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Modulation of periodontal biofilms by quorum sensing inhibition: A review

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Abstract:
Periodontitis is a chronic inflammatory disease driven by dysbiotic subgingival biofilms that resist conventional therapy. Therefore, it is of interest to evaluate the QSI against key periodontal pathogens and examines phytochemicals, furanones, quorum-quenching enzymes, probiotics, peptides and nanotechnology based approaches. Quorum sensing (QS) regulates biofilm maturation, virulence and microbial communication, making quorum sensing inhibition (QSI) a potential anti-biofilm strategy. Pre-clinical studies show reduced biofilm formation, virulence-associated gene expression and alveolar bone loss, but clinical evidence remains limited by methodological heterogeneity and agent instability. Thus, QSI is a promising adjunct to scaling and root planing, warranting well designed clinical studies to establish its efficacy and safety.

Keywords: Quorum sensing (QS), quorum quenching, periodontal biofilm, autoinducer-2, *Porphyromonas gingivalis*, anti-biofilm therapy

Background:
Periodontitis is a chronic multifactorial inflammatory disease characterized by progressive destruction of the tooth-supporting structures, including gingiva, periodontal ligament, cementum and alveolar bone **[1].** According to recent epidemiological estimates, severe periodontitis remains one of the most prevalent chronic diseases worldwide, affecting approximately 11.2% of the global population and constituting the sixth most prevalent human disease **[2].** Although conventional periodontal therapy including scaling and root planing (SRP) remains the cornerstone of treatment, complete eradication of pathogenic biofilms is often challenging because of the highly organised and resistant nature of the microbial communities residing within the periodontal pocket **[3].** Dental plaque is a structured polymicrobial biofilm embedded in an extracellular polymeric matrix, exhibiting markedly enhanced resistance to antimicrobial agents and host defence mechanisms compared with planktonic bacteria **[4]**. The pathogenicity of these communities depends not only on bacterial composition but also on coordinated microbial interactions that regulate virulence, metabolic activity and survival within the complex oral ecosystem **[5].** Quorum sensing (QS) is a cell density dependent communication system enabling bacteria to regulate gene expression collectively through the production and detection of autoinducer signaling molecules, facilitating biofilm maturation, virulence factor production and interspecies co-ordination **[6, 7].** Key periodontal pathogens including *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans*, *Treponema denticola* and *Tannerella forsythia* utilise the LuxS/autoinducer-2 (AI-2) system to coordinate community behaviour, establish synergistic polymicrobial interactions and promote dysbiosis **[8, 9].** Disruption of these QS pathways through quorum sensing inhibition (QSI), also termed quorum quenching, represents a mechanistically distinct anti-biofilm approach that suppresses virulence expression without exerting direct bactericidal effects, thereby minimizing selective pressure for antimicrobial resistance **[10, 11].** Diverse QSI agents have been investigated, including naturally derived phytochemicals such as quercetin, curcumin, catechins and cinnamaldehyde, as well as synthetic furanones, enzymatic quorum-quenching agents, probiotic-derived molecules, peptides and nanotechnology based delivery systems **[12].** Despite growing interest, the available literature remains heterogeneous with respect to study design, target organisms, intervention characteristics and outcome measures and a consolidated overview is lacking **[13].** Therefore, it is of interest to evaluate the principal QS circuits' operative among periodontal pathogens, appraises the major categories of QSI agents and their mechanisms of action and considers their translational potential, thereby providing a scientific basis for the development of innovative anti-biofilm therapies in periodontology.

