key bacteria; for example, a reduction in *Faecalibacterium prausnitzii* or*Bifidobacterium*, associated with increased intestinal permeability, microglial activation, and systemic inflammation.These alterations favor the circulation of lipopolysaccharides (LPS), increasing pro-inflammatory cytokines (IL-6, TNF-α) and activating the Hypothalamic-Pituitary-Adrenal (HPA) axis pathway, with increased cortisol release, which perpetuates chronic stress and neuropsychiatric symptoms. (HOMANN *et al*., 2022; KELLY *et al.*, 2022; MINAYO *et al.,* 2021)

According to Oliveira *et al.* (2025), diseases such as Alzheimer's and Parkinson's are associated with the relationship between neuroinflammation and dysbiosis, as well as neurodegenerative disorders. The study also proposes that Western dietary patterns may effectively reduce microbial diversity, significantly decreasing the production of short-chain fatty acids, such as butyrate, which is responsible for the integrity of the intestinal and blood barriers, as well as for neuroinflammation and cognitive decline.

Therefore, the influence of the gut microbiota is notable, revealing alterations in neuropsychiatric and inflammatory processes in adults. Thus, dysbiosis has also been associated with disorders such as depression, anxiety, and chronic inflammatory diseases. Gupta *et al.* (2023) and Gao *et al.* (2023) reiterate that, despite advances, there are still significant gaps in out understanding of the pathopsysiological mechanisms of this interaction.

Despite the evidence, there are still incipient studies that establish causality. According to Santos *et al.* (2024), Su *et al.* (2022) and Zhang *et al.* (2023), there is a methodological inconsistency that prevents ensuring the heterogeneity of

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clinical scales and the standardization of interventions (dosage, strains, duration) and, consequently, does not allow the verification of long-term follow-up in the assessment of lasting or temporary effects.

Thus, the present study is justified by the clinical, social, and scientific relevance of the topic. The increasing diagnosis os mental disorders and chronic inflammatory diseases in the adult population coincides with the growing identification of alterations in the gut microbiota as a possible contributing factor. However, the literature still lacks reviews that systematically compile evidence on this association and on therapeutic interventions, such as the use of probiotics, prebiotics, and dietary changes, which aim to modulate this axis.

Therefore, this study seeks to address this gap by answering the following fundamental question: What are the mechanisms through which the imbalance of the gut microbiota (dysbiosis) influences the manifestation of neuropsychiatric and inflammatory symptoms in adults?

1.1 General Objectives

To gather evidence on how the imbalance of the gut microbiota (dysbiosis) influences the manifestation of neuropsychiatric and inflammatory symptoms in adults, with emphasis on the gut-mind-body connection.

2. Literature Review

The understanding of the relationship between gut microbiota and mental health has advanced significantly in recent decades, mainly due to the development of studies on the microbiota-gut-brain axis. This system represents a complex network of bidirectional communication between the gastrointestinal tract and the central nervous system, involving neural, metabolic, immunological, and neuroendocrine pathways.Recent evidence demonstrates that metabolites produced by the gut microbiota, such as short-chain fatty acids and neurotransmitters, are capable of modulating inflammatory processes, neuronal activity, and mood regulation. Thus, alterations in this microbial balance may directly influence the pathopsysiology of neuropsychiatric and inflammatory

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disorders. (FOSTER; NEUFELD, 2013; WANG *et al*.,2023)

In this context, gut dysbiosis— characterizedby alterations in microbial composition and diversity — has been associated with the development os various clinical conditions, including depression, anxiety, and neurodegenerative deseases. Meta-analytical studies demonstrate that individuals diagnosed with major depressive disorder present specific patterns of gut microbiota alterations, including a reduction in butyrate-producting bacteria and an increase in pro-inflammatory species. These alterations may contribute to the activation of systemic inflammatory responses, which, in turn, interfere with brain function and neuroendocrine balance. (GAO *et al*., 2023; LIU *et al.,* 2024)

