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Review article

Interconnections of Oral Microbiota and Systemic Health: Insights from Recent Research on Periodontal Diseases

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Abstract

This review explores the intricate relationships between oral microbiota, periodontal diseases, and systemic health. Recent studies have revealed that alterations in the oral microbiome can significantly impact systemic conditions such as cardiovascular disease, diabetes, and rheumatoid arthritis. Pathogens such as *Porphyromonas gingivalis* and *Tannerella forsythia* are frequently implicated in these associations, contributing to systemic inflammation and disease progression. The review also examines how behavioral factors, particularly smoking and dietary habits, influence the composition of the oral microbiome and exacerbate periodontal conditions. Technological advancements in diagnostic methods, including multiplex real-time PCR and next-generation sequencing, have enhanced our understanding of microbial dysbiosis and its implications for disease severity. Furthermore, innovative therapeutic strategies such as Oral Microbial Transplantation (OMT) are being investigated to improve oral health outcomes. By elucidating these complex interactions, this review aims to inform healthcare professionals on effective strategies for the prevention and management of both periodontal diseases and their systemic implications.

Keywords: oral microbiota; periodontal diseases; systemic health; microbial dysbiosis

1. Introduction

The oral microbiome is a complex ecosystem that plays a crucial role in both oral and systemic health. Comprising over 700 species of bacteria, fungi, viruses, archaea, and protozoa, the oral microbiome serves as a gateway for microorganisms to enter the body and influence various physiological processes (Varoni & Rimondini, 2022; Kozak & Pawlik, 2023). This diverse community is primarily composed of six bacterial phyla: Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes, and Fusobacteria, accounting for approximately 94% of the detected taxa (Santonocito et al., 2022; D'Ambrosio et al., 2023). The composition varies across different oral sites, with interindividual similarities observed at the same sites (Santonocito et al., 2022).

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The oral microbiome maintains host health through several mechanisms. Commensal bacteria provide "colonization resistance" by competing for binding sites and nutrients, thus limiting pathogen access. They also contribute to immune system development and regulation, promoting immune cell recruitment and the synthesis of epithelial defenses (Irie et al., 2023). Maintaining balance within the oral microbiome is essential for oral health. Dysbiosis can lead to various oral diseases, including dental caries and periodontal disease (Baker et al., 2024). Recent research has highlighted the intricate relationship between oral and systemic health. Periodontal diseases, characterized by chronic gum inflammation, have been associated with increased systemic inflammation. Periodontal pathogens and their byproducts can enter the bloodstream, triggering a body-wide inflammatory response linked to cardiovascular disease, rheumatoid arthritis, and diabetes (Pisano et al., 2023). The composition of the oral microbiome has been found to differ between individuals with and without systemic diseases. Oral microbiome dysbiosis, marked by reduced diversity and pathogenic bacterial overgrowth, has been associated with metabolic disorders and neurodegenerative diseases (Georges et al., 2022). Interestingly, this relationship is bidirectional, with systemic diseases also influencing the oral microbiome (Peng et al., 2022).

Advancements in metagenomic and metatranscriptomic techniques have enhanced our understanding of the microbiome's role in health and disease. These studies reveal that certain beneficial bacteria, such as *Streptococcus* species, are more active in healthy conditions (Kozak & Pawlik, 2023). Research on germ-free mice has shown that while bacterial colonization is not necessary for survival, it is crucial for overall health and proper oral tissue development (Irie et al., 2023). Therefore, the oral microbiome is an integral component of human health, maintaining homeostasis through complex host-microbe and inter-microbial interactions. Understanding these relationships is crucial for developing new strategies to prevent and treat both oral and systemic diseases, as well as potentially using health-associated microorganisms as probiotics or biomarkers for various conditions (Baker et al., 2024).

2. The Role of Oral Microbiota in Systemic Diseases

The oral microbiota plays a critical role in overall health and is significantly influenced by systemic diseases (Table 1). For example, individuals with diabetes mellitus often exhibit changes in their oral microbiome, leading to an increase in pathogenic bacteria that can exacerbate periodontal disease. Matsha et al. (2020) found that diabetic patients display distinct oral microbiome signatures characterized by a higher prevalence of anaerobic bacteria, such as *Porphyromonas gingivalis* and *Tannerella forsythia*, which are closely associated with the progression of periodontal disease. The inflammatory environment present in diabetic patients shifts the oral microbiota towards a more pathogenic state, worsening periodontal conditions. In a study involving 128 South African individuals, researchers linked higher glycemic levels to a greater prevalence of specific bacterial phyla, demonstrating significant variations in the microbiome between prediabetic and diabetic individuals (Matsha et al., 2020).

Similarly, patients with rheumatoid arthritis (RA) exhibit distinct subgingival microbiomes compared to healthy individuals, indicating a bidirectional relationship between RA and oral health. Liu et al. (2020) utilized Illumina MiSeq technology to analyze subgingival bacterial diversity in 54 RA patients, 45 patients with periodontitis (PD), and 44 healthy controls. Their findings identified *P. gingivalis* as a crucial link between RA and periodontitis through immune responses. The study revealed that RA patients had a higher

