

THE ROLE OF ORAL MICROBIOTA IN SYSTEMIC HEALTH: EMERGING LINKS BETWEEN PERIODONTAL DISEASE AND CHRONIC ILLNESS

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ABSTRACT

Background: The human oral cavity harbours over 700 microbial species constituting one of the most complex and diverse microbiomes in the body. Disruption of this community, termed oral dysbiosis, is central to the pathogenesis of periodontal disease. Accumulating evidence demonstrates that periodontitis is not merely a localised infection but a systemic inflammatory condition with wide-ranging implications for chronic non-communicable diseases.

Objectives: This review critically appraises the mechanistic and epidemiological evidence linking oral microbiota dysbiosis and periodontal disease to cardiovascular disease, type 2 diabetes mellitus, rheumatoid arthritis, adverse pregnancy outcomes, Alzheimer's disease, and colorectal cancer, while evaluating pharmacological and non-pharmacological management strategies.

Methods: A structured narrative review of peer-reviewed literature published from 2020 to 2025 was conducted using PubMed, Scopus, and Web of Science databases.

Results: The keystone periodontal pathogen *Porphyromonas gingivalis* orchestrates immune subversion via complement manipulation and gingipain activity, enabling bacteraemia and systemic dissemination of pro-inflammatory mediators including IL-1 β , TNF- α , and CRP. Bidirectional relationships exist between periodontitis and T2DM, while molecular mimicry underpins the oral-RA axis. Emerging data implicates *P. gingivalis* gingipains in neuroinflammation relevant to Alzheimer's disease.

Conclusion: Periodontal treatment, including scaling and root planning, demonstrably reduces systemic inflammatory markers and improves glycaemic control, supporting the incorporation of oral health management into multidisciplinary chronic disease care. Future research should prioritise mechanistic causal studies and multicentre randomised controlled trials.

Keywords: Oral Microbiome; Periodontal Disease; Systemic Inflammation; Cardiovascular Disease; Diabetes Mellitus; Dysbiosis; *Porphyromonas Gingivalis*; Pharmaceutical Intervention.

1. INTRODUCTION

The oral microbiome constitutes one of the most diverse and complex microbial ecosystems in the human body, encompassing bacteria, fungi, archaea, and viruses collectively referred to as the oral microbiota.[1] Under homeostatic conditions, approximately 700 distinct microbial species maintain a symbiotic relationship with the host, contributing to nutrient metabolism, mucosal immunity, and pathogen exclusion. Perturbation of this balance, termed oral dysbiosis, precipitates inflammatory diseases including dental caries and, most significantly for systemic health, periodontal disease.[2]

Periodontal disease, encompassing gingivitis and periodontitis, affects approximately 1 billion people worldwide, making it among the most prevalent chronic inflammatory conditions globally.[3] The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases revised staging and grading criteria that stratify disease severity and systemic risk, reflecting an evolution in understanding periodontitis as a condition with far-reaching biological consequences.[4] Pathological biofilm accumulation at the gingival margin triggers an exaggerated host immune-inflammatory response involving neutrophil extravasation, cytokine release, and osteoclast-mediated alveolar bone destruction.

A growing body of epidemiological and mechanistic evidence establishes bidirectional relationships between oral dysbiosis and an expanding spectrum of chronic systemic illnesses including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), rheumatoid arthritis (RA), adverse pregnancy outcomes (APO), Alzheimer's disease (AD), and colorectal cancer (CRC).[5] The biological plausibility of these associations rests on three interrelated mechanisms: (i) bacteraemia and direct seeding of distant tissues, (ii) systemic dissemination of microbial products such as lipopolysaccharide (LPS), and (iii) chronic activation of the systemic inflammatory cascade mediated through pro-inflammatory cytokines.[6]

From a pharmaceutical and clinical management perspective, the evidence that effective periodontal treatment reduces surrogate markers of systemic disease, including HbA1c, CRP, and endothelial function parameters, opens a compelling avenue for integrative chronic disease management.[7] This review critically examines the mechanistic underpinnings of the oral-systemic axis, evaluates systemic disease associations, and appraises pharmacological strategies targeting the oral-systemic interface, with a focus on literature published between 2020 and 2025. Figure 1 presents a detailed medical illustration showing a cross-section of human anatomy.