Furthermore, the literature indicates that the reduction of beneficial bacteria, such as species of the genera *Bifidobacterium* and*Lactobacillus*, may promote increased intestinal permeability. This phenomenon allows the translocation of bacterial lipopolysaccharides into the systemic circulation, triggering an inflammatory response characterized by the release of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha. These inflammatory mediators may reach the central nervous system and stimulate microglial activation, contributing to processes of neuroinflammation and neuronal dysfunction associated with mood disorders and cognitive alterations. (CAI *et al.,* 2022; GUPTA *et al*., 2023)

Another relevant aspect concerns the role of the gut microbiota in the production and modulation of neurotransmitters involved in the regulation of behavior and emotions. Several intestinal bacteria participate in the metabolism of tryptophan, a precursor of serotonin, as well as influence the synthesis of Gamma-Aminobutyric Acid (GAMA) and dopamine. The alteration of these metabolic processes may result in neurochemical imbalancers that contribute to symptoms of depression, anxiety, and cognitive alterations. In this sense, the microbiota-gut-brain axis acts as an important mediator of communication between the immune, endocrine, and nervous systems. (ZHANG *et al.,* 2023;ORTEGA *et al.,* 2023)

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Regarding therapeutic approaches, several studies have investigated strategies aimed at modulating the gut microbiota, such as the use of probiotics, prebiotics, and symbiotics. Randomized clinical trials indicate that the administration of probiotics containing specific strains may contribute to the reduction of depressive and anxiety symptoms, possibly through the modulation of the inflammatory response and the restoration of intestinal homeostasis. Recent meta-analyses demonstrate that these interventions may promote significant improvement in clinical scales of depression and anxiety, reinforcing the therapeutic potential of the so-called psychobiotics. (HOFMEISTER *et al*., 2021; LIU *et al*., 2022).

Another emerging field involves Faecal Microbiota Transplantation (FMT), a technique that consists of transferring healthy gut microbiota to restore microbial balance in individuals with dysbiosis. Although this approach is already well established in the treatment of *Clostridioides difficile*infections, its application in neuropsychiatric disorders remains in the experimental phase. Initial studies indicate promising results; however, methodological heterogeneity and the scarcity of large-scale clinical trials still limit definitive conclusions regarding its effectiveness in this context. (SU *et al*., 2022; SANTOS *et al*., 2024).

In general, scientific evidence indicates that the gut microbiota plays a fundamental role in maintaning immunological and neuroendocrine homeostasis. Alterations in this microbial ecosystem may contribute to the development or worsening of inflammatory diseases and mental disorders, reinforcing the importance of understanding the microbiota-gut-brain axis in clinical practice and scientific research. However, despite the advances observed, there are still gaps related to the standardization of methodologies, the identification of specific microbial strains, and the definition of effective therapeutic protocols, highlighting the need for further studies with greater methodological rigor and longitudinal follow-up. (OLIVEIRA *et al.,* 2025; ALAGIAKRISHNAN; MORGADIHO; HALVERSON, 2024)

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3. Methodology

This is an integrative literature review, conducted in a systematized manner and guided by the recommendations of the PRISMA protocol (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*), with the aim of ensuring transparency, reproducibility, and methodological rigor in the study selection process – thus, the stages of identification, screening, eligibility, and inclusion of studies were carried out.

The search strategy was structured based on the definition of controlled descriptors using the Health Sciences Descriptors (DeCS), including the terms: “dysbiosis”, “gut microbiota”, “immune system”, “gut-brain-microbiota axis”, and “cell communication”. These descriptors were combined using boolean operators (AND, OR and NOT), in order to expand and refine the results according to thematic relevance.

The search was conducted in the MEDLINE, LILACS and PubMed databases, including publications from 2020 to 2024. Studies avaiable in Portuguese, English, and Spanish were included.

Duplicate articles, studies with pediatric populations, narrative reviews, letters to the editor, and studies without acess to the full text were excluded.

