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REVIEW ARTICLE

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Clinical studies on the interrelationship between gut microbiota and oral health for systemic homeostasis: a systematic review

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Abstract

Introduction: The oral microbiota has shown important actions in the physical and mental health of human beings. Oral diseases related to oral dysbiosis are studied, as well as systemic degenerative inflammatory diseases. Objective: It was to present and discuss the main considerations and results of clinical studies on the interrelationship between gut microbiota and oral health for systemic homeostasis. Methods: The PRISMA Guidelines were followed. The search was conducted from January to February 2026 across the Web of Science, Scopus, Embase, PubMed, ScienceDirect, SciELO, and Google Scholar databases. The quality of the studies was assessed using the GRADE instrument, and the risk of bias was evaluated according to the Cochrane instrument. Results and Conclusion: According to the GRADE instrument, most studies presented homogeneous results, with X2=67.5% > 50%. A total of 112 articles were found and submitted for eligibility analysis, with 18 final studies selected to compose the results of this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 35 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2 standards. It was concluded that there are distinct causal relationships between the microbiota and acute and chronic gingivitis. Oral microbiota dysbiosis not only induces local inflammation and exacerbates inflammation associated with metabolic diseases, but can also trigger systemic inflammation, leading to metabolic and neuropsychiatric disorders. Clinical studies have shown the effectiveness of anti-inflammatory treatments of the gut and oral microbiota in reducing periodontal disease and cognitive decline. The integration of advanced microbiome analysis and neuroimaging techniques may help to elucidate the mechanisms linking gut health, systemic inflammation, and cognitive function.

Keywords: Oral microbiota. Oral diseases. Oral dysbiosis. Gut microbiota. Diseases.

Introduction

The oral microbiota has been shown to play important roles in human physical and mental health. Oral diseases related to oral dysbiosis are studied, as well as systemic degenerative inflammatory diseases. In this sense, it is necessary to understand the communication mechanisms between the oral cavity and the different mucosal compartments, and to explain how alterations in the microbial composition can modify their balance, leading to the development of diseases **[1,2]**.

In this scenario, many bacteria can induce oral dysbiosis, notably *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. Other species, such as *Tannerella forsythia, Treponema denticola, Aggregatibacter actinomycetemcomitans*, and *Filifactor alocis*, are capable of causing local and systemic diseases through the release of toxins. The bidirectional communication system between the gut

and the central nervous system (CNS) can regulate many diseases along with the oral microbiota. Qualitative and quantitative changes in microorganisms present in the main mucosal compartments can lead the host to the development of systemic inflammatory diseases [3].

Recent research has elucidated the interconnection between masticatory function, oral microbiota, and intestinal health, suggesting that alterations in chewing ability can disrupt oral microbial communities, which, in turn, affects gastrointestinal health and systemic inflammation. The consequences of impaired chewing, including malnutrition, dysbiosis, and gastrointestinal disorders in aging, are a fact, making it necessary to develop strategies to improve masticatory function and maintain a healthy gut microbiome through interventions such as dietary modifications and oral care [4]. Therefore, the present study aimed to present and discuss the main considerations and results of clinical studies on the interrelationship between gut microbiota and oral health for systemic homeostasis.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed at: 02/18/2026. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed at: 02/18/2026.

Search Strategy and Search Sources

The literature search process was carried out from January to February 2026 and developed based on Web of Science, Embase, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors were used in health sciences (DeCS/MeSH terms): *"Oral microbiota. Oral diseases. Oral dysbiosis. Gut microbiota. Diseases",* and the Boolean "and" was used between the MeSH terms and "or" between the historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

A total of 112 articles were found and submitted to eligibility analysis, with 18 final studies selected to compose the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=67.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 35 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2.

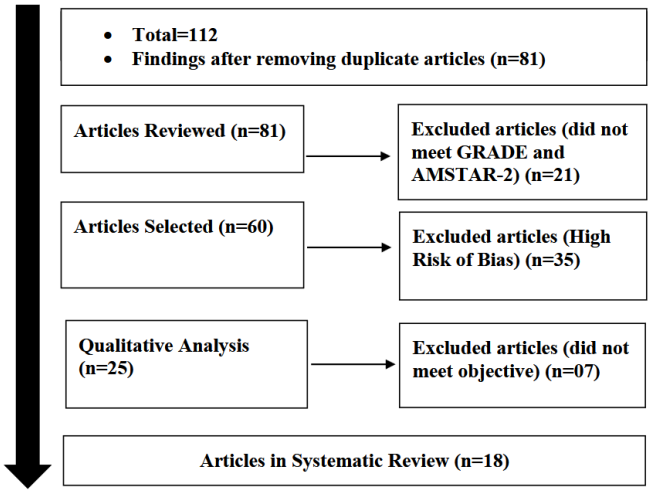

Figure 1. Flowchart showing the article selection process. Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph did not have a symmetrical behavior, suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that

are presented at the top.