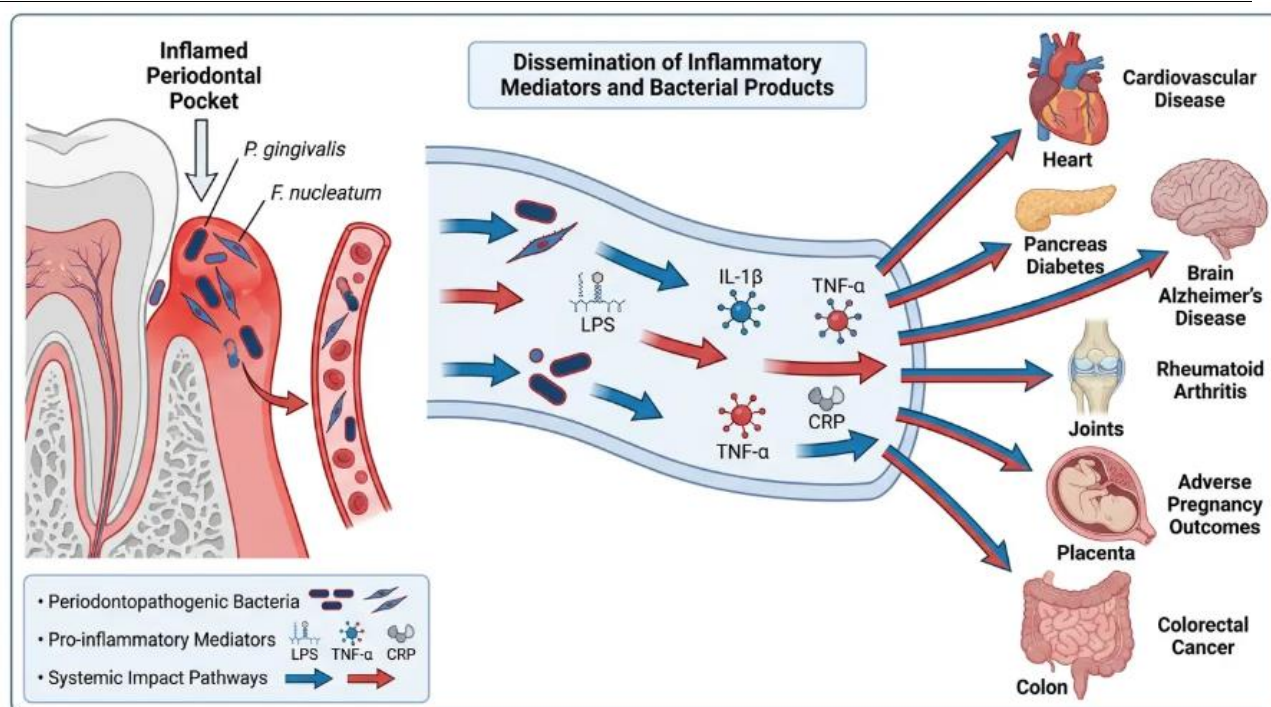


Figure 1. Schematic overview of the oral-systemic axis: from oral dysbiosis and periodontal pathogen dissemination to systemic chronic disease involvement.

Sources: Adapted from concepts in references [2, 5, 6]

The Oral Microbiome: Composition, Homeostasis, And Dysbiosis

Microbial Ecology of the Oral Cavity

The Human Oral Microbiome Database (HOMD) catalogues over 770 prokaryotic taxa colonising distinct oral niches including the supragingival plaque, subgingival sulcus, tongue dorsum, and buccal mucosa.[1] Dominant phyla include Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes, and Fusobacteria. The keystone pathogen *Porphyromonas gingivalis* (*P. gingivalis*) occupies a disproportionately disruptive ecological role relative to its numerical abundance, subverting complement-mediated innate immunity to create a permissive environment for polymicrobial dysbiosis.[2]

Early colonisers such as *Streptococcus* and *Actinomyces* species establish the scaffolding for biofilm maturation. Bridge species including *Fusobacterium nucleatum* facilitate coaggregation of late colonisers comprising the periodontal 'red complex': *P. gingivalis*, *Tannerella forsythia*, and *Treponema denticola*. These organisms constitute the principal drivers of subgingival dysbiosis and are the subjects of intense investigation regarding systemic disease linkage.[3]

Table 1. Key oral microorganisms implicated in periodontal disease and associated systemic conditions.

Table 1. Key oral microorganisms implicated in periodontal disease and associated systemic conditions.

Organism	Gram Status	Role in Periodontal Disease	Systemic Association
<i>Porphyromonas gingivalis</i>	Negative	Keystone pathogen; disrupts complement immunity	CVD, T2DM, RA, Alzheimer's
<i>Tannerella forsythia</i>	Negative	Degrades host tissue; synergistic with <i>P. gingivalis</i>	Adverse pregnancy outcomes, CVD
<i>Treponema denticola</i>	Negative	Invades gingival epithelium; stimulates cytokine release	CVD, chronic kidney disease
<i>Fusobacterium nucleatum</i>	Negative	Bridges early/late colonisers; promotes inflammation	Colorectal cancer, preterm birth
<i>Aggregatibacter actinomycetemcomitans</i>	Negative	Produces leukotoxin; promotes bone resorption	Infective endocarditis
<i>Streptococcus mutans</i>	Positive	Primary cariogenic species; aids biofilm maturation	Bacteraemia, endocarditis
<i>Prevotella intermedia</i>	Negative	Responsive to steroid hormones; elevated in pregnancy	Gestational periodontitis, preterm birth

GCF = gingival crevicular fluid; *CVD* = cardiovascular disease; *T2DM* = type 2 diabetes mellitus; *RA* = rheumatoid arthritis.

