The oral-gut axis in periodontitis: Current evidence and emerging therapeutic targets (Review)

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Abstract. The oral-gut axis has emerged as an important biological pathway linking periodontitis with gut microbiota dysbiosis and systemic immune-metabolic disturbances. In periodontitis, the expansion of oral pathobionts, such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* may promote enteric colonisation, impair gut barrier integrity, alter microbial metabolite profiles and sustain low-grade systemic inflammation. The present narrative review synthesises evidence from the PubMed, Scopus and Web of Science databases up to January, 2026 on oral-gut microbial crosstalk in periodontitis, with an emphasis on microbial translocation, barrier dysfunction, immune signalling, metabolite-mediated pathways and emerging therapeutic strategies. Unlike recent reviews, it also integrates Mendelian randomisation evidence, the oral-gut-bone axis, implant-related implications and a global-health perspective. Current evidence supports bidirectional interactions between oral and gut dysbiosis in periodontitis. Experimental and clinical studies indicate that oral pathobionts can reach the intestine, disrupt tight-junction integrity, reduce short-chain fatty acid production and promote Th17/Treg imbalance, thereby amplifying mucosal and systemic inflammation. These alterations are linked to osteoclastogenesis, alveolar and peri-implant bone loss, and broader associations with gastrointestinal, cardiometabolic, autoimmune and neuroinflammatory disorders. Adjunctive therapeutic approaches under investigation include probiotics, prebiotics, synbiotics, dietary modulation, faecal microbiota transplantation, and combined host- and microbiota-directed interventions. Conclusions: The oral-gut axis provides a biologically plausible framework connecting periodontitis with systemic disease through microbial, immune and metabolic pathways. However, a large amount of the currently available evidence remains observational or derived from animal models, and heterogeneity in study design limits formal comparison across studies. Large longitudinal human studies, standardised multi-omics approaches, and rigorously designed randomised trials are required to establish causality and to guide precision, microbiome-informed periodontal care.

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1. Introduction

The oral-gut axis has emerged as a key-biological pathway through which periodontitis modulates gut microbiota composition and systemic immune-metabolic responses (1-3). This axis denotes a bidirectional network linking the oral and gastrointestinal microbiomes, whereby microbial translocation, microbially derived metabolites and immune signalling jointly influence systemic health (2,4,5). In periodontitis, oral dysbiosis, characterised by the expansion of pathogensm such as *Porphyromonas gingivalis* (*P. gingivalis*) and *Fusobacterium nucleatum (F. nucleatum)*, leads to the continuous seeding of the gut via swallowed saliva, disrupting intestinal homeostasis and sustaining low-grade inflammation (6-9). Conversely, established gut dysbiosis can intensify periodontal tissue breakdown by altering host

immune responses and bone metabolism, thereby reinforcing a self-perpetuating loop that contributes to the development and progression of systemic diseases, such as rheumatoid arthritis (RA), diabetes and cardiovascular disease (3,10,11). The underlying mechanisms include the direct migration of oral taxa to the intestine, the disruption of short-chain fatty acid (SCFA) profiles, and an imbalance between T helper 17 (Th17) cells and regulatory T cells (Tregs). Collectively, these findings emphasise the oral cavity as a major gateway influencing the composition and function of the gut microbiome (1,2,12).

A central component of this axis is microbial translocation, whereby oral pathobionts survive gastric conditions and colonise the intestine, particularly when gut barrier function is compromised (4,6,9). Individuals with periodontitis are estimated to ingest 10^9-10^{10} bacteria daily, a burden that may exceed the colonisation resistance of the gut and favour the enrichment of organisms such as *P. gingivalis*. This pathogen downregulates tight junction proteins, including zonula occludens-1 (ZO-1) and occludin, thereby increasing intestinal permeability and endotoxemia (6,13,14). Murine models receiving oral gavage of *P. gingivalis* have demonstrated persistent gut colonisation, reduced microbial diversity, elevated levels of interleukin (IL)-17 and tumour necrosis factor-α (TNF-α), and bile-acid disturbances that predispose the host to non-alcoholic fatty liver disease and impaired glucose tolerance (2,6,15). *F. nucleatum* similarly exploits adhesins, such as *Fusobacterium* adhesin (FadA), to bind E-cadherin, activate β-catenin signalling pathways, and evade host immune responses through interactions between FadA protein 2 (Fap2) and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT). These mechanisms exacerbate colitis and colorectal carcinogenesis via the oral-gut route (7,16,17). Findings from human microbiota-associated mouse models and paired saliva-faeces sequencing analyses have shown that salivary taxa can account for up to 5.88% of the gut microbes in individuals with periodontitis, compared with only 0.6% in healthy subjects (8). Immune crosstalk constitutes another major pillar of the oral-gut axis, whereby dysbiotic oral communities prime systemic Th17 responses that recirculate to both gut and periodontal tissues, as detailed in subsequent sections (12,18). In models of high-fat-diet or antibiotic-induced gut dysbiosis, the expansion of Th17 cells and suppression of Tregs, together with upregulated IL-17 and receptor activator of nuclear factor κB ligand (RANKL), enhance osteoclastogenesis, alveolar bone loss and impaired osseointegration (10,11,19). Periodontal pathogens further aggravate these effects through the translocation of lipopolysaccharides (LPS) and gingipains, which compromise epithelial barrier integrity and create a pro-inflammatory milieu favouring the expansion of Enterobacteriaceae, while depleting SCFAs, particularly butyrate (4,14,20). The evaluation and modulation of the oral-gut microbiomes using probiotics and precision dietary interventions may help reduce the burden of systemic diseases. The present review aimed to clarify the role of the bidirectional oral-gut axis in periodontitis pathogenesis and to appraise emerging host- and microbiota-targeted therapeutic strategies for disrupting this inflammatory circuit. Furthermore, it integrates evidence from Mendelian randomisation studies with current understanding of oral-gut-bone axis mechanisms, including implant failure, within the broader context of the Sustainable Development Goals and global health priorities.