Table 1. Summary of systemic diseases associated with oral microbiota

Systemic Condition	Associated Pathogens	Proposed Mechanism	Clinical Evidence	Reference
Diabetes Mellitus	*P. gingivalis*, *T. forsythia*	Inflammatory environment worsening periodontal conditions	Higher glycemic levels linked to increased prevalence of specific bacterial phyla	Matsha et al. (2020)
Inflammatory Bowel Disease	Various dysbiotic profiles	Gut barrier disruption; immune response modulation	Altered microbial composition associated with IBD	Graves et al. (2019)
Systemic Lupus Erythematosus	*Prevotella*, *Selenomonas*	Elevated inflammation; interactions between immune responses	Increased inflammatory markers in patients with periodontal disorders	Graves et al. (2019)
Rheumatoid Arthritis	*P. gingivalis*, *Aggregatibacter actinomycetemcomitans*	Induce citrullination of host proteins, promote anti-citrullinated antibodies (ACPAs), and autoimmune reactions	RA treatment benefits periodontal health and correlates with RA autoantibody production	Hajishengallis (2022)
Respiratory Infections	*Fusobacterium nucleatum*, *Prevotella intermedia*	Aspiration of oral pathogens causing lung infections	Increased incidence of pneumonia linked to poor periodontal health	Hajishengallis (2022)
Type 1 Diabetes Mellitus	*P. gingivalis*, *Pr. intermedia*	Oxidative stress; immune dysregulation	Higher susceptibility to periodontitis in T1DM patients	Vlachou et al. (2024)
Crohn's Disease	Decreased Firmicutes; increased Bacteroidetes	Altered microbial composition affecting gut health	Significant differences in subgingival plaque compared to periodontitis alone	Chen et al. (2022a)
Cardiovascular Disease	*P. gingivalis*, *Streptococcus mitis*, *F. nucleatum*	Bacterial translocation leading to endothelial inflammation and atherosclerosis	Elevated levels of periodontal pathogens in atherosclerotic plaques	Emery et al. (2021)

abundance of Bacteroidetes and exhibited greater microbial evenness, as indicated by a higher Shannon index. Additionally, RA patients showed significantly elevated levels of *Spirochaetes*, including *Treponema* and *Tannerella*, alongside a greater prevalence of *P. gingivalis* compared to healthy controls.

The relationship between oral microbiota and systemic diseases extends beyond diabetes and RA. The oral microbiome has been implicated in the exacerbation of various systemic conditions such as atherosclerosis, inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE). Graves et al. (2019) highlighted that periodontal disorders in patients with RA, SLE, and diabetes were associated with increased inflammation. Specifically, elevated levels of *Prevotella* and *Selenomonas* were noted in RA and SLE patients, respectively, while diabetic patients exhibited increased levels of *Capnocytophaga*, *Porphyromonas*, and *Pseudomonas*. Dysbiosis within the oral microbiome—characterized by the presence of pathogens such as *Treponema denticola*, *P. gingivalis*, and *Bacteroides forsythus* (now *Tannerella forsythia*)—exacerbates inflammation and tissue damage. Studies suggest that the pathogenicity of the oral microbiome in diabetes may be reversible through the inhibition of interleukin-17 (IL-17).

Recent research also indicates that periodontal disease may heighten the risk of systemic conditions by affecting gut health. Periodontopathic bacteria like *P. gingivalis* have been shown to survive within the gut environment, inducing dysbiosis that contributes to systemic diseases by disrupting gut barrier function, immune responses, and metabolic processes. Yamazaki (2023) proposed that the oral-gut axis represents a novel biological mechanism linking periodontal disease to systemic health issues. Both animal models and human studies indicate that oral bacteria can exacerbate systemic conditions by colonizing the gut; chronic periodontitis has been associated with decreased gut microbiota diversity and dysbiosis. This relationship underscores the importance of managing gut health as part of comprehensive systemic disease treatment.

Moreover, the bidirectional relationship between periodontal disease and type 1 diabetes mellitus (T1DM) further emphasizes the interaction between oral microbiota and systemic health. A review by Vlachou et al. (2024) highlighted that T1DM patients are more susceptible to periodontitis, exhibiting higher levels of pathogens such as *P. gingivalis* and *Prevotella intermedia*, which adversely affect microbial diversity. Factors such as oxidative stress, immune dysregulation, and inflammatory cytokines influence this relationship. The review also suggests that gut dysbiosis observed in T1DM presents potential new avenues for treatment through microbiome modulation.

In patients with Crohn's disease (CD), significant differences in the oral microbiome have been observed compared to those with periodontitis alone. Chen et al. (2022a) reported that subgingival plaque from patients with both CD and periodontitis exhibited decreased levels of Firmicutes and Actinobacteria while showing increased levels of Bacteroidetes. Additionally, certain bacterial genera—such as *Streptococcus*, *Haemophilus*, and *Gemella*—were less abundant in the CD group, whereas *Actinomyces*, *Capnocytophaga*, *Treponema_2*, and *Porphyromonas* were more prevalent. These findings suggest that the oral microbiome may contribute to the pathogenesis of systemic diseases like CD, underscoring the importance of maintaining good oral health for managing systemic conditions.

Therefore, these studies illustrate the intricate interplay between oral microbiota and systemic diseases, emphasizing the necessity for a holistic approach to healthcare that recognizes the role of the oral microbiome in systemic health.

3. Impact of Behavioral Factors on Oral Microbiota

Behavioral factors, particularly smoking and dietary habits, play a significant role in shaping the oral microbiota and influencing periodontal health.

3.1 Smoking and its effect on subgingival microflora

Smoking significantly alters the composition of the oral microbiota, with smokers exhibiting reduced levels of the Actinobacteria phylum and lower abundances of genera such as *Leptotrichia, Actinomyces, Corynebacterium*, and *Lautropia*. In contrast, genera like *Fusobacterium* and *Campylobacter* were notably more abundant in smokers. This shift creates an anaerobically rich environment conducive to the proliferation of gram-negative anaerobic bacteria, including species such as *F. nucleatum, Campylobacter gracilis, Veillonella rogosae, F. canifelinum,* and *Actinomyces odontolyticus* (Prince et al., 2024).

