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Local and systemic effects of probiotic modulation of the oral microbiota

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Abstract

The oral cavity hosts a complex microbial ecosystem in which bacteria, fungi, viruses, and archaea interact with the host to maintain both local and systemic homeostasis. Increasing evidence indicates that disruption of this equilibrium can promote the overgrowth of opportunistic species such as Porphyromonas gingivalis, Fusobacterium nucleatum, and Streptococcus mutans, triggering chronic inflammatory processes with potential effects beyond the oral environment. This narrative review summarizes the mechanisms through which oral dysbiosis may influence immune, metabolic, and microbial pathways along the oral–gut and oral–lung axes, potentially contributing to systemic conditions including cardiovascular, respiratory, intestinal, and autoimmune disorders, cancer development, and preterm delivery. Within this framework, targeted modulation of the oral microbiota through probiotics, prebiotics, and postbiotics may represent a potential prophylactic strategy. Several strains (including *Lactobacillus reuteri*, *Streptococcus salivarius K12/M18*, *Bifidobacterium animalis BB-12*, and *Lactobacillus rhamnosus GG*) have been reported, based on current evidence, to exert beneficial effects by competing with pathogens, modulating inflammatory responses, and supporting mucosal barrier function, with possible downstream effects mediated through interactions with the intestinal microbiota. Prebiotics and postbiotics represent complementary approaches, promoting a more stable and less inflammatory oral microenvironment while offering advantages in terms of safety, stability, and applicability in oral care products. Despite these encouraging findings, the lack of long-term clinical studies with endpoints clearly demonstrating systemic benefits from probiotic interventions targeting oral health remains a limitation. Importantly, current evidence does not establish a consistent causal relationship between oral dysbiosis and the systemic diseases discussed in this review. Overall, these findings suggest that probiotic interventions may serve as a valuable adjunct to oral healthcare, with the potential, based on current evidence, to contribute to the prevention and management of systemic diseases through targeted modulation of the oral microbiome. Nevertheless, more comprehensive and rigorous research is required to confirm these potential effects.

Keywords Oral dysbiosis, Systemic disorders, Oral-gut axis, Oral-lung axis, Probiotic

1 Introduction

The oral cavity constitutes a complex biological ecosystem where bacteria, fungi, viruses, and other microorganisms coexist, playing a crucial role not only in oral health but also, as increasingly recognized, in systemic health [1]. Under homeostatic conditions, the oral microbiota supports essential physiological functions, including barrier protection, initial digestion, immune modulation, and defense against pathogens. However, disruption of this equilibrium, resulting in oral dysbiosis, can trigger localized or systemic inflammatory processes [2].

These processes not only compromise dental health (manifesting as caries, gingivitis, and periodontitis), but may also exert effects beyond the oral cavity, impacting the cardiovascular, metabolic, respiratory, neurological, and immune systems [2]. Recent literature has elucidated multiple pathogenic mechanisms through which oral microorganisms or their metabolites can transmit inflammatory signals or translocate systemically, thereby influencing distant organs and tissues [3–5].

Within this context, there is growing interest in strategies aimed at beneficially modulating the oral microbiota, among which the use of oral probiotics emerges as a promising intervention strategy [6]. Several studies have demonstrated that specific strains of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus salivarius* contribute to the restoration of microbial balance, reduction of oral pathogen colonization, and modulation of the local immune response [7, 8]. These effects extend beyond the oral cavity, as maintaining an eubiotic oral microbiota may attenuate low-grade systemic inflammation, offering potential benefits for the physiological health.

This narrative review aims to delineate the current understanding of the interplay between the oral microbiota, systemic health, and probiotic interventions by critically analyzing microbiological, immunological, and clinical evidence that supports an integrated perspective of oral health as a fundamental component of overall organismal well-being. The literature selection was conducted using PubMed, focusing on studies published between 2020 and 2025. Included were preclinical studies (animal and in vitro models), observational clinical studies, and meta-analyses. The search was performed using the following keywords: oral microbiota and systemic disease, oral dysbiosis and systemic disease, oral-gut axis, and oral-lung axis.

2 The link between oral dysbiosis and systemic diseases: the oral-gut axis and the oral-lung axis

The oral microbiota represents one of the most complex and diverse microbial ecosystems in the human body, colonizing multiple niches within the oral cavity (including the tongue, dental surfaces, gingiva, oral mucosa, and saliva) each characterized by specific environmental properties that selectively support distinct microbial communities [9–11].

This community includes bacteria, fungi, viruses, and archaea, with more than 700 estimated bacterial species per individual [2, 10]. Several reviews offer comprehensive and exhaustive descriptions of the components of the oral microbial community [12, 13]. Microbial communities adhere to surfaces and form biofilms whose structure and composition vary according to the niche (for example, the tongue harbors more complex and anaerobic communities compared with the buccal mucosa), making the oral habitat highly dynamic and selective [14].

Under healthy conditions, the oral microbiota acts in symbiosis with the host, contributing to the protection of the oral cavity from pathogen invasion [11], the initial digestion of food [12], and the local modulation of the immune response [15]. However, the composition and stability of the oral microbiota may be altered by a complex interplay of endogenous and exogenous factors, including oral hygiene, dietary habits, salivary flow, and systemic conditions such as diabetes or cardiovascular disease [16–18]. Environmental exposures, lifestyle habits (e.g., smoking and alcohol), and pharmacological treatments can further destabilize the ecological balance, promoting dysbiotic transitions [11].

