IJBPAS, September, 2026, 15(9): 4124-4138

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

THE ROLE OF ANTIMICROBIAL PEPTIDES IN PERIODONTITIS -A LITERATURE REVIEW

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Received 25th July 2025; Revised 16th Sept. 2025; Accepted 31st Jan. 2026; Available online 1st Sept. 2026

https://doi.org/10.31032/IJBPAS/2026/15.9.10408

ABSTRACT

Antimicrobial peptides (AMPs) have a long history and play a key role in natural defence mechanisms. AMPs constitute an organism's frontline defence against bacteria, fungi, viruses and other pathogens through direct killing and modulation of the immune system. For example, defensins, histatins, and cathelicidin LL-37 are produced and work synergistically in the oral cavity to protect periodontal tissues from infection and/or damage. Therefore, AMPs are important to oral health because they may directly enable clearance of infection and may also bolster immune responses. In periodontitis specifically, undirected AMP expression or function contributes to microbial persistence, inflammation, and periodontal tissue destruction. This review provides a comprehensive review of AMP structural characteristics, expression, biological roles, clinical significance in periodontal health and disease, and finally, the potential for therapeutically modulating AMP activities in treatment in contemporary periodontics.

Keywords: Antimicrobial Peptides, Defensins, Periodontitis, Anti-inflammation

INTRODUCTION:

If not treated, periodontitis is a chronic, slowly evolving infection of the supporting tissues of the teeth—gingiva, periodontal ligaments, and alveolar bone—that can eventually result in tooth mobility and loss **[1]**. The disease originates as a localized battleground between the host immune defenses and bacterial biofilms that colonizes the tooth surface. Although the immune response is protective initially, if the challenge from the microbes persists, the inflammatory response can become dysregulated, damaging the host tissue and targeting the microbes while slowly eroding the periodontal tissue support **[2-3]**.

The oral cavity is home to a uniquely diverse microbial community. The mouth is host to over 700 different microbial taxa that constantly interact to form complex ecological networks. These residents usually live in a state of harmony with the host to preserve oral health; however, disruptions in this equilibrium (dysbiosis) are associated with common oral diseases such as gingivitis and periodontitis **[4]**. The host has multiple defensive barriers against infection, including the physical barrier of the mucosal epithelium and biochemical barriers. Among the biochemical barriers, antimicrobial peptides (AMPs) play an important role. These small but diverse molecules help control microbial populations and protect the tissue within the oral environment **[5]**.

Over forty-five different AMPs have been identified in the oral compartments, such as saliva, the gingival crevicular fluid (GCF), and epithelial layers, and their expression patterns are dynamic and change depending on the physiological and inflammatory state of the host. Baseline expression levels are necessary for homeostasis; however, the expression of individual AMPs may increase or decrease with the presence of an inflammatory stimulus, respectively, affecting the progression of disease **[6]**. In addition to direct microbicidal activity, AMPs modulate immune responses and induce tissue repair, and their expression profiles may provide the earliest indications of gingival inflammation, supporting the development of clinical assay workflows.

CLASSIFICATION OF ANTIMICROBIAL PEPTIDES

AMPs display substantial diversity that can be classified by a number of criteria. They are derived from either microorganisms (including bacteriocins), plants (i.e. seeds, leaves, roots), or animals (i.e. invertebrates and vertebrates including fish, amphibians, reptiles, birds, and mammals). Regarding structural classification, AMPs order can generally be placed into structural groupings of α-helical, β-sheet, mixed α/β structure, extended/linear peptides, or cyclized

peptides (i.e. cyclotides and knottins), with distinct structural families belonging to certain plant peptide families -i.e. thionins, defensins, snakins. Regarding biological functionality, AMPs can possess antibacterial activity, antifungal activity, antiviral activity, antiparasitic activity, anticancer activity, and anti-inflammatory activity **(Table 1)**.