Sources: Compiled from references [1,2,3]

Pathogenesis: From Biofilm to Systemic Dissemination

P. gingivalis expresses a unique lipopolysaccharide that antagonises Toll-like receptor 4 (TLR4) while activating TLR2, effectively dampening bactericidal responses while amplifying the release of pro-inflammatory cytokines.[6] The organism elaborates cysteine proteases termed gingipains (RgpA, RgpB, Kgp) that degrade host defence proteins, dysregulate complement

activation, and facilitate periodontal tissue destruction. Gingipains have been identified in the brain tissue of Alzheimer's disease patients, providing direct histopathological evidence for systemic translocation.[12]

Bacteraemia arising from periodontal instrumentation, chewing, or spontaneous gingival bleeding provides a haematogenous route for oral pathogens to access remote anatomical sites. LPS from periodontal pathogens stimulates hepatic synthesis of acute-phase proteins including CRP and fibrinogen, elevates circulating IL-6 and TNF- α , and activates the nuclear factor- κ B (NF- κ B) pathway in vascular endothelium.[7] Chronic subthreshold systemic inflammatory activation constitutes a plausible biological mechanism linking chronic periodontitis to the pathophysiology of CVD, insulin resistance, and neurodegeneration.[8] Figure 2 presents the Molecular mechanisms of *P. gingivalis*-mediated immune subversion and systemic inflammatory cascade activation.

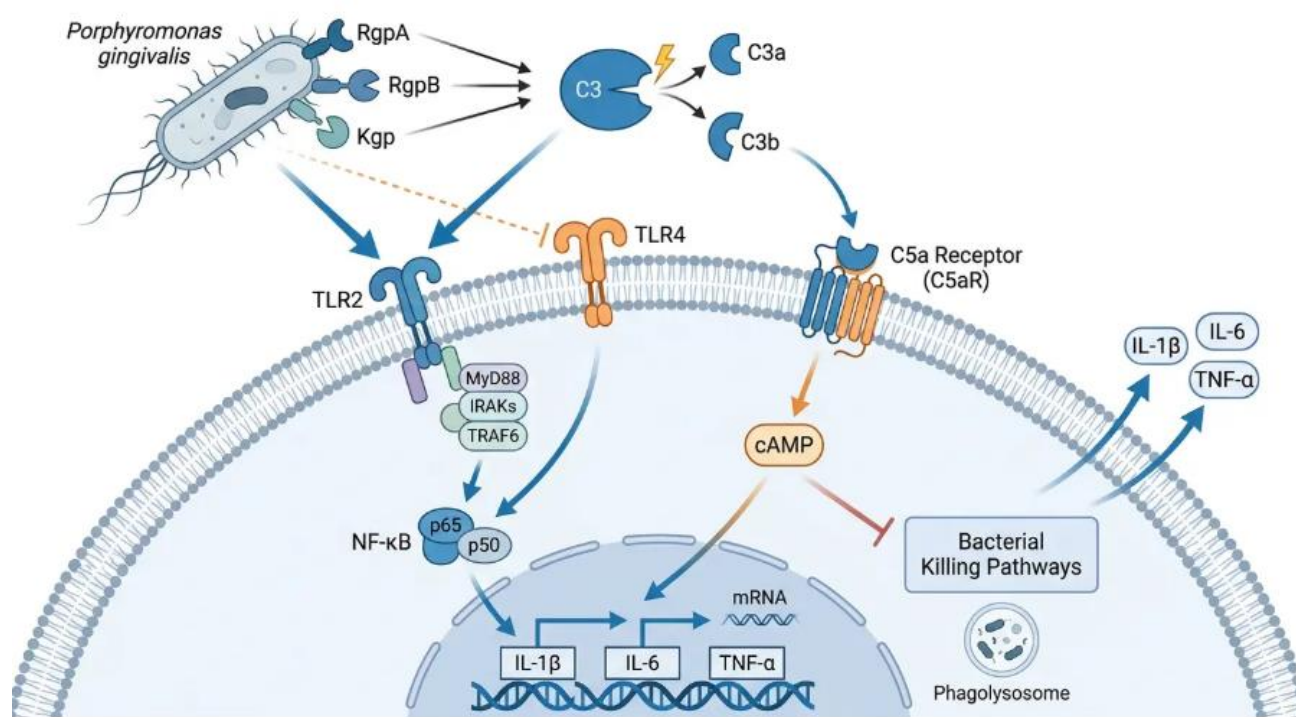


Figure 2. Molecular mechanisms of *P. gingivalis*-mediated immune subversion and systemic inflammatory cascade activation. The diagram illustrates gingipain activity, TLR2/TLR4 antagonism, complement evasion (C3 cleavage by gingipains), NF- κ B activation, and downstream cytokine (IL-1 β , IL-6, TNF- α) release.