In eubiotic conditions, the oral microbiota is characterized by high microbial diversity and functional balance, supporting immune homeostasis and tissue health. By contrast, dysbiosis involves a reduction in microbial richness and diversity, promoting the proliferation of opportunistic species that predispose the host to oral diseases (such as dental caries and periodontitis) and generating inflammatory responses with potential systemic implications [19, 20].

Table 1 summarizes the main bacterial genera and species commonly associated with oral health (eubiosis) and dysbiosis-related diseases. In eubiotic conditions, commensal taxa such as *Streptococcus*, *Veillonella*, *Actinomyces*, *Rothia*, and *Neisseria* contribute to biofilm homeostasis, maintenance of mucosal integrity, and modulation of local immune responses [21–24]. These microorganisms play essential roles in preserving ecological balance and preventing the overgrowth of pathogens.

Conversely, oral dysbiosis is marked by a shift toward pathogenic and opportunistic species, including *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Fusobacterium nucleatum*, and *Streptococcus mutans*, implicated in the pathogenesis of caries, gingivitis, and periodontitis [25, 26]. The production of pro-inflammatory metabolites and proteases contribute to tissue disruption and chronic inflammatory state.

Table 1 Main bacterial components of the oral microbiota in health and dysbiosis

Condition	Main families/genera	Role and characteristic	References
Oral eubiosis	*Streptococcus* spp. (es. *S. mitis*, *S. sanguinis*, *S. gordonii*)	Pioneer bacteria forming commensal biofilms; compete with pathogens; produce hydrogen peroxide and bacteriocins.	[9]
	Veillonella spp.	Metabolize acids produced by other bacteria; contribute to oral pH balance.	[11]
	Actinomyces spp.	Involved in initial biofilm formation; stimulate physiological immune response.	[10]
	Rothia spp. e *Neisseria* spp.	Associated with stable oral microbiota and reduced inflammatory risk.	[24]
Oral dysbiosis	*Porphyromonas gingivalis*	Keystone pathogen in periodontitis; produces proteases (gingipains) and induces chronic inflammation.	[25]
	Tannerella forsythia, *Treponema denticola*	Part of the "red complex" associated with severe periodontitis.	[26]
	Fusobacterium nucleatum	Promotes bacterial coaggregation and may facilitate systemic dissemination; associated with colon cancers.	[32, 33]
	Prevotella intermedia, *Campylobacter rectus*	Involved in gingivitis and periodontal infections; release pro-inflammatory metabolites.	[29, 30]
	Streptococcus mutans, *Lactobacillus* spp.	Acidogenic and aciduric bacteria, primary agents of dental caries.	[25]

In recent years, research has increasingly focused on the role of the oral microbiota not only in local diseases, but also as a potential key factor in systemic pathological conditions. A growing body of research suggests that the composition of the oral microbiota could potentially play a role as an early indicator of certain systemic diseases such as type 2 diabetes (T2DM), atherosclerosis, cardiovascular and respiratory disorders, autoimmune diseases, and digestive-related disorders [27]. Moreover, changes in oral microbiota during pregnancy seem to be correlated to the risk of pre-term delivery [28]. However, further investigation is needed to better understand the strength, consistency, and clinical relevance of this association.

In this long-distance dialogue, the so-called oral–gut axis and the oral-lung axis represent two communication pathways in which a dynamic and complex microbial network comes into play.

2.1 The oral-gut axis

This oral-gut axis is maintained through the continuous exchange of microorganisms, metabolites, and immune mediators that connect the oral cavity to the gastrointestinal tract, thereby influencing systemic homeostasis [29]. Saliva and swallowing are the main routes by which oral microorganisms reach the intestine, with approximately 10^{11} oral bacteria ingested daily [9]. Under physiological conditions, these microbes are rapidly neutralized or integrated into the intestinal microbial community. However, in the presence of oral dysbiosis opportunistic species like *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Campylobacter rectus* may translocate and alter the gut microbiota composition, promoting a chronic pro-inflammatory state [30, 31].

The circulating and enteral routes represent the two main pathways enabling bacterial dissemination within the digestive tract [32]. The oral–gut axis is further shaped by shared immune and metabolic pathways. Oral bacteria trigger inflammation by activating Toll-like receptor (TLR) pathways, creating a pro-inflammatory state, and producing metabolites that disrupt intestinal barrier integrity [33, 34]. Microbial products, such as lipopolysaccharides (LPS), can act as pro-inflammatory factors, activating pathways (including NF-κB, IL-6, and TNF-α) thereby amplifying or modulating systemic responses [4, 35].

2.2 The oral-lung axis

The pathophysiological integration between the oral microbiome and pulmonary homeostasis defines the oral-lung axis. The healthy lung is characterized by a low-density microbial ecosystem, whose composition is determined by the dynamic equilibrium between microbial immigration (primarily mediated by subclinical microaspiration and mucosal dispersion) and mucociliary clearance [36, 37]. The upper respiratory tract represents a direct anatomical extension of the oral cavity, which may therefore act as a possible source of respiratory pathogens. Complex immune responses and physical barrier mechanisms help limit the migration of microorganisms toward the lower airways.

Key periodontal pathogens such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans* promote inflammation via virulence factors like lipopolysaccharides [38, 39]. Oral streptococci including *Streptococcus pneumoniae*, *S. mitis*, and *S. oralis* may be aspirated into the lower airways and contribute to pneumonia [40]. Anaerobes such as

Veillonella, *Prevotella*, and *Actinomyces* species are enriched in chronic lung diseases and sustain airway inflammation [41]. Opportunistic bacteria like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* can colonize dental plaque and cause severe respiratory infections, especially in vulnerable patients [42]. Fungi such as *Candida albicans* may also disrupt biofilms and enhance inflammatory responses. These microbes reach the lungs mainly through microaspiration of saliva and plaque. Their presence triggers local immune activation and systemic cytokine release. Oral dysbiosis is therefore linked to pneumonia, COPD, and broader systemic conditions such as cardiovascular and metabolic diseases.