The identification process resulted in 1,462 potentially relevant studies. Subsequently, the screening stage was carried out, with the exclusion of 5 duplicate articles, 739 incomplete studies, and 84 studies with samples considered inadequate or insufficient, according to previously established criteria.

Subsequently, the remaining studies were subjected to eligibility analysis, considering inclusion criteria such as: thematic relevance, approach toe the relationship between gut microbiota and neuropsychiatric and/or inflammatory manifestations, adult population, and methodological design compatible with the objectives of the review.

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At the end of the process, 16 articles were selected to compose the final sample of the integrative review. The study selection flow followed the stages of identification, screening, eligibility, and inclusion, as recommended by the PRISMA protocol. Figure 1 presents, in a schematic manner, the stages of the review process.

Additionally, the GRADE approach *(Grading of Recommendations Assessment, Development and Evaluation)* was applied to assess the overall level of evidence, and the *Joanna Briggs Institute* (JBI) tools were used to evaluate the risk of bias-considering aspects such as consistency of findings, precision of results, directionality of effects, and clinical applicability. The quality of evidence was classified as high, moderate, low, or very low.

Data analysis was conducted in a descriptive and critical manner, allowing for the synthesis of evidence and the identification of gaps in the literature, as described in Table 1 – Assessment of the Methodological Quality of Studies (JBI/GRADE). Brazil, 2025.

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Table 1 – Assessment of the Methodological Quality of Studies (JBI/GRADE). Brazil, 2025.

Author/Year	Type of Study	JBI(Risk of Bias)	GRADE(Level of Evidence)
Alagiakrishnanet al., 2024	Narrative/clinical review	High	Very low
Caietal.,2022	Systematic review	Low	Moderate
Carretaetal., 2024	Integrative review	Moderate	Low
Foster&Neufeld, 2013	Theoretical review	High	Very low
Gao M.etal.,2023	Systematic review+meta-analysis	Low	High
GaoK.etal., 2023	Systematic review+meta-analysis	Low	High
Guptaetal.,2023	Narrative review	Moderate	Low
Hofmeisteretal., 2021	Systematic review+meta-analysis (RCT)	Low	High
Homannetal., 2022	Randomized clinical trial	Low	High
LiuP.etal., 2024	Experimental/biomolecular study	Moderate	Moderate
LiuR.T.etal.,2022	Systematic review+meta-analysis	Low	High
Minayoet al.,2021	Systematic review	Moderate	Moderate
Oliveiraetal.,2025	Narrative review	Moderate	Low
Ortegaetal.,2023	Systematic review	Low	Moderate
Santosetal., 2024	Narrative review	Moderate	Low
Zhangetal.,2023	Systematic review	Low	Moderate

Source:Prepared by the authors,2025.

The assessment of methodological quality revealed a predominance of studies with low risk of bias among systematic reviews and clinical trials, especially those that included meta-analyses, which presented levels of evidence classified as moderate to high according to the GRADE system. In contrast, studies of a narrative of theoretical nature demonstrated a higher risk of bias and lower methodological robustness, being classified with low or very low levels of evidence.

