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MICROBIOTA INTESTINAL E SUA INFLUÊNCIA NA SAÚDE HUMANA E NO TRANSTORNO DO ESPECTRO AUTISTA (TEA)

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REVISÃO DE LITERATURA

RESUMO

Introdução: A microbiota intestinal desempenha um papel crucial na saúde humana, influenciando a digestão, o metabolismo, o desenvolvimento do sistema imunológico e até mesmo o comportamento. Esta revisão visa explorar a relação entre a microbiota intestinal e o Transtorno do Espectro Autista (TEA), enfatizando seu potencial papel no desenvolvimento e manifestação dos sintomas do TEA através de vias imunológicas e metabólicas. Métodos: Os dados para esta revisão foram obtidos do PubMed e Science Direct, abrangendo literatura de 2011 a 2024. Os critérios de inclusão focaram em estudos originais, revisões sistemáticas e meta-análises que discutiam a composição da microbiota intestinal, disbiose e sua relação com o TEA. Os artigos foram selecionados com base na relevância, idioma (inglês ou português) e na presença de dados empíricos. Resultados: A revisão identificou 36 artigos que destacam a diversidade e as funções vitais da microbiota intestinal. A disbiose, um desequilíbrio na microbiota intestinal, está associada a problemas gastrointestinais, distúrbios metabólicos e condições neuropsiquiátricas, incluindo o TEA. Estudos indicam que crianças com TEA possuem composições de microbiota intestinal distintas, com redução da diversidade e desequilíbrios bacterianos específicos. Essas alterações podem contribuir para os sintomas do TEA através do eixo intestino-cérebro, afetando a produção de neurotransmissores e respostas imunológicas. Discussão: Manter uma microbiota intestinal equilibrada é essencial para a saúde geral, e a modulação da microbiota pode oferecer benefícios terapêuticos para o manejo dos sintomas do TEA. As alterações na microbiota intestinal observadas em indivíduos com TEA sugerem uma ligação potencial entre a saúde intestinal e os sintomas neuropsiquiátricos, destacando a importância de intervenções dietéticas e probióticas para manter a saúde intestinal. Conclusão: Esta revisão destaca o potencial da microbiota intestinal como um alvo terapêutico no TEA e a importância de intervenções dietéticas e probióticas na manutenção da saúde intestinal. É necessária uma pesquisa adicional para compreender completamente essas interações e desenvolver tratamentos eficazes baseados na microbiota, enfatizando a necessidade de abordagens personalizadas em aplicações clínicas.

Palavras-chave: Microbiota intestinal; Transtorno do Espectro Autista (TEA); Disbiose

INTESTINAL MICROBIOTA AND ITS INFLUENCE ON HUMAN HEALTH AND AUTISM SPECTRUM DISORDER (ASD)

ABSTRACT

Introduction: The intestinal microbiota plays a crucial role in human health, influencing digestion, metabolism, immune system development, and even behavior. This review aims to explore the relationship between gut microbiota and Autism Spectrum Disorder (ASD), emphasizing its potential role in the development and manifestation of ASD symptoms through immunological and metabolic pathways. Methods: Data for this review were obtained from PubMed and Science Direct, covering literature from 2011 to 2024. Inclusion criteria focused on original studies, systematic reviews, and meta-analyses discussing gut microbiota composition, dysbiosis, and its relationship with ASD. Articles were selected based on relevance, language (English or Portuguese), and the presence of empirical data. Results: The review identified 36 articles that highlight the diversity and vital functions of the gut microbiota. Dysbiosis, an imbalance in the gut microbiota, is associated with gastrointestinal issues, metabolic disorders, and neuropsychiatric conditions, including ASD. Studies indicate that children with ASD have distinct gut microbiota compositions, with reduced diversity and specific bacterial imbalances. These changes may contribute to ASD symptoms through the gut-brain axis, affecting neurotransmitter production and immune responses. Discussion: Maintaining a balanced gut microbiota is essential for overall health, and modulating the microbiota may offer therapeutic benefits for managing ASD symptoms. The changes in gut microbiota observed in individuals with ASD suggest a potential link between gut health and neuropsychiatric symptoms, highlighting the importance of dietary and probiotic interventions in maintaining gut health. Conclusion: This review underscores the potential of the gut microbiota as a therapeutic target in ASD and the importance of dietary and probiotic interventions in maintaining gut health. Further research is necessary to fully understand these interactions and develop effective microbiota-based treatments, emphasizing the need for personalized approaches in clinical applications.

Keywords: Gut microbiota; Autism Spectrum Disorder (ASD); Dysbiosis.

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INTRODUCTION

The microbiota, also known as the microbiome, is a complex community of microorganisms that coexist in specific environments such as the gut, skin, soil, and even the ocean. This community is composed of a variety of bacteria, archaea, fungi, viruses, and other microorganisms, each playing distinct and interdependent roles. These microorganisms not only occupy a particular space but also interact with each other and with the host, influencing a variety of physiological and metabolic processes [1].

This microbiota is composed of approximately 500-1000 different species, including Bacteria, Archaea, and Eukarya, forming about 1.5 kg of biomass in the human gut. This diversity is crucial for maintaining intestinal homeostasis and the individual's overall health [2]. Furthermore, the microbiota possesses significant genetic potential, potentially containing up to 100 times more genes than the human genome, considering the diversity of species present. This complex ecosystem performs various vital functions, contributing to the organism's homeostasis [3].

The gut microbiota is essential for digestion, metabolism, immune system development, and the regulation of mood and behavior. This dynamic interaction between microorganisms and the host is fundamental for maintaining health and homeostasis, impacting various physiological processes such as metabolism, immunity, and digestion. Maintaining the balance of this microbiota is crucial for overall health, and one effective way to achieve this is through a balanced diet rich in probiotics and prebiotics [4, 5].