The convergence and divergence between the oral-lung and oral-gut axes lie in their shared origin but distinct physiological transit routes and local environmental pressures. Both pathways converge on the hematogenous route and systemic immune priming, where oral-derived pathobionts or their metabolic byproducts (such as LPS) trigger a state of low-grade systemic inflammation, often characterized by the migration of oral-primed Th17 cells to distal mucosal sites. However, they diverge significantly in their primary mode of translocation: the oral-lung axis is predominantly driven by microaspiration, allowing oral biofilms to bypass gastric acidity and directly colonize the respiratory tree, whereas the oral-gut axis relies on the enteral route via deglutition. Furthermore, while the lung microenvironment is a high-oxygen, low-biomass system where dysbiosis is defined by a shift in microbial density and diversity, the gut is a high-biomass anaerobic environment where oral invaders must compete with a dense resident microbiota and survive the selective pressure of bile acids and digestive enzymes. Table 2 summarizes a comparative analysis on pathogenic mechanism in oral and lung or gut axis.

3 Systemic implications of oral dysbiosis: mechanisms and clinical relevance

Clinical and experimental evidence increasingly supports the involvement of oral bacteria in various chronic pathological conditions (including cancer, systemic diseases, metabolic and respiratory disorders) [30], as well as in transient conditions such as pregnancy, in which oral dysbiosis may act as a contributing factor and/or serve as a biomarker for preterm delivery [43, 44]. Evidence from diverse clinical settings indicates that oral dysbiosis functions as a systemic mediator involved in multiple disease pathways. The

Table 2 Comparative analysis of oral-gut and oral-lung pathogenetic mechanisms

Mechanism	Pathophysiological description	Target system	Systemic implication
Microaspiration	Direct inhalation of oral biofilms/pathobionts into the lower respiratory tract.	Lung	Direct shift toward pulmonary dysbiosis; impaired surfactant function.
Hematogenous Route	Translocation of oral bacteria (e.g., *P. gingivalis*) into the bloodstream via sulcular epithelium.	Both	Systemic endotoxemia; promotion of atherosclerotic plaques and distal organ seeding.
Enteric Route (Swallowing)	Daily ingestion of bacteria, surviving the gastric acid barrier in dysbiotic states	Gut	Alteration of intestinal microbiota; breakdown of the gut epithelial barrier ("Leaky Gut").
Immune Priming / Cell Trafficking	Migration of oral-primed Th17 cells or Th1 cells to mucosal sites.	Both	Hyper-inflammation; exacerbation of RA (Rheumatoid Arthritis) or IBD (Inflammatory Bowel Disease).
Molecular Mimicry	Cross-reactivity between oral bacterial antigens and host proteins.	Both	Triggering of autoimmune responses (e.g., Citrullination in the lungs and joints).

presence of oral taxa in distant tissues supports a mechanistic role beyond the oral cavity and highlights the close link between microbial communities and host physiology. Overall, oral dysbiosis may act as an early driver of systemic inflammation and immune imbalance, positioning the oral microbiome as both a promising biomarker and a modifiable therapeutic target. Nevertheless, causal relationships in humans remain largely hypothesis-generating.

3.1 Digestive tract disorders

3.1.1 Cancer

Fusobacterium nucleatum, a common oral opportunistic bacterium [45], has been identified within intestinal tumor tissues, where it appears to modulate cell proliferation and local immune responses implicated in colorectal cancer [46]. Oncogenic mechanisms involve the activation of Wnt/β-catenin signaling via its adhesin FadA and the immune evasion through Fap2–TIGIT interactions [47], as well as its contribution to inflammation in the tumor microenvironment. A recent study reported a significant overrepresentation of oral-origin bacterial taxa (*Peptostreptococcus*, *Streptococcus*, and *Solobacterium* spp.) in both salivary and fecal microbiomes of individuals with colon carcinoma when compared with healthy controls [48]. A current systematic review investigating the potential association between the oral microbiota and the development of colon carcinoma underscored the need for further research and validation to determine the applicability of oral microbiota as diagnostic biomarkers for colorectal cancer [49].

Oral dysbiosis, is increasingly recognized as a contributing factor in the pathogenesis of head and neck cancers [50]. Patients with head and neck squamous cell carcinoma frequently exhibit a shift toward a microbiota enriched in pro-inflammatory taxa (such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Prevotella*) accompanied by a reduction in commensal species typically associated with oral health [51]. This altered microbial landscape promotes a pro-tumorigenic microenvironment characterized by chronic inflammation, oxidative stress, and immune modulation, all of which facilitate cellular transformation and tumor progression [16]. Notably, periodontal pathogens like *P. gingivalis* and *F. nucleatum* have been implicated in specific oncogenic mechanisms, including inhibition of apoptosis, enhancement of epithelial proliferation, and increased invasiveness. In particular, Binder-Gallimidi and collaborators demonstrated a direct interaction of the two pathogens with oral epithelial cells through Toll-like receptors, leading to increased tumor aggressiveness [52]. Moreover, oral dysbiosis may exacerbate the carcinogenic effects of established risk factors, such as tobacco use, alcohol consumption, and HPV infection, whose combined presence is known to potentiate the individual carcinogenic effects in head and neck malignancies [53, 54]. Interesting, a pilot study showed that 55% of heavy drinker patients affected by upper aero-digestive tract carcinoma presented in the oral cavity acetaldehyde-producing bacteria (*Neisseria subflava*, *Streptococcus mitis*, *Candida albicans*, *and glabrata*). Notably, the presence of these microorganisms was found to correlate with increased oxidative stress compared to patients without such bacteria, supporting the hypothesis of the association of several factors could increase the risk of cancer onset [55]. Despite the compelling evidence available, the causal relationship between oral cavity dysbiosis and cancer remains a matter of debate, warranting further investigation and more robust experimental validation.