Table 1: Classification of Antimicrobial Peptides

Category	Representative Peptides	Primary Source in Oral Tissues	Structural Class	Major Functions in Periodontal Health
α-Defensins (Human Neutrophil Peptides, HNP1–6)	HNP-1, HNP-2, HNP-3	Neutrophils (azurophilic granules)	β-sheet (disulfide-stabilized)	Bactericidal activity against Gram+ and Gram− bacteria; immune cell recruitment
β-Defensins (Human Beta-Defensins, hBD1–4)	hBD1, hBD2, hBD3, hBD4	Gingival epithelial cells	β-sheet (disulfide-stabilized)	Broad antimicrobial action, LPS neutralization, cytokine modulation
Cathelicidin Family	LL-37 (hCAP-18 precursor)	Neutrophils, epithelial cells, fibroblasts	α-helical	Membrane disruption, chemotaxis, wound healing, LPS neutralization
Histatins	Histatin-1, -3, -5	Salivary glands (parotid, submandibular)	Extended linear peptide	Antifungal (Candida albicans), bacterial adhesion control, promotes epithelial migration
Secretory Leukocyte Protease Inhibitor (SLPI)	SLPI	Epithelial cells, neutrophils	Small cysteine-rich peptide	Anti-protease activity, anti-inflammatory, promotes healing post-therapy
Adrenomedullin	Adrenomedullin (ADM)	Gingival epithelial and endothelial cells	Linear peptide	Vasodilatory, antimicrobial, immunomodulatory
Statherin	Statherin	Salivary glands	Phosphoprotein	Regulates mineral homeostasis, inhibits crystal growth, bacterial adhesion control
Bacteriocins (Microbial AMPs)	Nisin, subtilin	Oral commensal Streptococcus spp.	Cyclic/lanthionine-containing	Competitively inhibits pathogenic bacteria; maintains microbial balance
Synthetic / Engineered AMPs	Peptidomimetics, LL-37 analogs	Laboratory-derived	Variable (α/β/modified)	Enhanced stability, targeted antimicrobial activity, biofilm disruption

STRUCTURE AND PHYSICOCHEMICAL FEATURES OF AMPS

Typically, antimicrobial peptides (AMPs) are short polypeptides—primarily ranging from 12 to 50 amino acids—with a net positive charge overall. The cationic nature of AMPs allows for subsequent electrostatic attraction to negatively charged bacterial membranes, the initial and critical step of their mode of action. AMPs are amphipathic, bearing both hydrophilic and hydrophobic segments permitting bacterial membrane disruption alongside associate interactions with membranes and bacterial membranes. The amino acid composition of AMPs is enriched, overall, in lysine and arginine residues contributing to membrane binding and facilitating insertion into lipid bilayers resulting in membrane destabilization, pore formation, and exposed cell death **[7-8]**.

Four general structural classes are of particular relevance to oral health: (i) α-helical peptides like LL-37 that create flexible helical conformations; (ii) β-sheet peptides like defensins that stabilized by disulfide bonds; (iii) extended peptides that are rich in particular amino acids like indolicidin; and (iv); looped peptides that fold into small rings by disulfide bridges. AMPs compromise membranes by various mechanisms or models ranging from the "carpet" model where peptides coat the membrane and solubilize, to the "toroidal pore" model where peptides facilitate continued pore formation by bending lipid monolayers. Some AMPs are also capable of penetrating the cell and disrupting intracellular processes such as nucleic acid or protein synthesis differentially, and will thus exert multiple layers of antimicrobial activity **[9-11]**.

EXPRESSION AND LOCALIZATION IN THE ORAL CAVITY

Various oral cell populations generate endogenous antimicrobial peptides (AMPs). Gingival and oral epithelial cells are constantly producing and seeding peptides into the oral cavity that provide protection against pathogens. Professional immune cells, such as neutrophils and macrophages, provide the most abundant source of AMPs during active immune defence; these cells can mobilize stored AMPs stored in granules to the gingival sulcus to prevent pathogens from invading deeper tissues. Salivary glands produce AMPs contained in saliva as a source of constant supply AMPs at the mucosal surface to further contribute to a baseline antimicrobial environment. Collectively, epithelial cells, immune cells, and salivary glands provide a continuous output of AMPs that works in concert to form a spatial and chemical dependent barrier that controls bacteria density at mucosal surfaces and gingival crevice. Under healthy conditions, constitutive AMP

expression maintains balanced exposure to opportunistic pathogens while controlling a dense population of commensals **[12-14]**.

In the case of microbial invasion or inflammatory stimuli, pathogen associated molecular patterns (e.g., lipopolysaccharide; LPS) and host-derived cytokines (e.g., interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α)) rapidly stimulate AMP expression. This results in a rapid localized antimicrobial response, alongside civilian immune cells, to control the infection, or in the case of LPS, stimulus to initiate an inflammatory response. The response is tightly regulated to contain the infection and limit damage to the surrounding tissues **[15]**. Gingival epithelial cells provide the largest amounts of β-defensins and LL-37 acting at the epithelial surface to protect the gingiva. Neutrophils add α-defensins and LL-37 into the gingival crevicular fluid, providing a deeper level of antimicrobial defence in the periodontal sulcus. The combination of these secretions provides layered defence against microbial colonization at multiple levels of the oral cavity **[16]**.

