Oral Microbiota and the Gut–Brain Axis with Autism Spectrum Disorder: A Systematic Review

Willy Rilston Souza de Jesus, Marcos Fernandes Morales, Júlia Cunha Gonzales, Nataly Emanuelle Ament de Souza, Alinne Pereira de Castro

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Authors:
Willy Rilston Souza de Jesus
MSc in Biotechnology
Affiliation: Dom Bosco Catholic University (UCDB)
Address: Av. Tamandaré, 6000, Seminário, Campo Grande - MS, ZIP Code: 79117900, Brazil
Orcid ID: https://orcid.org/0009-0006-5905-8276
Email: willirilston@gmail.com

Marcos Fernandes Morales
MSc in Biotechnology
Affiliation: Dom Bosco Catholic University (UCDB)
Address: Av. Tamandaré, 6000, Seminário, Campo Grande - MS, ZIP Code: 79117900, Brazil
Orcid ID: https://orcid.org/0000-0001-7469-8542
Email: marcos.morales221b@live.com

Júlia Cunha Gonzales
PhD in Biotechnology
Affiliation: Dom Bosco Catholic University (UCDB)
Address: Av. Tamandaré, 6000, Seminário, Campo Grande - MS, ZIP Code: 79117900, Brazil
Orcid ID: https://orcid.org/0000-0003-1060-5727
Email: juliacunhagonzales@gmail.com

Nataly Emanuelle Ament de Souza
BSc student in Biomedicine
Affiliation: Dom Bosco Catholic University (UCDB)
Address: Av. Tamandaré, 6000, Seminário, Campo Grande - MS, ZIP Code: 79117900, Brazil
Orcid ID: https://orcid.org/0009-0001-5208-6083
Email:ra197827@ucdb.br

Alinne Pereira de Castro
PhD in Molecular Biology
Affiliation: Dom Bosco Catholic University (UCDB)
Address: Darcy Ribeiro University Campus, Asa Norte, Brasília-DF, ZIP Code: 70910900, Brazil
Orcid ID: https://orcid.org/0000-0002-9703-0577
Email: p.alinne@gmail.com

***Corresponding author:** Willy Rilston Souza de Jesus (willirilston@gmail.com.br)

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Abstract

Objective: To systematically review the literature on the association between the oral microbiota and the gut-brain axis in the context of Autism Spectrum Disorder (ASD), investigating whether alterations in the oral microbial ecosystem reflect systemic processes related to the disorder. **Methods:** This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Electronic searches were performed in Embase, PubMed, Scopus, and Web of Science using descriptors related to oral microbiota, ASD, and the gut-brain axis. Human studies published between 2015 and 2025 that evaluated the oral microbiota (saliva, dental plaque, or oral swab) and its association with ASD-related outcomes were included. Methodological quality was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists, and study selection was managed using Rayyan software. Twelve studies met the eligibility criteria and were included in the qualitative synthesis. **Results:** The included studies consistently demonstrated alterations in the composition, diversity, and richness of the oral microbiota in individuals with ASD compared with healthy controls, indicating a dysbiotic microbial profile. The predominant bacterial phyla identified were *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteriota, and Fusobacteriota*. These microbial alterations were associated with clinical, behavioral, inflammatory, and metabolic outcomes. Furthermore, studies simultaneously evaluating the oral and gut microbiota suggested systemic interactions, with shared dysbiotic profiles supporting the role of the oral cavity as a potential source of biomarkers and as a component of the oral-gut-brain axis. **Conclusions:** The oral microbiota appears to be an integral component of the gut-brain axis in ASD and should not be investigated in isolation. Current evidence indicates that oral microbial dysbiosis is associated with the clinical manifestations and pathophysiological mechanisms of ASD. Although further studies involving larger populations and standardized methodologies are required, the available findings support the oral microbiota as a promising target for the development of diagnostic biomarkers and complementary therapeutic strategies for personalized ASD care.

Keywords: autism spectrum disorder; oral microbiota; gut-brain axis; systematic review.

RESUMEN

Objetivo: Realizar una revisión sistemática de la literatura para analizar la asociación entre la microbiota oral y el eje intestino–cerebro en el contexto del Trastorno del Espectro Autista (TEA), investigando si las alteraciones en el ecosistema microbiano oral pueden reflejar procesos sistémicos relacionados con el trastorno. **Métodos:** La revisión se llevó a cabo de acuerdo con las directrices PRISMA 2020. Se realizaron búsquedas en las bases de datos Embase, PubMed, Scopus y Web of Science, utilizando descriptores relacionados con la microbiota oral, el TEA y el eje intestino–cerebro. Se incluyeron estudios en humanos publicados entre 2015 y 2025 que evaluaron la microbiota oral (saliva, placa dental o hisopo) y su relación con los desenlaces del TEA. La calidad metodológica fue evaluada mediante las listas de verificación del Joanna Briggs Institute (JBI), y el proceso de selección fue gestionado con el software Rayyan. Doce estudios cumplieron los criterios de elegibilidad para la síntesis cualitativa. **Resultados:** Los estudios demostraron de manera consistente alteraciones en la composición, diversidad y riqueza de la microbiota oral en individuos con TEA en comparación con los controles, caracterizando un estado de disbiosis. Los principales filos identificados fueron *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteriota* y *Fusobacterium*. El análisis reveló que estas alteraciones microbianas orales se correlacionan con desenlaces clínicos, conductuales, inflamatorios y metabólicos. Además, las evidencias provenientes de estudios que analizaron simultáneamente las microbiotas oral e intestinal sugieren una interacción sistémica, con perfiles compartidos de disbiosis, reforzando la relevancia de la cavidad oral como un sitio de potenciales biomarcadores y como un componente del eje oral–intestino–cerebro. **Conclusiones:** La microbiota oral se presenta como un componente integrado del eje intestino–cerebro en el TEA y no debe analizarse de forma aislada. Los hallazgos indican que el desequilibrio microbiano oral está asociado con la expresión clínica y fisiopatológica del trastorno. Aunque se requieren nuevos estudios con poblaciones más amplias y una mayor estandarización metodológica, los resultados respaldan a la microbiota oral como un objetivo prometedor para el desarrollo de biomarcadores diagnósticos y de futuras estrategias terapéuticas complementarias en la atención individualizada del autismo.