The bacterial microbiota is established in humans after birth, influenced by the type of delivery and breastfeeding, colonizing various surfaces. Throughout life, dietary habits, hospitalization, and antibiotic use affect the composition of the microbiota. Factors such as pH, temperature, oxygenation, and nutrients, along with peristaltic movements, saliva, enzymes, and immune response, determine the microbiota composition in different body parts [3].

On the other hand, dysbiosis can cause digestive problems such as irritable bowel syndrome and inflammatory bowel disease, metabolic disorders such as obesity and type 2 diabetes, and increase the risk of autoimmune diseases, chronic inflammation, and neuropsychiatric diseases. Each of these diseases presents specific symptoms and pathogenic mechanisms, highlighting the importance of a balanced microbiota for preventing these conditions [6, 7].

Additionally, the communication between the gut and the brain, known as the gut-brain axis, plays an important role in mental health, given that gut dysbiosis has been associated with neuropsychiatric disorders, including autism spectrum disorder (ASD). Studies suggest that the gut microbiota can influence the development and manifestation of autism through immunological and metabolic mechanisms. Thus, modulating the microbiota may represent a promising strategy for managing autism symptoms, although more research is needed to fully understand this relationship [8, 9].

METODOLOGY

Search Strategy

To conduct this systematic review, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed. The search was conducted in the PubMed and Science Direct databases, covering the period from 2011 to 2024. The descriptors used included: “intestinal microbiota,” “gut microbiota,” “microbiota composition,” “dysbiosis,” “autism spectrum disorder,” “gastrointestinal diseases,” and “immune modulation.” The search strategy combined the terms using the boolean operators “AND” to link different domains of interest and “OR” to include synonyms or related terms within the same domain.

Inclusion and Exclusion Criteria

Original studies, systematic reviews, and meta-analyses that discussed the composition of the gut microbiota, its health benefits, the causes and consequences of gut dysbiosis, and the relationship between microbiota and autism were included. Articles not available in English or Portuguese were excluded. Studies that did not specifically focus on the gut microbiota were excluded, as well as those that did not present empirical data or comprehensive reviews on the topic.

Review articles, commentaries, editorials, conference reports, and studies not directly related to the defined descriptors were excluded. Studies lacking empirical data or full accessibility were also excluded. Additionally, other articles were included for contextualization, enrichment, and justification of the topic addressed. The identified studies were initially screened based on titles and abstracts. Team members independently reviewed the titles and abstracts to identify potentially relevant studies. Following the initial screening, studies deemed potentially relevant were selected for full evaluation. The final selection of studies was based on comprehensive analysis of the articles and application of previously established inclusion and exclusion criteria. Peer review was conducted, where two independent reviewers examined the titles and abstracts of articles identified in the initial search. Potentially relevant studies were selected for full-text review. Discrepancies were resolved through consensus or by a third reviewer.

All records related to the search and study selection were systematically documented. A bibliographic reference management system was utilized to organize the identified studies and facilitate the review process. This stage of the methodological process followed PRISMA guidelines to ensure transparency, rigor, and replicability in identifying relevant studies for the proposed systematic review. The methodological quality of the included studies was assessed using a tool adapted for observational studies.

Results

Initially, using the expressions associated with the search terms, a total of 562 articles were obtained, 380 from PubMed and 182 from Science Direct. Subsequently, inclusion and exclusion criteria were added to the database filters, and the search revealed 128 articles related to the study's subject. In the selection of duplicate articles, 8 articles were excluded. After reading the titles and abstracts, 36 articles were selected for this review. The research results are represented in Figure 1.