2. Literature search strategy and scope of the review

A literature search was conducted using the PubMed, Scopus and Web of Science databases up to January, 2026, focusing on studies published from 2000 onwards that examined oral-gut microbial crosstalk in the context of periodontitis. Search terms comprised a combination of Medical Subject Headings (MeSH) and free-text key words related to periodontitis, oral microbiome, gut microbiota, oral-gut axis, microbial translocation and probiotics/synbiotics, combined using Boolean operators. Original human and experimental studies, as well as key narrative and systematic reviews reporting data on microbial translocation, immune-metabolic signalling, barrier dysfunction, or therapeutic modulation of the oral-gut axis, were included. Moreover, case reports and non-English publications were excluded. The present review is narrative rather than systematic in nature. Therefore, the substantial heterogeneity in study designs, populations and microbiome analysis methodologies precluded a formal quantitative comparison of the reported findings.

3. Evidence for oral-gut translocation and colonisation of periodontal pathobionts

The oral cavity harbours a diverse microbial community that continuously supplies bacteria to the gastrointestinal tract via swallowed saliva. Under healthy conditions, this microbial flux contributes to the maintenance of a stable ecological equilibrium. By contrast, periodontal diseases, such as periodontitis enrich pathogenic species, including *P. gingivalis*, *F. nucleatum*, and *Treponema denticola*, which can translocate and establish within the intestine (4,6,7). SourceTracker analyses have shown that saliva-derived *Porphyromonadaceae* account for ~5.88% of the faecal microbiota in patients with periodontitis, compared with only 0.6% in healthy individuals, confirming distal intestinal seeding by oral pathobionts (8,21).

Mechanistic insights from animal models strongly support the enteral translocation and mucosal persistence of oral microorganisms (10). The oral gavage of *P. gingivalis* in mice has been shown to lead to its persistence throughout the gastrointestinal tract and induces alterations in the resident microbial communities by downregulating the tight-junction proteins, ZO-1 and occludin, thereby weakening intestinal barrier function (6,13,14). Proof-of-concept analyses using carboxyfluorescein succinimidyl ester (CFSE)-labelled salivary bacteria have further demonstrated that fluorescent oral microbes remain detectable within the gut lumen and mucosa for >24 h, providing direct evidence of survival after oral-gut migration (8). *P. gingivalis* exhibits acid tolerance and adherence to the colonic epithelium via gingipain-mediated mechanisms, while *F. nucleatum* employs FadA-E-cadherin and Fap2-TIGIT interactions to facilitate ectopic colonisation, particularly in the presence of pre-existing gut dysbiosis (13,16,17,22).

Human cohort studies have corroborated these findings. Individuals with periodontitis display an increased faecal

abundance of oral taxa, including *Prevotella intermedia*, *Treponema* and *Porphyromonas*, which is associated with reduced microbial diversity and altered *Bacteroidetes*/*Firmicutes* ratios (23-25). Longitudinal follow-up studies following non-surgical periodontal therapy have demonstrated a partial reversal of these changes, with reductions in salivary pathobionts paralleling improved faecal composition and lower systemic levels of IL-17 and TNF-α (26,27). In addition, Mendelian randomisation analyses support a causal contribution of specific oral-gut migrants to the risk of developing periodontitis. For example, taxa such as *Anaerotruncus* were found to be inversely associated with periodontitis through genetically determined abundance (28-30).

Colonisation by these oral pathobionts drives functional dysbiosis with systemic consequences. These effects include the remodelling of gut metabolic pathways, elevated trimethylamine N-oxide levels and diminished SCFA production. In addition, faecal microbiota transplantation (FMT) from donors with periodontitis has been shown to transfer the dysbiotic phenotype to germ-free recipients, resulting in barrier leakage and the upregulation of the chemokines, CXCL2 and CCL5 (12,20,31,32). Despite this substantial evidence, the durability of engraftment and its dependence on host diet, baseline gut ecology, and medication exposure remain incompletely defined (33).

Bidirectional causality is evident in clinical cohorts. Patients with periodontitis exhibit persistent gut dysbiosis, characterised by an enrichment of Erysipelotrichaceae and a depletion of *Akkermansia*. These alterations mirror the overgrowth of salivary *Porphyromonadaceae*. Notably, periodontal therapy realigns both the oral and gut microbiomes toward a healthy state (8,24,25). Furthermore, Mendelian randomisation studies have revealed that gut microbes, such as *Prevotella* increase the risk of developing periodontitis, whereas *Butyricicoccus* exerts a protective effect, emphasising a causal association between the gut microbiota and periodontitis rather than a simple association (28,29). In individuals with comorbid RA and periodontitis, the enrichment of salivary *Prevotella* and *Streptococcus* is associated with Disease Activity Score-28 (DAS28) values. Conversely, gut *Fusobacterium* abundance is inversely related to the inflammatory status, suggesting oral-specific biomarkers (27). Experimental models of periodontitis extend these observations to the oral-gut-brain axis, where the gavage of *P. gingivalis* induces cognitive deficits via gut-mediated neuroinflammation in mice (34,35). Taken together, evidence from both clinical and experimental studies provides strong support for sustained oral-to-gut colonisation in periodontitis. Nevertheless, the long-term microbial engraftment and its dependence on factors, such as diet, baseline gut ecology and medication exposure remain incompletely understood.