Palabras clave: trastorno del espectro autista; microbiota oral; eje intestino–cerebro; revisión sistemática.

RESUMO

Objetivo: Realizar uma revisão sistemática da literatura para analisar a associação entre a microbiota oral e o eixo intestino-cérebro no contexto do Transtorno do Espectro Autista (TEA), investigando se alterações no ecossistema microbiano oral podem refletir processos sistêmicos relacionados ao transtorno.**Métodos:**A revisão foi conduzida conforme as diretrizes PRISMA 2020. Foram realizadas buscas nas bases Embase, PubMed, Scopus e Web of Science, utilizando descritores relacionados à microbiota oral, TEA e o eixo intestino-cérebro. Foram incluídos estudos em humanos publicados entre 2015 e 2025 que avaliaram a microbiota oral (saliva, placa ou *swab*) e sua relação com desfechos do TEA. A qualidade metodológica foi avaliada pelos checklists do Joanna Briggs Institute (JBI), e a triagem foi gerenciada via software Rayyan. 12 estudos preencheram os critérios de elegibilidade para a síntese qualitativa.**Resultados:**Os estudos demonstraram de forma consistente alterações na composição, diversidade e riqueza da microbiota oral em indivíduos com TEA em comparação aos controles, caracterizando um estado de disbiose. Os principais filos identificados foram *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteriota* e *Fusobacterium*. A análise revelou que essas alterações microbianas orais correlacionam-se com desfechos clínicos, comportamentais, inflamatórios e metabólicos. Além disso, evidências de estudos que analisaram simultaneamente as microbiotas oral e intestinal sugerem uma interação sistêmica, com perfis de disbiose compartilhados, fortalecendo a relevância da cavidade oral como um sítio de biomarcadores potenciais e como componente do eixo oral-intestino-cérebro.**Conclusões:**A microbiota oral apresenta-se como um componente integrado ao eixo intestino-cérebro no TEA, não devendo ser analisada isoladamente. Os achados indicam que o desequilíbrio microbiano oral está associado à expressão clínica e fisiopatológica do transtorno. Embora novos estudos com populações maiores e padronização metodológica sejam necessários, os resultados sustentam a microbiota oral como um alvo promissor para o desenvolvimento de biomarcadores diagnósticos e futuras estratégias terapêuticas complementares no cuidado individualizado ao autismo.

Palavras-chave: transtorno do espectro autista; microbiota oral; eixo intestino–cérebro; revisão sistemática.

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by persistent deficits in social communication and interaction, along with restricted and repetitive patterns of behavior, interests, or activities (Frazier et al., 2021). The global prevalence of ASD has increased substantially over recent decades, prompting growing interest in identifying not only its well-established genetic determinants but also the environmental and epigenetic factors involved in its etiology (Lord et al., 2020).

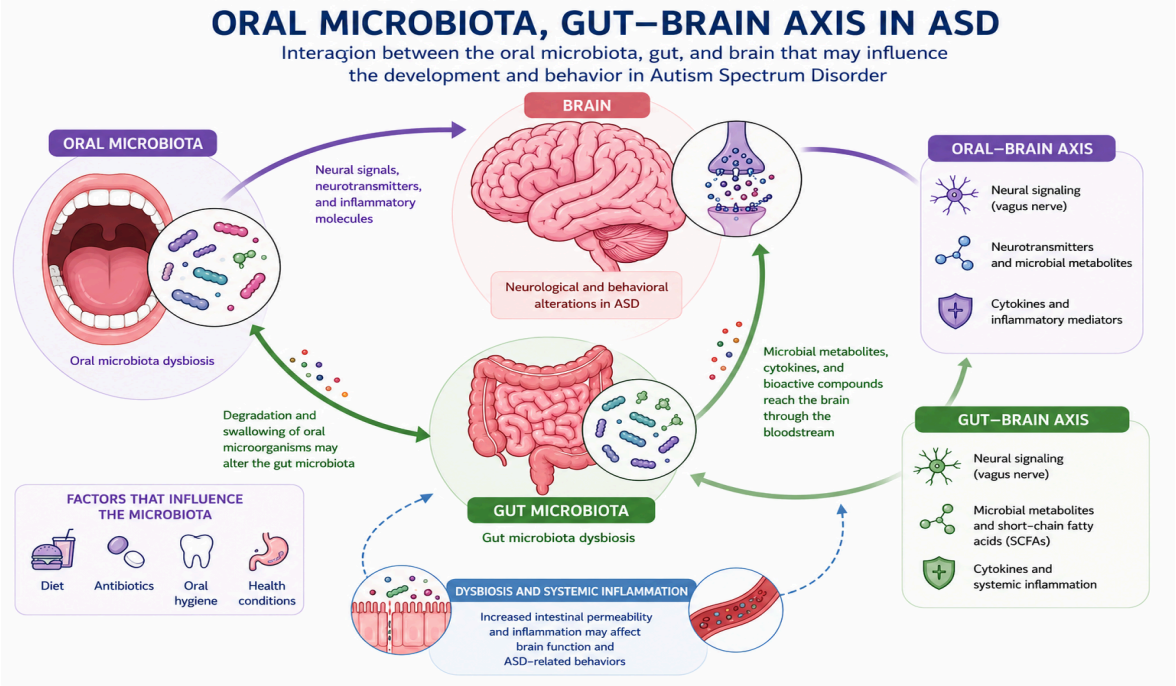
In recent years, the gut-brain axis has emerged as a key bidirectional neuroendocrine, immune, and neural communication network in which the resident microbiota plays a fundamental role in maintaining host homeostasis (Cryan et al., 2019). Although research on microbial dysbiosis in ASD has historically focused on the lower gastrointestinal tract, the oral cavity constitutes the gateway to the digestive system and harbors the second most diverse microbial community in the human body (Madra et al., 2020). Oral microorganisms and their metabolites may disseminate systemically or signal through the vagus nerve, thereby influencing central neuroinflammatory responses (Schmidt et al., 2019).

This evidence supports the hypothesis of an oral-brain axis, in which microbial metabolites and inflammatory mediators may contribute to neurological processes. Oral bacteria can produce bioactive compounds capable of modulating immune responses and promoting systemic inflammation, which may directly or indirectly affect central nervous system function. Alterations in the oral microbiota may also influence the production of molecules involved in immune-brain communication, suggesting a potential role in neurodevelopment (Lewandowska-Pietruszka et al., 2025).