Smoking has a profound impact on the subgingival microbiota, creating an environment favorable for periodontal pathogens such as *P. gingivalis*. Research by Jiang et al. (2020) demonstrated that smoking leads to distinct microbial profiles in smokers, irrespective of their periodontal health status, as revealed by advanced 16S rRNA sequencing. Components of cigarette smoke, including nicotine and cigarette smoke extract (CSE), induce phenotypic changes in pathogens like *P. gingivalis*, promoting upregulation of specific proteins and altering inflammatory responses. These smoking-induced shifts in the microbiota contribute to exacerbated periodontal inflammation and compromised host-pathogen interactions. These microbial changes suggest a potential link between smoking and an increased risk of periodontal disease, as the altered microbiome fosters conditions that may promote its onset and progression. However, these microbial changes are reversible with smoking cessation, with studies showing a reduction in periodontal pathogens and a restoration of beneficial bacteria. Additionally, smoking impacts the immune system, altering cytokine responses and further aggravating periodontal disease.

A comprehensive review by Hanioka et al. (2019) assessed the impact of smoking on periodontal microorganisms by analyzing data from 42 selected studies out of 1,099 reviewed. The methodologies employed included colony counting, qPCR, DNA hybridization, microarray analysis, and 16S rRNA sequencing, with a particular focus on *P. gingivalis* and other oral microbes. The findings indicated that smoking elevates levels of bacteria such as *Streptococcus sobrinus* and *Eubacterium brachy* in saliva, adversely affecting both oral and respiratory health.

Moreover, a pilot study by Al Kawas et al. (2021) examined the effects of various tobacco products—including cigarettes, medwakh, and shisha—on subgingival microbiota and periodontal health among 40 participants categorized by their periodontal status. Results indicated that cigarette and medwakh smokers exhibited a higher prevalence of moderate to severe periodontitis compared to shisha smokers and non-smokers. This study also identified specific microbial shifts associated with each type of smoking, revealing that cigarette smokers had lower microbial diversity than non-smokers.

Further research by Beklen et al. (2022) explored demographic factors associated with smoking and their impact on periodontal health, finding significant differences in periodontal status based on smoking habits. Smokers displayed higher rates of periodontal disease severity and elevated DMFT (Decayed, Missing, and Filled Teeth) scores, indicating poorer overall oral health. While Soldati et al. (2022) found that smoking alters beta-defensin levels, crucial for the innate immune response in the oral cavity. A

systematic review by Alwithanani (2023) demonstrated that smoking significantly elevates the risk of developing periodontitis by 85%, establishing it as a critical factor in the progression of periodontal disease. This review examined the effects of smoking on periodontitis, focusing on its role in disrupting vascular and immune mechanisms that exacerbate periodontal inflammation. A thorough search of databases, including EMBASE, MEDLINE, PUBMED, and SCOPUS, identified 15 relevant studies, with 14 included in a meta-analysis. The review included prospective longitudinal studies with a minimum follow-up period of 12 months and assessments of at least two periodontal parameters: clinical attachment level, probing depth, or alveolar bone loss. Statistical evaluations, such as meta-regression and heterogeneity analysis, were conducted using Stata 14.2. The results indicated that smoking increases periodontitis risk by 85% (risk ratio 1.845, 95% CI = 1.5-2.2), with variations attributable to factors like age (54.2%), follow-up duration (10.7%), disease severity (13.5%), and participant attrition (2.1%). These findings highlight the importance of documenting patients' smoking status during initial visits and advocating for smoking cessation to mitigate periodontal inflammation and slow disease progression.

3.2 Dietary factors and the oral microbiome

Dietary habits, particularly prebiotic fibers, influence the oral microbiome by promoting a balance between pathogenic and beneficial bacteria. A systematic review by Tailor et al. (2023) on animal studies showed that prebiotics like β-(1,3/1,6)-glucan and mannan oligosaccharides reduced alveolar bone loss and lowered pro-inflammatory cytokines in ligature-induced periodontitis models, suggesting their potential as adjunctive therapies for periodontal disease. Additionally, inulin-type fructans were linked to increased levels of beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, which help protect against periodontal pathogens.

The shift from hunter-gatherer diets to agrarian lifestyles introduced dairy, refined carbohydrates, vegetable oils, and alcohol, leading to significant changes in the oral microbiome and increased prevalence of dental and periodontal diseases. Plaque samples from agricultural populations, starting from the Neolithic era, show a predominance of caries-associated microbes like those in the Veillonellaceae family, alongside periodontal pathogens such as *P. gingivalis*, *T. forsythia*, and *T. denticola*. Macronutrients also play a critical role in oral and periodontal health. Diets high in processed, fermentable carbohydrates encourage pro-inflammatory responses and the proliferation of saccharolytic bacteria like *Streptococcus*, *Actinomyces*, and *Veillonella*, which contribute to enamel demineralization, caries, and a favorable environment for periodontal pathogens. Protein consumption affects the oral environment differently; while animal protein can influence carcinogenesis, vegetable protein offers protective health benefits. During periodontitis, protein degradation in deepened gingival pockets produces short-chain fatty acids that neutralize acidity, fostering periodontal pathogen growth (Takahashi et al, 2015). Similarly, while saturated fats and trans fats are linked to worsening periodontal conditions, omega-3 fatty acids exert anti-inflammatory effects (Stein et al, 2021) though the overall impact of dietary lipids on the oral microbiome remains unclear.

The composition of the oral microbiome is heavily influenced by diet, with changes in food texture and macronutrient composition playing a significant role in the development of caries and periodontal diseases. A balanced diet rich in anti-inflammatory and microbiome-friendly nutrients may help mitigate the risks associated with periodontal disease and maintain oral health (Santonocito et al., 2022).

In summary, behavioral factors such as smoking and dietary choices significantly impact the oral microbiome's composition and function. The evidence indicates that smoking not only alters microbial diversity but also adversely affects immune responses, heightening the risk and severity of periodontal diseases. Effective strategies for smoking cessation combined with dietary modifications—such as incorporating prebiotics—are essential for maintaining a healthy oral microbiome and preventing recurrence of periodontal disease.