4. Oral microbiome dysbiosis and gut alterations in periodontitis

Oral microbiome dysbiosis plays a central role in periodontitis, driving a shift from symbiotic communities to pathogenic biofilms that sustain chronic inflammation and progressive tissue destruction. Health-associated supragingival sites are typically dominated by commensals, such as *Streptococcus* and *Neisseria*, whereas disease-associated plaque maturation favours the proliferation of Gram-negative anaerobic bacteria, including *P. gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Fusobacterium* and *Prevotella*. These microorganisms thrive in the low-oxygen environment of deep periodontal pockets (5,21). Periodontitis is consistently linked to the enrichment of *Porphyromonadaceae* and *Treponema* species in saliva and plaque. Their increased abundance is associated with probing depth and bleeding on probing, thus exemplifying the polymicrobial synergy and dysbiosis model. Accordingly, keystone pathogens, such as *P. gingivalis* subvert host defences, increase the production of virulence factors (e.g., gingipains), disrupt epithelial junctions and promote osteoclastogenesis. Overall, these shifts in the oral community create a reservoir of pathobionts capable of subsequently reshaping gut microbial ecology (22).

Alterations in the oral microbiome are accompanied by distinct changes in gut microbial composition in individuals with periodontitis. Faecal microbiome analyses reveal an enrichment of taxa, such as Erysipelotrichaceae, Lachnospiraceae and *Blautia*, alongside a reduction in beneficial genera, including *Akkermansia*. These alterations in gut composition have been linked to systemic inflammatory status and may be associated with the severity of periodontal disease (36). Emerging evidence from Mendelian randomisation and experimental models suggests that specific gut taxa can modulate susceptibility to periodontitis, with certain genera (e.g., *Anaerotruncus* and *Eisenbergiella*) demonstrating protective associations, while others (e.g., Lachnospiraceae *UCG-008* and *Fusicatenibacter*) have been linked to enhanced inflammatory responses and an increased risk of disease development. Furthermore, gut dysbiosis may influence periodontal outcomes through immune and metabolic pathways, including Th17/Treg imbalance, altered bone metabolism and systemic inflammatory priming (37). Notably, dysbiotic gut profiles may persist even after periodontal therapy, indicating that gut alterations can become established over time and contribute to a self-sustaining oral-gut inflammatory axis.

5. Gut barrier dysfunction and mucosal inflammation

Periodontal dysbiosis exerts profound effects on gut barrier integrity and the local inflammatory status (8). In mice receiving salivary microbiota from patients with periodontitis, the colonic mucosal barrier was impaired (8,9). This is evidenced by a significant reduction in crypt depth and decreased ZO-1 expression, as determined by immunofluorescence staining, despite a compensatory upregulation of tight-junction-related gene transcripts (8,9). The levels of pro-inflammatory mediators, including IL-1β, TNF-α and IL-17, and various chemokines, were elevated, indicating the presence of low-grade inflammation and impaired neutrophil function. The administration of *P. gingivalis* further decreases the expression of ZO-1 and occludin, thus promoting endotoxemia and skewing toward Th17-dominant immune responses (6,13,14). The resulting barrier disruption facilitates the translocation of LPS into the systemic circulation, amplifying systemic inflammation and contributing to the development of comorbidities such as RA and implant failure (27,38). Locally, *Fusobacterium* adheres to

intestinal epithelium and forms biofilms that perpetuate dysbiosis. Persistence assays confirm that CFSE-labelled salivary bacteria can survive gastric passage and remain viable in the gut for at least 24 h, thereby enabling colonisation. Probiotic interventions have been shown to restore microbial balance, attenuate inflammation, and support epithelial barrier repair in experimental models (39,40). Thus, periodontal dysbiosis promotes a state of low-grade colonic inflammation and barrier dysfunction that facilitates systemic dissemination of microbial products.

6. Immune and molecular mechanisms linking oral-gut dysbiosis and periodontitis

Salivary pathobionts that translocate across the gut barrier reprogramme local and systemic immune responses towards a pro-inflammatory, Th17-dominant profile. This invasion amplifies inflammation through the upregulation of IL-1β, TNF-α and IL-17, and drives systemic Th17 responses, which recirculate to both gut and periodontal tissues (12,18).

In murine models, oral exposure to *P. gingivalis* results in its persistence for >24 h. This colonisation is accompanied by an enrichment of *Porphyromonadaceae* and *Fusobacterium*, shallower crypts and heightened chemokine expression, reflecting mucosal disruption and immune activation (8,13). Conversely, gut dysbiosis intensifies periodontal damage. High-fat-diet-induced imbalances elevate serum uric acid levels and drive alveolar bone resorption through hyperuricemia and Th17/Treg dysregulation. In addition, neutrophil defects arising from gut dysbiosis, such as impaired chemotaxis and the excessive formation of neutrophil extracellular traps, compromise gingival defence. The trafficking of T-cells from the gut to the gingiva via adhesion molecules, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, further contributes to oral inflammation (41). Collectively, these findings demonstrate that the oral-gut axis mediates bidirectional immune crosstalk in which oral pathobionts prime intestinal macrophages for inflammasome activation, thereby amplifying systemic Th17 responses that subsequently re-enter periodontal tissues and perpetuate a self-sustaining inflammatory loop.