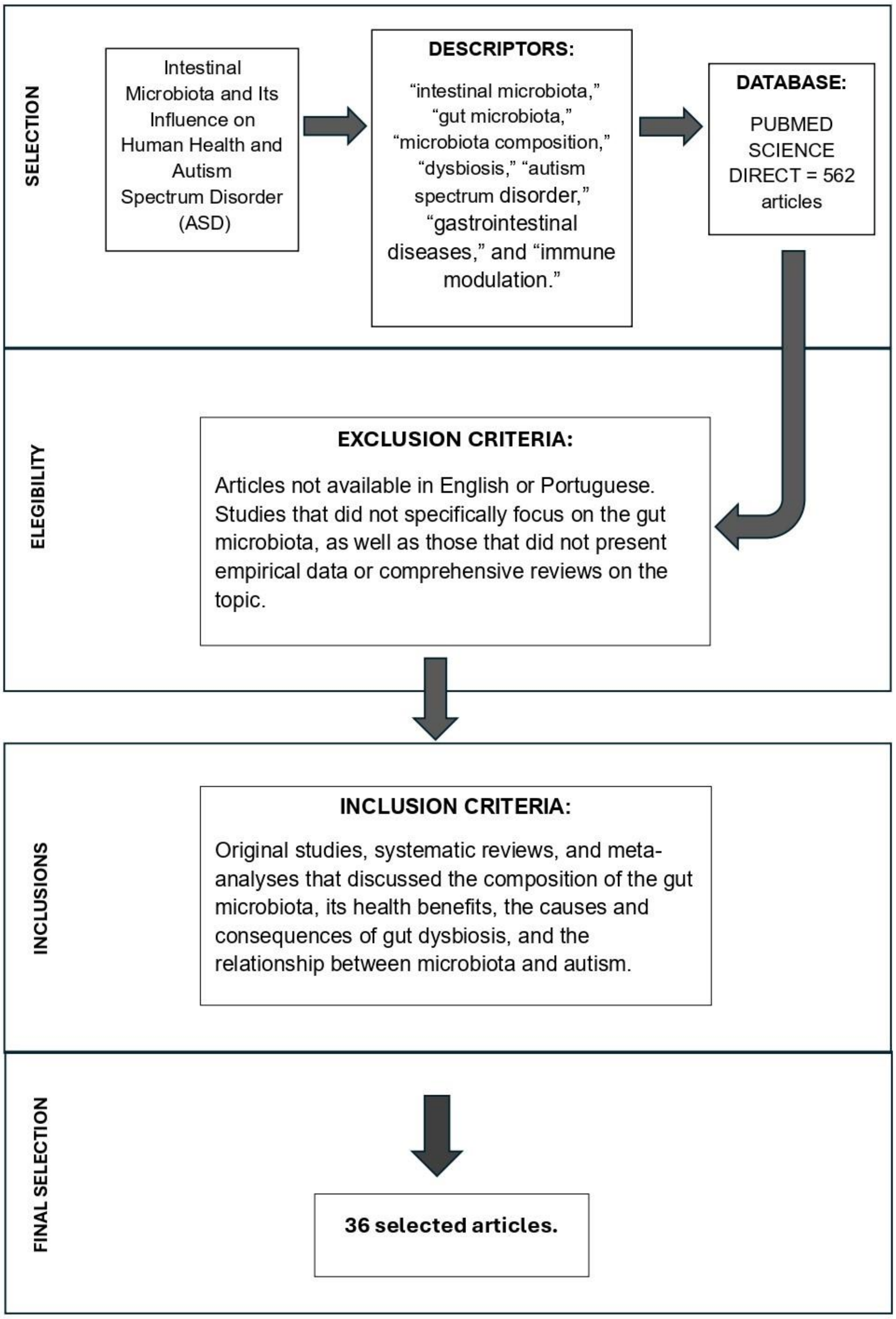

Figure 1. Flowchart of the article search and selection process. Source: Authors.

The Table 1 presents the description of the articles according to the author, year of publication, type of study, objective, results, and conclusion. These studies explore the diversity of the gut microbiota and its vital functions, analyzing the benefits of a balanced microbiota, and investigating the causes and consequences of gut dysbiosis, examining the relationship between microbiota and gastrointestinal, metabolic, immunological, and neuropsychiatric diseases.

Title	Author/year of publication	Type of study	Conclusion
Antibiotic-associated dysbiosis affects the ability of the gut microbiota to control intestinal inflammation upon fecal microbiota transplantation in experimental colitis models	Strati et al. (2021)	Experimental Study	Diverse antibiotic regimens affect the ability of the gut microbiota to control intestinal inflammation in experimental colitis by altering the microbial community structure and microbiota-derived metabolites.
Gut microbiome–targeted therapies in nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression	Sharpton et al. (2019)	Literature Review and Meta-analysis	Probiotics/synbiotics were associated with improvement in liver-specific markers of hepatic inflammation, liver stiffness measurement, and steatosis in persons with non-alcoholic fatty liver disease (NAFLD). Further well-designed randomized controlled trials (RCTs) are needed to define the efficacy of probiotics/synbiotics for treatment of NAFLD.
Multi-omic approaches for host-microbiome data integration	Chetty, A.; Blekhman, R. (2024)	Literature Review	Multi-omic studies of the microbiome provide insights into host-microbe interactions, but standardization across approaches is needed. Integrating multiple omics layers requires sophisticated statistical methods.
The links between gut microbiota and obesity and obesity related diseases	Geng et al. (2022)	Literature Review	Gut microbiota plays a crucial role in the onset and progression of obesity and obesity-related diseases. Modulating the gut microbiome composition and targeting relevant metabolic pathways can provide therapeutic benefits.

Title	Author/year of publication	Type of study	Conclusion
Roles of the cell surface architecture of *Bacteroides,* and *Bifidobacterium* in the gut colonization	Nishiyama et al. (2021)	Literature Review	The cell surface architecture of *Bacteroides,* and *Bifidobacterium* plays a critical role in their ability to colonize the gut. These structures facilitate interactions with the host and other microbes, impacting gut health and disease.
Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health	Oliphant, K.; Allen-Vercoe, E. (2019)	Literature Review	The human gut microbiome plays a critical role in breaking down complex macronutrients, producing metabolites that can significantly impact host health. Understanding these metabolic processes is crucial for developing microbiome-targeted therapies.
Metabolic influences of gut microbiota dysbiosis on inflammatory bowel disease	Sultan et al. (2021)	Literature Review	Gut microbiota dysbiosis in inflammatory bowel disease (IBD) is characterized by depleted diversity, reduced abundance of short-chain fatty acids (SCFAs) producers, and enriched proinflammatory microbes. This dysbiosis may contribute to inflammation through immune system modulation or metabolic pathway alterations.
Understanding the gut–brain axis and its therapeutic implications for neurodegenerative disorders	Zheng et al. (2023)	Literature Review	The gut–brain axis is a complex bidirectional communication network. Alterations in gut microbiota composition, known as gut dysbiosis, have been associated with dysfunction and neurodegeneration. Therapeutic approaches targeting the gut–brain axis have shown promising outcomes in ameliorating neurodegenerative disorders.

Title	Author/year of publication	Type of study	Conclusion
Profiles of autism characteristics in thirteen genetic syndromes: a machine learning approach	Bozhilova et al. (2023)	Experimental Study	Genetic syndromes are associated with different but overlapping autism-related profiles. The study highlights the need for greater precision in the assessment of autistic characteristics in individuals with genetic syndromes associated with intellectual disability.
Autism spectrum disorder research: knowledge mapping of progress and focus between 2011 and 2022	Jiang et al. (2023)	Literature Review	Research on autism spectrum disorder (ASD) has significantly increased in the last decade, focusing on causal mechanisms, clinical characteristics, and interventions. Immunological dysbiosis and intestinal microbiota are new frontiers of development.
Prevalence and characteristics of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 Sites, United States, 2020	Maenner et al. (2024)	Epidemiological Study	The prevalence of ASD among 8-year-old children in the United States is 1 in 36. The condition is more common in boys than in girls and varies significantly among different racial and ethnic groups.
The potential pathogenic role of gut microbiota in rheumatic diseases	Mahroum et al. (2023)	Literature Review	Dysbiosis of the gut microbiota may play an important role in the pathogenesis of rheumatic diseases, including rheumatoid arthritis, by influencing immune system activation and joint inflammation. Microbiota modulation strategies can be therapeutic, but personalized approaches are needed.

