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# Unveiling the Molecular Crosstalk Between Periodontal and Cardiovascular Diseases: A Systematic Review

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## ADMINISTRATIVE INFORMATION

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**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202510055

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 January 2025 and was last updated on 15 January 2025.

## INTRODUCTION

**Review question / Objective** P (Population/ Problem): Individuals with periodontal disease (PD), with or without systemic conditions such as cardiovascular disease (CVD).
I (Intervention/Exposure): Oral microbiome dysbiosis and the presence of periodontal pathogens contributing to systemic inflammation, immune modulation, endothelial dysfunction, and microbial dissemination.
C (Comparison): Individuals with or without periodontal disease and cardiovascular disease.
O (Outcome): Systemic inflammation and endothelial dysfunction as mechanisms linking PD to CVD. Molecular and microbial mechanisms, including inflammatory pathways, immune modulation, and microbial dissemination, affecting systemic health.
Research questions:

How does oral microbiome dysbiosis in periodontal disease influence systemic health through inflammatory pathways, immune modulation, endothelial dysfunction, and microbial dissemination, potentially linking PD to cardiovascular disease? How the dysbiosis of the oral microbiome in periodontal disease (PD) contributes to systemic inflammation and endothelial dysfunction, linking PD to the pathogenesis of cardiovascular disease (CVD)..

**Condition being studied** Periodontal disease (PD) is a chronic inflammatory condition with significant systemic implications, driven by the complex interplay of the oral microbiome and host immune responses. At the center of its pathogenesis is the dysbiosis of the oral micro-biome, where specific bacterial consortia dominate and contribute to tissue destruction. Among these, the "Red Complex" bacteria—Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola—are

particularly implicated. Furthermore, oral microbial dysbiosis is not confined to local infections, but can have systemic implications. Oral pathogen can spread from the subgingival biofilm into the bloodstream, allowing them to reach various organs and tissues. This dissemination may play a role in the development of multiple systemic diseases by contributing to inflammation and pathogenic processes beyond the oral cavity. These include respiratory diseases such as asthma, gastrointestinal disorders like inflammatory bowel disease, cardiovascular diseases, diabetes, obesity, metabolic disorders, autoimmune diseases, Alzheimer's disease and certain cancers. The mechanisms underlying these associations involve complex interactions between oral pathogens, host immune responses, and systemic inflammation.

Understanding the composition and dynamic interactions of the oral microbiota is essential for elucidating the mechanisms by which these microorganisms influence both oral and systemic health. This review emphasized how the dysbiosis of the oral micro-biome in periodontal disease (PD) contributes to systemic inflammation and endothelial dysfunction, linking PD to the pathogenesis of cardiovascular disease (CVD).

## METHODS

**Participant or population** Individuals with periodontal disease (PD), with or without cardiovascular disease (CVD).

**Intervention** Oral microbiome dysbiosis and the presence of periodontal pathogens contributing to cardiovascular disease, immune modulation, endothelial dysfunction, and microbial dissemination.

**Comparator** Individuals with or without periodontal disease and cardiovascular disease.

**Study designs to be included** Study conducted in accordance with the PRISMA guidelines. The search strategy employed a combination of keywords such as periodontitis, oral microbiome, cardiovascular diseases, underlying mechanisms, atherosclerosis, and red complex bacteria. The literature search was performed in two major databases: PubMed and ScienceDirect.

**Eligibility criteria** The screening process began with an evaluation of titles and abstracts to determine the relevance of the articles to the research objectives.

Inclusion Criteria: To ensure the inclusion of relevant and high-quality studies, the following eligibility criteria were applied:

1. Studies must explicitly examine the association between periodontal disease and cardiovascular disease, focusing on mechanisms linking pathogenic oral bacteria to the development of cardiovascular conditions.
2. Sufficient data must be available for extraction and analysis.
3. Articles must be peer-reviewed, written in English, and published within the last decade.
4. Article must be freely available in a full text format.