This immunological dysregulation carries direct consequences for bone metabolism and implant outcomes. However, it should be acknowledged that the majority of available human data remain observational, warranting cautious mechanistic interpretation. A gut-primed Th17/Treg imbalance facilitates elevated RANKL signalling, osteoclast hyperactivation and compromised osseointegration. Consistent with this, germ-free mice colonised with saliva from individuals with periodontitis exhibit increased serum C-terminal telopeptide of type I collagen (CTX) levels, reduced osteocalcin concentrations and impaired implant osseointegration, reflecting disrupted SCFA homeostasis (42). Mechanistically, dysbiotic gut-expanded Th17 cells secrete IL-17 and TNF-α to directly enhance osteoclast differentiation. Concurrently, it suppresses the production of Treg-derived IL-10 and TGF-β. In addition, LPS translocation elevates the systemic RANKL/OPG ratio, establishing a coherent molecular framework through which oral-gut dysbiosis orchestrates pathological bone remodelling at both periodontal and implant interfaces.

7. Systemic immune dysregulation

Periodontitis imposes a substantial global health burden, and its association with systemic inflammation underscores the importance of integrating oral health into broader strategies for the prevention of non-communicable diseases. Epidemiological and mechanistic evidence converges to demonstrate that periodontitis co-clusters with cardiovascular disease, type 2 diabetes mellitus (T2DM), RA inflammatory bowel disease (IBD) and colorectal cancer. These conditions share common pathophysiological mechanisms, encompassing gut microbial dysbiosis, chronic endotoxemia and immune dysregulation propagated via the oral-gut axis (43,44). The clinical relevance of this framework is particularly apparent in the dissemination of periodontal pathobionts and the disruption of gut barrier integrity. These processes manifest as discrete, yet mechanistically interconnected pathological consequences across multiple organ systems and disease categories.

Autoimmune/inflammatory diseases. In RA-periodontitis cohorts, salivary *Porphyromonas* levels are strongly associated with the erythrocyte sedimentation rate, C-reactive protein (CRP) levels, probing depth and DAS28 scores (27). Similarly, patients with IBD demonstrate exacerbated colitis severity and increased relapse rates linked to periodontal pathogen colonisation (45).

Metabolic disorders. Periodontitis has been shown to be associated with insulin resistance, obesity, T2DM progression and non-alcoholic fatty liver disease through chronic low-grade endotoxemia, elevated IL-6/CRP levels, and visceral adiposity mediated by gut-derived LPS (12,18,19).

Gastrointestinal/oncological conditions. Oral pathobionts, specifically *F. nucleatum,* contribute to the progression of colorectal cancer by promoting tumour proliferation, metastatic potential and chemoresistance. These effects are mediated via gut colonisation and the activation of *Fusobacterium*-Toll-like receptor 4 (TLR4) signalling pathways. Furthermore, the severity of colitis has been reported to increase when periodontal disease remains untreated (7,16).

Neurological manifestations. Emerging evidence from oral-gut-brain axis research demonstrates that periodontitis is linked to cognitive decline, altered Alzheimer's disease biomarkers (phosphorylated tau/amyloid-β ratios) and neuroinflammation. These effects are considered to arise from microglial priming by circulating pathobionts and systemic cytokines (34,35,46,47).

Despite these converging mechanistic insights, the interplay between oral, gut and systemic diseases remains critically underrepresented in global clinical and public health frameworks. Moreover, the supporting evidence spanning cross-sectional associations, animal models, and Mendelian randomisation studies underscores the urgent need for robust prospective trials to substantiate causal inference and guide the development of integrated preventive strategies.

8. Microbial metabolites and host signalling

Microbial metabolites and host signalling pathways constitute a third, interconnected axis through which oral-gut dysbiosis