Sources: Based on concepts in references [2, 6, 8]

Periodontal Disease and Systemic Chronic Illness

Cardiovascular Disease

The association between periodontitis and CVD is among the most extensively studied in dental medicine. A 2020 joint workshop statement from the European Federation of Periodontology and the American Heart Association concluded that periodontitis independently increases cardiovascular risk, with atherosclerosis being the principal mediating pathology.[2] Multiple

mechanisms are implicated: *P. gingivalis* has been identified in atherosclerotic plaques, capable of inducing foam cell formation and endothelial inflammation. In addition, platelet aggregation stimulated by oral streptococci contributes to thrombus formation relevant to acute coronary events.[9]

A systematic review and meta-analysis by Leira et al. demonstrated that individuals with periodontitis exhibit a 1.34-fold increased risk of major adverse cardiac events.[10] Importantly, periodontal treatment has been shown to reduce CRP, endothelin-1, and intima-media thickness, surrogate markers of cardiovascular risk, providing mechanistic support for the causal hypothesis rather than mere association.[11]

Type 2 Diabetes Mellitus

The bidirectional relationship between periodontitis and T2DM is perhaps the best characterised oral-systemic interaction. Hyperglycaemia promotes advanced glycation end-product (AGE) formation, impairing neutrophil function and enhancing pro-inflammatory cytokine production in periodontal tissues.[5] Reciprocally, periodontitis-derived TNF- α and IL-6 interfere with insulin receptor signalling, aggravating insulin resistance and worsening glycaemic control. A 2021 systematic review demonstrated that non-surgical periodontal therapy reduces HbA1c by a weighted mean difference of approximately 0.43%, a magnitude comparable to adding a second pharmacological agent.[5]

Rheumatoid Arthritis

The oral-RA axis is mechanistically grounded in molecular mimicry and shared autoantigens. *P. gingivalis* uniquely expresses a peptidylarginine deiminase (PPAD) enzyme capable of citrullinating host and bacterial proteins, generating neo-epitopes that drive anti-citrullinated protein antibody (ACPA) production, the hallmark autoantibody of RA.[8] Cross-reactive immune responses between citrullinated bacterial antigens and joint-specific proteins provide a compelling hypothesis for periodontitis as a potential initiating event in RA pathogenesis in genetically susceptible individuals.[13]

Alzheimer's Disease

The neuropathological role of oral pathogens in AD has gained traction following landmark studies demonstrating *P. gingivalis* DNA and gingipain immunoreactivity in post-mortem hippocampal tissue of AD patients.[12] Gingipains co-localise with amyloid- β deposits and tau tangles, suggesting an active role in neuroinflammation rather than passive translocation. A 2022 prospective cohort study found that individuals with chronic periodontitis had a 1.7-fold increased risk of developing dementia over a 10-year follow-up period.[14] The blood-brain barrier disruption mediated by systemic IL-6 and LPS challenge provides the mechanistic conduit for central nervous system involvement.

Adverse Pregnancy Outcomes

Maternal periodontitis has been associated with preterm birth, low birth weight, and pre-eclampsia through haematogenous translocation of periodontal pathogens to the fetoplacental unit.[18] *Fusobacterium nucleatum* and *Prevotella intermedia* have been cultured from placental tissue, amniotic fluid, and neonatal gastric aspirates of women with periodontitis. Prostaglandin

E2 released in response to subgingival LPS may induce premature cervical ripening and uterine contractions, constituting a plausible mechanism for preterm birth.[19]

Colorectal Cancer

Fusobacterium nucleatum has emerged as a significant oncogenic driver in CRC, enriched in tumour tissue relative to adjacent normal mucosa. The FadA adhesin of *F. nucleatum* activates Wnt/ β -catenin signalling by binding E-cadherin, promoting tumour cell proliferation, invasion, and immune evasion.[20] Epidemiological studies demonstrate a significantly higher prevalence of tooth loss, a proxy for cumulative periodontal disease burden, among CRC patients, supporting a clinical oral-gut oncological axis, plausibly mediated by salivary bacterial transit through the gastrointestinal tract. Table 2 shows the Summary of evidence linking periodontal disease to major chronic systemic diseases.

Table 2. Summary of evidence linking periodontal disease to major chronic systemic diseases.

Systemic Disease	Key Mechanism	Strength of Evidence	Proposed Mediators	Selected Reference
Cardiovascular Disease	Bacteraemia, platelet aggregation, endothelial dysfunction	Strong (meta-analyses, RCTs)	IL-6, CRP, P. gingivalis gingipains	Sanz et al. [2]
Type 2 Diabetes Mellitus	Bi-directional: periodontitis worsens HbA1c; hyperglycaemia increases inflammation	Strong (systematic reviews)	TNF- α , IL-1 β , advanced glycation end-products	Polak & Shapira [5]
Rheumatoid Arthritis	Molecular mimicry; citrullinated proteins from P. gingivalis	Moderate-Strong	ACPA, citrullinated fibrinogen	Potempa et al. [8]
Alzheimer's Disease	P. gingivalis invasion of brain; gingipain-mediated neurodegeneration	Emerging	Gingipains, amyloid- β aggregation	Dominy et al. [12]
Adverse Pregnancy Outcomes	Haematogenous spread to fetoplacental unit;	Moderate	PGE2, IL-8, LPS from oral pathogens	Zi et al. [18]

Systemic Disease	Key Mechanism	Strength of Evidence	Proposed Mediators	Selected Reference
	prostaglandin induction			
Colorectal Cancer	F. nucleatum promotes tumour microenvironment; E-cadherin dysregulation	Emerging-Moderate	FadA adhesin, Wnt/ β -catenin pathway	Gur et al. [20]
Chronic Kidney Disease	Shared inflammatory pathways; uraemia alters oral microbiome	Moderate	CRP, IL-6, oxidative stress markers	Wahid et al. [21]

CVD = cardiovascular disease; T2DM = type 2 diabetes mellitus; RA = rheumatoid arthritis; CRC = colorectal cancer; ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein.