3.1.2 Gut inflammatory disease

Inflammatory Bowel Disease (IBD), including Crohn's disease and ulcerative colitis, is marked by chronic intestinal inflammation driven by disrupted host–microbiota interactions. Emerging evidence implicates oral bacteria in IBD pathogenesis through various mechanisms [56]. Pathobionts such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Klebsiella* spp. have been identified in the gut of IBD patients [57, 58]. Notably, oral-derived *Klebsiella* strains can colonize the intestine and trigger Th1-mediated inflammation [59]. These microorganisms activate Toll-like receptors (TLRs) and NF-κB signaling, inducing pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, Th17) and impairing the intestinal barrier by reducing tight junction protein expression [60]. This disruption increases gut permeability, facilitating microbial translocation and sustaining a chronic inflammatory cycle. Additionally, *Fusobacterium nucleatum* and *Campylobacter concisus* worsen mucosal integrity and contribute to cytokine release [61], while *Klebsiella pneumoniae* activates inflammasomes to amplify inflammation [62]. Oral fungi such as *Candida albicans* may also exacerbate disease by promoting epithelial permeability and inflammation, highlighting the complex role of oral dysbiosis in gut health [63].

3.2 Metabolic disorders

In the metabolic context, evidence from systematic analyses involving numerous patients with type 2 diabetes mellitus (T2DM) indicates that oral dysbiosis is characterized by an increased abundance of *Streptococcus*, *Porphyromonas*, *and Treponema spp*., along with alterations in overall microbial diversity, which are associated with heightened systemic inflammation and insulin resistance [17, 18]. Supporting this, a bioinformatic study revealed that genes linked to periodontitis and thus to its associated oral pathogens are enriched in T2DM, reinforcing a mechanistic connection between periodontal disease and metabolic dysregulation. Collectively, these findings support the notion that oral dysbiosis associated with T2DM represents a bidirectional relationship, as T2DM can modify the oral environment, promoting the proliferation of specific bacterial species that, in turn, can exacerbate insulin resistance and trigger systemic inflammation [64]. Evidence remains associative, and bidirectional interactions where systemic metabolic changes influence oral microbiota cannot be ruled out. Further research could determine whether targeted modulation of the oral microbiome may represent an effective strategy for the prevention of T2DM.

3.3 Cardiovascular disease

The oral microbiome is implicated in cardiovascular disease and contribute to atherosclerotic progression, through several interrelated biological mechanisms, most notably systemic inflammation and the translocation of oral bacteria into the bloodstream [3, 65]. Oral infections and microbial dysbiosis can elicit a systemic inflammatory response, thereby promoting pathophysiological processes such as atherosclerosis by impairing endothelial function and facilitating plaque development [16]. Moreover, specific oral microorganisms [66–68] are capable of entering the circulatory system, primarily because of dental procedures, periodontal inflammation (chronic inflammatory disease characterized by Gram-negative bacteria), or even routine activities such as chewing, and they may directly contribute to atherogenic processes or precipitate infections such as endocarditis [16]. Among these, *viridans* group Streptococci (particularly

Streptococcus sanguinis, *S. mitis*, *S. oralis*, and *S. mutans*) are the most frequently implicated, owing to their pronounced ability to adhere to damaged endothelium and participate in the formation of endocardial vegetations [69]. Interesting, periodontitis was found highly prevalent in both stable and unstable abdominal aortic aneurysm patients (AAA), but severe and progressive periodontitis tended to be more frequent in the group of patients with unstable AAA [70]. Additional taxa, including *Granulicatella*, *Abiotrophia*, *Gemella*, and members of the HACEK group (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*), are also commonly associated with subacute forms of the disease [68]. Although less characteristic of the oral microbiome, *Staphylococcus aureus* may be present in the oral cavity and represents a particularly aggressive etiological agent for endocarditis [71]. Collectively, these findings underscore the extent to which oral health and microbiota composition can significantly influence the risk of developing infective endocarditis. Oral dysbiosis is plausibly linked to cardiovascular disease, especially infective endocarditis, supported by mechanistic and observational evidence. However, causality is not yet definitive and required gurther longitudinal and interventional studies to establish causality more conclusively.

3.4 Autoimmune disorders

In autoimmune conditions such as systemic lupus erythematosus (SLE), high-throughput sequencing studies have characterized distinct oral microbiome alterations. One large study of tongue-coating samples in SLE patients vs. matched controls found that *Prevotella* and *Veillonella* were enriched, while *Streptococcus* and *Porphyromonas* were reduced; moreover, the authors developed a microbial classifier based on operational taxonomic units that strongly distinguished SLE from healthy controls [72]. In addition, a comparative study found that SLE and Sjögren's syndrome (autoimmune disorders characterized by chronic dryness due to immune-mediated deterioration od mucous membranes and moisture-secreting glands of your eyes and mouth) patients display disease-specific differences in oral microbiota composition, suggesting that oral dysbiosis could serve as a biomarker for autoimmune disease phenotypes [73]. These observations derive from sequencing studies in human cohorts and suggest potential microbial biomarkers, but causality is unproven. Mechanistic pathways remain speculative based on immune-modulatory plausibility derived from in vitro models.