Title	Author/year of publication	Type of study	Conclusion
Prebiotics and probiotics for autism spectrum disorder: a systematic review and meta-analysis of controlled clinical trials	Song et al. (2022)	Systematic Review and Meta-analysis of Controlled Clinical Trials	The meta-analysis found that probiotics and prebiotics did not significantly improve ASD symptoms, gastrointestinal issues, or comorbid psychopathology. Due to the limited number of included trials, further clinical verification is needed. Future randomized controlled studies with larger populations and specialized professionals may yield more robust results.
Autism spectrum disorder associated with gut microbiota at immune, metabolomic and neuroactive Level	Garcia-Gutiérrez et al. (2020)	Literature Review	The review highlights increasing evidence linking ASD with gut microbiota through immune, metabolomic, and neuroactive pathways. It underscores the need for further research to identify robust biomarkers and develop effective microbiota-based treatments for ASD symptoms.
Altered gut microbial profile is associated with abnormal metabolism activity of autism spectrum disorder	Dan et al. (2020)	Research Paper	Children with ASD have a distinct gut microbiota with altered diversity and specific bacteria. These changes are linked to abnormal neurotransmitter metabolism, suggesting potential interventions targeting specific bacteria.
Altered gut microbiota in chinese children with autism spectrum disorders	Ma et al. (2019)	Original Research	The study found that children with ASD have less diversity and richness in their gut microbiota compared to neurotypical children. Specifically, children with ASD exhibited a lower relative abundance of certain bacterial families and genera, indicating intestinal microbial dysbiosis in ASD.

Title	Author/year of publication	Type of study	Conclusion
Composition of gut microbiota in children with autism spectrum disorder: a systematic review and meta-analysis	Iglesias-Vázquez et al. (2020)	Systematic Review and Meta-Analysis	The meta-analysis shows that children with ASD have significant gut microbiota dysbiosis, with increased bacteroidetes, firmicutes, and certain genera. This may affect ASD symptoms. More research is needed to confirm microbiota-based treatments.
The impact of gut microbiota on autoimmune thyroiditis and relationship with pregnancy outcomes: a review	Song et al. (2024)	Literature Review	The review suggests gut microbiota dysbiosis may significantly influence autoimmune thyroiditis (AITD) and related pregnancy complications. Further research is needed to confirm if modifying gut microbiota can improve pregnancy outcomes in AITD patients.
Gut microbiota alteration and modulation in psychiatric disorders: Current evidence on fecal microbiota transplantation	Settanni et al. (2021)	Literature Review	The review suggests FMT may help treat psychiatric disorders by modulating gut microbiota. While initial data is promising, more research is needed to standardize procedures and confirm effectiveness.
The role of gut microbiota in gastrointestinal symptoms of children with autism spectrum disorder	Martínez-González A. E.; Andreo-Martínez P. (2019)	Literature Review	Evidence links gastrointestinal symptoms and ASD, but specific gut microbes are not yet identified due to limited studies. Children with ASD show more *Candida* and less *Prevotella, Veillonella*, and *Streptococcus.* Future research should use a multidisciplinary approach.

Title	Author/year of publication	Type of study	Conclusion
Introduction to the human gut microbiota	Thursby, E., Juge, N. (2017)	Literature Review	The symbiotic relationship between the gut microbiota and the host is crucial, and dysbiosis is linked to various diseases. Metabolomic approaches advance the understanding of this interaction. Therapeutic strategies, including microbiome modulators and microbial solutions, aim to restore symbiosis. Combined therapies may be necessary due to the host's genetic influence.
Human microbiomes and their roles in dysbiosis, common diseases, and novel therapeutic approaches	Belizário J. E., Napolitano M. (2015)	Literature Review	The use of novel pharmaceuticals and nutraceuticals to modulate microbial colonization and development of a healthy gut microbial community in early childhood will support healthy adult human body functions and prevent the occurrence of several diseases.
Enterotypes of the human gut microbiome	Arumugam et al. (2011)	Literature Review and Meta-analysis	While individual host properties don’t explain the enterotypes, the latter might be driven by a complex mixture of functional properties, by host immune modulation or by hitherto unexplored physiological conditions such as transit time or pH of luminal contents.
The gut microbiota and host health: a new clinical frontier	Marchesi et al. (2015)	Literature Review	The potential of manipulating the gut microbiota in these disorders is assessed, with an examination of the latest and most relevant evidence relating to antibiotics, probiotics, prebiotics, polyphenols and faecal microbiota transplantation.

Title	Author/year of publication	Type of study	Conclusion
The international scientific association for probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics	Gibson et al. (2017)	Expert Consensus Document	Engender appropriate use of the term 'prebiotic' by relevant stakeholders so that consistency and clarity can be achieved in research reports, product marketing and regulatory oversight of the category.
Intestinal microbiota and cardiometabolic risk: mechanisms and diet modulation	Moraes et al. (2014)	Literature Review	There is evidence that the relationship between diet, inflammation, insulin resistance, and cardiometabolic risk are, in part, mediated by the composition of intestinal bacteria. Knowledge about the gut microbiota may result in different strategies to manipulate bacterial populations and promote health.
Gut microbiota functions: metabolism of nutrients and other food components	Rowland et al. (2018)	Literature Review	The gut microbiota expands the host's biochemical capacity to process dietary substrates, affecting the metabolism of carbohydrates, proteins, and phytochemicals. Functional redundancy and metabolic communication between the microbiota and the host influence health. Metabolites like acetate and butyrate regulate appetite and energy homeostasis, highlighting the need for further research.
Microbiota in the gastrointestinal tract	Dieterich et al. (2018)	Literature Review	The gut-associated lymphatic tissue balances tolerance to harmless microbes and pathogen defense. Individual gut microbiota composition and its interaction with the host's immune system are essential for homeostasis.