Several studies have reported significant differences in the diversity and composition of the oral microbiota in individuals with ASD compared with neurotypical controls (Qiao et al., 2018; Hicks et al., 2018). These microbial alterations have been associated with inflammatory, immunological, and neurobiological mechanisms potentially involved in ASD pathophysiology (Kong et al., 2021; Zhang et al., 2024). However, the relationship between the oral microbiota and the gut-brain axis in ASD remains poorly understood and has not yet been comprehensively synthesized.

Therefore, the present systematic review aimed to examine the association between the oral microbiota and the gut-brain axis in ASD, investigating whether alterations in the oral microbial ecosystem may reflect systemic processes involved in the pathophysiology of the disorder.

Figure 1: Interaction between the oral microbiota and the gut-brain axis in autism spectrum disorder (ASD).



Source: Created by the authors with the assistance of artificial intelligence (Gemini, 2026)
Note: The schematic illustrates the proposed interaction between the oral microbiota and the gut-brain axis, highlighting how oral microorganisms may modulate intestinal permeability and systemic inflammation, ultimately influencing brain function and behavioral manifestations in individuals with autism spectrum disorder (ASD).

Methods

Study design

This systematic review was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The complete PRISMA 2020 checklist is provided as Supplementary Material. The review was designed to address the following research question, formulated according to the Population, Interest, and Context (PICo) framework: What is the association between the oral microbiota and the gut-brain axis in autism spectrum disorder (ASD)?

Search strategy and information sources

The literature search was independently conducted by three reviewers, who performed the searches without prior communication regarding the retrieved studies. To maximize the sensitivity and comprehensiveness of the search, a strategy based on Boolean operators was employed. Different terms and synonyms were combined using the operators AND and OR to broaden or refine the search according to the study objective. The final search strategy was as follows: ("oral microbiota" OR "gut microbiota" OR "oral microbiome") AND "autism

spectrum disorder" AND "gut-brain axis".

Eligibility criteria and study selection

Studies published in English between 2015 and 2025 were eligible if they investigated the association between the oral microbiota (saliva, dental plaque, or oral mucosal swab), autism spectrum disorder (ASD), and the gut-brain axis in human participants. Studies exclusively evaluating the gut microbiota without assessing the oral microbiota were excluded. Studies that did not investigate the relationship between the oral microbiota and ASD or mechanisms related to the gut-brain axis were also excluded. The screening process, including title and abstract screening followed by full-text assessment, was managed using the Rayyan QCRI platform. No disagreements were identified among the three independent reviewers during the study selection process.

Data extraction and outcome assessment

Data were extracted using a standardized form that included the following information: first author, year of publication, study design, oral sampling site, and main biological outcomes. The primary outcomes comprised the taxonomic characterization of the oral microbiota in individuals with ASD, including alpha diversity, beta diversity, and the relative abundance of bacterial phyla, genera, and species. Secondary outcomes included associations between oral microbial profiles and clinical characteristics, behavioral measures, and biomarkers related to the gut-brain axis.

Methodological quality assessment and risk of bias

Methodological quality was independently assessed by three reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Tools, according to the study design. Analytical cross-sectional studies were evaluated using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies (Table 1), which comprises eight domains addressing sample definition, participant description, exposure measurement, objective assessment of the condition, identification and management of confounding factors, outcome measurement, and statistical analysis. Case-control studies were assessed using the JBI Critical Appraisal Checklist for Case-Control Studies (Table 2), consisting of ten domains evaluating group comparability, matching procedures, exposure measurement, identification and control of confounding factors, outcome assessment, exposure period, and statistical analysis. Each study was assessed using the checklist appropriate for its methodological design. The appraisal items were rated as "Yes," "No," "Unclear," or "Not applicable," according to JBI recommendations. Complete agreement was achieved among the three reviewers throughout the quality assessment process. Overall, the included studies demonstrated satisfactory

methodological quality, fulfilling most of the criteria established by the JBI appraisal tools. The main methodological limitations were related to the identification and control of potential confounding factors in some observational studies. Despite these limitations, all studies were considered methodologically adequate and were included in the qualitative synthesis.

Table 1: Methodological quality assessment of analytical cross-sectional studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies.

Author / Title	2	3	4	5	6	7	8	9
Hicks et al., 2018 miRNA salivar	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tong et al. (2022)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Berbé et al., 2024	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Lewandowska-Pietruszka et al. (2025)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Note: Column numbers correspond to the criteria of the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies: (2) inclusion criteria; (3) description of study participants and setting; (4) valid and reliable measurement of exposure; (5) use of objective and standardized criteria for condition assessment; (6) identification of confounding factors; (7) strategies to address confounding factors; (8) valid and reliable outcome measurement; and (9) appropriate statistical analysis. Abbreviations: Yes, criterion met; No, criterion not met; N/A, not applicable.

Table 2. Methodological quality assessment of case-control studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case-Control Studies.

Author/ Title	2	3	4	5	6	7	8	9	10	11
Qiao et al., 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Hicks et al., 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Kong et al., 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhang &	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes

Author/ Title	2	3	4	5	6	7	8	9	10	11
Qiao et al., 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Zhang, 2022										
Tang et al., 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Manghi et al., 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Evenepoel et al., 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhong et al., 2025	Yes	Yes	Yes	Yes	Yes	Not	Yes	Yes	Yes	Yes
Meng et al., 2025	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Note: Column numbers correspond to the criteria of the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case-Control Studies: (2) comparability between groups; (3) appropriate matching of cases and controls; (4) use of the same criteria for the identification of cases and controls; (5) valid and reliable measurement of exposure; (6) exposure measured in a standard, valid, and reliable way for both cases and controls; (7) identification of confounding factors; (8) strategies to address confounding factors; (9) valid and reliable outcome assessment; (10) sufficient exposure period; and (11) appropriate statistical analysis. Abbreviations: Yes, criterion met; No, criterion not met; N/A, not applicable.