Inflammatory Mediators of the Oral-Systemic Interface

The mechanistic bridge between oral dysbiosis and systemic pathology is constituted by a network of pro-inflammatory cytokines, acute-phase proteins, and tissue-degrading enzymes that are elevated both locally in gingival crevicular fluid (GCF) and systemically in the circulation.[7] IL-1 β and TNF- α are principal drivers of osteoclastogenesis in periodontal tissue and simultaneously impair insulin receptor substrate signalling, directly linking periodontitis to metabolic dysregulation.[15]

CRP, synthesised by the liver in response to IL-6, serves as a clinically measurable biomarker of the systemic inflammatory burden attributable to periodontal disease. Multiple intervention studies demonstrate reductions in high-sensitivity CRP (hs-CRP) following non-surgical periodontal therapy, corroborating a causal contribution.[16] Matrix metalloproteinases, particularly MMP-8 measurable in point-of-care salivary assays, represent both markers of periodontal tissue destruction and potential mediators of vascular extracellular matrix remodelling in atherosclerosis.[17] Table 3 presents the Principal inflammatory mediators at the oral-systemic interface and their clinical significance, while Figure 3. Cytokine network mediating the oral-systemic inflammatory axis.

Table 3. Principal inflammatory mediators at the oral-systemic interface and their clinical significance.

Inflammatory Marker	Source	Role in Oral-Systemic Axis	Clinical Relevance
Interleukin-1 β (IL-1 β)	Macrophages, gingival fibroblasts	Drives osteoclast activation; amplifies systemic inflammation	Elevated in GCF; correlates with disease severity
Tumour Necrosis Factor- α (TNF- α)	Macrophages, T-cells	Induces insulin resistance; promotes endothelial dysfunction	Serum levels correlate with periodontitis + T2DM
C-Reactive Protein (CRP)	Liver (acute-phase)	Biomarker of systemic inflammatory burden	Reduced after periodontal treatment in RCTs
Matrix Metalloproteinase-8 (MMP-8)	Neutrophils, fibroblasts	Degrades collagen; marker of periodontal tissue destruction	Point-of-care diagnostic potential in saliva
Interleukin-6 (IL-6)	Multiple immune cells	Hepatic CRP induction; atherosclerosis progression	Elevated in both periodontitis and CVD cohorts
Prostaglandin E2 (PGE2)	Macrophages, gingival cells	Bone resorption mediator; labour onset involvement	Implicated in preterm birth mechanism
RANKL/OPG Ratio	Osteoblasts, T-cells	Regulates osteoclastogenesis in alveolar bone	Elevated ratio in chronic periodontitis patients

GCF = gingival crevicular fluid; MMP = matrix metalloproteinase; RANKL = receptor activator of nuclear factor- κ B ligand; OPG = osteoprotegerin; CRP = C-reactive protein.

Sources: Compiled from references [7,15,16,17]