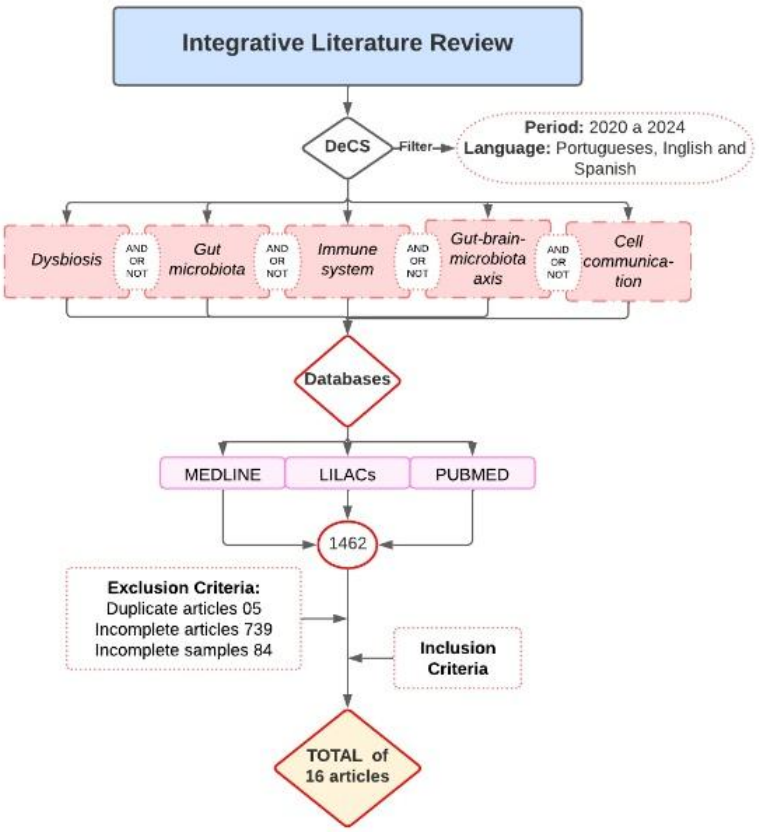
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It was observed that studies with greater methodological rigor were concentrated on the analysis of probiotic interventions and their relationship with depressive and inflammatory symptoms, while experimental and mechanistic studies contributed to the understanding of pathophysiological mechanisms, although with limitations regarding direct clinical applicability.

Figure 1 – Schematic representation of the stages of the review process. Brazil, 2025.



Source:Prepared by the authors,2025.

4. Results and discussion

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The analysis of the 16 included studies (Table 2) allowed the identification of consistent patterns, as well as relevant divergences, organized into three central thematic axes: **(i) inflammation and intestinal permeability**, **(ii) neurochemical modulation and the gut-brain axis**, and **(iii) therapeutic interventions and their clinical effects**. This organization enables not only the description of the findings, but also an integrated critical interpretation of the evidence.

Table 2 – Articles included in the review by author, year of publication, intervention/exposure, population and main outcome.

Author/Year	Type of Study	Population	Intervention/Exposure	Main Outcome	Evidence
Alagiakrishnan, 2024	Narrative review	Adults	Dysbiosis	Association with inflammation and mental health	Very low
Cai,2022	Systematic review	Adults	Gut microbiota	Association with depression	Moderate
Carreta,2024	Integrative review	Adults	Dysbiosis	Relationship with ADHD	Low
Foster,2013	Theoretic al review	Adults	Gut-brain axis	Influence on anxiety and depression	Very low
GaoM.,2023	SR+Meta-analysis	Adults	Gut microbiota	Alterations in depression	High
GaoK.,2023	SR+Meta-analysis	Adults	Microbiota	Association with MDD	High
Gupta,2023	Narrative review	Adults	Microbiotaanddiet	Modulation in neurodegenerative diseases	Low
Hofmeister, 2021	SR+Meta-analysis	Adults	Probiotics	↓ Depressive symptoms	High
Homann,2022	Clinical trial	Adults	Probiotics	↓ Symptoms + neuroimaging alterations	High
Liu P.,2024	Experimental study	Adults	Microbiota	Inflammatory modulation	Moderate
LiuR.,2022	SR+Meta-analysis	Adults	Probiotics	↓ Depressive symptoms	High
Minayo,2021	Systematic review	Adults	Probiotics	↓Anxiety and depression	Moderate
Oliveira,2025	Narrative review	Adults	Gut-brain axis	Association with mood	Low
Ortega,2023	Systematic review	Adults	Microbiota	Relationship with bipolar disorder	Moderate
Santos,2024	Narrative review	Adults	Microbiota	Therapeutic modulation	Low

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Zhang,2023	Systematic review	Adults	Microbiota	Association with mood disorders	Moderate

Source:Prepared by the authors,2025.