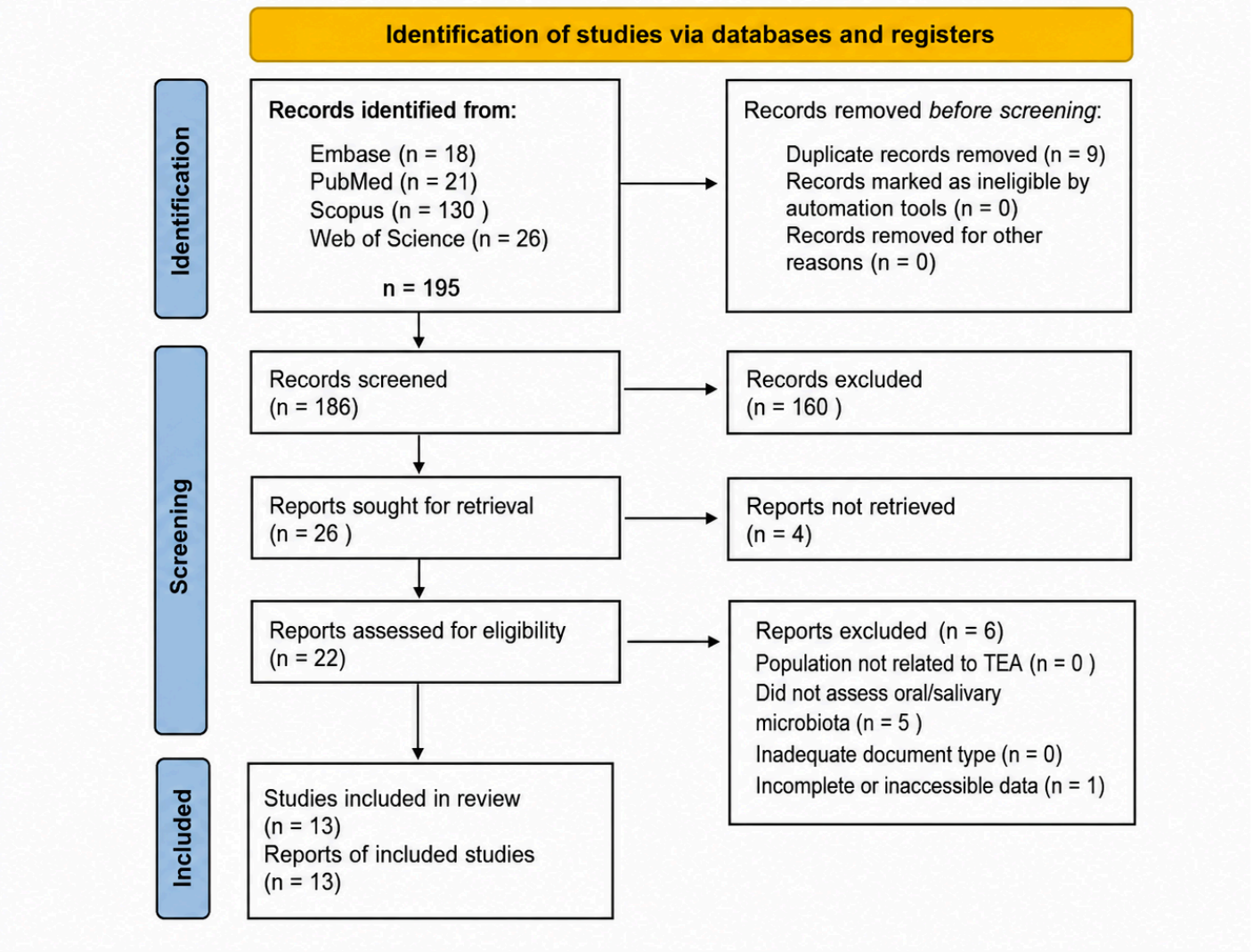
Results

Study selection

The comprehensive search of Embase, PubMed, Scopus, and Web of Science identified 194 potentially relevant records. After the removal of nine duplicates, 185 unique records were screened by title and abstract using the Rayyan software, with full agreement among the reviewers. Of these, 160 records were excluded for not meeting the eligibility criteria, leaving 25 articles for full-text assessment. During the full-text review, 12 studies were excluded, primarily because they did not investigate the relationship between the oral microbiota and the gut-brain axis in the context of autism spectrum disorder (ASD) or because the full text was not accessible. Ultimately, 13 studies met all eligibility criteria and were included in the qualitative synthesis (Figure 2). The limited number of eligible studies reflects the specificity of the research topic, the methodological heterogeneity among the available studies, and the

still limited body of evidence regarding the relationship between the oral microbiota and the gut-brain axis in ASD.

Figure 2: PRISMA 2020 flow diagram of the study selection process.



Source: Adapted from the PRISMA 2020 flow diagram template, available at the PRISMA Statement website (https://www.prisma-statement.org).

Characteristics of the included studies and main findings

The characteristics and main findings of the 13 studies included in this systematic review are summarized in Table 3. The studies investigated the relationship between the oral microbiota and autism spectrum disorder (ASD), with some also exploring its interaction with the gut-brain axis. Most were observational case-control studies conducted primarily in children diagnosed with ASD. The biological samples analyzed included saliva, dental biofilm, and oral swabs. The most commonly used analytical method was 16S rRNA gene sequencing, although shotgun metagenomics, metatranscriptomics, and bioinformatic analyses were also employed.Overall, the included studies consistently demonstrated

alterations in the composition and diversity of the oral microbiota in individuals with ASD compared with neurotypical controls, indicating a dysbiotic microbial profile associated with the disorder. Several studies also reported changes in metabolic pathways, inflammatory processes, immune responses, and neurotransmitter metabolism, suggesting that the oral microbiota may contribute to mechanisms involved in the gut-brain axis. Furthermore, some studies identified shared dysbiotic profiles between the oral and gut microbiota, supporting the existence of interactions between these two microbial ecosystems. The most frequently reported bacterial phyla were *Firmicutes, Bacteroidota, Proteobacteria, Actinobacteriota, and Fusobacteriota, with recurrent alterations in the genera Streptococcus, Prevotella, Veillonella, Neisseria, Haemophilus, Rothia, Gemella, Porphyromonas, and Fusobacterium.* Although differences in the relative abundance of these microorganisms were observed across studies, all studies reported associations between oral microbiota alterations and clinical, cognitive, behavioral, or physiological outcomes related to ASD. None of the included studies investigated the oral microbiota as an isolated biological system, independently of systemic or disease-related mechanisms.