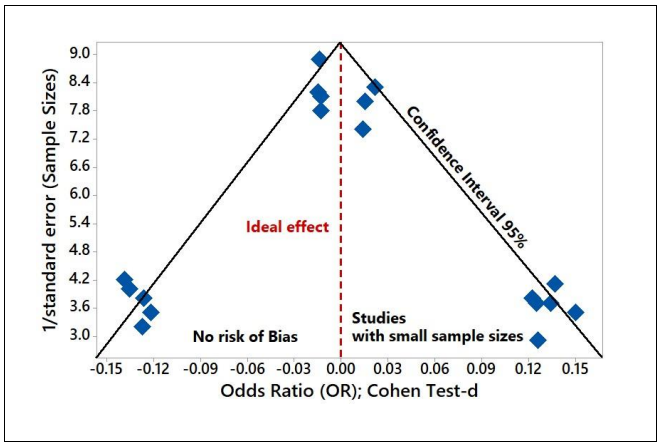

Figure 2. The non-symmetrical funnel plot suggests risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=18 studies). Source: Own Authorship.

Major Considerations and Findings

According to scientific evidence, the loss of oral microbiota homeostasis can cause chronic inflammatory oral diseases and contribute to the development of systemic diseases such as endocarditis, rheumatoid arthritis, osteoporosis, obesity, diabetes, and psychiatric and neurological disorders. Furthermore, it can contribute to several degenerative diseases, including colorectal cancer and esophageal cancer **[1,2]**.

Studies discuss the concept of an oral-gut-brain axis as an important relationship in the management of neurodegenerative and systemic diseases. Oral dysbiosis can alter the composition of the gut microbiota, damage the integrity of the intestinal barrier, and trigger systemic inflammation **[3,4]**.

Authors have shown that periodontal inflammation can lead to an increase in Klebsiella and Enterobacter **[5]**. These bacteria interact with the gut microbiota and have adapted their metabolism to grow in an inflamed intestinal environment. These interactions favor the expansion of Th17-inducing microbial consortia, thus remodeling immune-microbiota interactions, sustaining mucosal inflammation, and causing epithelial barrier dysfunction. Ectopic colonization by oral pathobionts exacerbates intestinal inflammation directly through IL-1β activation and indirectly as cognate antigens for orally sensitized effector T cells that migrate to the intestine. Oral pathogens and their molecular derivatives, such as lipopolysaccharide (LPS) and extracellular vesicles (exosomes), can translocate to the gastrointestinal tract and enter the systemic circulation, causing blood-brain barrier dysfunction, as well as microglia activation and inflammatory processes **[6-8]**.

In this respect, LPS from the oral microbiota can reach the brain directly through the vascular system. Furthermore, LPS can reach the intestine and indirectly affect brain functions, generating neurovascular changes, increased BBB permeability, neuroinflammation, and neurodegeneration **[9]**. The oral microbiota can interact with the central nervous system (CNS) not only through the vagal system but also through the trigeminal nerve, responsible for transmitting signals between the oral cavity and the brain. These signals overlap with those of the vagus nerve through the main sensory nucleus **[10]**. Neuroinflammation is strongly associated with significant cognitive and neurological decline, as well as multiple psychiatric CNS disorders, such as depression, anxiety, and bipolar disorder, in addition to Parkinson's disease, multiple sclerosis, and Alzheimer's disease **[11]**.

In the oral cavity, *Porphyromonas gingivalis* stands out, which can reach the brain via the bloodstream and release a neurotoxic protease (gingipain). This protease is directly involved in the generation of β-amyloid (Aβ) protein plaques. Animal models have shown that oral administration of *Porphyromonas gingivalis* can lead to intestinal dysbiosis and cognitive impairment **[2]**. Furthermore, *Porphyromonas gingivalis* has been shown to promote neuroinflammation and neurodegeneration through microglia activation and M1 macrophage stimulation, resulting in increased expression of IL-1β, IL-6, and TNF-α. The increase in these molecules at the central level leads to synaptic dysfunction due to the accumulation of Aβ, which is generated by the activation of the NF-κB/cathepsin B pathway. These processes can lead to dementia and progression to Alzheimer's disease **[11,12]**.