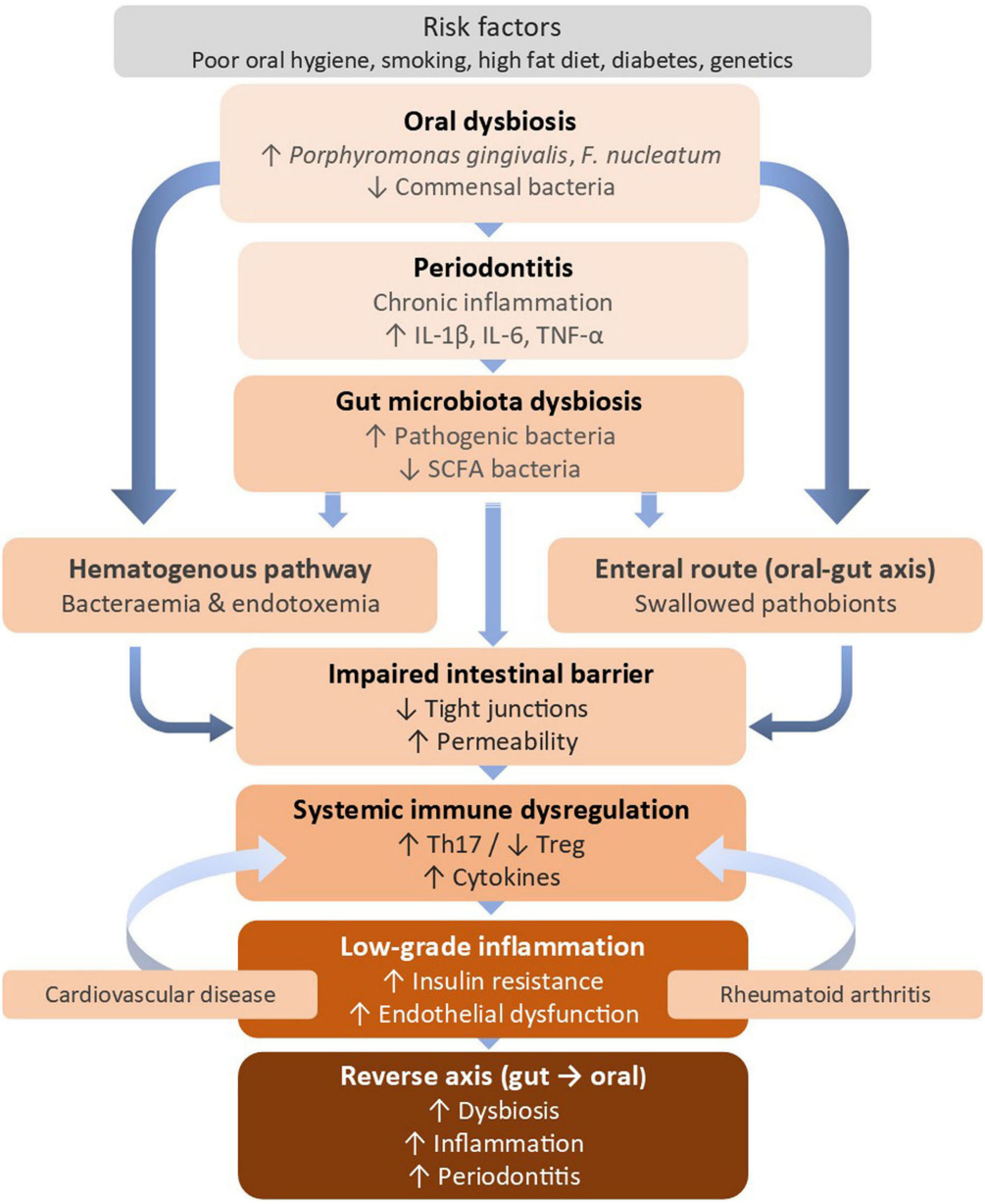

Figure 1. Schematic diagram illustrating the pathways linking oral dysbiosis, periodontitis, gut dysbiosis and systemic inflammation. The figure illustrates the bidirectional oral-gut axis in the pathogenesis of periodontitis, depicting risk factors that lead to oral dysbiosis, gut barrier impairment, systemic inflammation, and reverse feedback loops that exacerbate periodontal disease. SCFA, short-chain fatty acid.

alters SCFA availability, bile acid and amino acid metabolism and hormone-related pathways, thereby perpetuating immune imbalance and skeletal and metabolic dysfunction. The levels of SCFAs, such as butyrate, are markedly reduced in periodontitis-associated dysbiosis, which impairs Treg differentiation, diminishes colonocyte energy supply and increases osteoclast activity via histone deacetylase inhibition (20,31,48). Concurrently, gut dysbiosis elevates the levels of oxidative stress markers, including malondialdehyde and 8-hydroxy-2'-deoxyguanosine. These changes sensitise gingival tissues to infection and promote reactive oxygen species-driven osteoclast activation. In addition, LPS derived from translocated *Fusobacterium* stimulates TLR4/NF-κB signalling, inducing IL-6 and IL-1β production and amplifying the existing cytokine milieu to reinforce systemic inflammation (16,27).

The disruption of the estrobolome by shared oral-gut taxa, including β-glucuronidase-producing microorganisms, may alter oestrogen metabolism and increase the risk of periodontitis in women. Conversely, metabolites produced by *Eisenbergiella* support barrier function by replenishing SCFAs (37). Microbiota-targeted therapies, including probiotics that restore *Lactobacillus* and *Bifidobacterium* populations, have been shown to reduce Th17 cell expansion and RANKL expression, highlighting the potential of metabolite-focused interventions (40,49). Taken together, the available evidence suggests that both gut-directed approaches (e.g., FMT) and oral-biofilm-directed interventions may beneficially modulate systemic metabolic and inflammatory profiles. The schematic diagram depicted in Fig. 1 illustrates the bidirectional oral-gut axis involved in periodontitis pathogenesis, depicting risk factors leading to oral dysbiosis, gut barrier impairment and

systemic inflammation, as well as the reverse feedback loops exacerbating periodontal disease.

9. Emerging host- and microbiota-targeted therapies

Therapeutic strategies targeting the oral-gut axis in periodontitis focus on addressing both host immune dysregulation and microbial dysbiosis. These approaches are designed to restore barrier integrity, reduce systemic inflammation and prevent the risk of associated comorbidities, such as implant failure. The following sections discuss host-focused, microbiota-centred and integrated therapeutic interventions aimed at modulating the oral-gut axis.

Host-focused approaches. Host-focused approaches aim to modulate immune responses and promote tissue repair through the oral-gut axis. Therapeutic selection should be guided by patient-specific comorbidity profiles and immunological phenotypes. Non-surgical periodontal therapy, including scaling and root planing, serves as a first-line intervention across all patient strata. The method reduces oral pathogen loads and partially normalises gut microbiota. In ApoE mice, such treatment has been shown to improve intestinal barrier function and reduce the levels of inflammatory markers (50). In patients with concurrent RA, systemic agents, such as methotrexate attenuate IL-6 and IL-1β-mediated pathways. These agents have also been associated with improvements in periodontal status through the restoration of Th17/Treg balance, although current evidence is derived primarily from animal models (27,33). This patient subgroup may additionally benefit from biologic therapies targeting TNF, which limit osteoclast activation, a pathogenic mechanism shared by both conditions. In postmenopausal or oestrogen-deficient patients exhibiting disproportionate alveolar bone loss, oestrogen-based interventions may be considered to address the dysregulation of gut microbial genera, such as *Fusicatenibacter*, that are implicated in the gut-bone axis (51). Patients with IBD or T2DM represent a distinct high-risk stratum. In these individuals, gut microbiome profiling may further refine the selection of host-targeted therapeutic regimens by identifying those most likely to benefit from combination-based approaches (52,53).