Table 3: Characteristics of the included studies and the main findings regarding the oral microbiota and the gut-brain axis in autism spectrum disorder (ASD).

Author (Year)	**Population (N)**	**Objective**	**Methodology**	**Main findings**
Hicks et al. (2018)	346 children (180 ASD, 60 DD, and 106 controls)	To evaluate the oral microbiota in children with ASD.	Saliva; metatranscriptomic analysis (shotgun RNA sequencing).	Alterations in the oral microbiota and metabolic pathways; high diagnostic accuracy for distinguishing ASD from controls.
Qiao et al. (2018)	32 children with ASD and 27 controls (N = 59)	To compare the oral microbiota between children with ASD and healthy controls.	16S rRNA gene sequencing of saliva and dental plaque.	Oral dysbiosis characterized by reduced bacterial diversity and alterations in bacterial genera associated with ASD.

Hicks et al. (2018)	120 saliva samples; validation cohort of 140 children with ASD (77 with sleep disorders and 63 without)	To investigate circadian oscillations of salivary miRNAs and microbial transcription and their association with health and disease.	Next-generation sequencing (NGS), salivary miRNA profiling, and microbial RNA sequencing at different time points.	Circadian patterns of salivary RNAs were identified.
Kong et al. (2019)	114 participants (children with ASD and their first-degree relatives)	To compare the oral and gut microbiota in ASD.	16S rRNA gene sequencing of saliva and fecal samples.	Alterations in both the oral and gut microbiota were associated with ASD.
Tong et al. (2022)	52 participants (26 ASD and 26 matched neurotypical controls)	To characterize the oral phageome in ASD.	Shotgun metagenomic sequencing of dental plaque and fecal samples.	Reduced viral diversity and increased bacteriophage abundance in individuals with ASD.
Zhang & Zhang (2022)	20 children (10 ASD and 10 controls), aged 2–6 years	To compare the salivary microbiota of children with ASD and healthy controls.	Salivary 16S rRNA gene sequencing and correlation analysis with the gut microbiota.	Fourteen different bacterial taxa were identified; *Bacteroides fragilis* was suggested as a potential biomarker.
Manghi et al. (2024)	7,812 participants (2,154 children with ASD, siblings, and parents)	To investigate oral microbiota biomarkers associated with ASD.	Shotgun metagenomic sequencing of saliva samples.	The oral microbiota discriminated against individuals with ASD and was associated with cognitive impairment.

Tang et al. (2024)	55 children (25 ASD and 30 controls)	To identify oral microbiota biomarkers for ASD.	Dental plaque; 16S rRNA gene sequencing.	Reduced bacterial diversity and six microbial biomarkers with high diagnostic performance.
Berbé et al. (2024)	30 adults with ASD	To evaluate periodontal disease and the oral microbiota in adults with ASD.	Cross-sectional study with periodontal examination and microbiological analysis by PCR/qPCR.	Periodontal disease was observed in 86.7% of participants, with a high prevalence of periodontal pathogens, indicating alterations in the oral microbiota.
Evenepoel et al. (2024)	120 children (80 ASD and 40 controls), aged 8–12 years	To evaluate the association between the oral microbiota and ASD symptoms.	Oral microbiome sequencing and statistical analyses.	Higher abundance of *Solobacterium*, *Tannerella*, and other taxa associated with ASD symptoms.
Lewandowska-Pietr uszka et al., 2025	45 children with ASD, aged 2–18 years	To evaluate the relationship between the oral microbiota, behavior, gastrointestinal symptoms, and cortisol levels.	Cross-sectional study; 16S rRNA gene sequencing and salivary cortisol analysis.	Pro-inflammatory taxa were associated with poorer functional outcomes, whereas greater microbial diversity was associated with better adaptation.
Meng et al. (2025)	64 children (30 ASD and 34 controls)	To evaluate the oral microbiota and the influence of dental caries in ASD.	Saliva and dental plaque; 16S rRNA gene sequencing	Reduced microbial diversity and alterations in bacterial composition

				associated with ASD.
Zhong et al. (2025)	100 participants (54 ASD and 46 controls)	To investigate oral microbiota and oxidative stress in ASD.	Salivary 16S rDNA sequencing.	Oral dysbiosis associated with increased oxidative stress.

Source: Prepared by the authors (2026).
Note: This table summarizes the findings of the selected studies regarding the correlation between oral microbiota dysbiosis and alterations in the gut-brain axis. The main outcomes include systemic inflammatory biomarkers, levels of oral microbial metabolites, and their potential influence on intestinal permeability and behavioral phenotypes observed in individuals with autism spectrum disorder (ASD).

Discussion

For many years, the relationship between the microbiota and Autism Spectrum Disorder (ASD) has attracted increasing interest due to evidence that microorganisms colonizing the human body play essential roles in regulating immune responses, metabolism, and communication between the gut and the central nervous system. Initially, investigations focused almost exclusively on the gut microbiota, mainly because individuals with ASD have a high prevalence of gastrointestinal symptoms, including constipation, diarrhea, and abdominal pain. However, more recent studies have demonstrated that the oral microbiota also exhibits important alterations in this population, expanding the understanding of the role of the oral cavity in the gut–brain axis. As the entry point of the gastrointestinal tract and the site harboring the second most complex microbial community in the human body, the oral cavity represents an important reservoir of microorganisms capable of influencing both the intestinal microbiota and systemic immune and metabolic processes (Kong et al., 2019; Tong et al., 2022; Lewandowska-Pietruszka et al., 2025).

The included studies showed differences regarding the evaluated populations and the methodologies employed, although they presented similar findings regarding the presence of oral dysbiosis in individuals with ASD. Among the 13 studies analyzed, 11 were conducted in children, one evaluated adults, and one included participants aged between 2 and 18 years, demonstrating the predominance of research focused on pediatric populations. Regarding methodological approaches, 16S rRNA gene sequencing was the most frequently used technique, being applied in seven studies, followed by shotgun metagenomics or metatranscriptomics in three investigations. Saliva was the most commonly used biological sample, whereas dental plaque and fecal samples were also analyzed to investigate the relationship between the oral microbiota and the gut–brain axis.