Exclusion Criteria:

1. Irrelevant topics such as studies not focused on periodontal disease, cardio-vascular disease, or their relationship.
2. Non-rodent models: Studies conducted in species other than rodents.
3. Irrelevant outcomes: Studies that did not report relevant outcomes related to cardiovascular health.
4. Unrelated systemic conditions: Studies addressing systemic conditions not directly linked to periodontal disease or cardiovascular disease.

**Information sources** The literature search was performed in two major databases: PubMed and ScienceDi-rect. The search strategy employed a combination of keywords such as "periodontitis, oral microbiome, cardiovascular diseases, underlying mechanisms, atherosclerosis, and red complex bacteria".

**Main outcome(s)** Central to the pathogenesis of periodontal disease (PD) is the activation of immune cells and the subsequent release of pro-inflammatory cytokines, including IL-1, IL-6, TNF-α, and PGE2. These mediators, alongside oxidative stress driven by excessive reactive oxygen species (ROS), orchestrate tissue inflammation, degradation, and systemic immune dysregulation. Furthermore, chemokines such as IL-8 and MCP-1 direct immune cell infiltration to the affected periodontal tissues, amplifying the inflammatory response. Matrix metalloproteinases (MMPs) and arachidonic acid metabolites exacerbate tissue damage, while the disrupted redox balance contributes to the progression of PD and its systemic consequences. Periodontal pathogens, particularly "Red complex" (P. gingivalis, T. denticola, T. forsythia) and other keystone bacteria such as A. actinomycetemcomitans, and F. nucleatum induce endothelial oxidative stress and systemic inflammation through mechanisms involving Toll-like receptors (TLRs), the NF-κB signaling pathway, and nitric oxide (NO) dysregulation. These processes promote

endothelial dysfunction, a precursor to atherosclerosis, by increasing reactive oxygen species (ROS), impairing NO bioavailability, and triggering inflammatory cascades. The involvement of inflammatory biomarkers such as C-reactive protein (CRP), interleukins, matrix metalloproteinases (MMPs), and fibrinogen further reinforces the association between periodontitis and systemic inflammation, contributing to vascular pathology and atheroma formation. While substantial evidence supports the link between PD and CVD the precise molecular mechanisms underlying these associations remain incompletely understood, necessitating further investigation.

**Quality assessment / Risk of bias analysis** Titles and abstracts of all retrieved articles were independently screened by two reviewers to assess their relevance to the research objectives. Full-text articles were obtained for studies meeting the inclusion criteria, and eligibility was independently confirmed by the reviewers.
The risk of bias was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework, ensuring a structured and transparent evaluation of the quality of evidence. Two reviewers independently evaluated each study across the following domains:
1. Risk of Bias: Assessment of study methodology.
2. Inconsistency: Variability in study results.
3. Indirectness: Relevance of evidence to the review question.
4. Imprecision: Uncertainty in effect estimates.
5. Publication Bias: Potential overrepresentation of positive findings.
No automation systems were used for this assessment. Manual evaluations were conducted to ensure objectivity and minimize bias. Discrepancies were resolved through discussion, with involvement from a third reviewer when necessary, to reinforce the reliability and validity of the assessments. Outcomes were synthesized using narrative summaries.

**Strategy of data synthesis** The strategy for data synthesis involved a combination of narrative synthesis and visual presentation to comprehensively analyze and interpret the findings. Narrative synthesis provided a structured summary of the data, identifying patterns, relationships, and key themes across studies, particularly focusing on the molecular and microbial mechanisms linking periodontal disease to systemic health outcomes such as cardiovascular disease. Visual presentations, including tables, and network diagrams, were employed to illustrate the relationships between periodontal pathogens, inflammatory pathways, and systemic effects, enabling a clear and concise representation of complex interactions. This integrative approach ensured a balanced and accessible synthesis of qualitative and quantitative findings.

**Subgroup analysis** Not applicable.

**Sensitivity analysis** Not applicable.

**Language restriction** Articles that are published in English language are considered for review.

**Country(ies) involved** United States.

**Keywords** Periodontal disease, Oral microbiota, Red complex bacteria, Cardiovascular disease, Endothelial dysfunction, Systemic inflammation.

**Dissemination plans** Open access journal publication.

**Contributions of each author**
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