Quorum sensing systems in periodontal pathogens:
Bacteria communicate through three broad classes of autoinducer signals. Gram negative organisms typically employ acyl-homoserine lactones (AHLs, autoinducer-1) synthesized by LuxI-type enzymes and detected by LuxR-type receptors; Gram-positive organisms generally use oligopeptide autoinducing peptides (AIPs); and both groups produce autoinducer-2 (AI-2), a furanosyl-borate diester generated by the LuxS enzyme that functions as a universal signal for interspecies communication **[14]**. In the oral cavity, the LuxS/AI-2 circuit is regarded as the dominant driver of interspecies coordination within multispecies biofilms. Early work by researchers showed that periodontal isolates, including *F. nucleatum*, *Prevotella intermedia* and *P. gingivalis*, produce AI-2-like signaling activity, establishing QS as a feature of the subgingival community **[15].** *P. gingivalis* possesses a LuxS orthologue and uses AI-2 to modulate the expression of virulence determinants such as gingipains and fimbriae, as well as to regulate its incorporation into developing biofilms**.** AI-2 further mediates the coaggregation and metabolic partnerships that allow *F. nucleatum* to bridge early and late colonisers, promoting maturation of the pathogenic "red complex" **[16].** Although classical LuxI/LuxR AHL circuits were long thought to play only a minor role in the oral environment, AHLs have now been detected in subgingival plaque and saliva and their concentrations have been reported to correlate with periodontal disease severity, reinforcing QS as a rational therapeutic target **[17].** Collectively, these signaling systems govern biofilm architecture, virulence and community resilience

and their interruption offers a means of disarming rather than eradicating the biofilm.

Rationale for quorum sensing inhibition:
Mechanical debridement through SRP physically disrupts the biofilm but cannot reliably reach all anatomical niches and residual organisms readily re-establish mature, QS-coordinated communities**.** Adjunctive systemic and local antibiotics carry the well-recognised risks of dysbiosis and the selection of resistant strains **[18].** Quorum sensing inhibition offers a conceptually different, anti-virulence approach: by interfering with bacterial communication rather than viability, QSI attenuates biofilm formation and virulence expression while exerting minimal direct growth pressure, thereby reducing the selective advantage for resistant mutants **[19].** Because QSI aims to preserve commensal organisms and re-establish eubiosis rather than to sterilise the pocket, it aligns closely with the contemporary ecological understanding of periodontitis as a dysbiotic rather than a purely infectious disease **[20].**

Quorum sensing inhibition strategies:
Phytochemical and naturally derived inhibitors:
Plant-derived compounds are among the most extensively studied QSI agents owing to their biocompatibility and multi-target activity. Quercetin, a dietary flavonoid, competitively binds LuxR-type receptors and reduces biofilm formation, exopolysaccharide production and virulence expression; photoactivated quercetin has additionally been shown to inhibit *P. gingivalis* biofilms and to downregulate the key virulence gene encoding the lysine-specific gingipain Kgp **[21].** Curcumin, the principal polyphenol of *Curcuma longa*, interferes with autoinducer production and downregulates QS-regulatory genes such as luxS, while also destabilizing the extracellular matrix and impairing bacterial motility **[22].** Catechins, including those from green tea and *Azadirachta indica* (neem), reduce LuxS activity in oral pathogens and cinnamaldehyde and carvacrol interfere with AI-2 and AHL signaling respectively. Coumarin has been reported to inhibit AI-2 activity, disperse late-stage *P. gingivalis* biofilms and downregulate biofilm-associated genes. The main limitations of phytochemicals are variable bioavailability, a lack of standardisation and, in some cases, difficulty in distinguishing genuine signal interference from non-specific antibacterial effects **[23]**.

Synthetic halogenated furanones:
Halogenated furanones, originally isolated from the marine alga *Delisea pulchra*, are prototypical synthetic QSI molecules that accelerate LuxR turnover and block AI-2-mediated signalling **[24].** In an experimental periodontitis model, a brominated furanone combined with D-ribose inhibited AI-2-induced biofilm formation and the coaggregation of red-complex species, suppressed adhesion molecules such as FadA, RgpA, Msp and BspA and reduced alveolar bone destruction and bacterial load in mice **[25].** Concerns regarding the cytotoxicity of some furanone derivatives have motivated the search for safer structural analogues.

Enzymatic quorum quenching:
Quorum-quenching enzymes inactivate signal molecules directly. AHL-lactonases hydrolyse the lactone ring of AHLs, abolishing their signalling capacity**.** The broad-spectrum lactonase Aii20J, derived from the marine bacterium *Tenacibaculum sp.* 20J, has been shown to modify *in vitro* periodontal biofilm formation generated from subgingival samples **[26].** The lactonase Est816 similarly inhibits biofilm formation by *A. actinomycetemcomitans* and by polymicrobial subgingival plaque derived biofilms and acts synergistically with minocycline, metronidazole and amoxicillin, improving biofilm eradication **[27].** The chief translational obstacle for enzymatic strategies is instability within the proteolytic, pH-fluctuating subgingival environment, which has prompted interest in enzyme engineering and protective delivery vehicles.