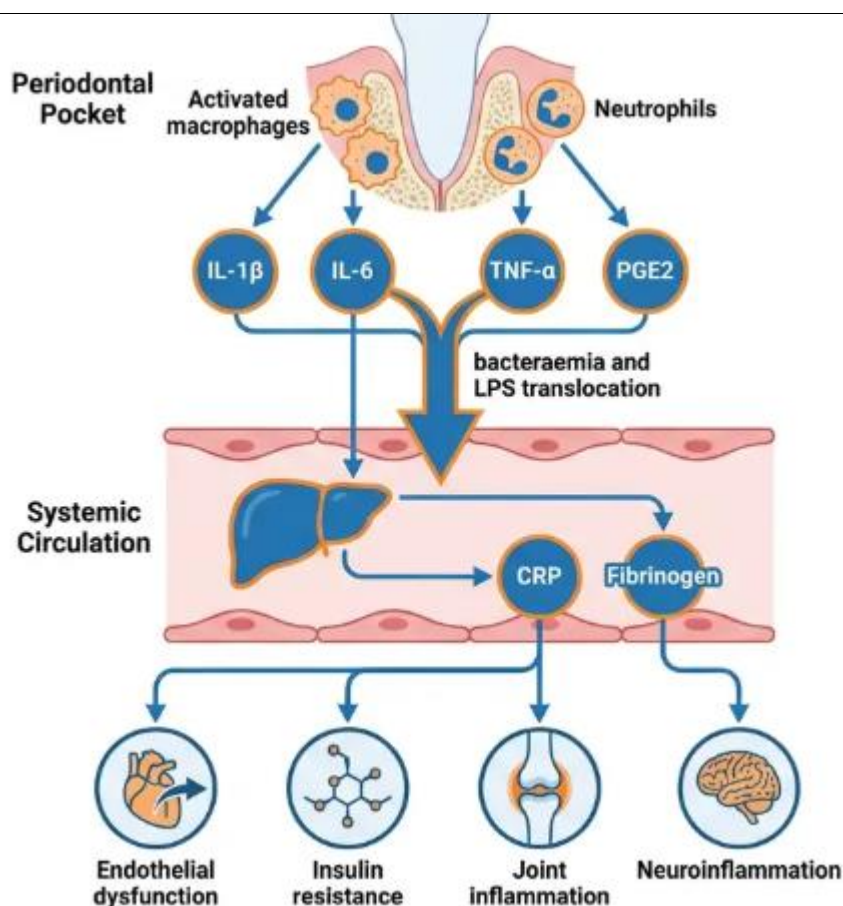


Figure 3. Cytokine network mediating the oral-systemic inflammatory axis. The figure shows local (gingival) cytokine production (IL-1 β , IL-6, TNF- α , PGE2, MMP-8) with bidirectional arrows demonstrating amplification of systemic inflammatory markers (CRP, fibrinogen) and their downstream effects on target organs.

Sources: Based on concepts in references [7, 15, 16]

Pharmacological And Non-Pharmacological Management Strategies

Mechanical Periodontal Therapy and Systemic Outcomes

Scaling and root planing (SRP) constitutes the gold standard non-surgical intervention for chronic periodontitis, mechanically disrupting the subgingival dysbiotic biofilm and reducing the inflammatory burden.[2] A landmark 2020 meta-analysis demonstrated that SRP produces a statistically significant reduction in HbA1c of 0.43% in patients with comorbid T2DM, a magnitude clinically comparable to adding a second oral hypoglycaemic agent.[5] Additionally, SRP reduces hs-CRP, IL-6, and endothelin-1 concentrations in peripheral blood, indicating measurable attenuation of systemic inflammatory activation.[16]

Host-Modulation Pharmacotherapy

Sub-antimicrobial dose doxycycline (SDD; 20 mg twice daily) represents the only FDA-approved host modulation agent for periodontitis. Its mechanism operates through inhibition of

matrix metalloproteinases, particularly MMP-8 and MMP-13, independent of any antibiotic activity.[28] Clinical trials demonstrate statistically significant improvements in probing pocket depth and clinical attachment level with SDD adjunctive to SRP, with concurrent reductions in GCF MMP-8 concentrations. The systemic anti-inflammatory effects of SDD are of particular interest given the role of MMPs in cardiovascular plaque vulnerability.

Adjunctive Systemic Agents

Metformin, the first-line pharmacological agent for T2DM, has been evaluated as an adjunct to SRP in diabetic patients with periodontitis. A systematic review found that metformin-adjunctive SRP produced greater improvements in clinical attachment levels and probing depths compared to SRP alone, mediated through AMPK activation, reducing oxidative stress in periodontal tissues.[29]

Statins, particularly atorvastatin and simvastatin, exert pleiotropic anti-inflammatory and anti-osteoclastic effects beyond their lipid-lowering action. Locally delivered atorvastatin administered as an adjunct to SRP has demonstrated superior reductions in pocket depths, bone fill, and IL-6 serum concentrations compared to SRP alone in randomised controlled trials.[30] Omega-3 polyunsaturated fatty acid supplementation mediates production of specialised pro-resolving mediators (SPMs), including resolvins and protectins, facilitating resolution of periodontal inflammation.[31]

Probiotics and Microbiome-Targeted Therapies

The emerging concept of microbiome restoration as a therapeutic strategy has prompted investigation of oral probiotic formulations. *Lactobacillus reuteri* lozenges as an adjunct to SRP have demonstrated reductions in subgingival *P. gingivalis* counts, GCF IL-1 β , and bleeding on probing in double-blind RCTs.[32] Antimicrobial photodynamic therapy (aPDT) and locally delivered antimicrobials (chlorhexidine, minocycline microspheres) represent additional adjunctive modalities with varying levels of evidence.[33] Table 4 shows the Pharmacological and non-pharmacological interventions targeting the periodontal-systemic axis, while Figure 4 presents the Therapeutic landscape for managing the periodontal-systemic interface.

Table 4. Pharmacological and non-pharmacological interventions targeting the periodontal-systemic axis.

Intervention / Drug Class	Mechanism of Action	Evidence Level	Outcome on Periodontal / Systemic Parameters	Key Study
Sub-antimicrobial doxycycline (SDD)	MMP inhibition; anti-inflammatory (not antibiotic)	Level I RCT	Reduces probing depth, MMP-8; may lower CRP	Caton et al. [28]
Metformin (adjunct to SRP)	AMPK activation reduces oxidative stress	Level II Systematic Review	Improved CAL, PPD in T2DM patients with periodontitis	Tsobgny-Tsague et al. [29]