Title	Author/year of publication	Type of study	Conclusion
Research progress on the regulation mechanism of probiotics on the microecological flora of infected intestines in livestock and poultry	Shi et al. (2022)	Literature Review	The advent of high-throughput sequencing technology has given us a clearer understanding and has facilitated the development of research methods to investigate the intestinal microecological flora.
Crosstalk between the gut microbiota and innate lymphoid cells in intestinal mucosal immunity	Guo et al. (2023)	Literature Review	Studies on innate lymphoid cells (ILCs) and their interaction with the gut microbiota have great clinical significance owing to their potential for identifying pharmacotherapy targets for multiple related diseases.
Gut microbiota and its metabolic products in acute respiratory distress syndrome	Zhang et al. (2024)	Literature Review	The interaction between the gut microbiota and acute respiratory distress syndrome (ARDS) affects disease progression, causing microbial imbalances and inflammation. Metabolites like butyrate and propionate have therapeutic effects. Modulating the gut microbiota emerges as a promising treatment for ARDS. Rigorous studies are needed to understand the mechanisms and develop microbiota-based interventions to improve ARDS prognosis.
Fight them or feed them: how the intestinal mucus layer manages the gut microbiota	Schroeder (2019)	Literature Review and Meta-analysis	Understanding the molecular details of this host–microbe interaction may contribute to the development of novel treatment options for diseases involving a dysfunctional mucus layer, such as ulcerative colitis.

Title	Author/year of publication	Type of study	Conclusion
The human intestinal microbiome in health and disease	Lynch, S. V.; Pedersen, O. (2016)	Literature Review	The composition and function of the microbiota can influence susceptibility to various health conditions, including inflammatory, metabolic, and infectious diseases. The article emphasizes the need for further research to fully understand these interactions and to develop therapies based on modulating the gut microbiota.
Current understanding of dysbiosis in disease in human and animal models	DeGruttola et al. (2016)	Literature Review	Dysbiosis is a complicated disorder in the intestinal microbiota that is strongly believed to play a role in the pathogenesis of inflammatory bowel disease as well as other disorders like colorectal cancer and allergic disorders, however future work must be done to confirm this hypothesis.
Interactive relationships between intestinal flora and bile acids	Guo et al. (2022)	Literature Review	The bidirectional interaction between gut microbiota and bile acids is crucial for maintaining normal physiology. Gut microbiota influences bile acid synthesis, metabolism, and composition, while bile acids regulate microbial diversity. Imbalances contribute to diseases like inflammatory bowel disease,colorectal cancer, polycystic ovary syndrome and type 2 diabetes mellitus. Treatment strategies include altering bile acids, supplementing beneficial bacteria, and fecal microbiota transplantation (FMT) to restore balance and prevent disease.

Title	Author/year of publication	Type of study	Conclusion
Mechanisms and consequences of intestinal dysbiosis	Weiss, G.A.; Hennet, T. (2017)	Literature Review	The gut microbiota, crucial for host regulation, reacts to internal and environmental changes. Despite clear links between dysbiosis and disease, specific pathogenic mechanisms remain uncertain. Advances in sequencing and bioinformatics are enhancing our understanding of microbial diversity and metabolism. Comprehensive data integration will improve dysbiosis management and health outcomes for various conditions.

Table 1: Description of Articles Used for the Review. Source: Authors

In the studies summarized, it was demonstrated that antibiotic regimens can significantly alter the microbial community structure and microbiota-derived metabolites, thereby affecting the gut microbiome's ability to control intestinal inflammation in experimental colitis models [10]. Additionally, it was reviewed how the gut microbiome plays a crucial role in the onset and progression of obesity and related diseases, emphasizing the importance of modulating the gut microbiome composition for therapeutic benefits [11].

Similarly, it was shown through a meta-analysis study that the use of probiotics and synbiotics is associated with improvements in specific markers of liver inflammation, hepatic stiffness measurement, and steatosis in individuals with non-alcoholic fatty liver disease (NAFLD) [12]. In the same vein, it was emphasized through a literature review that multi-omic studies of the microbiome provide valuable insights into host-microorganism interactions, underscoring the need for standardization among approaches to integrate multiple omic layers [13].

The importance of maintaining a balanced gut microbiota, dominated by anaerobic bacteria such as Bacteroides and Bifidobacterium, is emphasized, as this microbial balance is crucial for host health [14, 15]. The rapid renewal of intestinal cells contributing to microbial diversity is also discussed, with over 99.9% of the adult gut microbiota consisting of obligate anaerobic bacteria, and their population density increasing towards the colon. This provides a broader perspective on the microbial population dynamics [2, 3].

Additionally, the role of gut microbiota in vitamin production and energy metabolism is explored, highlighting the production of essential vitamins and the breakdown of indigestible carbohydrates [16, 17]. This role is further supported by the emphasis on the production of short-chain fatty acids (SCFAs) and their impact on energy metabolism and gut health. Additionally, the immune functions of gut bacteria are discussed, showing how they enhance organ resistance and prevent colonization by harmful agents. The roles of Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD) proteins in microbial threat recognition and immune response are also explained [18, 19, 20, 21, 22].