4. Microbial Dysbiosis and Periodontal Disease Severity

Research employing advanced diagnostic techniques, such as multiplex real-time PCR, has revealed significant variations in the abundance and diversity of periodontopathic bacteria across different stages of periodontal disease severity (Table 2). A study by Choi et al. (2020) involved 114 individuals with varying degrees of periodontal disease, from gingivitis to severe periodontitis. The researchers used three sampling methods—mouthwash, paper points, and gingival retraction cords—to collect samples, which were then analyzed using multiplex PCR to quantify bacterial DNA. The findings demonstrated notable differences in bacterial counts and prevalence among the severity groups, particularly between severe periodontitis and moderate periodontitis or gingivitis/mild periodontitis cases. Interestingly, the most pronounced variations were observed in severe periodontitis patients, and there was a strong correlation between mouthwash samples and subgingival samples, suggesting the potential utility of non-invasive sampling methods in assessing periodontal disease severity.

Figure 1 provides a glimpse of the stages of progression of periodontal disease, from healthy gums to severe periodontitis, highlighting microbial shifts and immune responses. Healthy gums maintain a balanced microbiome with commensal bacteria like *S. mitis*, *S. salivarius*, and *Actinomyces*. Gingivitis marks the onset of dysbiosis, with increased pathogens such as *F. nucleatum*, *P. intermedia*, and *Capnocytophaga*, triggering inflammation. Mouse molar gingivitis models have demonstrated early inflammation and tissue destruction caused by *P. gingivalis*, *T. denticola*, and *T. forsythia*. Early periodontitis features virulent species (*P. gingivalis*, *T. denticola*, *F. nucleatum*) and immune activation, progressing to advanced periodontitis with deep pockets and pathogens like *Aggregatibacter actinomycetemcomitans*, exacerbating tissue destruction. Diagnostic techniques such as PCR, NGS, microbiome analysis, oral care chips, and microarrays play a critical role in identifying pathogens and understanding disease progression.

Further insights into the microbial shifts associated with different stages of periodontal disease have been provided by compositional data analysis (CoDA). This approach, combined with next-generation sequencing (NGS), has enabled researchers to identify distinct microbial communities linked to specific disease stages. A study by Sisk-Hackworth et al. (2021) reanalyzed multi omics data from previous studies using NGS and CoDA, revealing novel relationships between particular bacteria and disease severity. The researchers found that advanced stages of periodontal disease were associated with a more diverse microbiome, with significant interactions among bacteria, cytokines, and metabolites. These findings highlight the complex microbial networks involved in periodontal disease progression and the potential for identifying biomarkers to predict treatment response.

Table 2. Key periodontal pathogens and their virulence factors

Bacterial Species	Virulence Factors	Pathogenic Mechanisms	Associated Disease Severity	Reference
P. gingivalis	Gingipains (proteases), Lipopolysaccharides (LPS), Fimbriae	Tissue degradation, immune evasion, disruption of host immune responses	Moderate to Severe Periodontitis	Naginyte et al. (2019)
T. denticola	Dentilisin, Major outer sheath protein (Msp)	Degradation of extracellular matrix, inhibition of neutrophil function	Severe Periodontitis	Schulz et al. (2019)
T. forsythia	BspA protein, S-layer proteins	Induction of pro-inflammatory cytokines, adherence to host tissues	Aggressive Periodontitis	Choi et al. (2020)
A. actinomycetemcomitans	Leukotoxin, Cytolethal distending toxin (CDT)	Destruction of leukocytes, inhibition of cell cycle	Localized Aggressive Periodontitis	Lochman et al. (2020)

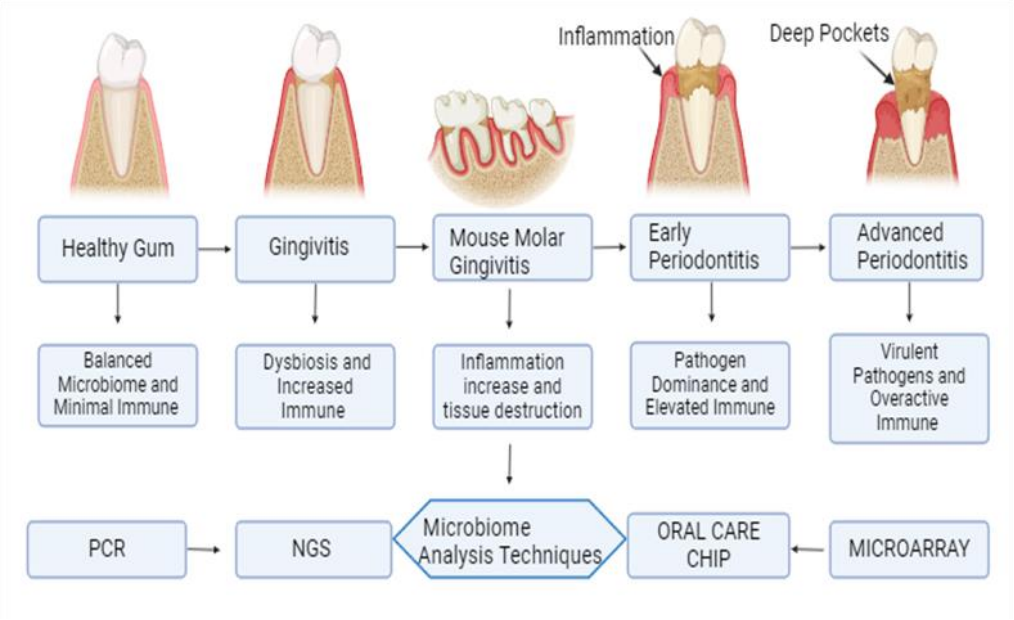

Figure 1. Insights into the progression of periodontal disease and the techniques used

Key periodontal pathogens, such as *P. gingivalis*, *T. denticola*, and *T. forsythia*, have been strongly linked to severe periodontal disease. These bacteria possess various virulence factors that contribute to tissue destruction and inflammation, exacerbating periodontal conditions. Naginyte et al. (2019) conducted a study that enriched periodontitis-associated taxa from biofilms of healthy adults, observing a shift in microbial composition towards these pathogenic species. These findings underscore the importance of understanding microbial dysbiosis in periodontal disease to develop targeted treatment strategies.