Intervention / Drug Class	Mechanism of Action	Evidence Level	Outcome on Periodontal / Systemic Parameters	Key Study
Statins (local/systemic)	Anti-inflammatory; inhibits osteoclast activity	Level II RCT	Adjunctive atorvastatin reduces pocket depth and IL-6	Kumari et al. [30]
Omega-3 supplementation	Specialised pro-resolving mediators (SPMs); reduces TNF- α	Level II RCT	Modest improvement in clinical attachment level	Elkhouli [31]
Probiotics (Lactobacillus reuteri)	Competitive exclusion of pathogens; immunomodulation	Level II Systematic Review	Reduces P. gingivalis load; improves GI and systemic markers	Martin-Cabezas et al. [32]
Scaling and Root Planing (SRP)	Mechanical debridement; disrupts dysbiotic biofilm	Level I Systematic Review	Reduces HbA1c by ~0.4%; lowers CRP, IL-6	Sanz et al. [2]
Azithromycin (adjunct)	Macrolide antibiotic; immunomodulatory effects	Level II RCT	Short-term benefit in aggressive periodontitis; systemic impact unclear	Hirsch et al. [33]

SRP = scaling and root planing; CAL = clinical attachment level; PPD = probing pocket depth; MMP = matrix metalloproteinase; T2DM = type 2 diabetes mellitus; RCT = randomised controlled trial.

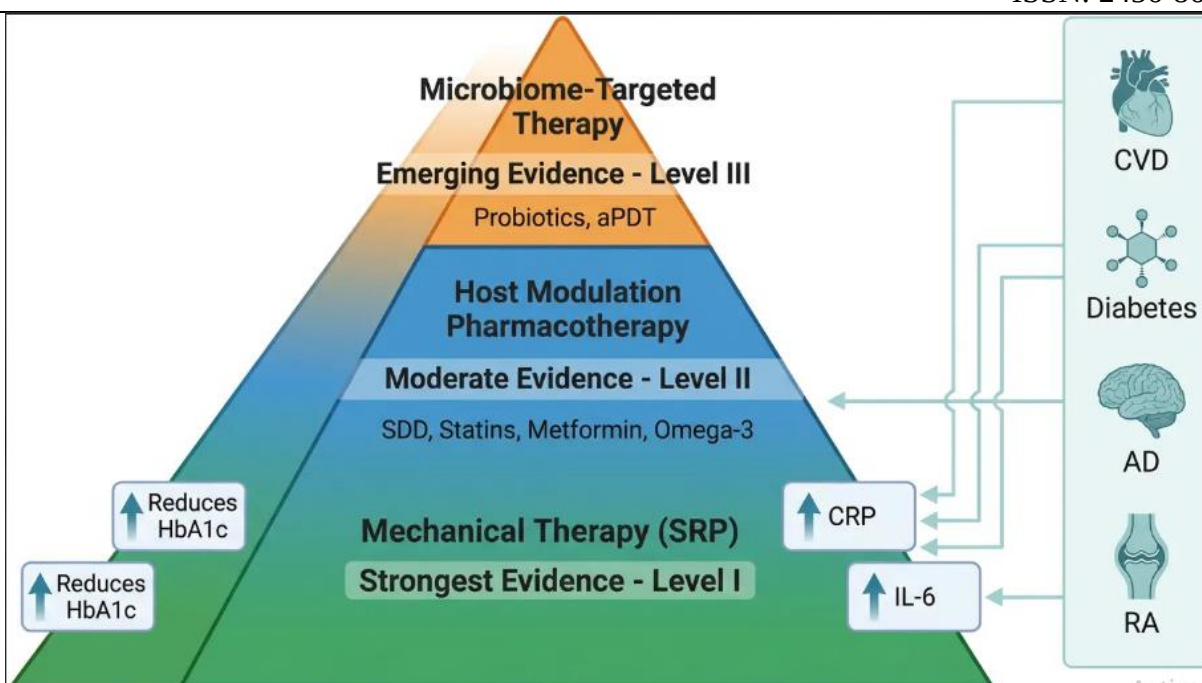


Figure 4. Therapeutic landscape for managing the periodontal-systemic interface. An evidence pyramid showing interventions from mechanical therapy (SRP) at the base, through host modulation (SDD, statins, omega-3), to microbiome-targeted strategies (probiotics, aPDT) at the apex, with corresponding systemic outcome benefits annotated at each level.

Sources: Based on concepts in references [2, 28, 29, 30, 31, 32]

Future Directions and Research Priorities

Despite significant advances, several critical gaps preclude definitive causal inferences. Most epidemiological evidence is cross-sectional, precluding temporal attribution. The majority of intervention trials are limited by short follow-up durations, small sample sizes, and heterogeneous periodontal diagnostic criteria.[22] Future research priorities include: (i) large-scale, multicentre RCTs with standardised periodontal staging/grading, (ii) longitudinal microbiome profiling using metagenomic sequencing to characterise dysbiosis signatures predictive of systemic risk, and (iii) mechanistic studies utilising humanised murine models to delineate causality.[23]

The advent of salivary diagnostics offers transformative potential for non-invasive systemic disease screening. Salivary exosome proteomics, volatile organic compound analysis, and cell-free DNA profiling may enable simultaneous oral and systemic disease biomarker detection.[24] Integration of oral health assessment into multidisciplinary chronic disease management pathways, encompassing cardiology, endocrinology, rheumatology, and obstetrics, represents a priority recommendation from international periodontal societies.[25]