The concept of gut dysbiosis is examined, linking it to gastrointestinal and metabolic disorders [23]. This is expanded upon by associating dysbiosis with inadequate immune responses and an increased risk of autoimmune diseases [24]. Furthermore, the gut-brain axis is explored, showing how the microbiota influence mental health through neurotransmitter production [4]. This is reinforced by discussions on the microbiota's role in neurodegenerative diseases [25].

Moreover, it is suggested that gut dysbiosis may contribute to autism spectrum disorder (ASD) symptoms through the microbiota-gut-brain axis [8, 9]. The link between gastrointestinal symptoms in ASD and changes in gut microbiota composition is also highlighted [26].

These key studies illustrate the critical role of gut microbiota in various health aspects, emphasizing the potential for microbiota modulation as a therapeutic strategy. Further research is essential to effectively translate these findings into clinical practice.

DISCUSSION

Host and Microbiota

The relationship between the host and gut microbiota is beneficial and depends on a healthy balance. The predominant bacteria in the gastrointestinal tract are anaerobes, with notable genera including Bacteroides, Bifidobacterium, Eubacterium, Clostridium, Peptococcus, Peptostreptococcus, Ruminococcus, and Fusobacterium [14, 15]. The intestinal environment is dynamic, with rapid cell renewal both in the small intestine and colon, maintaining different areas for various types of cells that continuously renew [3]. In healthy individuals, each area of the intestine is occupied by diverse members of the microbiota, some permanently and others temporarily. It is known that more than 99.9% of the adult gut microbiota consists of obligate anaerobic bacteria, with a population density that significantly increases towards the colon [2].

Certain gut bacteria, such as Escherichia coli, and Bacteroides, play a crucial role in the production of vitamins K and B complex in the intestine, providing essential sources of these vitamins. Recent studies also suggest that the gut microbiota can aid in the breakdown of carbohydrates indigestible by the human body, influencing energy storage from sugars and fats [16, 17].

Human gut microorganisms ferment complex carbohydrates, resulting in the production of short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, which are important energy sources for the host and have regulatory functions in energy metabolism. The presence of these SCFAs has a significant impact on host health. They can be absorbed by intestinal cells and used as an energy source, as well as influence lipogenesis and fat storage in adipose tissue. Thus, dietary modulation, such as increased fiber intake, can alter the microbiota composition and increase SCFA production, promoting metabolic benefits [17, 18].

Moreover, the microbiota's ability to ferment indigestible carbohydrates helps maintain the integrity of the intestinal barrier and regulate immune response, highlighting the importance of a fiber-rich diet for maintaining a healthy and functional microbiota. A specific bacterium, Bacteroides thetaiotaomicron, found in the end of the intestine in healthy individuals, can digest polysaccharides found in dietary fibers, such as xylan, pectins, and arabinose, which are not usually digested by the human diet [17].

In the small intestine, the duodenum contains few microorganisms due to exposure to acids and digestive enzymes, while the jejunum mainly presents gram-positive cocci and rods, as well as yeasts like Candida albicans. In the distal ileum, the microbiota resembles that of the colon, with predominant gram-negative anaerobic bacteria [27]. In the large intestine, or colon, there is significant diversity of gram-negative and gram-positive anaerobes, spore-forming and non-spore-forming, with predominance of Lachnospiraceae (Firmicutes) and Bacteroidetes [17, 27]. In addition to bacteria, some fungi and protozoa like Candida albicans and Trichomonas hominis can be present in a commensal relationship. Physiological processes such as peristaltic movement and mucus production help maintain the intestinal microbiota, which is influenced by factors such as stress, environmental changes, parasites, and the use of antimicrobials and probiotics [17].

Benefits of the Gut Microbiota

The gut microbiota plays a fundamental role in maintaining health and preventing diseases. The good performance and integrity of various systems and the body's connectivity depend on a healthy microbiome. The gut-brain-central nervous system axis has a rich and complex communication channel. This is due to the production of neurotransmitters and hormones like dopamine, serotonin, and GABA (gamma-aminobutyric acid) occurring from the gut microbiota. Regarding the performance of symbiotic bacteria in metabolic processes, the synthesis of vitamin K and B complex vitamins are extremely important and essential for the proper functioning of the body and maintaining health [4].

This microbiota performs the essential function of anti-infective protection, increasing organ resistance and preventing colonization by exogenous agents. It also contributes to maintaining homeostasis among the resident microbial population. However, some pathogenic bacteria can overcome antimicrobial barriers and the protective mucus wall, competing for nutrients and habitat, hindering the spread of pathogenic agents [20]. Additionally, the epithelial cells of the intestinal mucosa play a crucial role in the immune system, being responsible for the initial recognition of threats. Direct contact with the intestinal lumen is essential for the rapid and effective identification of risks by innate tissue receptors, allowing the identification of structural components of fungi, yeasts, and bacteria [21].

Inside the cells, the immune system manifests through proteins with nucleotide-binding and oligomerization domain (NOD) present in the cytosol. On the cell surface, Toll-Like receptors (TLRs) play an important role in the immune response. When bacteria invade the body, these sensors are activated, leading to gene expression responsible for the synthesis of pro-inflammatory proteins, such as cytokines and enzymes that promote the inflammatory response [22].

When the body's defense system is activated, secretory IgA immunoglobulin plays a fundamental role, preventing bacteria from adhering to the gastrointestinal tract's mucosal barrier. Macrophages and neutrophils act in the phagocytosis of bacteria, while antibodies help destroy pathogens and neutralize bacterial toxins [19].