Despite methodological differences, the studies included in this review demonstrated reduced microbial diversity and alterations in the composition of the oral microbiota in individuals with ASD. Meng et al. (2025) observed a predominance of the phyla Bacillota and Actinomycetota and the genera *Streptococcus* and *Porphyromonas*, while also demonstrating that dental caries significantly influences the composition of the oral microbiota. Similarly, Tang et al. (2024) identified reduced bacterial diversity and species with potential value as biomarkers for ASD. Furthermore, Evenepoel et al. (2024) and Lewandowska-Pietruszka et al. (2025) associated alterations in the oral microbiota with the severity of clinical and gastrointestinal symptoms, whereas Zhong et al. (2025) demonstrated a relationship between oral dysbiosis and increased oxidative stress. Collectively, these findings reinforce the involvement of the oral microbiota and the gut–brain axis in the pathophysiology of ASD and highlight their potential as sources of biomarkers for the disorder.

The studies identified in this review further support this perspective by demonstrating that microbial alterations observed in ASD are not restricted to the intestine but involve the entire digestive tract. Kong et al. (2019), by simultaneously evaluating saliva and fecal samples, identified significant differences in the composition of the oral and intestinal microbiota of children with ASD compared with controls, suggesting that both ecosystems undergo concurrent alterations. These findings highlight that the oral microbiota may represent an important component of the gut–brain axis, participating in bidirectional communication between the oral cavity, the intestine, and the central nervous system. Similarly, Tong et al. (2022) demonstrated that alterations in the oral phageome, characterized by reduced viral diversity and increased abundance of specific bacteriophages, are also associated with ASD, indicating that not only bacteria but the entire oral microbial community may contribute to this process. Taken together, these results suggest that dysbiosis observed in ASD involves complex modifications in microbial ecology, encompassing different microorganisms and their functional interactions.

Another important aspect highlighted by the included studies is the reduction in microbial diversity, which is considered one of the main indicators of dysbiosis. Qiao et al. (2018), Hicks et al. (2018), Zhang and Zhang (2022), Tang et al. (2024), and Meng et al. (2025) reported lower bacterial diversity in individuals with ASD compared with neurotypical controls, despite using different sample types and sequencing approaches. Under physiological conditions, high microbial diversity contributes to the stability of the bacterial community, limits the colonization of potentially pathogenic microorganisms, and supports the balance of metabolic and immune functions. Therefore, reduced microbial diversity may

compromise microbiota homeostasis, promoting inflammatory processes, metabolic alterations, and changes in the interactions among different microorganisms inhabiting the oral cavity.

Although decreased bacterial diversity was one of the most consistent findings in this review, the available evidence indicates that the main aspect associated with ASD does not appear to be the presence or absence of a single specific bacterium, but rather the overall imbalance of the microbial community. Tang et al. (2024), for instance, identified significant differences in the composition of the oral microbiota of young children with ASD, as well as six bacterial species, including *Microbacterium flavescens*, *Prevotella jejuni*, and *Porphyromonas* sp. HMT-278, which demonstrated discriminatory potential for distinguishing individuals with ASD from controls. The authors suggested that these alterations in the oral microbiota may contribute to ASD pathophysiology through mechanisms involving inflammation, immune dysregulation, and alterations in the gut–brain axis, although causal relationships remain to be fully established. Similarly, Hicks et al. (2018) demonstrated that changes in the functional activity of the oral microbiota are associated with alterations in metabolic pathways related to energy metabolism and lysine degradation, suggesting that the impact of dysbiosis depends not only on the taxonomic composition of the bacterial community but also on its metabolic activity.

The analysis of the included studies also revealed recurrent alterations in the taxonomic composition of the oral microbiota of individuals with ASD. The main microorganisms identified belonged to the phyla Bacillota (formerly Firmicutes), Bacteroidota, Proteobacteria, Actinomycetota (formerly Actinobacteriota), and Fusobacteriota, as well as frequent modifications in genera such as *Streptococcus*, *Prevotella*, *Veillonella*, *Neisseria*, *Haemophilus*, *Rothia*, *Gemella*, *Porphyromonas*, and *Fusobacterium*. However, the findings suggest that the impact of these alterations does not result from the increased or decreased abundance of a single bacterial phylum, but rather from an imbalance of the microbial community as a whole. This observation is consistent with the findings of Kong et al. (2019), Zhang and Zhang (2022), Tang et al. (2024), and Meng et al. (2025), who demonstrated relevant differences in the oral microbiota composition between individuals with ASD and neurotypical controls, accompanied by reduced bacterial diversity and changes in the relative abundance of different taxa.

Among the identified phyla, Bacillota (Firmicutes) stood out because it includes several genera frequently reported in the analyzed studies, including *Streptococcus*, *Veillonella*, and *Gemella*. Meng et al. (2025) observed that Bacillota remained among the

predominant phyla in both saliva and dental plaque samples from children with ASD, whereas Tang et al. (2024) identified significant alterations in the abundance of species belonging to this group compared with controls. Similar results were reported by Qiao et al. (2018), who observed increased abundance of *Haemophilus* in saliva and *Streptococcus* in dental plaque from children with ASD, while Zhang and Zhang (2022) reported differences involving *Bacteroides fragilis* and other microorganisms potentially associated with ASD. Collectively, these findings suggest that different bacterial groups may act in an integrated manner, influencing oral microbiota stability and contributing to metabolic and immune alterations observed in the disorder.

These findings indicate that among the bacterial phyla reported in the included studies, Bacillota was one of the most frequently identified groups. Meng et al. (2025), for example, identified Bacillota and Actinomycetota as predominant phyla in the oral microbiota of children with ASD, while Kong et al. (2019) also observed alterations in oral microbiota composition consistent with an imbalance involving this phylum. These results suggest that modifications in Bacillota may reflect disturbances in oral microbiota equilibrium, as many representatives of this group participate in carbohydrate fermentation, bacterial metabolite production, and maintenance of microbial homeostasis. Therefore, alterations in this phylum may affect the metabolic activity of the bacterial community and influence processes related to inflammation, metabolism, and microbiota–host communication, contributing to the oral–gut–brain axis.

Alterations in Bacteroidota (formerly Bacteroidetes) were also observed across different studies, mainly through changes in genera such as *Prevotella* and *Porphyromonas*. Tang et al. (2024) identified increased abundance of *Prevotella jejuni* and *Porphyromonas* sp. HMT-278 in children with ASD compared with controls, whereas Meng et al. (2025) reported higher abundance of *Porphyromonas* in individuals with ASD. These microorganisms play important roles in the organization of oral biofilms and participate in protein and carbohydrate metabolism. Changes in their abundance may reflect alterations in oral microbial balance and promote local inflammatory conditions, contributing to the disruption of microbial community organization observed in ASD.