Microbiota-centred therapies. Microbiota-centred therapies should be stratified according to disease severity, the burden of systemic comorbidities, and individual gut microbial composition. A summary of key clinical trials and reviews evaluating probiotics, prebiotics and synbiotics in periodontitis is presented in Table I. In patients with mild-to-moderate periodontitis and peri-implant mucositis, probiotic formulations containing *Lactobacillus* and *Bifidobacterium* represent a clinically accessible first-line adjunct, promoting Treg differentiation through butyrate production and improving microbial diversity (1,40,46). 16S rRNA profiling has revealed a significant reduction in SCFA-producing taxa, such as *Anaerotruncus* and *Phascolarctobacterium*; in such instances, targeted prebiotic fibre supplementation may be indicated, given its association with a lower risk of periodontitis and improved osseointegration outcomes (40,44). Synbiotic formulations may be preferentially reserved for patients with high-fat diet-associated metabolic comorbidities or those demonstrating an inadequate response to probiotic monotherapy, with experimental data indicating augmented *Eubacterium xylanophilum* enrichment and reduced gingival bleeding (40). In refractory cases characterised by confirmed pathobiont dominance, emerging therapeutic strategies, including oral microbiota transplantation, phage therapy targeting *P. gingivalis* and dietary patterns preferentially supporting SCFA-producing microbial communities, warrant consideration (54). The rationale for FMT as a microbiome-targeted intervention remains predominantly preclinical. Animal models have demonstrated that lower gastrointestinal tract FMT eliminates orally derived *F. nucleatum* and its virulence factor, FadA, restores microbial diversity and enriches anti-inflammatory taxa, hence attenuating colonic inflammation (32). Similarly, the *Akkermansia muciniphila*-mediated restoration of gut microbial homeostasis has been reported to alleviate periodontal inflammation in murine models (36). However, the complete absence of human periodontal trial data implies that FMT remains an investigational approach. Its clinical application should therefore be confined to rigorously designed, placebo-controlled randomised trials incorporating comprehensive safety surveillance until sufficient evidence is available to support its broader clinical adoption (55).

Combined interventions. Combined interventions targeting both host responses and microbial ecosystems exhibit considerable promise, particularly when patient selection is guided by systemic comorbidity status and oral-gut microbial signatures. In patients with moderate-to-severe periodontitis accompanied by systemic inflammation, clinical trials have demonstrated that periodontal therapy augmented with probiotics, such as *Lactobacillus reuteri*, yields significantly greater reductions in probing depth and lower systemic CRP levels than mechanical debridement alone. These findings support the application of this approach in this specific patient subgroup (40,46). In patients with causally implicated microbial deficiencies, Mendelian randomisation analyses support the targeted supplementation of protective bacterial genera, including *Eisenbergiella* and *Lachnoclostridium*, as a rational precision-medicine strategy (29,37). Nevertheless, the interpretation of these findings should consider the inherent limitations of Mendelian randomisation, including susceptibility to weak instrument bias, horizontal pleiotropy and population stratification bias, all of which may influence causal relevance (56-59). For implant patients with a history of implant failure or established gut dysbiosis, personalised therapeutic regimens guided by 16S rRNA gene sequencing or metagenomic profiling may optimise treatment selection by correcting dysbiotic patterns predictive of peri-implant complications (38). However, the majority of available data are derived from small-scale trials or animal models. Consequently, robust clinical evidence supporting the routine personalised approaches remains limited. The schematic diagram depicted in Fig. 2 illustrates a therapeutic framework for periodontitis-associated oral-gut dysbiosis, integrating oral niche-targeted, gut microbiota-targeted, and systemic host-directed interventions to reduce pathobiont burden, restore barrier integrity and improve oral-gut homeostasis.

Table I. Key clinical trials and reviews evaluating probiotics, prebiotics and synbiotics in periodontitis.

