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NARRATIVE REVIEW

The Oral Microbiome and Systemic Disease: From Microbial Dysbiosis to Therapeutic Opportunities

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ABSTRACT

The oral microbiome is a complex community of microorganisms that maintain oral homeostasis and continuously engage host immune and metabolic pathways. The disruption of this ecosystem can lead to dysbiosis, a condition that is increasingly linked to systemic diseases relating to the cardiovascular, metabolic, respiratory, gastrointestinal, neurological, and reproductive systems. This review discusses the biological mechanisms linking oral dysbiosis to systemic disease, such as microbial dissemination, disruption of the epithelial barrier, changes in microbial metabolites, immune activation, and oral–gut microbial interactions. It also highlights the difference between epidemiological association and causality, and the role of longitudinal, multi-omics, and interventional studies. Selective antimicrobials, probiotics, postbiotics, bacteriophages, host-directed therapies, and delivery systems such as nanotechnology are considered potential solutions to restore the microbial and inflammatory balance. Further, with an increasing number of studies investigating microbiome profiling and multi-omics, personalized risk assessment and intervention can be achieved. In conclusion, the oral microbiome is a potentially modifiable interface between local microbial ecology and systemic health, but more compelling evidence of causation, standardized assessment of the oral microbiome, and mechanism-based clinical trials will be necessary to develop clinically effective therapies.

Keywords: Dysbiosis; Inflammation; Microbiota; Mouth; Periodontitis; Precision Medicine.

INTRODUCTION

The oral cavity harbors a highly complex and diverse microbial ecosystem with bacteria, archaea, fungi, viruses, and other microorganisms in their own ecological niche. These communities constantly interact with host tissues and signaling pathways and contribute to the maintenance of oral homeostasis and other physiological processes, which is why the oral microbiome is considered an organized microbial community rather than a collection of individual pathogens [1]. Disruption of this ecological balance may lead to oral microbial dysbiosis, characterised by alterations in the composition, structure and function of the oral microbial community. Factors that influence dysbiosis include age, oral hygiene, smoking, systemic conditions, and host immunity, and this dysbiosis can contribute to chronic oral inflammation and periodontal tissue damage [1, 2]. Importantly, dysbiosis can impact more than the oral cavity. Oral dysbiosis may influence distant tissues through microbial products, immune signaling, and oral–gut interactions [3].

Oral dysbiosis and periodontal inflammation have been linked to cardiovascular, metabolic, respiratory, gastrointestinal, neurological, and other systemic diseases based on the accumulating evidence. However, these relationships are not always causal, and shared risk factors, reverse causality, and methodological differences have complicated the interpretation of these relationships [3, 4]. The oral–gut axis has also broadened the field by showing that microorganisms from the mouth can invade the gut and potentially influence the gut microbial communities, although the extent to which these processes drive systemic disease remains incompletely established [3]. PubMed and Google Scholar were searched to identify relevant studies published between 2012 and 2026. Search terms included "oral microbiome," "oral dysbiosis," "periodontitis," "systemic diseases," "oral–gut axis," "inflammation," "microbial dissemination," and "therapeutic interventions." Boolean operators (AND/OR) were used to combine keywords and broaden the search. Relevant publications addressing the biological mechanisms linking oral dysbiosis to systemic diseases, evidence for causality, microbiome-based risk assessment, and emerging therapeutic strategies were considered. Priority was given to recent original research, systematic reviews, meta-analyses, and mechanistic studies, alongside foundational publications relevant to the scope of this narrative review.

In this context, the oral microbiome is a potential therapeutic interface between the local microbial ecology and health outcomes. This review explores how oral microbial dysbiosis progresses to systemic disease and therapeutic opportunity, discusses how microbial communities from the oral cavity can impact distant organs, assesses evidence for causality, discusses evolving interventions directed at modifying microbial communities, and the opportunities for precision oral–systemic medicine.

THE ORAL MICROBIOME: AN ECOLOGICAL SYSTEM RATHER THAN A COLLECTION OF PATHOGENS

The oral microbiome is a spatial ecosystem in which microbes are located in various niches, such as the tongue, saliva, tooth surfaces, and the gingival sulcus and periodontal pocket. The oral sites are heterogeneous in oxygen availability, nutrient content, pH, host-derived substrates, and interactions with microorganisms, leading to significant differences in community composition. Oral microorganisms do not live alone; community stability and function depend on metabolic cooperation, competition, and signaling between microorganisms [5, 6]. In health-associated conditions, these communities help support the body's ability to resist colonization, maintain mucosal barrier function, regulate nutrient absorption and metabolism, and maintain immune homeostasis. Oral biofilms are particularly important because their spatial organization allows microorganisms to exchange metabolites and signaling molecules while adapting to changing host conditions. Therefore, microbial numbers cannot be used to measure oral health alone; the structure and activity of the community are also important [9].