5. Systemic Health Implications of Periodontal Disease

Periodontal diseases have been increasingly recognized for their associations with various systemic conditions, including cardiovascular diseases, respiratory disorders, and neurodegenerative diseases. Research indicates that periodontal pathogens can enter the bloodstream, contributing to systemic inflammation and disease progression. For instance, a study comparing blood bacterial communities in individuals with periodontal health versus those with periodontal disease found that oral bacteria, particularly *S. mitis* and *Staphylococcus epidermidis*, were predominant in blood samples. Also. *P. gingivalis* and *T. forsythia*, major periodontal pathogens, have been linked to late-onset Alzheimer's disease through elevated IgG antibodies in plasma and the detection of *P. gingivalis* in brain tissues, suggesting a blood-borne route of bacterial translocation from the periodontium to the brain. These findings imply that periodontitis contributes to Alzheimer's pathology. While oral species like *S. mitis* and *S. epidermidis* are more abundant in blood, *P. gingivalis* and *T. forsythia* remain significant due to their potential to enter systemic circulation, trigger immune responses, and invade distant tissues like the brain. However, *P. gingivalis* was detected at low levels (0.6% in healthy controls, 0.8% in periodontitis), and *T. forsythia* was absent in the analyzed blood samples, likely due to their anaerobic nature or limitations in detection methods. This emphasizes that, although present in low abundance, these pathogens play a critical role in Alzheimer's progression (Emery et al., 2021). This highlights the potential role of oral bacteria in systemic conditions such as cardiovascular disease, Alzheimer's disease, and rheumatoid arthritis (Emery et al., 2021), and an overview is provided in Table 3.

The connection between oral health and systemic health is further emphasized by innovative therapeutic strategies such as Oral Microbial Transplantation (OMT). OMT is a novel therapeutic strategy aimed at restoring oral microbial homeostasis by transferring beneficial oral microbiota from a healthy donor to an individual with dysbiosis. This approach has potential applications in managing conditions such as periodontitis, dental caries, halitosis, and oral candidiasis, which are associated with an imbalanced oral microbiome. Inspired by the success of fecal microbiota transplantation in gastrointestinal disorders (Chen et al., 2022b), OMT involves donor screening, microbiota harvesting, and application via rinses, gels, or sprays. While early evidence suggests its efficacy in reducing pathogenic overgrowth and inflammation, challenges such as standardization of protocols, donor selection, and regulatory considerations remain significant barriers to clinical translation. Ongoing research in Australia is exploring the feasibility, safety, and efficacy of OMT using supragingival plaque samples from healthy individuals. The aim is to develop a hydrogel-based delivery system for OMT therapy to improve oral health outcomes, especially in underserved populations with limited access to dental care (Nath et al., 2021). Individuals suffering from periodontal disease are at an elevated risk of

Table 3. Systemic health implications of periodontal disease and pathogenesis

Systemic Condition	Pathogenesis and Connection to Periodontal Disease	Details
Cardiovascular Diseases	Periodontal pathogens, such as *S. mitis* and *S. epidermidis*, can enter the bloodstream and trigger systemic inflammation. This leads to the formation of atherosclerotic plaques, contributing to cardiovascular conditions like heart attacks and strokes.	Chronic inflammation due to periodontal disease can exacerbate plaque formation in blood vessels, increasing the risk of cardiovascular events.
Respiratory Disorders	Periodontal pathogens can be aspirated into the lungs, leading to conditions such as pneumonia and chronic obstructive pulmonary disease (COPD). Inflammation from periodontal disease can also exacerbate existing respiratory conditions.	Studies indicate that oral bacteria may reach the lungs and promote infections, especially in individuals with compromised immune systems or pre-existing lung conditions.
Neurodegenerative Diseases	Oral bacteria entering the bloodstream can reach the brain, potentially triggering inflammatory responses and contributing to conditions like Alzheimer's disease. Pathogens such as *P. gingivalis* have been implicated in neuroinflammatory processes.	The inflammatory process linked to periodontitis may lead to an increase in amyloid plaques and tau tangles, characteristic of Alzheimer's disease.
Rheumatoid Arthritis (RA)	The chronic inflammation associated with periodontal disease may share common pathways with RA. Oral pathogens can enter the bloodstream and affect joints, leading to immune system dysregulation.	Research has shown that periodontal bacteria can induce systemic inflammation that exacerbates joint inflammation and RA progression.

developing cardiovascular conditions due to the systemic dissemination of periodontal pathogens and their byproducts. These pathogens can trigger inflammatory responses that contribute to the formation of atherosclerotic plaques, thereby increasing the risk of heart attacks and strokes. While significant associations between periodontitis and systemic diseases have been identified, further studies are needed to confirm the impact of periodontal treatment on these associated conditions (Hajishengallis, 2022).

6. Current Status: Periodontal Disease Prevalence and Its Significance in Public Health

Recent studies have shed light on the prevalence and impact of periodontal disease across various populations, highlighting its significance as a public health concern. A study focusing on Serbian schoolchildren revealed notable oral health issues among 12 and 15-year-olds. While 36% of 12-year-olds and 22% of 15-year-olds had no caries, the mean DMFT index increased significantly from 2.32 in 12-year-olds to 4.09 in 15-year-olds. Gingival bleeding occurred in 26% of 12-year-olds and 18% of 15-year-olds, with dental plaque present in 63% of both age groups. These findings underscore the need for improved preventive measures and modifications to school-based oral health programs (Peric et al. 2022). The impact of periodontal disease extends to specific patient groups, as evidenced by a study on adult hemophilia patients in Rotterdam. Despite high self-rated

oral health scores, 52% of participants experienced bleeding during or after dental treatments. Interestingly, patients with severe hemophilia demonstrated lower mean DMFT scores compared to those with mild hemophilia, suggesting a complex relationship between hemophilia severity and oral health outcomes (Mulders et al. 2023).