Authors, year of publication	Study design and sample size (N)	Intervention(s)	Main outcomes	Clinical significance	(Refs.)
Hardan *et al*, 2022	Systematic review and meta-analysis of RCTs; pooled n=600 patients with chronic periodontitis	*Lactobacillus reuteri* lozenges (probiotics), $2x10^8$ CFU/day, used as an adjunct to scaling and root planing	Additional reductions in probing pocket depth (PPD), clinical attachment level (CAL) gain, bleeding on probing (BOP), and gingival index (GI) compared with SRP alone; decreased salivary IL-1β levels in several included trials	Supports *L. reuteri* as an evidence-based adjunct to SRP in chronic periodontitis, with the largest benefit in moderate-severe cases and added anti-inflammatory effects	(49)
Sachelarie *et al*, 2025	Narrative review of RCTs and open-label clinical studies; individual trial N typically 20-120 participants	Various multi-strain probiotic supplements containing Lactobacillus and Bifidobacterium species, with different delivery forms, regimens and durations	Reported reductions in BOP and PPD, lower plaque indices, and improved peri-implant mucositis indices in several reviewed trials; some heterogeneity in response across strains and protocols	Indicates promising utility of multi-strain probiotics in both periodontal and peri-implant therapy, while emphasizing that optimal strain combinations, dosing and treatment duration still need standardization	(40)
Yang *et al*, 2025	Experimental murine RCT-equivalent model of diabetic periodontitis plus translational human correlation study; n=60 mice and 40 human participants	Butyrate supplementation as a prebiotic/synbiotic-type strategy targeting butyrate-producing microbiota in the context of diabetic periodontitis	Restoration of Treg/Th17 balance, reduction in alveolar bone loss, and decreased IL-17 and RANKL expression in mice; human data suggested association between improved butyrate status, better glycemic control (HbA1c), and periodontal parameters	Suggests that strategies enhancing butyrate production (prebiotics/synbiotics) may benefit diabetic patients with periodontitis via combined immunomodulatory and metabolic effects along the oral-gut axis	(31)
Di Stefano *et al*, 2023	Systematic review of clinical trials evaluating probiotics as adjuncts in periodontitis; pooled >400 patients	Probiotic strains such as *L. acidophilus*, *L. rhamnosus*, and *B. longum* used as adjuncts to SRP in different formulations and regimens	Overall reductions in periodontal pocket depth and improvements in clinical periodontal indices; several studies reported decreases in subgingival dysbiotic taxa and early evidence of shifts in gut microbial diversity markers	Reinforces the biological rationale for probiotic therapy in periodontitis within an oral-gut axis framework, while noting that gut microbiome endpoints remain underreported and require more systematic inclusion in future trials	(1)

CAL, clinical attachment level; BOP, bleeding on probing; GI, gingival index; PPD, probing pocket depth; SRP, scaling and root planing; RCT, randomised controlled trial; CFU, colony-forming units.

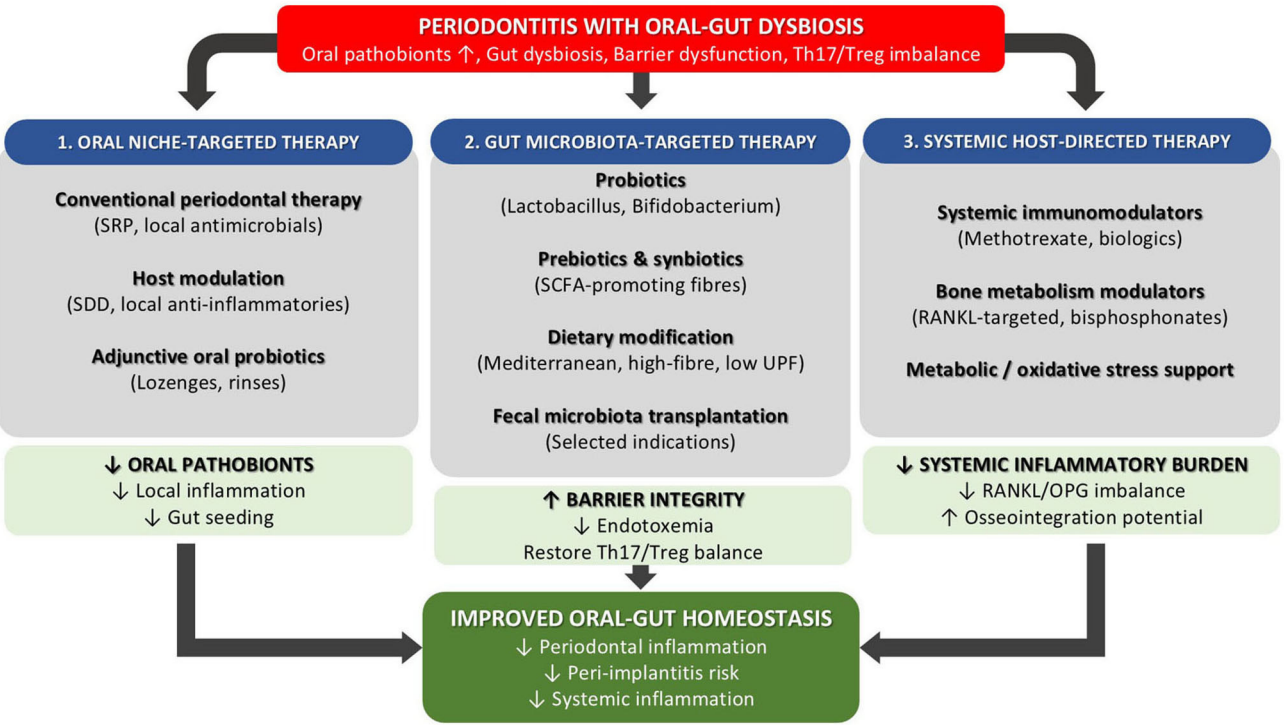

Figure 2. Therapeutic strategies targeting the oral-gut axis in periodontitis. The figure depicts a therapy framework for periodontitis-associated oral-gut dysbiosis that integrates oral niche-targeted, gut microbiota-targeted, and systemic host-directed interventions to reduce pathobiont burden, restore barrier integrity and improve oral-gut homeostasis. SRP, scaling and root planning; SDD, subantimicrobial dose doxycycline; SCFA, short-chain fatty acid; UPF, ultra-processed food; RANKL, receptor activator of nuclear factor kappa-B ligand; OPG, osteoprotegerin.