Composition and spatial organization: The oral microbiome is comprised of bacteria from many phyla, as well as fungi, archaea, viruses, and other microbial members. Saliva and tongue dorsum, supragingival and subgingival communities have different microbial profiles. This biogeographical arrangement makes it possible for the effects of the same microbial species to vary based on their location level, abundance, metabolic activity, and interactions with other organisms [10]. A very important example of microbial organization is dental plaque. Early colonizers attach to oral surfaces and establish conditions for recruitment of other species, which lead to the formation of mature, multispecies biofilms. These communities may show coordinated responses to environmental shifts and metabolic cross-feeding that enable them to survive mechanical clearance and host defences [8].

Eubiosis, dysbiosis and ecological transition: Oral health is more accurately described as an ecological balance and the absence of particular microorganisms. Dysbiosis is the disruption of this balance due to alterations of community structure or function that occur in response to environmental or host-related pressures. For example, in periodontal disease, inflammation alters the local environment and may promote the development of microbial communities that thrive in an inflammatory environment, establishing a cycle of microbial alteration and host tissue inflammation [10, 11]. This ecological approach also debunks the usual pathogen-driven model. Acquisition of a single pathogen may not be responsible for disease; instead, it might be a change in the behaviour and interactions of an established microbial community [7]. Poly-microbial changes may affect host immune responses, virulence potential, and metabolic activity, so community-level properties are important targets for understanding disease progression.

Drivers of oral dysbiosis: Local and systemic pressures affect the composition of the oral flora. These influences are not independent; dietary habits can alter the oral environment, which in turn can change the microbial community. Microbial metabolism can then reshape the local pH, redox conditions, and host signaling, which in turn can influence the availability of nutrients [9, 10]. Inflammation can also modify the nutrition available, and the metabolic condition of the host may influence the microbial community. It is therefore critical to grasp these ecological stressors in order to recognise when a health-associated microbiome becomes dysbiotic. Key ecological characteristics of the oral microbiome and their relevance to systemic health are summarized in **Table I**.

Table I: Ecological characteristics of the oral microbiome and their relevance to systemic health

Study	Focus	Key ecological characteristic	Relevance to dysbiosis/systemic health
Baker et al., 2024 [1]	Oral microbiome diversity	Distinct microbial communities occupy anatomically different oral niches	Establishes the oral cavity as a complex, spatially organized ecosystem
Lamont et al., 2018 [5]	Oral microbial communities	Multispecies biofilms involve metabolic cooperation, competition, and host interaction	Explains community-level behavior beyond individual pathogens
Lamont & Hajishengallis, 2015 [6]	Polymicrobial dysbiosis	Disease can arise from synergistic interactions among microbial communities and altered host responses	Provides a mechanistic basis for dysbiosis-associated inflammation
Mark Welch et al., 2016 [7]	Biofilm spatial organization	Oral biofilms exhibit defined spatial structures and microbial interactions	Spatial organization influences microbial function and ecological stability
Rosier et al., 2018 [8]	Oral microbial ecology	Oral microbial communities are shaped by environmental and host-associated factors	Helps explain transitions between health-associated and dysbiotic states
Abusleme et al., 2013 [9]	Subgingival microbiome	Periodontal health and disease are associated with distinct microbial community structures	Supports a community-level rather than single-pathogen model of periodontal dysbiosis
Griffen et al., USA, 2012 [10]	Oral microbiome composition	Healthy individuals harbor diverse and site-specific oral microbial communities	Demonstrates substantial interindividual and ecological variation

FROM THE MOUTH TO DISTANT ORGANS: MECHANISMS OF ORAL–SYSTEMIC COMMUNICATION

Oral dysbiosis is not likely to have a single pathway of effect on systemic health. Oral dysbiosis may influence systemic health through interconnected mechanisms, including microbial dissemination, epithelial barrier disruption, altered microbial metabolites, immune activation, and oral–gut microbial exchange. Their relative contribution is likely to vary according to the disease and host context (**Figure 1**) [1, 3]. Periodontal tissue inflammation can lead to exposure of oral microorganisms and products to the circulation. Disruption of the periodontal epithelial barrier may facilitate the entry of bacterial components, including lipopolysaccharides, proteins, and nucleic acids, into local tissues and blood [4]. However, it is important to note that persistent bacteremia is not a necessary condition for systemic effects. Chronic exposure to microbial products and inflammatory mediators may be enough to generate chronic host responses, especially in metabolically or vascular susceptible individuals [12].