MAJOR FAMILIES OF ORAL ANTIMICROBIAL PEPTIDES

Defensins:

Human a-defensins (human neutrophil peptides HNP1–6) are contained in neutrophil azurophilic granules and are released rapidly during infection, furthering the antimicrobial work in infected areas. While α-defensins have limited activity against some important periodontal pathogens (e.g., Porphyromonas gingivalis), they play essential roles in the modulation of immune cell recruitment and inflammatory tone. The gingival epithelium expresses b-defensins (hBD1–6): hBD1 is constitutively expressed at baseline, while hBD2 and hBD3 are inducible in response to microbial challenge in inflammation. hBD3 is the most potent of the b-defensins against periodontal pathogens P. gingivalis and Fusobacterium nucleatum, and b-defensins also have immunoregulatory functions including recruitment of dendritic cells and macrophages and neutralizing bacterial components (e.g., LPS) to limit excessive toll-like receptor activation **[17-21]**.

Cathelicidin (LL-37):

LL-37 is the only human cathelicidin, generated as the precursor hCAP-18 and activated by proteases from neutrophils. The peptide displays broad antimicrobial activity against a variety of bacteria, viruses and fungi, and has important immunomodulatory properties. The amphipathic α-helical structure of LL-37 enables interaction with and penetration of membranes, while LL-37 can neutralize endotoxins (such as LPS) and alter gingival fibroblast response to pro-inflammatory cytokines such as IL-6 and IL-8. Additionally, LL-37 enhances wound healing processes through angiogenic and

pro-migratory effects of epithelial cells, making LL-37 critical for repair after injury. Moreover, clinical syndromes that feature mutations in neutrophil function—Kostmann syndrome and Papillon-Lefèvre syndrome—exhibit deficient production or maturation of LL-37 and are associated with severe periodontal disease, illustrating the clinical importance of LL-37 **[22-28]**.

Histatins:

Histatin peptides, particularly histatin-5, are abundant in histidine residues and are predominantly produced by the parotid and submandibular glands. Histatins are well known for their potent antifungal properties against Candida albicans, as well as displaying antibacterial effects against Streptococcus spp. and P. gingivalis. Additionally, histatins may facilitate migration and adhesion of epithelial cells to assist in mucosal healing, as well as contribute to the formation of an enamel pellicle, thereby assisting in mineral homeostasis. Histatin concentrations in saliva (e.g., histatin-1 and -3) are typically between 10 and 30 µg/mL **[29-31]**.

Other peptides:

SLPI, adrenomedullin, and statherin. Secretory leukocyte protease inhibitor (SLPI) protects tissues from the virulent proteases that are released during inflammation and has shown to have antimicrobial activity; levels of SLPI often increase after periodontal therapy, which coincides with less inflammation and healing. Gingival epithelial cells secrete adrenomedullin whose expression also increases with inflammation and contributes to balancing host defense and tissue-preserving activity. Statherin is secreted by salivary glands, will inhibit inappropriate calcium phosphate crystal growth, and will also modulate bacterial adhesion to surfaces, which slows the accumulation of dental plaque and dental caries **[32-35]**.

These peptide families comprise an important area of the molecular network that integrates together to maintain oral microbial homeostasis and modulate host activity to restore periodontal health.

ROLE OF AMPS IN PERIODONTAL PATHOGENESIS

Microbial defense and biofilm regulation:

AMPs are capable of targeting significant periodontal pathogens: *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans, P. gingivalis, and Prevotella intermedia*, through membrane permeabilization and interference with their intracellular functions. Produced by epithelial cells, neutrophils, and salivary glands, AMPs not only directly kill microbes but also promote host tissue repair and stimulate immune responses. Specific pathogens have evolved pathways to escape AMP function, and AMPs continue to be important in supporting periodontal homeostasis. LL-37 and hBD3 can penetrate

established biofilms, destabilize the bacterial membrane, and disrupt the quorum sensing pathways within bacterial populations that initiate biofilm maturation. This antimicrobial/anti-biofilm function provides a strategy to reduce chronic colonization associated with chronic periodontitis **[36-39]**.

Immunomodulation:

Antimicrobial peptides (AMPs) coordinate the recruitment of immune cells and serve as a link between innate and adaptive immune responses: they chemoattract T cells, monocytes, and neutrophils and engage with receptors, such as formyl peptide receptor-like 1 (FPRL1), to recruit immune effectors, as others have shown with LL-37. In addition, AMPs modulate the production of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-8, to maintain appropriate inflammatory responses and to avoid the types of responses that would lead to tissue destruction. Therefore, the combine antimicrobial and immunoregulatory roles of AMPs contribute to an effective means to contain infection while limiting damage to the host **[40-41]**.