3.5 Pre-term delivery

Accumulating scientific evidence indicates that dysbiosis of the oral microbiota may contribute to inflammatory pathways implicated in an increased risk of pre-term delivery.

In a retrospective clinical study, Song and collaborators show a clear difference between the oral microbiota of pregnant with threatened preterm birth and that of healthy ones, suggesting that characteristics of the oral microbiota may be associated with the risk of pre-term birth. In particular, *F. nucleatum* has been found frequently associated with pre-term birth [28]. Another recent a large case-control study including women with term and pre-term birth examined differences in the microbial richness, diversity, and differential abundance of specific taxa. The phyla *Firmicutes* and *Bacteroidetes* were relatively more abundant in women with a pre-term birth than in women with at term birth, while *Proteobacteria* was less prevalent in women with a pre-term birth [74].

Oral microbiota may contribute to pre-term delivery through several interconnected mechanisms. Bacteria originating from the oral cavity, particularly those associated with periodontal disease, can disseminate through the bloodstream, and reach the placenta, where they can trigger localized inflammation and potentially lead to preterm rupture of the fetal membranes [75].

3.6 Respiratory disorders

In contexts of oral dysbiosis, particularly during chronic periodontitis, an ecological transition occurs toward highly virulent obligate and facultative anaerobic taxa, such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Prevotella intermedia*. These pathogens, beyond aerogenic migration, can induce transient bacteremia, facilitating the systemic translocation of endotoxins (LPS) and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α).

Upon reaching the pulmonary microenvironment, these agents alter the local immune gradient, promoting neutrophil recruitment and the upregulation of matrix metalloproteinases (MMPs), which are central mechanisms in connective tissue degradation and airway remodeling [76]. This bio-molecular axis not only exacerbates the inflammatory phenotype of chronic pathologies such as chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis but also acts as a critical determinant in the pathogenesis of nosocomial pneumonias and the modulation of susceptibility to lung neoplasms through the activation of oncogenic pathways mediated by chronic inflammation [77]. Recent evidence from a large cohort study revealed a strong association between oral microbiome diversity and composition and chronic respiratory diseases (COPD, asthma, emphysema, or chronic bronchitis), encouraging further study on its potential as non-invasive biomarkers for respiratory health [78]. In a mouse model, oral infection with the periodontal pathogens *Porphyromonas gingivalis* and *Fusobacterium nucleatum* led to migration of these bacteria into lung tissue, causing COPD-like lesions, airway inflammation, reduced lung function, and increased pro-inflammatory cytokines, demonstrating a causal link in animals [79]. Other rodent studies showed that oral exposure to *P. gingivalis* exacerbates experimental COPD with neutrophil recruitment and activation of inflammatory pathways in lung tissue [80]. Mixed infection models in mice combining commensal oral *Streptococcus* and *Prevotella intermedia* products worsened pneumonia severity and inflammatory dysfunction, highlighting synergistic pathogenic effects of oral microbes [81]. Most evidence linking oral dysbiosis to respiratory diseases is observational, limiting causal inference due to confounding factors (smoking, age, comorbidities). Microbial detection in the lungs does not necessarily prove direct pathogenic activity, as microaspiration can occur in healthy individuals without causing disease. Moreover, heterogeneity in sampling methods, microbiome analysis techniques, and small sample sizes reduce reproducibility and make it difficult to establish a clear cause–effect relationship. Nevertheless, the biological plausibility and emerging experimental data strongly encourage further well-designed longitudinal and mechanistic studies.

Despite the growing number of studies linking oral dysbiosis to systemic diseases, it is crucial to interpret the results with caution due to potential sources of bias. Most evidence comes from selected clinical cohorts, often small and not representative of the general population, limiting the generalizability of the findings. Confounding factors such as smoking, diet, oral hygiene, medication use, and comorbidities can influence

both oral microbiota composition and the development of systemic diseases, making it difficult to distinguish cause from effect. Furthermore, the observed dysbiosis may be both a consequence and a causal factor of disease, introducing the risk of reverse causality. Differences in sampling methods, sequencing platforms, and bioinformatic pipelines further contribute to data heterogeneity. Therefore, it is essential to clearly distinguish between statistical associations, biological plausibility supported by experimental mechanisms, and demonstrated causality, particularly when considering the oral microbiota as a biomarker or therapeutic target.

Table 3 summarizes the studies linking oral microorganisms with systemic diseases, including key biases, limitations, and interpretation of evidence.

Despite several limitations, emerging evidence of crosstalk between oral dysbiosis and systemic diseases suggests that modulating the oral microbiota, through probiotics, prebiotics, postbiotics, or targeted nutritional strategies, may not only enhance oral health but also serve as a potential preventive approach to support overall systemic well-being. Figure 1 summarizes the interplay between oral dysbiosis and systemic diseases, highlighting the main mechanistic pathways and the potential beneficial effects of using "biotics" as modulatory tools.

4 Oral probiotics: mechanisms of action and potential impact on systemic health

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [82]. Within the oral environment, their primary objective is to restore microbial balance (eubiosis), counteract pathogenic colonization, and mitigate chronic low-grade inflammation [83]. To define a specific strain as an oral probiotic, direct evidence is required to demonstrate that the strain can effectively colonize the oral environment and significantly improve oral health-related metrics, such as plaque index, degree of gingival inflammation, or counts of specific oral pathogens.