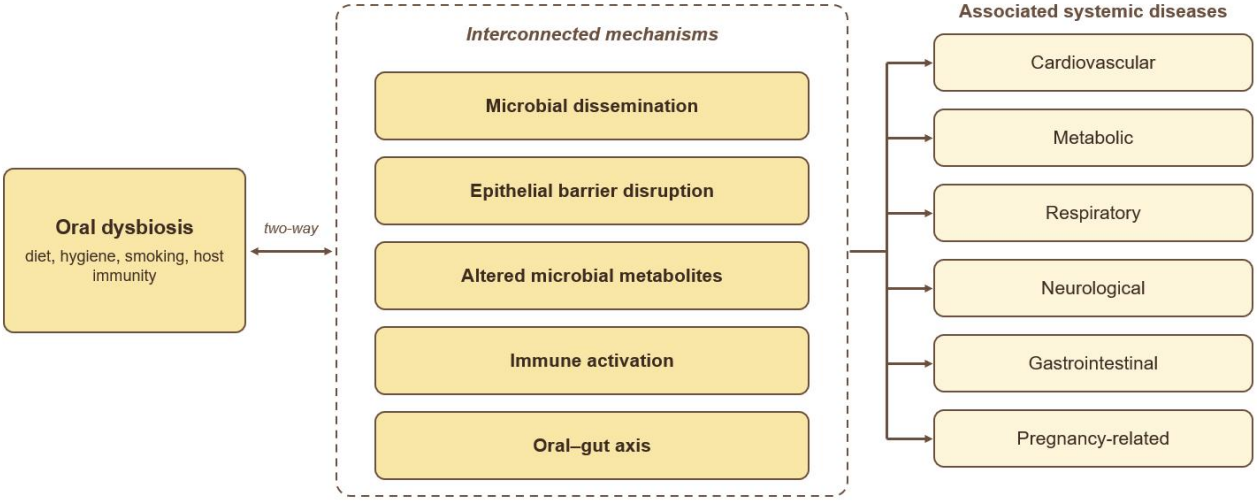


Figure 1: Oral dysbiosis reaches distant organs through interconnected mechanisms. *Oral dysbiosis, driven by factors such as diet, hygiene, smoking, and host immunity, engages five interconnected mechanisms: microbial dissemination, epithelial barrier disruption, altered microbial metabolites, immune activation, and the oral–gut axis. These mechanisms act together rather than as a single pathway, and inflammation feeds back on the oral microbiome (two-way arrow). They are associated with cardiovascular, metabolic, respiratory, neurological, and gastrointestinal disease and with pregnancy-related outcomes, although causality has not been established for most of these links.*

Barrier disruption and epithelial permeability: The periodontal epithelium is an important barrier of physical and immune defense that interfaces oral biofilm and host tissues. These dysbiotic communities can lead to epithelial damage and to inflammatory signaling, which can be mediated by increased permeability of the epithelium, and allow microbial products to reach deeper tissues, thus increasing the microbial load for immune cells [1, 4]. The barrier dysfunction is also applicable outside of the oral cavity. In the oral-gut axis, ingested microorganisms and microbial products interact with the intestinal epithelial barrier, with potentially different effects depending on the existing gut microbial community and immune status of the host [13].

Microbial metabolites and molecular signaling: Dysbiosis can modify not only which microorganisms are present but also their metabolic output. In comparison to direct microbial dissemination and inflammatory signaling, the association of specific oral metabolites with systemic disease is not well understood [14]. This distinction is significant because systemic effects may not be well predicted by the composition of the microbiota. A functional profile of two people with similar microbial taxa can vary due to diet, host physiology, host-microbial interactions, and environmental conditions [1, 14]. Host immune activation is an important mechanistic link between oral dysbiosis and systemic inflammation. These alterations in the activity of the various types of leukocytes and in the levels of circulating inflammatory mediators, caused by an ongoing periodontal inflammation, may affect distant tissues. Recent studies also indicate that periodontal inflammation may have an effect on the function of innate immune cells outside the periodontium. Systemic immune reprogramming can offer a mechanism by which a remote organ can be affected by inflammatory conditions without requiring chronic colonization of the organ [15].