Gut Dysbiosis

On the other hand, gut dysbiosis, characterized by an imbalance in the microbiota due to an increase in harmful bacteria, is associated with various gastrointestinal and metabolic disorders, as well as immunological and neuropsychiatric issues. Factors such as the indiscriminate use of antibiotics, excessive consumption of processed foods at the expense of raw foods, laxative abuse, exposure to environmental toxins, consumptive diseases (such as cancer and Acquired Immune Deficiency Syndrome - AIDS), liver and pancreatic dysfunctions, stress, and diverticulosis contribute to this condition [10, 23].

This alteration in the gut microbiota can lead to a range of digestive issues including irritable bowel syndrome, inflammatory bowel disease, constipation, and functional diarrhea, as well as metabolic disorders such as obesity, insulin resistance, and type 2 diabetes. Furthermore, dysbiosis is associated with inadequate immune responses, increasing the risk of autoimmune diseases, allergies, and chronic inflammation [24].

Regarding gastrointestinal diseases, they can be divided into infections, caused by pathogen invasion, and intoxications, resulting from the ingestion of toxins. Major diseases include Staphylococcal Enterotoxicosis, Shigellosis, Salmonellosis, Typhoid Fever, Cholera, and Gastroenteritis caused by Escherichia coli. Ongoing investigation of these diseases has revealed the complexity of interactions between pathogens and the gut microbiota and how these interactions can influence the severity and progression of the diseases [6, 7].

Additionally, recent studies have deepened the understanding of the role of the microbiota in regulating metabolism and modulating the immune system. For instance, the composition of the microbiota can influence nutrient absorption and the production of bioactive metabolites that directly affect energy homeostasis and immune function [11]. In this context, dysbiosis has been implicated in conditions such as non-alcoholic fatty liver disease (NAFLD), where alterations in the microbiome may promote liver inflammation and insulin resistance [12].

Moreover, the communication between the gut and the brain, known as the gut-brain axis, plays an important role in mental health. Gut dysbiosis has been associated with neuropsychiatric disorders, including depression, anxiety, autism, and Parkinson's disease [24]. These connections highlight the relevance of integrative approaches in treating health conditions, considering gut health as a key component for overall well-being. Modulating the gut microbiota through probiotics, prebiotics, and specific diets has shown therapeutic potential in improving symptoms of mental disorders [12].

Thus, the prevention and treatment of gastrointestinal diseases and the maintenance of gut microbiota health are areas of intense study and innovation. New therapies are being developed, including fecal microbiota transplantation (FMT), which has shown efficacy in conditions such as recurrent Clostridioides difficile infection and potential in other dysbiosis-related disorders. Identifying specific microbiological markers is also paving the way for more accurate diagnoses and personalized treatments [13].

Autism and Gut Microbiota

Autism, or Autism Spectrum Disorder (ASD), is defined in the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition, DSM-5) as a heterogeneous group of neurodevelopmental disorders characterized by the three main features of impaired communication, social interaction disorder, and repetitive behavior. Within this spectrum, Kanner's autism, Asperger's syndrome, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) are included, all characterized by persistent deficits in social communication interaction and restricted-repetitive patterns of behavior, interests, or activities [28]

The characteristics of autism vary widely among individuals, making each case unique. Some key signs include difficulties in verbal and non-verbal communication, repetitive behaviors, restricted interests, and problems with social interaction. These symptoms usually manifest before the age of three and can range from mild to severe. The prevalence of autism has increased in recent years, with recent estimates indicating that 1 in 36 children in the United States is diagnosed with ASD. This increase may be attributed to better awareness, more accurate diagnostic methods, and greater inclusion of different autism profiles in diagnostic criteria [29, 30].

Additionally, the relationship between gut microbiota and ASD has been the subject of intense research in recent years. The human gut harbors a complex community of microorganisms, known as the gut microbiota, which plays a crucial role in regulating the immune system, metabolism, and even the development of the central nervous system. Recent studies suggest that alterations in the composition and function of the gut microbiota may be associated with the development of neuropsychiatric disorders, including autism [8, 9].

Relationship Between Gut Microbiota and Autism

Individuals with ASD often develop various comorbidities, including gastrointestinal (GI) symptoms such as diarrhea, constipation, abdominal pain, and bloating, which are correlated with the severity of the disorder. These GI symptoms are often associated with gut microbiota dysbiosis, characterized by an alteration in the composition of gut bacteria [31].

Studies suggest that the gut microbiota may influence the development and manifestation of autism through immunological and metabolic mechanisms [8]. In this context, gut dysbiosis, or an imbalance in the gut microbiota, may lead to changes in intestinal permeability, known as "leaky gut," allowing toxins and inflammatory substances to enter the bloodstream, which can trigger systemic inflammatory responses and impact brain function [9].

Furthermore, genetic conditions such as Fragile X Syndrome, tuberous sclerosis, and Rett syndrome have a higher association with ASD, reinforcing the influence of genetic factors in the development of the condition [32]. Thus, modulating the microbiota may represent a promising strategy for managing autism symptoms, although more research is needed to fully understand this relationship [8, 9]. Bidirectional communication between the gut and the brain, known as the gut-brain axis, is mediated by various mechanisms, including the production of neurotransmitters, cytokines, and metabolites by the gut microbiota. Dysfunctions in this axis can lead to changes in intestinal permeability ("leaky gut"), allowing toxins and inflammatory substances to enter the bloodstream, triggering systemic inflammatory responses and impacting brain function [31].

In this scenario, it is known that the gut microbiota plays a crucial role in the homeostasis of the central nervous system (CNS), modulating the immune system and regulating the production of molecules and metabolites that affect the nervous and endocrine systems. Moreover, the composition of the gut microbiota can significantly influence mental health, with studies indicating that gut dysbiosis is associated with neurodegenerative diseases such as Alzheimer's and Parkinson's [25]. These inflammatory substances, including pro-inflammatory cytokines, can cross the blood-brain barrier and cause inflammation in the brain, contributing to the neuropsychiatric symptoms observed in individuals with ASD. The production of neurotransmitters by the gut microbiota, such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), directly influences behavioral symptoms associated with autism [31].