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4.1. Systemic Inflammation and Intestinal Permeability

The studies converge in demonstrating that gut dysbiosis is directly associated with increased intestinal permeability and the activation of systemic inflammatory pathways. Systematic reviews and meta-analysis indicate that the reduction of bacteria with anti-inflammatory function, such as*Faecalibacterium prausnitzii* and*Bifidobacterium*, favors the translocation of lipopolysaccharides (LPS), triggering an immune response mediated by pro-inflammatory cytokines, such as IL-6 e TNF-α. (Gao et al., 2023; Hofmeister et al., 2021; Liu et al., 2024)

However, divergence is observed regarding the magnitude of this effect. While studies with greater methodological rigor (meta-analysis) indicate a robust association between inflammation and depressive symptoms, narrative and experimental studies present more heterogeneous results, especially in relation to causality. This difference may be explained by methodological variability, including sample type, inflammatory markers used, and control of confounding variables.

From an interpretative perspective, the findings suggest that inflammation does not act in isolation, but as part of a complex system that integrates immunological, metabolic, and neuroendocrine factors. Thus, dysbiosis may be understood as a modulatory factor —rather thanan exclusively determining one— of clinical manifestation.

4.2. Neurochemical Modulation and the Gut-Brain Axis

Within the neurobiological axis, the analyzed studies reinforce the hole of the gut microbiota in regulating the central nervous system through the gut-brain axis. Consistent evidence indicates that dysbiosis is associated with alterations in the synthesis of neurotransmitters, including serotonin, dopamine, and GABA, directly impacting mood, behavior, and cognition. (Cai et al., 2022; Wang et al., 2023; Zhang et al., 2023)

Furthermore, the chronic activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, with the consequent elevation of cortisol levels, has been widely described as a central mechanism in the maintenance of chronic stress and in the

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pathophysiology of depression and anxiety. (Gao et al., 2023; Liu et al., 2024)

However, a critical analysis reveals important inconsistences. Experimental studies suggest biologically plausible mechanisms, but their translation into clinical practice remains limited. On the other land, clinical studies demonstrate an association between microbiota and neuropsychiatric symptoms, but with a lower capacity to elucidate the underlying mechanisms.

Thus, the literature highlights a gap between mechanistic robustness and clinical applicability, indicating the need for translational studies that integrate these two dimensions.

4.3. Therapeutic Interventions and Clinical Effects

Regarding interventions, studies demonstrate growing interest in the modulation of the gut microbiota as a therapeutic strategy. Randomized clinical trials and meta-analysis indicate that the use of probiotics, especially strains of *Lactobacillus* and*Bifidobacterium*, is associated with a significant reduction in depressive and anxiety symptoms. (Hofmeister et al., 2021; Homann et al., 2022; Liu et al., 2022)

However, there are relevant divergences among the studies. While Hofmeister *et al.* (2021) identified a statistically significant effect across multiple clinical scales (HAM-D e BDI), Liu *et al.* (2022) observed a more modest effect that was dependent on the instrument used. This discrepancy suggests that the results may be influenced by methodological factors, such as the type of scale, duration of the intervention, and sample profile.

Furthermore, interventions such as Faecal Microbiota Transplantation (FMT), although promising, still present incipient and heterogeneous evidence, limiting their clinical recommendation in the current context.(Gupta et al., 2023; Su et al., 2022)

Another critical point concerns the lack of standardization in intervention protocols, including dose, duration, and combination of strains, wich makes it difficult to compare studies and to generalize the results.

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4.3.1. Interpretative Synthesis of the Findings

The integration of the three axes shows that the gut microbiota acts as a central component in a complex network involving inflammation, neuroendocrine regulation, and neurochemical modulation. The studies with greater methodological robustness support the hypothesis that dysbiosis is associated with the worsening of neuropsychiatric symptoms, while the interventions demonstrate therapeutic potential, although with limitations.