Oral–gut axis: The gastrointestinal tract is constantly exposed to oral microorganisms as saliva and oral fluids are continuously swallowed during the day. While most oral organisms cannot survive in the intestine, others might be able to survive or interact with the intestinal microbiota or be enriched in an environment of dysbiosis or compromised intestinal colonization resistance [3, 13]. There is increasing experimental and clinical evidence supporting this oral–gut connection. The consequences might involve changes in the integrity of the intestinal barrier, production of microbial metabolites, and activation of mucosal immunity [16].

Immune and metabolic cross-talk: The above-described pathways are not mutually exclusive. This establishes a potential feedback loop whereby oral dysbiosis can trigger immune pathways, inflammation can disrupt epithelial barriers, and changes in microbial metabolism can affect the microbial community and host signalling [1, 3,4]. Thus, the oral–systemic connection is best viewed as a multidirectional microbial–host network, rather than a simple movement of oral pathogens into distant organs. It is important to determine which parts of this network are causal, disease-specific, and therapeutically modifiable.

ORAL DYSBIOSIS AND SYSTEMIC DISEASE: CONVERGENT BIOLOGICAL PATHWAYS

There is a link between oral dysbiosis and systemic disease in multiple organ systems, although this evidence is not consistent. These pathways could overlap in different diseases, and the clinical relevance relies on host susceptibility and disease-specific factors.

Cardiovascular disease: Cardiovascular disease is among the most extensively studied systemic conditions in relation to periodontal disease. Oral microorganisms and products can have an impact on vascular tissues through recurring bacteremia, activation of the endothelial cells, platelet interactions, and systemic inflammation, and some recent evidence indicates that changes in the oral microbiome may be linked to pathways that could lead to atherosclerosis and other cardiovascular diseases, though it is not clear whether specific microbe changes are causal [17]. Shared risk factors such as smoking, diabetes, age, and socioeconomic factors also affect the relationship. For this reason, the relationship between periodontal disease and cardiovascular disease should not be taken for granted as evidence of an oral dysbiosis-cardiovascular disease link.

Diabetes and metabolic disease: The association between periodontitis and type 2 diabetes mellitus (T2DM) is now considered to be bidirectional. Hyperglycemia has been shown to cause a decrease in immune function and cause an increase in periodontal inflammation, while ongoing periodontal infection has been shown to add to systemic inflammatory burden and poor metabolic control [18]. This bidirectional association was confirmed by another large population-based cohort study, which reported associations between periodontitis and T2DM but did not implicate specific microbial changes as being responsible for metabolic dysfunction [19]. The oral microbiome may instead be a part of a larger inflammatory–metabolic network.

Respiratory disease: Oral microorganisms could influence pulmonary health by being transmitted via the anatomical connection between the oral cavity and the respiratory tract. Oral microbial communities can also be aspirated into the lower respiratory tract, especially in those at risk for aspiration due to swallowing impairments or other risk factors [20]. A systematic review and meta-analysis reported associations between periodontitis and respiratory diseases, with evidence particularly relevant to chronic obstructive pulmonary disease and obstructive sleep apnoea [21].

The oral–gut axis and gastrointestinal disease: The gastrointestinal tract is constantly exposed to oral microorganisms via ingestion, providing an interface between the oral microbial ecology and the systemic physiology, and oral-derived microorganisms can interact with the foregut barrier and mucosal immune responses and affect gut barrier integrity and immune responses when colonization resistance is compromised [3]. The oral microbiome has attracted particular interest in colorectal cancer, where changes in oral microbial composition and enrichment of organisms such as *Fusobacterium nucleatum* have been reported, although it is difficult to rule out whether the changes are causative or simply a result of the disease, treatment, diet, or changes in host physiology [22, 23].

Neurological and neurodegenerative diseases: The proposed oral–brain connection involves several mechanisms, including systemic inflammation, microbial or microbial-product dissemination, blood–brain barrier dysfunction, and neuroinflammatory signaling [24]. Periodontal pathogens have been especially noted in Alzheimer's disease research for their ability to trigger chronic inflammatory responses and to modulate neuronal or glial pathways. Previous human studies have shown that there are changes in oral microbial composition in the Alzheimer's disease group compared to the cognitively healthy population, although these findings are mainly associative in nature [25]. It is unclear whether oral dysbiosis plays a direct role in the progression of the disease and neurodegeneration, or whether it is a result of changed health behaviour during disease progression or affected by common risk factors.