The gut microbiota plays an essential role in metabolizing nutrients such as carbohydrates, proteins, and fats. Alterations in the composition of the microbiota can affect the absorption of essential nutrients for the proper functioning of the CNS. Resulting nutritional deficiencies may contribute to neurobehavioral dysfunctions observed in individuals with ASD [33].

Studies have shown significant differences in the composition of the gut microbiota in children with autism compared to neurotypical children. For example, some authors found that alpha diversity of the gut microbiota did not significantly change with age in the ASD group, while in the typically developing (TD) group, diversity increased with age, suggesting that the development of the gut microbiota in children with ASD is inconsistent compared to TD children [34].

Furthermore, a depletion of beneficial species such as Sutterella, Prevotella, and Bacteroides was identified in children with ASD and constipation, linking these changes to dysregulated metabolic activities that may be involved in the pathogenesis of ASD [34]. Concurrently, authors found that the gut microbiota of children with ASD is predominantly composed of the phyla Bacteroidetes, Firmicutes, and Actinobacteria, with higher abundance of the genera Bacteroides, Parabacteroides, Clostridium, Faecalibacterium, and Phascolarctobacterium, and lower abundance of Coprococcus and Bifidobacterium compared to healthy controls [33].

This dysbiosis may influence the development and severity of ASD symptoms, not only GI symptoms but also neuropsychiatric symptoms, suggesting an important link between the gut microbiota and ASD symptoms through the microbiota-gut-brain axis [33]. Interventions aimed at modifying the gut microbiota, such as using probiotics, prebiotics, antibiotics,or fecal microbiota transplantation, have shown therapeutic potential for children with ASD. For example, researchers suggest that targeting specific bacteria associated with neurotransmitter metabolism may be a promising strategy [34]. Additionally, its necessary further studies to evaluate the efficacy of these interventions and provide robust evidence on the role of the gut microbiota in ASD [33].

Therefore, the relationship between the gut microbiota and autism involves a complex network of pathophysiological mechanisms that directly influence the functioning of the central nervous system and the behavior of individuals affected by this neuropsychiatric condition. Gut health plays a crucial role in the development and management of ASD, and interventions that modify the gut microbiota may offer new therapeutic approaches to improve behavioral and gastrointestinal symptoms associated with autism.

Current Knowledge on Gut Microbiota

Recent studies address the crucial role of the gut microbiota in various health conditions. Researchers analyzed changes in the gut microbiota in psychiatric disorders and reviewed the therapeutic potential of fecal microbiota transplantation (FMT) in this context. FMT has emerged as a promising intervention for various health conditions, particularly those related to gut dysbiosis, involving the transfer of healthy fecal microbiota from a donor to the gastrointestinal tract of a recipient, with the aim of restoring the recipient's microbiota composition and function. The authors highlighted the need for personalized approaches in FMT, considering individual patient microbiome characteristics, ensuring that treatments are tailored to their specific needs. They also emphasized the need for further research to optimize the use of FMT in clinical practice, as although initial results are promising, standardizing FMT protocols and understanding the interactions between the microbiota and the brain are essential for significant advancements in this area [35].

Additionally, some studies investigated the impact of the gut microbiota on autoimmune thyroiditis and its effects during pregnancy. They found that alterations in the gut microbiota composition can influence immune responses and hormonal levels, affecting maternal and fetal health [26]. The studies highlight the importance of understanding these interactions to improve therapeutic strategies in pregnant women with autoimmune thyroiditis. The authors clarified that more longitudinal studies and clinical trials are needed to validate these findings and develop effective treatments [26].

Finally, the role of the gut microbiota in rheumatoid arthritis (RA) and its influence on immune system activation and joint inflammation was reviewed, discussing how gut dysbiosis may contribute to RA pathogenesis and exploring potential microbiota modulation strategies, such as using probiotics, prebiotics, and FMT, as therapeutic interventions. The need for personalized approaches for RA patients was highlighted, considering the individual microbiota composition and other genetic and environmental factors [36].

These studies underscore the complexity and importance of interactions between the gut microbiota and various health conditions, suggesting that interventions modifying microbial composition may have significant therapeutic roles. However, translating these findings into clinical practice requires more rigorous research to ensure the safety and efficacy of proposed interventions.

FINAL CONSIDERATIONS

This review highlights the complexity and importance of the gut microbiota in maintaining human health and modulating various pathological conditions, including Autism Spectrum Disorder (ASD). The microbiota, composed of a vast community of microorganisms, plays crucial roles in digestion, metabolism, immune system development, and even mood and behavior regulation. Dysbiosis, or an imbalance in the microbiota, has been associated with a range of gastrointestinal, metabolic, immunological, and neuropsychiatric disorders.

The relationship between gut microbiota and ASD is particularly notable, with growing evidence that gut dysbiosis may influence the development and manifestation of autism through immunological and metabolic mechanisms. Modulating the microbiota may represent a promising strategy for managing autism symptoms, but a deeper understanding of these interactions is needed to develop effective treatments.

Furthermore, it has been emphasized that gut microbiota modulation through interventions such as fecal microbiota transplantation (FMT), probiotics, and prebiotics offers significant therapeutic potential. However, translating these interventions into clinical practice requires more rigorous research to ensure their safety and efficacy. Personalized strategies, considering individual patient microbiome characteristics, are essential to optimize the benefits of these interventions.

In summary, the gut microbiota is a promising research area with the potential to significantly improve health and quality of life through dietary and therapeutic interventions based on microbial modulation. Continued research in this area is essential to fully explore these benefits and translate scientific discoveries into effective and safe clinical practices.

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