From a critical perspective, the main weakness of the literature lies in methodological heterogeneity and the difficult in establishing consistent causal relationships. In addition, there is a predominance of short-term studies, with small sample sizes and absence of longitudinal follow-up.

Despite these limitations, there is sufficient consistency to consider the modulation of the gut microbiota as a promising strategy in the integrated management of neuropsychiatric and inflammatory conditions. However, its incorporation into clinical practice requires greater evidential robustness, especially through large-scaleclinical trials and longitudinal studies.

5. Comparative Analysis of Interventions in Gut Microbiota Modulation

The analysis of the included studies (Table 2) shows that interventions aimed at modulating the gut microbiota — notably probiotics, faecal microbiota transplantation (FMT), and dietary interventions —present different levels of evidence, efficacy, and clinical applicability, and should be interpreted in a differentiated rather than aggregaded manner.

5.1. Probiotics:Greater Clinical Consistency and Higher Level of Evidence

Probiotics constitute the most widely investigated intervention, with a predominance of randomized clinical trials and meta-analysis. Studies such as those by Hofmeister *et al.*(2021) and Liu*et al.* (2022) demonstrate that supplementation with specific strains of *Lactobacillus*and*Bifidobacterium*is associated with a reduction in depressive and anxiety symptoms, with more

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consistent effects in populations with mild to moderate conditions.

From a methodological perspective, these studies present a **low risk of bias (JBI)** and a **moderate to high level of evidence (GRADE)**, which confers greater robustness to the findings. However, the critical analysis reveals significant heterogeneity in the protocols, including variations in the strains used, doses, duration of treatment, and assessment instruments, which limits the standardization of the results.

In addition, the magnitude of the observed effect is generally moderate, suggesting that probiotics act as an adjuvant rather than a substitutive strategy in the management of neuropsychiatric disorders.

5.1.2. Faecal Microbiota Transplantation (FMT): High Potential, Low Clinical Evidence

FMT emerges as a promising intervention, especially due to its ability to promote rapid reconstitution of the gut microbiota. Experimental studies and animal models demonstrate significant effects on the modulation of behavior, inflammation, and neuroendocrine function. (Gupta et al., 2023; Su et al., 2022)

However, evidence in humans is still limited, with a predominance of pilot studies, small sample sizes, and lack of protocol standardization. Consequently, FMT presents a **moderate to high risk of bias (JBI)** and a **low to very low level of evidence (GRADE)** in the context of neuropsychiatric disorders.

Additionally, issues related to safety, donor selection and potential adverse effects are not yet fully established, restricting its clinical application outside experimental settings.

5.1.3. Dietary Interventions: A Systemic Approach with Emerging Evidence

Dietary interventions, although less explored in the included studies, represent a relevant strategy as they act directly on the composition and functionality of the gut microbiota. Diets rich in fiber, prebiotics, and fermented foods have been associated with increased microbial diversity and the production of beneficial metabolites, such as short-chain fatty acids (SCFAs).

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From an evidence perspective, studies on diet present a **moderate level of evidence**, but with **variable risk of bias**, due to the difficulty of rigorously controlling dietary adherence and the influence of behavioral and environmental factors.

Compared to probiotics, dietary interventions present more gradual effects, but potentially more sustainable in the long term, as they promote structural changes in the intestinal ecosystem.

5.1.4. Comparative Synthesis of Interventions

The critical comparison between the interventions shows that:

- **Probiotics**→greater clinical evidence, better standardization, moderate and consistent effect.
- **FMT**→greater theoreticalpotential, but with limited clinical evidence and low current applicability.
- **Diet**→promising approach, with systemic and sustainable effects, but still methodologically underexplored.

This hierarchy suggests that, in the current context, probiotics represent the most established strategy for modulating the microbiota with an impact on neuropsychiatric symptoms, while FMT remains an experimental alternative and dietary interventions are configured as a complementary long-term approach.