From a pharmaceutical science perspective, the development of novel gingipain inhibitors, microbiome-restorative prebiotics, and targeted nano-drug delivery systems for subgingival administration represents emerging research frontiers.[26] The validation of mechanistic targets in human tissue, combined with rigorous clinical trial designs, is essential to translate mechanistic insights into evidence-based therapeutic guidelines.[27]

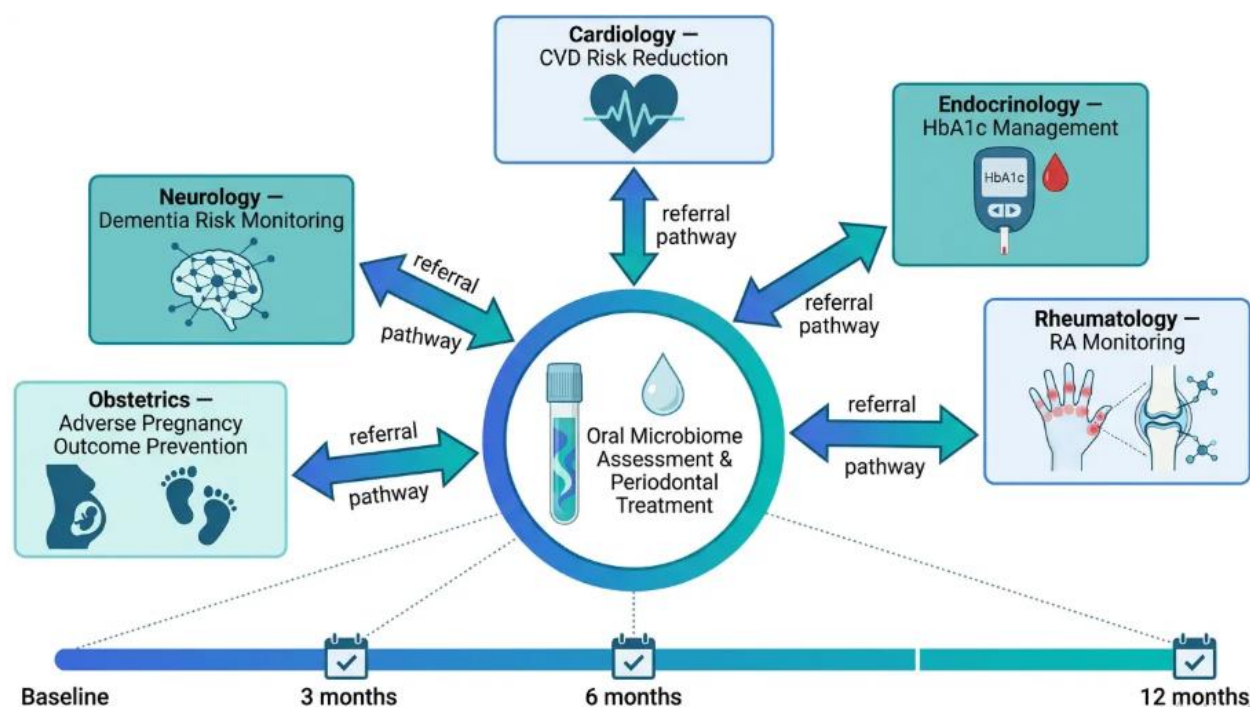


Figure 5. Proposed integrated care model for oral-systemic health management. The figure depicts a multidisciplinary team (periodontist, cardiologist, endocrinologist, rheumatologist, obstetrician) linked by shared patient care pathways, with oral microbiome screening as a central hub. Bidirectional referral arrows and a salivary biomarker monitoring loop are illustrated.

Sources: Based on concepts in references [22, 24, 25]

2. CONCLUSION

The evidence reviewed herein substantiates periodontal disease as a clinically significant systemic inflammatory condition whose biological consequences extend well beyond the oral cavity. The keystone pathogen *P. gingivalis*, through its repertoire of immune-subversive virulence factors, orchestrates a local dysbiotic microenvironment that perpetuates chronic systemic low-grade inflammation via bacteraemia and cytokine-mediated mechanisms.

The bidirectional relationship with T2DM, the mechanistic plausibility of the CVD and RA associations, and the emerging neuroinflammatory evidence for AD collectively position oral health as a determinant of systemic health outcomes. Critically, effective periodontal treatment demonstrably improves surrogate systemic endpoints, including HbA1c, CRP, endothelial function, and inflammatory cytokines.

From a pharmaceutical science perspective, host-modulation agents, adjunctive pharmacotherapy, and microbiome-targeted interventions represent viable and underutilised components of the periodontal management armamentarium with systemic health benefits. The integration of oral health assessment into multidisciplinary chronic disease management protocols is supported by current mechanistic and clinical evidence, and should be prioritised in both clinical practice guidelines and health policy formulation.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Micheal Abimbola Oladosu: Conceptualisation, Methodology, Supervision, Validation, Formal analysis, Writing-review and editing, Project administration.

Moses Adondua Abah: Methodology, Data analysis, Validation, Writing-review and editing.

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All authors contributed to the development of the manuscript, reviewed and approved the final version, and agreed to be accountable for the work.

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