The mechanisms through which probiotics exert their beneficial effects on oral health are multifactorial and closely interconnected. One of the most recognized actions involves competitive exclusion, whereby beneficial strains occupy ecological niches on the oral mucosa and dental surfaces, limiting the adhesion and proliferation of pathogenic microorganisms such as *Porphyromonas gingivalis* and *Streptococcus mutans* [83, 84]. Competition for adhesion sites and nutrients plays a key role in maintaining a stable microbial equilibrium in the oral cavity.

In addition to spatial competition, many probiotic species produce antimicrobial substances, including bacteriocins (antimicrobial peptides synthesized by bacterial ribosomes, exerting either bactericidal or bacteriostatic effects on pathogens), hydrogen peroxide (an antimicrobial agent that can suppress the growth of noxious microorganisms), and organic acids (which lower the local pH to create an unfavorable environment for many agents) [85]. These bioactive compounds not only suppress harmful bacteria but also promote a favorable microenvironment for the persistence of commensal and symbiotic microorganisms [86, 87].

Another important mechanism involves immune modulation, as oral probiotics have been shown to downregulate the expression of pro-inflammatory cytokines such as

IL-1β, IL-6, and TNF-α, while enhancing anti-inflammatory mediators like IL-10, both at the gingival and systemic level [88]. This immunoregulatory effect contributes to reduce tissue inflammation and improve periodontal health.

Furthermore, probiotics can fortify the mucosal barrier, thereby enhancing epithelial resilience to bacterial toxins and other deleterious metabolites. This effect is mediated through the reinforcement of mucosal integrity and the upregulation and proper assembly of tight junction proteins, such as occludin and claudin, which constitute essential components of the epithelial barrier. In turn, these mechanisms restrict microbial translocation and mitigate the dissemination of inflammatory mediators into systemic circulation [89].

Finally, an increasing body of evidence suggests that certain oral probiotic strains (particularly *Lactobacillus* and *Bifidobacterium* strains [90, 91]), when swallowed, may also interact with the oral–gut axis. Through this pathway, they can influence the composition and metabolic activity of the intestinal microbiota, thereby contributing to systemic anti-inflammatory effects and improved metabolic regulation [4, 92].

Taken together, these mechanisms highlight the multifaceted role of oral probiotics as biological modulators capable of influencing both local and systemic health. Their actions extend from direct microbial competition and antimicrobial production to immune and epithelial regulation, ultimately underscoring the integrated nature of the oral microbiome within the broader context of human physiology.

5 Key probiotic strains and clinical applications

In recent years, research on probiotics has identified several specific strains with documented beneficial effects on oral and, indirectly, systemic health. Among the most extensively studied are species belonging to the genera *Lactobacillus*, *Streptococcus*, and *Bifidobacterium*, each characterized by distinctive colonization properties and modes of interaction within the oral ecosystem.

One of the best-characterized strains is *Lactobacillus reuteri*, particularly *L. reuteri* DSM 17,938 and *L. reuteri* ATCC PTA 5289, which are frequently used in probiotic formulations [91, 93]. These bacteria exhibit a strong capacity to adhere to the oral mucosa and integrate into the commensal biofilm [94], effectively competing with pathogenic microorganisms such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, both well-known promoters of periodontitis. Controlled clinical studies have shown that *L. reuteri* administration can reduce periodontal pocket depth, improve gingival index scores, and decrease local inflammatory mediators such as IL-1β and TNF-α [95, 96]. Moreover, *L. reuteri* is capable of producing natural antimicrobial compounds, including reuterin, which inhibits the proliferation of opportunistic pathogens [97].

Another key member of the oral probiotic is *Streptococcus salivarius*, a dominant commensal species within the tongue and upper oral mucosa. The strains K12 and M18 have been widely investigated for their ability to stably colonize the oral cavity and produce bacteriocin-like inhibitory substances (BLIS), peptide-based antimicrobials capable of suppressing the growth of *Streptococcus pyogenes*, *Streptococcus mutans*, and other organisms associated with pharyngeal infections and dental caries [98, 99]. The K12 strain has been linked to a reduction in the frequency of recurrent pharyngitis and tonsillitis in children, while M18 has demonstrated benefits in reducing dental plaque and halitosis through the suppression of volatile sulfur compounds [100]. These effects point

Table 3 Summary of studies linking oral-originated microorganisms with systemic diseases, including evidence type, strength of association, key biases/limitations and interpretation

Condition/Disease	Oral bacteria involved	Evidence/Main mechanisms	References	Evidence type	Strength of association	Key biases/Limitations	Notes on interpretation
Colorectal Cancer	*Fusobacterium nucleatum*, *Streptococcus anginosus*, *Peptostreptococcus stomatis*, *Prevotella intermedia*, others	Oral *F. nucleatum* detected in intestinal tumor tissues. Activation of Wnt/β-catenin signaling via FadA adhesin Immune evasion through Fap2–TIGIT interactions Contribution to tumor microenvironment inflammation	[29, 35]	Mechanistic studies in vitro & animal models	Moderate	Small cohort sizes, confounding by diet/smoking, reverse causality	Associations observed in humans; mechanistic studies provide plausibility; causal role in humans remains **hypothesis-generating**
Gut inflammatory diseases	*Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Klebsiella spp. Campylobacter concisus*, *Candida albicans*	TLRs) and NF-κB signaling Pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, Th17) Reduction of tight junction protein expression	[57–63]	In vitro cell studies, observational clinical study	Moderate	Reverse causality (IBD affects oral microbiota), confounders (diet, medications)	Associations observed in humans; mechanistic studies provide plausibility; causal role in humans remains **hypothesis-generating**
Head and Neck Squamous Cell Carcinoma (HNSCC)	*Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella* *Neisseria subflava*, *Streptococcus mitis*, *Candida albicans*, *and glabrata*	Shift to pro-inflammatory microbiota Reduction of commensal species associated with oral health Chronic inflammation, oxidative stress, immune modulation Oncogenic mechanisms: apoptosis inhibition, epithelial proliferation, increased invasiveness	[16, 46–47, 55]	In vitro cell studies, observational clinical study	Low-Moderate	Confounding by tobacco, alcohol, HPV; heterogeneous sampling	Findings suggest plausible mechanisms; human evidence is **associative**, not causal
Type 2 Diabetes Mellitus	*Streptococcus*, *Porphyromonas* (especially *P. gingivalis*), *Treponema*	Increased abundance of pathogens and altered microbial diversity Associated with systemic inflammation and insulin resistance Periodontitis-related genes enriched in T2DM	[17, 18]	Observational human studies, bioinformatic analyses	Moderate	Reverse causality (T2DM affects oral microbiota), confounders (diet, medications)	Dysbiosis correlates with inflammation and insulin resistance; causal direction remains **uncertain**