Pregnancy and systemic maternal outcomes: Maternal periodontal disease has also been examined for negative pregnancy outcomes, and it was discovered that it is linked to low birth weight, pre-eclampsia, gestational diabetes and preterm birth. The suggested mechanisms are systemic inflammatory signaling and spread of microorganisms from periodontal tissues [26]. While observational studies have shown links to a number of adverse outcomes, it has not been proven that periodontal treatment will prevent these outcomes in intervention studies, so the association between periodontal disease and adverse outcomes may be due to shared risk factors for periodontal disease and the adverse outcomes in some settings.

Convergent pathways across systemic diseases: Across these conditions, several biological themes recur: microbial exposure beyond the oral cavity, barrier dysfunction, persistent inflammatory signaling, immune modulation, and interactions with other microbial ecosystems. These themes resonate with the idea of the oral microbiome as a systemic biological interface, but also underscore the importance of identifying the association, biological plausibility, and demonstrated causality for each disease. The available evidence across systemic diseases, including proposed mechanisms and major knowledge gaps, is summarized in **Table II**.

Table II: Oral dysbiosis and systemic disease: evidence, mechanisms, and knowledge gaps

Study	Systemic condition	Oral microbial/dysbiotic feature	Proposed mechanism	Evidence and major limitation
Tonelli et al., 2023 [17]	Cardiovascular disease	Periodontal dysbiosis and altered oral microbial communities	Endothelial activation, inflammation, microbial dissemination	Strong epidemiological and mechanistic interest; causality remains unresolved
Salhi & Reners, 2022 [18]	T2DM	Periodontal inflammation and dysbiosis	Bidirectional inflammatory and metabolic signaling	Supports a bidirectional relationship; microbial causality remains uncertain
Chien et al., 2023 [19]	T2DM	Periodontitis-associated inflammatory burden	Reciprocal effects between periodontal and metabolic inflammation	Large longitudinal cohort; microbiome-specific mechanisms not established
Pathak et al., 2021 [20]	Respiratory disease	Altered oral microbial communities	Aspiration and systemic/local immune activation	Biological plausibility is strong; disease-specific causality requires further study
Molina et al., 2023 [21]	Respiratory disease	Periodontal disease-associated dysbiosis	Aspiration, inflammation, immune modulation	Meta-analytic evidence; heterogeneity across respiratory outcomes
Camañes-Gonzalvo et al., 2024 [22]	Colorectal cancer	Altered oral microbiota, including *F. nucleatum*	Oral–gut transmission and microbial–tumor interactions	Association is increasingly documented; direction of causality remains uncertain
Pignatelli et al., 2023 [23]	Colorectal cancer	*F. nucleatum* and periodontal-associated microorganisms	Chronic inflammation and tumor–microbe interactions	Mechanistically plausible; clinical causality remains under investigation
Li et al., 2024 [24]	Alzheimer's disease	Periodontal pathogens and oral dysbiosis	Neuroinflammation and microbial-product dissemination	Mainly mechanistic/observational evidence; causal relationship remains unresolved
Fu et al., 2023 [25]	Alzheimer's disease	Altered oral microbial and serological profiles	Oral–systemic inflammatory signaling	Human association; directionality requires longitudinal evidence
Machado et al., 2023 [26]	Pregnancy outcomes	Maternal periodontal disease	Systemic inflammation and microbial dissemination	Associations reported; preventive effects of treatment remain inconsistent

BEYOND ASSOCIATION: ESTABLISHING CAUSALITY IN ORAL–SYSTEMIC DISEASE

There are many associations between dysbiosis in the oral cavity and systemic disease, but these associations are not sufficient to prove that oral microbial changes play a direct role in the development of disease. Causality cannot be inferred from observational studies alone, and supportive evidence should be gleaned from longitudinal studies, intervention trials, mechanistic experiments, and causal inference studies, as well.

Association versus causation: There is a majority of observational, rather than experimental, evidence on the association of periodontal disease with systemic diseases. While prospective cohorts can be used to create a temporal association, there may be residual confounding, especially for smoking, diet, socioeconomic status, diabetes, and access to health care. A recent epidemiological review of the association between periodontitis and cardiovascular disease found this association to be consistent across all studies, but evidence from intervention studies was not conclusive [27]. Microbiome studies present further challenges due to the fact that the microbial composition depends on the sampling location, method used for microbial sequencing, antibiotic exposure, diet, and host characteristics. Therefore, the presence of a microbial signature associated with disease is not necessarily a reflection of a microorganism causing disease.