10. Implications for clinical periodontal practice

Periodontal risk assessment should extend beyond conventional local factors to incorporate oral-gut considerations, as gut dysbiosis, gastrointestinal disorders, poor dietary quality and systemic inflammation can influence disease severity and therapeutic response. Referral to a gastroenterologist should be considered for patients with periodontitis presenting with recurrent or refractory disease that is disproportionate to local plaque burden. This is particularly relevant for individuals with concomitant IBD, unexplained gastrointestinal symptoms, or documented treatment failure despite optimal local periodontal care. Patients with comorbid RA, T2DM, obesity, or prior antibiotic exposure represent a high-risk dysbiotic subgroup that may benefit from early interdisciplinary consultation. Identification and management of underlying gut pathology may interrupt the bidirectional oral-gut inflammatory cycle, thereby improving periodontal therapeutic outcomes (60).

Dietary fibre recommendations. Patients with established gut comorbidities, metabolic syndrome, or T2DM should be prioritised for dietitian referral, as this subgroup demonstrates the greatest degree of dysbiosis and is likely to derive the greatest benefit from targeted dietary modification. Across all periodontal patient groups, a daily dietary fibre intake of ≥25-30 g is recommended, with an emphasis on diverse plant-based sources, legumes and whole grains. Such dietary patterns support SCFA-producing taxa, including *Anaerotruncus*, *Butyricicoccus* and *Phascolarctobacterium*, reduce systemic inflammatory markers, and promote periodontal stability (44). Furthermore, the reduction of ultra-processed food consumption should be strongly encouraged, particularly in obese and insulin-resistant patients, owing to its disproportionately detrimental effects on gut microbial diversity.

11. Future directions

Despite the growing body of evidence substantiating the involvement of the oral-gut axis in periodontitis, major knowledge gaps remain regarding dose-response associations, the temporal sequence of microbial and immune changes, and the extent to which oral-gut dysbiosis can be reversed through targeted interventions. Future research is thus warranted to prioritise large-scale longitudinal human studies employing standardised sampling protocols and analytical approaches to facilitate the transition from association-based observations to causal inference. Further investigations are warranted to integrate multi-omics approaches, including metagenomics, metabolomics, immunomics and proteomics, with systems biology frameworks, to elucidate how specific oral pathobionts alter gut barrier function, the Th17/Treg balance, and systemic inflammation responses. From a therapeutic perspective, priority should be given to rigorously designed randomised controlled trials (RCTs) assessing defined probiotic and prebiotic regimens, paraprobiotic mouth rinses, and diet-based strategies as adjuncts to scaling and root planning. Outcome measures should span periodontal clinical parameters, SCFA profiles and systemic cytokine levels. Non-invasive approaches that enhance SCFA production and support gut-bone homeostasis are particularly attractive compared with more invasive options, such as faecal microbiota transplantation. Mechanistic models should evolve toward gnotobiotic and humanised microbiota designs,

incorporating labelled oral inocula to track the persistence and metabolic impact of oral taxa in the gut.

Oral microbiota transplantation, defined as the standardised transfer of a healthy donor oral microbiome to recipients with established oral dysbiosis, represents an emerging and conceptually compelling frontier. However, it warrants rigorous preclinical validation and, ultimately, well-controlled human trials to assess its capacity to re-establish commensal oral microbial communities and to disrupt pathobiont-driven gut-periodontal inflammatory cascades. Future studies are required to adopt standardised case definitions for periodontitis, based on established clinical criteria, such as clinical attachment loss, probing depth, bleeding on probing, and radiographic bone loss. Likewise, gut dysbiosis should be defined using consistent microbiological and functional criteria, including alterations in alpha and beta diversity, the *Bacteroidetes*-to-*Firmicutes* ratios, and shifts in functionally relevant taxa, to enable reproducible and comparable assessments of the oral-gut axis. Achieving these goals will require close collaboration across dentistry, gastroenterology, immunology, and nutrition to translate mechanistic insights into practical, microbiome-centric clinical protocols.

12. Conclusion

The oral-gut axis represents a bidirectional biological framework in which periodontitis-associated dysbiosis promotes intestinal microbial imbalance, impairs gut barrier integrity and sustains systemic inflammation. Conversely, gut dysbiosis exacerbates periodontal tissue destruction through Th17/Treg imbalance, altered SCFA production, and upregulated RANKL-mediated osteoclastogenesis. Strong mechanistic evidence demonstrates that oral pathobionts, particularly *P. gingivalis* and *F. nucleatum*, translocate to the gut, disrupt tight-junction proteins and amplify mucosal immune activation. The durability of oral pathobiont engraftment in the gut, along with its clinical determinants, remains poorly defined. It is also unclear whether oral or gut dysbiosis serves as the primary driver within the bidirectional oral-gut axis across distinct patient subgroups. Although Mendelian randomisation studies provide hypothesis-generating evidence, their interpretation is constrained by weak instrumental variables, pleiotropy, and limited population diversity. In addition, the safety, regulatory and ethical frameworks governing FMT in periodontal contexts are underdeveloped. At present, personalised microbiome-based treatment algorithms lack a robust evidence base for routine clinical implementation. Addressing these gaps will require well-designed longitudinal studies, standardised multi-omics methodologies, and rigorously conducted RCTs to translate the biological plausibility of oral-gut interactions into measurable improvements in both periodontal and systemic patient outcomes.

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Authors' contributions

All authors (STP, NS and BG) contributed to the conceptualisation of the study, data collection, data analysis, literature data review, writing the first draft of the manuscript, preparation of graphical work and drawing figures. NS and BG critically revised the manuscript. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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