The authors Lin et al. (2025) **[13]** developed a two-sample Mendelian randomization (MR) using GWAS summary statistics from FinnGen data (149 cases of acute gingivitis, 850 cases of chronic gingivitis, and 195,395 controls) to explore the causal role of oral and intestinal microbiota. In the gut microbiota, inverse variance results showed that the class Negativicutes, Verrucomicrobiae, the genus Butyricicoccus, Eubacterium, Lactobacillus, the order Selenomonadales and Verrucomicrobiales were associated with a higher risk of acute gingivitis, while the family Peptostreptococcaceae, the genus Coprococcus2 and the genus Lachnospiraceae UCG001 were associated with a lower risk of acute gingivitis ($p<0.05$). The classes Erysipelotrichia,

Methanobacteria, Verrucomicrobiae, the families Defluviitaleaceae, Erysipelotrichaceae, Methanobacteriaceae, Verrucomicrobiaceae, the genera Akkermansia, Christensenellaceae R 7group, Defluviitaleaceae UCG011, Methanobrevibacter, the genera Paraprevotella, Senegalimassilia, the order Erysipelotrichales, Methanobacteriales, Verrucomicrobiales and the phylum Cyanobacteria were associated with a higher risk of chronic gingivitis, while the family Clostridiales vadin BB60 group, the genera Allisonella, Dorea and Lachnospiraceae UCG004 were associated with a lower risk of chronic gingivitis ($p<0.05$). In the oral microbiota, unknown species of Porphyromonas (ASV0008) and the genus Porphyromonas were associated with a higher risk of acute gingivitis ($p<0.05$). Unknown species of Neisseria (ASV0004) and Veillonella (ASV0001) were associated with a higher risk of chronic gingivitis, while the Bacilli class was associated with a lower risk of chronic gingivitis ($p<0.05$). Also, the gut-brain-oral axis is important in oral health, exploring how changes in the gut microbiota influence oral and cognitive health. It is essential to investigate the impact of probiotic supplementation and dietary modifications on the composition of the gut microbiota, systemic inflammation, and its influence on both cognitive and oral health. Exploring specific strains of the gut microbiota that regulate systemic inflammation and cognitive function may lead to targeted probiotic therapies, potentially alleviating neuroinflammation and improving cognitive performance. Furthermore, understanding the role of oral probiotics in periodontal health and their effects on the gut microbiota and systemic inflammation may contribute to the development of innovative treatment approaches **[14]**.

Moreover, oral microbiota dysbiosis not only induces local inflammation but can also trigger systemic inflammation, leading to metabolic and neuropsychiatric diseases. Although the main evidence indicates that oral microbiota dysbiosis induces changes in the gut microbiota, which exacerbate inflammation associated with metabolic diseases (obesity, dyslipidemia, diabetes, non-alcoholic fatty liver disease, and insulin resistance), other studies have revealed the contribution of the oral microbiota-brain axis in the pathogenesis of neuropsychiatric diseases. Dysbiosis of the gut microbiota and inflammation also induce epigenetic changes in cytokine genes, such as IL-1β, IL-6, TNF-α, NF-κB, BTLA, IL-18R1, TGF-β, PI3K/Akt1, Ctnnb1, and Hsp90aa1, as well as in DNMTs, HDACs, and DAT1, associated with the development and progression of metabolic disorders and/or neurodegenerative diseases. Therefore, the epigenome can serve as a target for preventive or therapeutic interventions **[15]**.

The authors Clasen et al. (2025) **[16]** generated 228 metagenomic samples from random sequencing of the gut and oral microbiomes of patients with Parkinson's disease (PD) with mild cognitive impairment (MCI-PD) or dementia (DCI), and from a healthy control group, to investigate the role of gut and oral microbiomes in cognitive impairment in patients with PD. In addition to revealing compositional and functional signatures, the role of pathobionts and dysregulated metabolic pathways of the oral and intestinal microbiome in DP-DCL and DPD, the importance of oral-intestinal translocation in increasing the abundance of virulence factors in DP and DCL was also revealed. Oral-intestinal virulence was further integrated into salivary metaproteomics and demonstrated its potential role in host immunity dysfunction and brain endothelial cells.

Finally, Fusobacterium functions both as a commensal and as a pathogen, connecting the oral-intestinal axis to various diseases, including cancer. Evidence shows that it modulates microbial balance, promotes dysbiosis, and contributes to carcinogenesis by driving inflammation, proliferation, invasion, and immune evasion **[17,18]**.

Conclusion

It was concluded that there are distinct causal relationships between the microbiota and acute and chronic gingivitis. Oral microbiota dysbiosis not only induces local inflammation and exacerbates inflammation associated with metabolic diseases, but can also trigger systemic inflammation, leading to metabolic and neuropsychiatric disorders. Clinical studies have shown the effectiveness of anti-inflammatory treatments of the gut and oral microbiota in reducing periodontal disease and cognitive decline. The integration of advanced microbiome analysis and neuroimaging techniques may help to elucidate the mechanisms linking gut health, systemic inflammation, and cognitive function.

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