Evidence from intervention studies: Interventional evidence is more powerful evidence that periodontal inflammation is a risk factor for systemic outcomes. Randomized trials suggest that periodontal treatment may improve some inflammatory or glycemic measures, but results are inconsistent. Evidence that periodontal therapy prevents cardiovascular disease remains insufficient, highlighting the distinction between improving systemic biomarkers and preventing clinical disease outcomes [28, 29].

Multi-omics and causal inference: Recent approaches increasingly integrate microbiome profiling with metabolomics, inflammatory proteomics, and host genomic data. This allows a shift from microbial associations to the testing of possible intermediate pathways between oral microorganisms and host phenotypes [30]. Another way to study causality is via Mendelian randomization (MR), which analyses the genetic variants that are linked to the exposure as instrumental variables. A bidirectional MR study conducted in 2024 revealed some possible causal links between individual taxa of gut microbes and periodontitis, demonstrating the potential to use genetic epidemiology in addition to traditional observational studies, but also highlighting the need to account for horizontal pleiotropy, population differences, and microbiome GWAS data limitations [31].

Major methodological challenges: There are still several limitations that limit the ability to draw causal conclusions. First, the methods for sampling the oral microbiome vary significantly, and so do the methods used in the laboratory, making it difficult to compare the studies directly. Second, the abundance of microorganisms need not correspond to the number of living organisms or microorganisms that are pathogenic. Third, systemic diseases can influence oral behaviour, medication use, diet, immune function, or microbial composition, which can also influence systemic diseases. Finally, there can be microbial communities and host responses, rather than individual organisms, involved in causal relationships, which are difficult to reduce to individual members. Moving forward, future studies need to combine longitudinal measurements of microbiomes with standardization of sampling, multi-omics characterization, mechanistic validation, and well-designed clinical interventions. These can be used to help establish if oral dysbiosis is a cause, consequence, mediator, or biomarker of systemic disease.

THERAPEUTIC OPPORTUNITIES: TARGETING THE ORAL MICROBIOME–SYSTEMIC DISEASE AXIS

The therapeutic implications of the oral–systemic connection extend beyond conventional elimination of periodontal pathogens. Nonetheless, as the understanding of dysbiosis and host responses evolves, new treatment modalities are emerging that focus on restoring microbial balance, controlling microbial function, host modulation, and localized delivery of anti-inflammatory drugs, which may be more applicable to treatment aimed at decreasing systemic inflammatory exposure without significantly altering the resident oral microbiome [32].

Conventional periodontal treatment: Mechanical plaque control and subgingival instrumentation remain the foundation of periodontal therapy, directly reducing microbial burden and inflammation. The growing awareness of antimicrobial resistance and alteration of commensal organisms, however, has fostered the development of more selective adjunctive strategies [32].

Precision antimicrobial strategies: Microbiome-directed therapies target disease-associated organisms or ecological functions, instead of broadly suppressing oral bacteria. Bacteriophages are one such approach because they can recognize specific bacterial hosts and potentially reduce selected members of dysbiotic communities while preserving unrelated commensals [33]. Alternative strategies are the use of antimicrobial peptides, quorum-sensing inhibitors, and compounds that disrupt biofilm growth and microbial virulence or toxicity. These approaches could offer more ecological selectivity than conventional antibiotics, but their systemic effects have yet to be proven.

Probiotics, prebiotics and postbiotics: Probiotics have been studied as an adjunct to periodontal treatment, as selected beneficial microorganisms could potentially inhibit the growth of pathogenic microorganisms, alter their metabolism, and regulate immune responses within the host. A network meta-analysis of 33 studies involving 1290 individuals reported that probiotic supplementation alongside professional mechanical plaque removal (PMPR) might improve some periodontal outcomes, although effects varied by probiotic strain and treatment duration [34]. Postbiotics involve the use of inactive microorganisms or microbes themselves, or their metabolites, to provide a benefit. Standardized definitions, dosing strategies, and long-term clinical evidence are limited, which may decrease concerns over the introduction of live microorganisms, while retaining some immunomodulatory or antimicrobial effects [35].

Microbiome-directed and phage-based approaches: Bacteriophage and other precision microbial approaches aim to selectively target disease-associated organisms within dysbiotic biofilms while minimizing disruption of commensal communities. Their potential is particularly relevant to biofilm-associated periodontal disease, although host range, biofilm penetration, bacterial resistance, formulation and regulatory requirements remain major barriers to clinical translation [33]. Current therapeutic strategies targeting the oral microbiome–systemic disease axis and their translational limitations are summarized in **Table III**.