Another recurrent finding was the involvement of bacteria belonging to the phylum Proteobacteria, mainly represented by the genus *Haemophilus*. Tang et al. (2024) highlighted that metabolites produced by *Haemophilus parainfluenzae* may, under certain conditions, reach the central nervous system following alterations in blood–brain barrier integrity, potentially contributing to neuroinflammatory processes. Although this mechanism still

requires clinical confirmation, the authors suggested that the interaction between oral bacteria, the immune system, and the gut–brain axis represents one of the possible pathways through which the microbiota may influence ASD pathophysiology.

Similarly, alterations in Actinomycetota and Fusobacteriota were identified in different studies, although less frequently. Meng et al. (2025) observed Actinomycetota among the predominant phyla in the oral microbiota, whereas Tang et al. (2024) reported differences in the abundance of species belonging to the genera *Actinomyces* and *Fusobacterium* between individuals with ASD and controls. Although the specific mechanisms associated with these microbial groups remain poorly understood, their involvement emphasizes that dysbiosis observed in ASD comprises changes in multiple components of the microbial community rather than alterations restricted to a single bacterial group.

The findings of this review indicate that the main characteristic of the oral microbiota in ASD is not the isolated increase or decrease of a specific bacterial phylum or genus, but rather the presence of dysbiosis characterized by reduced microbial diversity and reorganization of the bacterial community. This pattern has been observed across different studies, regardless of the evaluated population or methodology employed, suggesting that disruption of oral microbiota balance represents one of the most consistent findings associated with ASD. Reduced diversity may favor the predominance of certain microorganisms and the loss of others, decreasing microbial community stability and impairing important functions, such as resistance to pathogen colonization, metabolite production, and immune response modulation. Consequently, this microbial reorganization may promote inflammatory processes and alter communication between the oral microbiota and the host, reinforcing the potential role of oral microbiota alterations, directly or indirectly, in the mechanisms involved in the oral–gut–brain axis.

In addition to the taxonomic alterations observed in the oral microbiota, the studies included in this review suggest that the clinical relevance of dysbiosis is mainly associated with the functional consequences of these microbial changes on the oral–gut–brain axis. Although a causal relationship between microbial alterations and ASD development cannot yet be established, several authors have proposed that dysbiosis may modify metabolic, immunological, and neurochemical pathways capable of influencing the pathophysiology of the disorder (Hicks et al., 2018; Lewandowska-Pietruszka et al., 2025). Lewandowska-Pietruszka et al. (2025) emphasized that microbiota disruption may impair the production of bacterial metabolites, particularly short-chain fatty acids (SCFAs), which are essential molecules for maintaining intestinal homeostasis and communication between the

gut and the central nervous system. Among these metabolites, butyrate plays an important role in maintaining intestinal barrier integrity and modulating inflammatory responses, whereas alterations in propionate production have been associated with activation of inflammatory pathways and modulation of neuronal activity. Changes in microbiota composition may alter the availability of these metabolites, promoting immunological and neurological alterations potentially involved in ASD pathophysiology.

Another mechanism discussed by the authors involves increased intestinal permeability, commonly described as “leaky gut.” Disruption of intestinal barrier integrity may facilitate the translocation of bacterial components and metabolites into systemic circulation, stimulating immune responses and the release of pro-inflammatory cytokines. According to Lewandowska-Pietruszka et al. (2025), this process may contribute to a persistent inflammatory state capable of influencing the central nervous system through the oral–gut–brain axis, potentially affecting synaptic plasticity, neurogenesis, and neuronal communication.

The included studies also suggest that the microbiota may interfere with the production and metabolism of neurotransmitters involved in behavioral regulation. Hicks et al. (2018) demonstrated that functional alterations in the oral microbiota were associated with metabolic pathways related to energy metabolism and amino acid degradation, whereas Lewandowska-Pietruszka et al. (2025) highlighted that microbiota modifications may influence tryptophan metabolism and consequently serotonin synthesis, in addition to affecting pathways related to gamma-aminobutyric acid (GABA) and dopamine. Although these mechanisms require further confirmation through clinical studies, they provide a biologically plausible explanation for the association between dysbiosis and behavioral alterations observed in ASD.

Tang et al. (2024) reinforce the discussion that specific oral bacteria may influence neuroimmune processes. The authors highlighted that metabolites produced by *Haemophilus parainfluenzae* may reach the central nervous system when the integrity of the blood–brain barrier is compromised, potentially contributing to neuroinflammatory alterations. Furthermore, they reported experimental evidence showing that the transfer of oral microbiota from individuals with ASD to animal models was able to induce deficits in social interaction and increased repetitive behaviors, accompanied by changes in the expression of serotonin-related genes. Although these findings cannot be directly extrapolated to humans, they strengthen the hypothesis that the oral microbiota may participate in communication between the immune system, the gut, and the brain.

This interpretation is also supported by studies evaluating the association between microbiota alterations and clinical manifestations of ASD. Qiao et al. (2018) observed that bacteria from genera such as *Haemophilus*, *Streptococcus*, and *Rothia* were correlated with ASD clinical severity and oral health indicators, suggesting that alterations in the oral microbiota may reflect clinically relevant aspects of the disorder. Zhong et al. (2025) reported that individuals with higher abundance of inflammation-associated taxa exhibited increased oxidative stress, whereas Evenepoel et al. (2024) identified associations between specific bacterial genera and greater severity of behavioral symptoms. Similarly, Meng et al. (2025) demonstrated that genera such as *Streptococcus* and *Porphyromonas* remained associated with ASD even after considering the influence of dental caries on oral microbiota composition. These findings suggest that microbial alterations may not only characterize ASD but may also be related to the intensity of clinical manifestations observed in some individuals.

It is important to emphasize that current evidence does not allow the conclusion that a single bacterial phylum, genus, or species is responsible for ASD development. Instead, the analyzed studies indicate that the main phenomenon observed is the loss of microbial diversity and the functional reorganization of the bacterial community. Therefore, dysbiosis should be understood as a multifactorial process resulting from the interaction among genetic, immunological, environmental, behavioral, and metabolic factors, capable of modifying communication along the oral–gut–brain axis.