Table 3 (continued)

Condition/Disease	Oral bacteria involved	Evidence/Main mechanisms	References	Evidence type	Strength of association	Key biases/Limitations	Notes on interpretation
Cardiovascular Disease /Infective Endocarditis	Viridans group streptococci: *S. sanguinis*, *S. mitis*, *S. oralis*, *S. mutans*; also *Granulicatella*, *Abiotrophia*, *Gemella*, HACEK group; sometimes *Staphylococcus aureus*	Oral bacteria translocation Systemic inflammation and atherosclerosis Adhesion to damaged endothelium and form endocardial vegetations Dental procedures and periodontal inflammation as entry points	[3, 16, 66–70]	Observational and mechanistic studies	Moderate-Strong	Confounding by comorbidities, heterogeneous microbiome methods, small cohorts	Mechanistic plausibility exists; human evidence shows associations; causal inference is **hypothesis-generating**
Autoimmune Diseases (SLE, Sjögren's Syndrome)	Increased: *Prevotella*, *Veillonella* Decreased: *Streptococcus*, *Porphyromonas*	Distinct oral microbiome alterations in SLE patients Disease-specific differences between SLE and Sjögren's Oral dysbiosis as potential biomarker	[72, 73]	Observational sequencing studies	Low-Moderate	Small cohorts, disease heterogeneity, reverse causality	Findings suggest microbial differences may serve as biomarkers; causality remains **speculative**
Pre-term delivery	*F. nucleatum* Increased: *Firmicutes* and *Bacteroidetes* Decreased: *Proteobacteria*	Association with periodontal disease Oral bacteria may reach the placenta and trigger localized inflammation	[28, 74, 75].	Observational clinical studies, animal models	Low-Moderate	Confounding by maternal health, heterogeneous sampling, small sample sizes	Human studies show associations; animal studies provide mechanistic plausibility; conclusions are hypothesis-generating
Respiratory Diseases	*Porphyromonas gingivalis*, *Fusobacterium nucleatum* *Prevotella intermedia*	Transient bacteremia, systemic translocation of endotoxins LPS and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α).	[76–80]	Observational clinical studies, animal models	Moderate	Confounding factors, heterogeneous sampling, small sample sizes	Human studies show associations; animal studies provide mechanistic plausibility; conclusions are **hypothesis-generating**

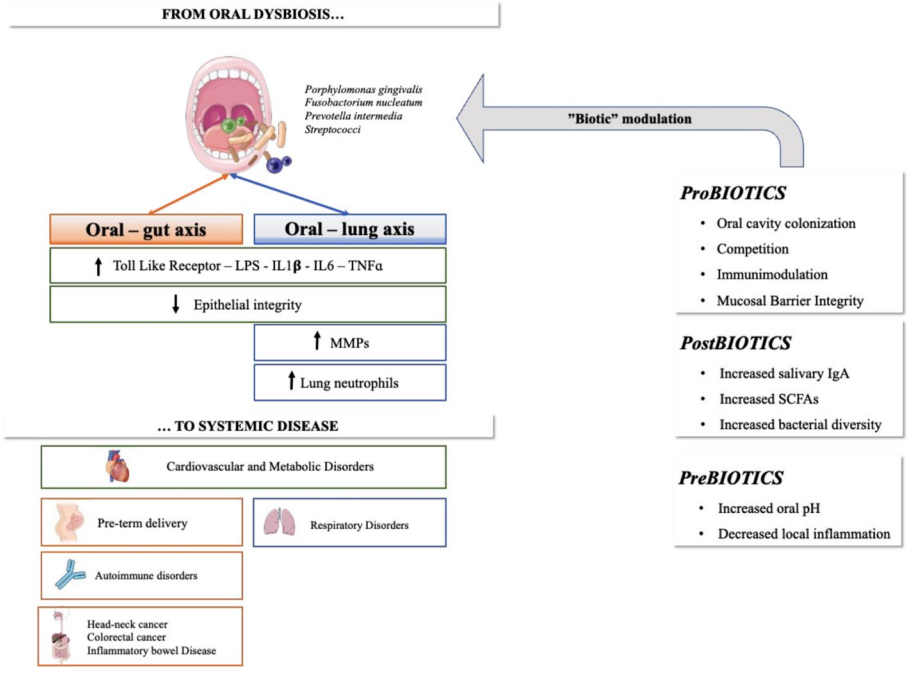

Fig. 1 Interplay between oral dysbiosis and systemic diseases, showing key mechanistic pathways and the potential modulatory effects of probiotics, prebiotics, and postbiotics

to a dual antimicrobial and immunomodulatory role, fostering a more balanced oral microenvironment less prone to chronic inflammation [101].