Host-directed therapies: An alternative therapeutic approach is to inhibit inflammation without eradicating the whole microbial community, as tissue destruction is due to interactions between microbial communities and an exaggerated host response. One example is inhibition of complement. Experimental and early clinical studies with C3-targeting agents like AMY-101 have shown the potential of complement modulation to decrease periodontal inflammation and suggested host-directed treatment as an adjunct to microbial control [36]. Host modulation

may ultimately be of particular benefit to those patients in whom microbial dysbiosis remains despite mechanical therapy. But systemic safety and interference with protective immune functions must be considered.

Nanotechnology and targeted delivery: Local delivery systems can deliver therapeutic agents directly into periodontal pockets and decrease systemic exposure. The use of antibacterial, anti-inflammatory, and regeneration agents has been studied with the aid of nanoparticles such as polymeric nanoparticles, liposomes, nanofibers, hydrogels, and other nanocomposites [37, 38]. This approach could be particularly relevant to oral–systemic disease because localized treatment may reduce the microbial and inflammatory burden at its source without requiring prolonged systemic antimicrobial exposure. However, the vast majority of the nanoparticle strategies are still in the preclinical or early translational phase, and potential toxicity, formulation stability, tissue penetration, and efficacy in humans are all in question. The long-term goal is to tailor therapy to individual microbial and inflammatory phenotypes. Such personalization will require validated microbiome biomarkers, reproducible dysbiosis signatures, and clinical trials demonstrating meaningful systemic benefit.

Table III: Therapeutic strategies targeting the oral microbiome–systemic disease axis

Study	Therapeutic approach	Primary target	Potential mechanism	Current evidence	Key translational limitation
Li et al., 2023 [32]	Probiotic adjunctive therapy	Periodontal microbial community	Microbial modulation and ecological support	Meta-analysis supports improvement in several periodontal outcomes	Strain-, dose-, and duration-dependent effects
Łasica et al., 2024 [33]	Bacteriophage/predatory bacteria therapy	Selected periodontal bacteria	Selective bacterial killing within dysbiotic biofilms	Mainly experimental	Limited phage characterization and clinical evidence
Duarte de Mendonça et al., 2024 [34]	Probiotics	Periodontal microbial community	Competition, microbial modulation and host effects	Network meta-analysis supports adjunctive benefit for several periodontal outcomes	Strain-, dose-, and duration-dependent effects
Moraes et al., 2022 [35]	Postbiotics	Microbial metabolites/cell components	Antimicrobial and immunomodulatory effects without viable organisms	Early clinical/preclinical evidence	Limited standardization and human data
Kajikawa et al., 2022 [36]	Host modulation/complement inhibition	Complement C3 pathway	Reduces excessive inflammatory tissue damage	Early clinical evidence with AMY-101	Long-term safety and broader validation
Wang et al., 2024 [37]	Nanoparticle delivery	Local microbial and inflammatory targets	Targeted and controlled delivery of therapeutic agents	Predominantly preclinical	Toxicity and translation to human therapy
Kumaar & Nair, 2023 [38]	Intra-periodontal nanodelivery	Periodontal pocket	Localized antimicrobial/anti-inflammatory delivery	Preclinical and limited clinical evidence	Formulation, retention and clinical validation

From Oral Microbiome Profiling to Precision Therapeutics: The growing availability of microbiome sequencing and multi-omics approaches creates an opportunity to move from broad descriptions of dysbiosis toward individualized microbial and host profiles [1, 3]. Metagenomics, metabolomics, transcriptomics, and spatial analyses can not only describe which microbes are present, but also their function and relationship to host tissue (**Figure 2**). Oral samples, particularly saliva, are useful sources of non-invasive biomarkers as they can be easily collected repeatedly and contain microbial, metabolic, inflammatory, and host-derived information. A study of 692 healthy individuals identified oral microbial signatures that were associated with metabolic and hematological biomarkers and suggested further investigation is needed before they can be used clinically [40]. Precision approaches will likely involve microbial profiles in combination with host inflammatory markers, clinical phenotypes, metabolomics, and genomics. To separate clinically relevant dysbiosis from normal inter-individual variation, multi-omics approaches can help identify functional pathways [39].

Predicting systemic disease risk: Oral microbiome profiles may not be the best suited for use as stand-alone diagnostic tests, but may be better suited to risk stratification and early detection. Microbial signatures in conjunction with the traditional clinical markers may be able to distinguish those who need more frequent follow-up for cardiometabolic, inflammatory or other systemic diseases. But there is a need for reproducibility across populations and standardized sampling. A precision approach in the future might include microbiome profiling, definition of the predominant dysbiotic pattern, characterization of the underlying biological mechanism, choice of specific intervention, and then monitoring of microbiome and clinical response. This approach may lead to moving oral–systemic therapy from broad–spectrum microbial suppression to targeted microbial–inflammation therapies.