Another relevant aspect identified in this review concerns the potential of the oral microbiota as a source of biomarkers for ASD. Unlike current diagnostic approaches, which are predominantly based on clinical and behavioral assessments, several studies suggest that specific oral microbiota profiles may contribute to early identification of the disorder. Hicks et al. (2018), Tang et al. (2024), and Manghi et al. (2024) demonstrated that distinct microbial profiles were able to differentiate individuals with ASD from controls with high diagnostic performance. Tang et al. (2024), for example, identified species such as *Microbacterium flavescens*, *Prevotella jejuni*, and *Porphyromonas* sp. HMT-278, among others, and developed a classification model with high accuracy for distinguishing children with ASD from neurotypical children. Similarly, Manghi et al. (2024), using a large cohort comprising more than seven thousand participants, observed that oral microbiota profiles showed potential for identifying individuals with ASD and were associated with cognitive impairment. Comparable results were reported by Qiao et al. (2018), who developed a diagnostic model based on bacterial genera such as *Haemophilus*, *Streptococcus*, and *Rothia*, achieving 96.3% accuracy in distinguishing children with ASD from neurotypical controls.

Despite the promising results, there is still no universal microbiological profile capable of characterizing ASD. The differences observed among studies likely reflect the influence of factors such as age, dietary habits, oral hygiene, medication use, geographic location, sample collection procedures, and sequencing techniques employed (Qiao et al., 2018; Kong et al., 2019; Evenepoel et al., 2024; Meng et al., 2025). In addition, the clinical heterogeneity of ASD itself may contribute to the variability of microbiological findings, making it difficult to identify a single set of biomarkers applicable to different populations (Manghi et al., 2024; Lewandowska-Pietruszka et al., 2025; Zhong et al., 2025). Although the oral microbiota represents a promising strategy to support early diagnosis, its clinical application still depends on multicenter studies using standardized methodologies and external validation of the identified biomarkers (Hicks et al., 2018; Tang et al., 2024; Manghi et al., 2024).

Another important aspect highlighted by this review concerns the influence of oral health conditions on the composition of the oral microbiota. Berbé et al. (2024) observed a high frequency of periodontal disease in adults with ASD, accompanied by a higher prevalence of periodontopathogens, such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*, indicating that inflammatory alterations in the oral cavity may significantly modify microbiome composition. Similarly, Meng et al. (2025) demonstrated that the presence of dental caries also influences oral microbiota diversity and composition, identifying differences between children with ASD with and without carious lesions. The authors found that genera such as *Streptococcus* and *Porphyromonas* were associated with both caries development and ASD, emphasizing the importance of controlling this factor in studies investigating microbiological biomarkers.

Children and adults with ASD frequently experience difficulties related to oral hygiene, food selectivity, sensory hypersensitivity, and continuous medication use, conditions that may favor the development of oral diseases and consequently alter the oral microbiota (Berbé et al., 2024; Evenepoel et al., 2024; Lewandowska-Pietruszka et al., 2025; Meng et al., 2025). Therefore, some of the microbial alterations observed may reflect not only mechanisms related to the disorder itself but also clinical and behavioral characteristics inherent to this population. This aspect reinforces the need to consider potential confounding factors when interpreting current findings and designing future investigations (Evenepoel et al., 2024; Meng et al., 2025).

Despite the substantial growth in investigations regarding oral microbiota and ASD, this review identified important limitations in the available literature. Most studies presented a

cross-sectional design, preventing the establishment of causal relationships between dysbiosis and disorder development. Furthermore, differences were observed regarding sample size, participants' age range, diagnostic criteria, type of biological sample analyzed (saliva, dental plaque, or oral biofilm), sequencing techniques, and bioinformatic analysis methods. These methodological differences limit direct comparisons among studies and may explain part of the heterogeneity observed in the reported results.

Another important limitation concerns the limited number of studies that simultaneously investigated clinical, behavioral, gastrointestinal, and microbiological factors. Although some authors have identified associations between microbiota alterations and greater ASD symptom severity, it remains unclear whether dysbiosis represents a contributing factor in the pathophysiology of the disorder or a consequence of the behavioral, dietary, and systemic characteristics of these individuals. Longitudinal studies, with follow-up from early childhood, may help clarify this temporal relationship and identify potential mechanisms involved in the interaction between oral microbiota, intestinal microbiota, and neurodevelopment, collectively referred to as the oral–gut–brain axis.

CONCLUSION

Overall, this review demonstrates that the oral microbiota and the gut–brain axis are closely interconnected and should be understood through an integrated perspective. Although many questions remain to be elucidated, the analyzed studies indicate that microbial alterations may influence immunological, metabolic, and neurological processes associated with ASD. Further investigation in this field may contribute to the development of more reliable biomarkers and complementary therapeutic strategies, expanding the possibilities for early diagnosis and personalized care for individuals with ASD.

Declaration on the Use of Artificial Intelligence

During the preparation of this manuscript, Google Gemini was used exclusively to assist with spelling and grammar revision and the organization of the reference list. The tool was not used to generate research hypotheses, design the study, select studies, extract data, analyze results, interpret the evidence, or draft the scientific content. The authors critically reviewed all outputs generated with the assistance of the tool and assume full responsibility for the accuracy, integrity, and content of this manuscript.

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Author Contributions

WRSJ: Conceptualization, Methodology, Literature search, Study selection and analysis, Data curation, Writing – original draft, Visualization.

MFM: Conceptualization, Methodology, Data analysis, Validation, Writing – review and editing.

JCG: Methodology, Data analysis, Validation, Critical revision of the manuscript, Writing – review and editing.

NEAS: Study selection support, Writing – review and editing.

APC: Supervision, Scientific guidance, Validation, Writing – review and editing.

Data Availability Statement: All data supporting the findings of this study are included in the manuscript. If additional information or supporting data are required, or if verification of any reported data is needed, they are available from the corresponding author upon reasonable request.

Ethics Statement: Not applicable. This study constitutes a systematic review based on secondary data previously published and publicly available in scientific databases. No direct interventions involving human participants or animal models were performed by the authors. Therefore, formal approval by an institutional research ethics committee and informed consent were not required.

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