Probiotic-derived and microbial molecules:
Certain commensal and probiotic organisms produce quorum quenching molecules or otherwise interfere with pathogen signalling and they may additionally restore ecological balance through competitive exclusion. Clinically, adjunctive administration of *Lactobacillus reuteri* alongside SRP has been associated with improved microbiological and clinical outcomes in chronic periodontitis, supporting probiosis as a biologically plausible route to biofilm modulation **[28].** The specific QS-quenching contribution of probiotics, as distinct from their broader ecological effects, requires further mechanistic clarification.

Anti-biofilm peptides and signal analogues:
Synthetic peptides and structural analogues of native autoinducers offer a further avenue for signal interference. Broad-spectrum anti-biofilm peptides such as peptide 1018 target the intracellular stress-response nucleotide (p) ppGpp and disperse established biofilms across diverse species **[29].** AHL and autoinducing-peptide analogues can act as competitive antagonists at their cognate receptors; for example, N-acyl-homoserine-lactone analogues have been reported to inhibit *P. gingivalis* biofilm formation. Peptide-based approaches must nonetheless contend with proteolytic degradation and potential host immunogenicity **[30]**.

Nanotechnology-based delivery systems:
Nanotechnology addresses several pharmacokinetic shortcomings of QSI agents by improving their stability, controlling their release and enhancing biofilm penetration. Polymeric, lipid-based, silver and chitosan nanocarriers loaded with quorum-sensing inhibitors can achieve sustained intrapocket delivery and better retention at the target site and nanoparticles may themselves possess intrinsic anti-biofilm properties **[31].** Rigorous evaluation of biocompatibility and long-term safety remains essential before clinical adoption.

Clinical and translational implications
Because QSI attenuates virulence without eliminating the microbiota, it is best conceptualized as an adjunct to rather than

a replacement for mechanical debridement. Local intrapocket delivery of QSI agents after SRP could suppress the re-formation of pathogenic, QS-coordinated biofilms while sparing beneficial commensals, potentially reducing disease recurrence. Combination regimens, in which QSI agents restore antimicrobial susceptibility or act synergistically with low dose antiseptics and antibiotics, are a particularly promising direction, as illustrated by the enhanced biofilm eradication achieved when lactonase is combined with conventional antibiotics **[32].**

Future directions:
Future research should prioritise structure-based design of selective inhibitors guided by molecular docking against defined targets such as LuxS, gingipain Kgp and the haem-acquisition protein HmuY **[13],** rational combination strategies pairing QSI agents with mechanical therapy, host-modulation or low-dose antimicrobials; and protective nanocarrier systems that stabilise labile enzymes and peptides for sustained intrapocket release. Above all, the field requires standardised methodology and adequately powered clinical trials to establish whether the consistent preclinical benefits of QSI translate into meaningful improvements in periodontal outcomes.

Challenges and limitations:
The current evidence base is dominated by *in vitro* and animal studies that differ widely in target organisms, agents, concentrations and outcome measures, limiting direct comparison and quantitative synthesis**.** Several practical barriers hinder translation: the instability of enzymes and peptides in the hostile subgingival milieu; uncertain bioavailability and standardisation of phytochemicals; difficulty in separating true signal interference from non-specific antibacterial or cytotoxic effects; and a near-absence of well-designed randomised clinical trials with patient centred endpoints. Long-term safety, potential effects on the wider oral and systemic microbiota and regulatory pathways also remain incompletely defined.

Conclusion:
Quorum sensing inhibition is a promising strategy for modulating periodontal biofilms by reducing microbial communication, virulence and biofilm maturation without strong bactericidal pressure. Phytochemicals, synthetic furanones, quorum-quenching enzymes, probiotics, peptides and nanotechnology-based systems have showed encouraging preclinical anti-biofilm effects. Further research should address agent stability, safety and standardisation and establish clinical efficacy before QSI can be integrated as an adjunct to scaling and root planing.

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