TRANSLATIONAL CHALLENGES AND FUTURE DIRECTIONS

Despite increasing evidence linking oral dysbiosis with systemic disease, translation into clinical practice remains limited by variability in microbiome phenotyping, sampling procedures, sequencing platforms, and patient populations. Reproducible microbial signatures and clinically validated biomarkers are still needed before oral microbiome profiles can support routine risk stratification or treatment selection [39, 40]. Therapeutic translation also requires evidence that modifying a specific microbial or host pathway produces meaningful systemic benefits. Future studies should therefore prioritize longitudinal designs, standardized microbiome assessment, mechanism-based interventions, and clinical outcomes rather than surrogate biomarkers alone [34].

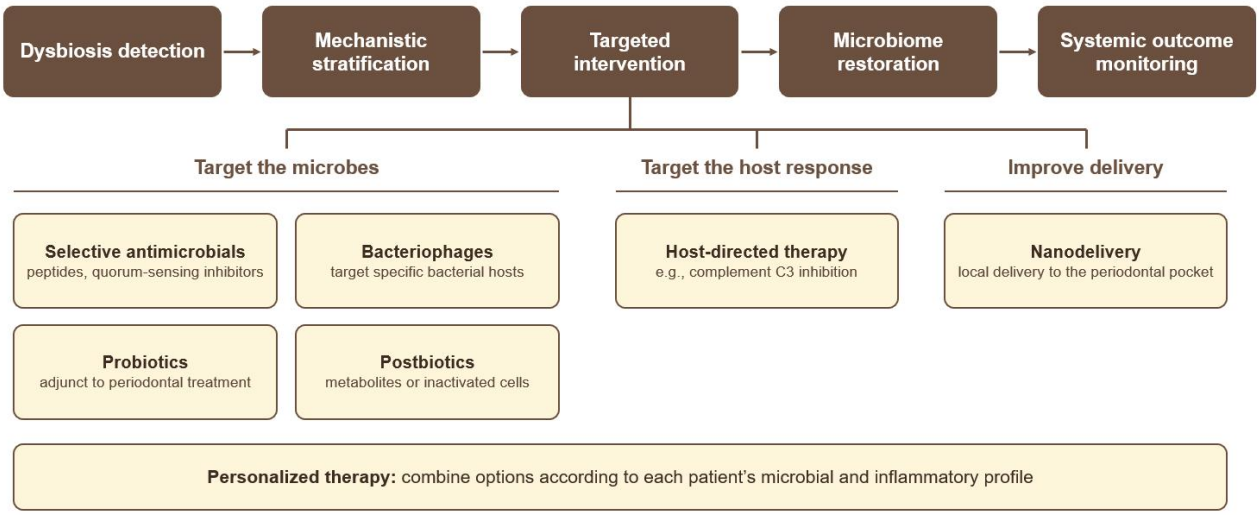


Figure 2. Therapeutic roadmap: matching intervention to the dysbiotic mechanism. *A precision approach proceeds from detection of dysbiosis and mechanistic stratification to targeted intervention, microbiome restoration, and monitoring of systemic outcomes. Interventions can target the microbial community (selective antimicrobials, bacteriophages, probiotics, and postbiotics), the host inflammatory response (host-directed therapy), or the delivery of therapeutic agents (nanodelivery), and may ultimately be combined in a personalized approach guided by each patient's microbial and inflammatory profile.*

CONCLUSION

The oral microbiome represents an important interface between oral and systemic health. Microbiological dissemination, disruption of epithelial barriers, microbial metabolites, and the presence of persistent immune activation are all mechanisms that may play a role in the spread of dysbiosis to distant organs, and there is growing evidence that dysbiosis may affect cardiovascular, metabolic, respiratory, gastrointestinal, and neurological systems and may also be associated with adverse pregnancy outcomes. But the associations found should not be interpreted as causes, and disease-specific mechanisms should be further validated. Challenges for future progress include integrating microbiome profiling with host and clinical information to define clinically relevant microbiome dysbiosis and identify suitable therapeutic interventions. Determining when oral dysbiosis represents a causal driver rather than a marker of systemic disease will be essential for integrating microbiome-based oral therapies into precision systemic medicine.

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