Socioeconomic factors play a crucial role in periodontal health, as demonstrated by a study conducted in the Tokyo Metropolitan District. Among 1033 participants, those from the lowest income bracket had significantly fewer remaining teeth and a higher proportion of teeth with probing pocket depth ≥ 4 mm. This disparity was intensified among current smokers, highlighting the compounding effect of lifestyle factors on socioeconomic-related oral health inequalities (Mikami et al., 2023). Several studies explored the relationship between systemic health conditions and periodontal disease. A comprehensive review of children living with HIV (CLWH) undergoing antiretroviral therapy revealed mixed results on dental caries but consistently higher periodontal disease prevalence compared to healthy controls. HIV-related orofacial manifestations were more common in CLWH, with CD4+ T-cell counts below 250 cells/mm³ associated with a higher likelihood of HIV-related oral lesions (Lam et al., 2022). Another study utilizing NHANES data from 2003 to 2018 found a significant association between periodontitis severity and hepatitis virus infection. This relationship was particularly pronounced in specific subgroups, including individuals aged 20-40, females, and Non-Hispanic Whites. The consistency of this association across various demographic and lifestyle factors underscores the complex interplay between systemic infections and oral health (Chen et al., 2024). The COVID-19 pandemic has also brought attention to potential links between severe respiratory infections and oral health. A pilot study of younger patients (≤60 years) hospitalized in ICU for severe COVID-19 found that all participants had periodontal issues, with nearly half showing advanced periodontitis. While the sample size was limited, these findings suggest a potential association between severe COVID-19 and periodontal health that warrants further investigation (Gardelis et al., 2022).

Educational attainment has emerged as a significant factor in periodontal health outcomes. The Hamburg City Health Study, involving 10,000 participants, revealed a clear association between lower education levels and increased periodontitis severity. This relationship persisted even after adjusting for various confounding factors, highlighting the profound impact of educational disparities on oral health (Walther et al., 2022). In developing countries, the prevalence of periodontal disease remains high, as evidenced by a study conducted in the Sunsari district of Nepal. Among 440 adult participants, the overall prevalence of periodontitis was 71.6%, with severity increasing with age. Tobacco use represents a significant risk factor, with 46.6% of individuals aged 21-65 reporting tobacco consumption. The strong link between tobacco use and higher prevalence and severity of periodontitis emphasizes the need for targeted interventions in public health strategies (Goel et al., 2021). Studies on immigrant populations reveal significantly higher rates of periodontal issues compared to local populations in host countries, with gingivitis prevalence ranging from 5.1% to 100%, and up to two-thirds of adults experiencing periodontitis. These disparities reflect broader health inequities, influenced by factors such as access to care, socioeconomic status, and cultural differences. The findings emphasize the need for tailored oral health strategies to address these diverse challenges. Future research and interventions should focus on integrating oral health into broader public health policies to reduce disparities and improve health outcomes across populations (Rad et al., 2024).

7. Future Directions and Clinical Implications

Emerging therapies for oral health and related systemic conditions are focusing on novel approaches to restore microbial balance and modulate host responses. These innovative strategies aim to address the complex interplay between the oral microbiome and overall health.

7.1 Microbiome modulation

Probiotics and prebiotics have emerged as promising interventions for managing oral dysbiosis and related conditions. Probiotics, particularly strains of *Lactobacillus* and *Bifidobacterium*, have shown potential in reducing periodontal pathogens and inflammation (Moreno et al., 2023). These beneficial bacteria can enhance intestinal barrier function, downregulate pro-inflammatory cytokines, and increase beneficial metabolites such as short-chain fatty acids (SCFAs) (Elzayat et al., 2023). While some studies have demonstrated improvements in periodontal health with probiotic use, results have been inconsistent, highlighting the need for further research to optimize dosage and application methods (Santonocito et al., 2022). Prebiotics, substrates that selectively nourish beneficial microorganisms, are often used in conjunction with probiotics. This symbiotic approach aims to enhance the effectiveness of microbiome modulation therapies (Santonocito et al., 2022).

7.2 Advanced antimicrobial strategies

Targeted antimicrobial therapies are increasingly being developed to address specific bacterial profiles implicated in aggressive periodontitis (Moreno et al., 2023). Among these, bacteriophage-based treatments are gaining attention for their ability to selectively eliminate pathogenic bacteria while sparing beneficial microbiota. Despite their promise, concerns regarding the emergence of phage-resistant strains and the potential for unintended microbiome disruptions highlight the need for further investigation (Paule et al., 2018; Moreno et al., 2023). The global rise of extensively drug-resistant (XDR) and multidrug-resistant (MDR) bacterial strains, such as *Campylobacter* and *Enterococcus*, represents a significant public health threat. *Campylobacter*, a leading cause of foodborne illness, has developed resistance to multiple antibiotic classes, including fluoroquinolones, macrolides, tetracyclines, and β-lactams. Key resistance mechanisms include point mutations in the *gyrA* gene and the overexpression of efflux pumps like CmeABC, with horizontal gene transfer further facilitating the dissemination of resistance genes, even across species. Contaminated poultry is a primary vector for human transmission, reflecting the role of livestock in the emergence of resistant strains (Urban-Chmiel et al., 2022).