Bifidobacterium animalis subsp. *lactis* BB-12 and *Lactobacillus rhamnosus* GG, traditionally associated with gut health, have also shown promising oral applications. Evidence suggests that these strains can reduce salivary concentrations of *S. mutans*, agent of dental caries, and modulate the acidity of the dental biofilm, creating conditions less favorable to enamel demineralization [102, 103]. Furthermore, *B. lactis* BB-12 supplementation has been associated with an increase in salivary bacterial diversity, a marker of ecological stability and resistance to pathogenic invasion [104].

Collectively, these findings indicate that oral probiotics exert strain-specific effects, with their benefits depending on the particular microorganism and microbial niche of colonization. *Lactobacillus* and *Streptococcus* strains appear to be more effective in controlling plaque accumulation and gingival inflammation, while *Bifidobacterium* species contribute to pH regulation and caries prevention. Increasing attention could be directed toward multi-strain formulations, which may produce synergistic effects by enhancing oral microbiota resilience and strengthening the barrier against dysbiosis.

6 Prebiotics and postbiotics

In addition to probiotics, growing interest has been directed toward prebiotics (non-digestible substances that selectively stimulate the growth or activity of beneficial microorganisms) and postbiotics, which are non-viable microbial products or metabolites that retain biological activity and confer health benefits to the host [105].

With respect to oral applications, several prebiotic compounds such as xylitol, arginine, and urea have been investigated. These molecules increase oral pH and promote the growth of alkalinizing commensal bacteria, thereby reducing the prevalence of

acidogenic species like *Streptococcus mutans* and limiting enamel demineralization. Such effects not only contribute to caries prevention but may also reduce local inflammatory stimuli that can have systemic repercussions [106–108].

Postbiotics, on the other hand, are gaining prominence due to their greater stability, safety, and suitability for incorporation into oral hygiene products such as toothpastes and gels [109–111]. In a randomized controlled trial, the use of a toothpaste containing postbiotic components (specifically inactivated strains of *Lactobacillus salivarius* LS97, *Lactobacillus paracasei* LC86, and *Lactobacillus acidophilus* LA85) was associated with increased salivary IgA levels, higher concentrations of SCFAs, and enhanced bacterial diversity, along with a reduction in potentially pathogenic genera such as *Klebsiella* and *Escherichia* [110]. These parameters reflect not only localized modulation of the oral microbiota and mucosal immune response but also suggest potential systemic influences, given that microbial diversity, mucosal immunity, and metabolite production are key factors in controlling low-grade inflammation along the oral–systemic axis.

The practical applications of these biological approaches extend beyond caries and periodontitis. Oral microbiota modulation through prebiotics and postbiotics may beneficially influence the oral–gut axis by reducing bacterial translocation from the mouth to the intestine and preventing the activation of systemic inflammatory cascades [112, 113]. A recent review emphasized that, although still preliminary, such interventions could play a role in preventing chronic dysbiosis-associated conditions, including cardiovascular, metabolic, and gastrointestinal diseases [108]. Nevertheless, most current studies on prebiotics and postbiotics focus on surrogate markers of oral health (such as plaque index, caries incidence, pH, and biofilm composition) while robust clinical trials assessing systemic endpoints (e.g., inflammation, metabolic function, cardiovascular outcomes) remain limited.

7 Limitations, conclusions and future perspectives

Growing evidence indicates that the oral microbiota should not be considered simply a local health indicator, but rather a potentially critical factor in modulating systemic inflammatory and metabolic processes. Recent studies have linked alterations in oral microbial composition to a wide range of systemic diseases, including cardiovascular, metabolic, autoimmune, and neurological disorders, suggesting a bidirectional interconnection between the oral cavity and the rest of the body.

Despite the increasing body of evidence linking oral dysbiosis to systemic diseases, most data remain associative. Although current models suggest possible causality or even bidirectionality in the temporal relationships (dysbiosis versus disease or disease versus dysbiosis), further evidence is needed to confirm these connections.

The use of probiotics, prebiotics, and postbiotics is emerging as a promising strategy to modulate the oral ecosystem and, consequently, potentially reduce systemic risk.

Recent clinical trials provide growing support for the role of probiotics in modulating the oral microbiota and improving various aspects of oral health. On the other hand, evidence from several meta-analyses suggests that probiotic supplementation may exert beneficial effects on systemic health parameters, including inflammation, lipid and glucose metabolism, and blood pressure.

However, despite these positive signals, the overall strength of the evidence remains limited due to the lack of long-term clinical studies with clinical endpoints, including

cardiovascular events or progression of systemic diseases, demonstrating systemic benefits from probiotic interventions aimed at oral health.

Overall, these promising findings highlight the potential of probiotic-based interventions as a valuable adjunct in oral healthcare, with the possibility of contributing to the prevention and management of systemic diseases through targeted modulation of the oral microbiota.

Acknowledgements
BANK OF ITALY for Liberal Donation 'Potenziamento Ambulatorio di Rinologia Traslazionale" assigned to Azienda Sanitaria Locale –ASL Rieti Prot. N.1500764/24 date 22/07/2024.

Author contributions
CP and CB: conceptualization, investigation, manuscript writing - original draft preparation; AM, CL, FZ, GR: conceptualization, visualization, writing - review and editing. All authors reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

Funding
This manuscript has received no specific funding.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 2 December 2025 / Accepted: 20 March 2026
Published online: 01 April 2026

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