5.1.5. Implications for Clinical Practice and Research

The analysis shows that the choice of intervention should consider not only potential efficacy, but also the level of avaiable evidence, safety, and feasibility of implementation. Furthermore, the lack of standardization among studies reinforces the need for more robust clinical trials that directly compare these interventions, enabling the development of evidence-based therapeutic protocols.

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6. Assessment of Methodological Quality and Risk of Bias of the Studies

In order to strengthen the robustness of the present integrative review, a critical evaluation of the methodological quality of the included studies was carried out, as well as an analysis of the risk of bias, using the **Joanna Briggs Institute (JBI)** tools, specific to each methodological design (clinical trials, observational studies, and systematic reviews). Additionally, the **GRADE** approach **(Grading of Recommendations Assessment, Development and Evaluation)** was applied to classify the overall level of evidence.

The analysis showed that studies with experimental designs, especially randomized clinical trials and systematic reviews with meta-analysis, mostly presented a **low risk of bias**, with adequate methodological description, control of confounding variables, and consistency in the evaluated outcomes. These studies were predominantly classified with a **moderate to high level of evidence**, contributing more robustly to the systesis of the findings.

In the other hand, observational and cross-sectional studies, as well as narrative reviews, presented a **moderate to high risk of bias**, mainly due to the lack of rigorous control of confounding factors, limitations in sample size, and methodological heterogeneity. These studies were classified with a **low or very low level of evidence** and should be interpreted with greater caution.

Among the main biases identified, selection bias stands out, resulting from non-representative samples; information bias, related to the use of different clinical assessment instruments; and publication bias, considering the predominance of studies with positive results. In addition, significant variability was observed in intervention protocols, including differences in the probiotic strains used, doses, follow-up duration, and outcome assessment criteria.

This methodological heterogeneity directly impacts the comparability between studies and limits the generalization of the results. In this sense, although the findings point to a consistent association between gut microbiota and neuropsychiatric manifestations, the strength of this evidence should be interpreted in light of the methodological quality of the included studies.

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Thus, the present review acknowledges that the reported results are influenced by the variability and limitations of the analyzed studies, reinforcing the need for future investigations with more robust designs, larger sample sizes, methodological standardization, and longitudinal follow-up.

7. Final Considerations

The present integrative review allowed a critical analysis of the avaiable evidence regarding the relationship between gut microbiota, neuropsychiatric manifestations, and inflammatory processes in adults, highlighting the gut-brain axis as an emerging and relevant field in the understanding of these complex phenomena.

The findings suggest a consistent association between gut dysbiosis and immunoneuroendocrine alterations, including increased intestinal permeability, activation of inflammatory pathways, and modulation of neurotransmitters. Such mechanisms present biological plausibility to explain the relationship between microbiota and neuropsychiatric symptoms; however, the predominance of observational studies and methodological heterogeneity limit the inference of direct causality.

With regard to interventions, it is observed that the use of probiotics presents more consistent evidence and more immediate clinical applicability, with moderate effects in reducing depressive and anxiety symptoms. On the other hand, strategies such as faecal microbiota transplantation still lack robust evidence, while dietary interventions emerge as promising alternatives, but with a need for greater methodological standardization.

The assessment of study qualityrevealed variability in the risk of bias and levels of evidence, which directly impacts the reability of the results and reinforces the need for cautions interpretation of the findings. In this context, the gut microbiota should be understood as an important modulator of neurobiological and inflammatory processes, rather than as an isolated or determining factor.

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Thus, it is recommended that future research prioritize more robust methodological designs, including randomized clinical trials with larger sample sizes, standardization of interventions, longitudinal follow-up, and rigorous control of confounding variables, such as diet, medication use, and lifestyle. Furthermore, the use of integrated approaches, sush as metagenomic sequencing and neuroimaging techniques, may contribute to advancing the understanding of the mechanisms involved.

Finally, the modulation of the gut microbiota represents a promising therapeutic strategy in the context of mental and inflammatory health, with potential impact on clinical practice and public health. However, its incorporation should be based on robust scientific evidence, respecting the current limits of knowledge and avoiding undue extrapolations.

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