Similarly, *Enterococcus*, a natural constituent of the human gut microbiota, is a significant pathogen in severe infections such as endocarditis, bloodstream infections, and urinary tract infections. Resistance mechanisms in *Enterococcus* include alterations in penicillin-binding proteins (PBPs), β-lactamase production, and changes in peptidoglycan precursors. For instance, resistance to glycopeptides like vancomycin involves the substitution of D-Ala-D-Ala with D-Ala-D-Lac or D-Ala-D-Ser in cell wall precursors, thereby reducing antibiotic binding and efficacy (Almutairy, 2024). The spread of resistance genes is exacerbated by inappropriate antibiotic use in healthcare and agriculture, where sub-therapeutic dosing promotes the development and transmission of resistant strains. Horizontal gene transfer mechanisms, including transformation, transduction, and

conjugation, play a crucial role in this process. Addressing the growing threat posed by these resistant pathogens requires coordinated global strategies that emphasize antimicrobial stewardship, enhanced infection control measures, and the development of innovative therapeutic approaches (Urban-Chmiel et al., 2022; Almutairy, 2024).

7.3 Immunomodulatory approaches

Therapies targeting specific inflammatory pathways, such as IL-17 inhibitors, are being investigated to mitigate the pathogenic effects of oral dysbiosis in conditions including diabetes (Moreno et al., 2023). The NLRP3 inflammasome, a critical component of the innate immune response, has been identified as a potential therapeutic target in periodontal disease (Didilescu et al., 2024). Host modulation therapies, including the use of tetracyclines, NSAIDs, and bisphosphonates, aim to alter the host's immune response to prevent excessive tissue destruction. Newer approaches target specific molecular pathways such as MAPK, NF-kB, and JAK/STAT (Yadalam et al., 2022).

7.4 Novel therapeutic agents

Advanced glycation end products (AGEs) are being targeted with innovative approaches in periodontitis treatment. Dickkopf-related protein 1 (DKK-1) of Wnt pathway have shown promise *in vitro* for ameliorating the negative impacts of AGEs on osteogenesis. AGE inhibitors such as aminoguanidine and cross-link breakers like N-phenacylthiazolium bromide (PTB) are being explored to reduce AGE accumulation in periodontal tissues (Plemmenos & Piperi, 2022). Antioxidants such as magnolol, astaxanthin, and vitamin C have demonstrated potential in modulating the Nrf2 signaling pathway to counteract AGE-induced oxidative stress (Plemmenos & Piperi, 2022).

7.5 Gene therapy and regenerative approaches

Gene therapy is being explored to promote tissue regeneration and repair in periodontal disease. Gene Activated Matrix (GAM) technology is being used to deliver growth factors such as BMP and PDGF to regenerate bone and periodontal tissues (Yadalam et al., 2022).

7.6 Antiviral agents

For periodontal diseases associated with viral infections, antiviral agents such as valacyclovir and acyclovir are being used alongside conventional therapies to reduce viral load and improve clinical outcomes (Yadalam et al., 2022).

Bacterial-viral co-infections may worsen periodontal disease severity, as viruses like EBV and cytomegalovirus are implicated in disease progression. Antiviral agents such as valacyclovir improve patient symptoms by reducing viral load, enhancing the clinical status of periodontal lesions, and improving outcomes when combined with non-surgical therapy. Acyclovir has also been shown to resolve lesions in herpetic infections. However, further research is needed to confirm the efficacy of antiviral agents in enhancing mechanical debridement and reducing pathogenic activity (Yadalam et al., 2022).

Advanced non-surgical treatments, including scaling, root planing, and adjunctive therapies like photodynamic therapy, are being investigated, particularly for special populations such as individuals with Down’s syndrome or obstructive sleep apnea (Ghaffarpour et al., 2024).

7.7 Microbiota transplantation

While still in the exploratory phase, oral microbiota transplants (OMTs) have been proposed as a potential treatment for gum disease, drawing inspiration from the success of fecal microbiota transplants in treating gut dysbiosis (Elzayat et al., 2023; Moreno et al., 2023).

These emerging therapies represent a shift towards more personalized and targeted approaches in oral health management, addressing the complex interactions between the oral microbiome, host response, and systemic health. As research progresses, these innovative strategies may offer new avenues for preventing and treating oral diseases and their associated systemic conditions.

Table 4 summarizes emerging therapeutic approaches aimed at managing periodontal disease effectively. These innovative strategies reflect ongoing advancements in understanding the pathophysiology of periodontal disease and highlight the need for tailored interventions based on individual patient profiles. In conclusion, understanding the systemic health implications associated with periodontal diseases is crucial for developing comprehensive healthcare strategies that address both oral and systemic health. By recognizing the interconnectedness of these domains, healthcare providers can implement more effective prevention and treatment protocols that ultimately improve patient outcomes across multiple facets of health

Table 4. Emerging therapeutic approaches for periodontal disease management

Therapeutic Approach	Mechanism of Action	Target Population	Clinical Outcomes	Reference
NLRP3 Inflammasome Inhibitors (e.g., AMY-101)	Modulation of innate immune response by inhibiting inflammasome activation	Patients with chronic periodontitis	Reduction in inflammation and tissue destruction; improved clinical parameters	Didilescu et al. (2024)
Oral Microbiome Transplantation (OMT)	Restoration of healthy microbial balance through transplantation of beneficial microbiota	Individuals with recurrent periodontitis and dental caries; underserved communities	Preliminary studies show improved oral health and reduced pathogenic bacteria	Nath et al. (2021)
Probiotic Therapy	Introduction of beneficial bacteria to suppress pathogenic species	Patients with Down's syndrome and other special needs	Decreased gingival inflammation; enhanced periodontal stability	Ghaffarpour et al. (2024)
Photodynamic Therapy	Destruction of pathogens using light-activated antimicrobial agents	Adjunctive treatment for moderate to severe periodontitis	Enhanced effectiveness of scaling and root planing; reduced bacterial load	Ghaffarpour et al. (2024)

8. Technological Advances in Microbiome Research

Recent innovations in microbiome research have significantly enhanced the understanding of the oral microbiota, particularly concerning periodontal diseases (Table 5). These technological advancements not only enhance diagnostic capabilities but also contribute to a deeper understanding of microbial dysbiosis and its implications for periodontal disease severity. Multiplex real-time PCR has emerged as a pivotal tool, allowing for the simultaneous detection and quantification of various periodontal pathogens within a single assay. This technology has been instrumental in identifying specific bacterial species associated with periodontal infections, thereby improving diagnostic accuracy and treatment monitoring. For instance, a study involving children with severe gingivitis utilized multiplex PCR to differentiate between healthy and affected teeth, revealing notable differences in microbial composition, such as increased levels of *T. forsythia* and *Parvimonas micra* in diseased samples (Lochman et al., 2020). Additionally, multiplex PCR has revealed that the diversity and abundance of periodontopathic bacteria vary significantly across different stages of periodontal disease (Choi et al., 2020). By identifying specific bacterial profiles associated with aggressive forms of periodontitis, targeted antimicrobial therapies can be developed to improve treatment outcomes (Schulz et al., 2019).

Table 5. Summary of studies utilizing advanced diagnostic technologies in periodontal disease research

Diagnostic Method	Sample Population	Key Findings	Reference
Multiplex Real-Time PCR	60 children (2-6 years) with severe gingivitis and early childhood caries	Identified significant differences in microbial composition between healthy and diseased teeth, highlighting the prevalence of *T. forsythia*, *F. nucleatum*, and *P. micra* in affected samples	Lochman et al. (2020)
Next-Generation Sequencing (NGS)	Systematic review of 12 studies	Demonstrated shifts from Gram-negative pathogens to Gram-positive commensals post-periodontal intervention; methodological variability limited quantitative analysis	Zhang et al. (2021)
Oral Care Chip Microarray	204 plaque samples from periodontitis patients and healthy individuals	Quantified 17 subgingival bacterial species; identified changes associated with pocket depth and disease progression; post-SRP analysis showed microbiota resembling healthy states	Nozawa et al. (2020)

Additionally, innovative diagnostic tools like the Oral Care Chip have shown promise in clinical applications by enabling the early detection of pathogenic bacteria linked to periodontal disease. A study involving this chip analyzed subgingival samples from patients with periodontitis and healthy controls, successfully correlating bacterial changes with disease severity. The chip employs microarray technology to detect multiple bacterial species simultaneously, providing a holistic view of the oral microbiota within a single assessment (Nozawa et al., 2020). Microarray chip technology, while innovative and valuable in detecting and quantifying specific bacteria, has notable limitations. The technology often suffers from cross-hybridization issues, where probes may bind to non-target sequences due to similarities in genetic sequences, leading to inaccuracies. Additionally, its quantitative accuracy can be compromised by varying hybridization efficiencies among different probes. This variation necessitates extensive standardization and validation, increasing complexity. The limited dynamic range of detection and the potential for signal saturation further constrain its utility in differentiating high-abundance from low-abundance targets. Moreover, the analysis is reliant on pre-selected probes, which limits its ability to detect novel or unexpected sequences. These drawbacks emphasize the need for complementary methods to achieve comprehensive and reliable microbial analyses (Nozawa et al., 2020)

Another significant advancement is next-generation sequencing (NGS), which facilitates comprehensive profiling of the oral microbiome before and after periodontal treatments. Next-Generation Sequencing (NGS) offers the capability to sequence entire genomes or multiple genes simultaneously, providing unparalleled depth in analyzing microbial diversity and metabolic pathways. This capability is essential for understanding complex microbial ecosystems, such as the oral microbiome. Systematic reviews leveraging NGS data have demonstrated substantial shifts in microbial populations post-intervention, highlighting the dynamic nature of the oral microbiome. These studies indicate a reduction in harmful bacteria alongside an increase in beneficial microbial diversity following treatment, although they also point out challenges related to methodological variability and the intricate nature of microbial interactions (Zhang et al., 2021).

Unlike PCR, which is constrained to specific, predefined targets, NGS delivers high taxonomic resolution, enabling species- or even strain-level identification without prior knowledge of the microbial community. Its unbiased approach, free from reliance on predefined primers or probes, facilitates the discovery of novel or unexpected microbial species, making it invaluable for comprehensive genomic studies. Moreover, NGS extends beyond mere identification of microbial composition by revealing functional changes in microbial communities, such as shifts in metabolic pathways—an important aspect of studies focusing on interventions like those targeting periodontal health (Zhang et al., 2021). Furthermore, NGS surpasses PCR in taxonomic resolution, with the ability to identify microbial species and even strain-level variations, making it a superior choice for in-depth genomic analyses (Lochman et al., 2020; Zhang et al., 2021). A comparative analysis was provided in Table 5. These technological developments are revolutionizing microbiome research by providing more accurate diagnostics and insights into the complex relationships between oral health and systemic conditions.

9. Conclusions

The interplay between oral microbiota and systemic health is a critical area of research that underscores the importance of maintaining oral health as a component of overall well-being. Periodontal diseases not only affect the oral cavity but also have far-reaching

consequences, highlighting the need for a multidisciplinary healthcare approach. The evidence presented in this review indicates that microbial dysbiosis is a key factor linking periodontal disease with various systemic ailments, necessitating targeted interventions to restore microbial balance. Furthermore, understanding the influence of behavioral factors such as smoking and diet on the oral microbiome can guide public health strategies aimed at reducing the prevalence of periodontal disease. As research continues to evolve, integrating advanced diagnostic technologies and innovative therapeutic approaches will be essential for improving patient outcomes. Ultimately, prioritizing oral health within broader healthcare policies will be vital for addressing health disparities and enhancing quality of life across diverse populations.

10. Conflicts of Interest

The authors declare that there is no conflict of interest

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