Dysregulation in periodontitis:

Persisting infection and inflammation disturb the finely-tuned antimicrobial peptide (AMP) network to create a surrounding in which peptides may not be sufficient; be degraded too much; or be dysregulated. With reduced efficacy of AMPs, microbial suppression and inflammation can no longer be effectively retained, which can lead to unregulated cellular damage. Upregulated dependant peptides (e.g. hBD2, hBD3, LL-37) frequently reflects an active immune response, whereas decreased dependent peptides (e.g. hBD1, mucin-7) indicates depleted baseline immunity, or are tied to inflammatory disease severity. In addition, reactive pathogens can influence and create dysregulation by utilizing proteases - P. gingivalis gingipains and T. forsythia karilysin degrade LL-37; resulting in decreased host defense, but contributes to an active cycle of inflammation and tissue destruction **[42-44]**.

Vitamin D and AMP regulation:

Vitamin D is essential for controlling AMP expression in the periodontal tissue. When the vitamin D receptor (VDR) in gingival cells is engaged, it increases the transcription of genes like CAMP and DEFB1 that encode the LLC-37 and hBD1 antimicrobial peptides, which supports local antimicrobial function and regulates immune responses to periodontal pathogens. Adequate serum 25-hydroxyvitamin D [25(OH)D] levels are associated with higher levels of both LL-37 and hBD1, in both circulation and in gingival tissue, while vitamin D deficiency is associated with lower AMPs and increased risk of

periodontitis. Thus, vitamin D supplementation may be a potential adjunct to increase endogenous AMP production in periodontal tissue, as well as responsible immune responses to periodontal disease **[45-47]**.

AMPs as diagnostic biomarkers

Given that AMP concentrations are indicative of host–microbe dynamics and inflammatory status, they may serve as diagnostic and prognostic indicators of periodontal disease. Increased concentrations of AMP such as LL-37, hBD2, and SLPI in gingival crevicular fluid or saliva are associated with active inflammation, whereas reduced hBD1 may indicate a compromised innate defence. The use of proteomic panels that include AMP patterns can discriminate healthier and diseased periodontal conditions with high sensitivity and specificity and allow for real-time non-invasive monitoring. Furthermore, normalization of certain AMPs (e.g., increased SLPI and stable LL-37) post periodontal therapy may serve as a novel biomarker for successful resolution and healing of tissue **[48-50]**.

THERAPEUTIC IMPLICATIONS AND NOVEL APPLICATIONS

Direct therapeutic applications:

The interest in synthetic and recombinant AMPs is growing as an adjunct to nonsurgical periodontal therapy. Topical products—gels, coatings, and localized delivery products—containing LL-37 or some other peptides have shown promise in preclinical or early clinical trials for accelerating the wound healing process, reducing probing depth, and limiting microbial recolonization. Randomized clinical studies comparing AMP adjuncts when used in conjunction with scaling and root planing have shown improvements in clinical attachment, as well as reductions in pocket depth, which suggest the therapeutic potential of AMPs **[51-52]**.

Biomaterial functionalization:

Embedding antimicrobial peptides (AMPs) within biomaterials such as coatings for implants, hydrogels, and scaffolds can impart antimicrobial effects while also promoting tissue integration and repair. AMP-functionalized surfaces can decrease peri-implant biofilm formation and chances of developing peri-implantitis while maintaining biocompatibility; therefore, utilizing AMPs is a promising approach to preserve dental implants and support peri-implant health **[53]**.

Combination therapies:

Using AMPs alongside other biologically-based interventions—such as specific probiotics (e.g., Streptococcus salivarius) or vitamin D supplementation—can assist in restoring a healthy and balanced oral microbiome and augment immune modulation, which may lead to improve clinical outcomes in periodontal therapy.

Additionally, strategies to facilitate endogenous expression of AMPs (e.g., using small-molecule enhancers or through nutritional support) may add to the impact of direct peptide therapies and provide more sustainable host-mediated defence **[54-55]**.

CHALLENGES AND FUTURE DIRECTIONS

There are multiple hurdles that must be met to transfer AMP-based approaches into everyday clinical practice. Stability is a primary issue: AMPs can be degraded by proteolytic action by both host and bacterial proteases in the oral cavity. To improve peptide stability and bioavailability, there are revealing lines of inquiry in applied technological methods (chemical modifications, use of non-natural amino acids, cyclization, and protective delivery modalities such as encapsulation) **[56]**.

Manufacturing costs and scalability will be limitations to broad clinical use. If AMP-based treatments are considered economically acceptable, there should be attention given to realizing an environmentally sustainable method of manufacture for widespread implementation. The exact delivery of AMPs in the local area also needs to be precise, by local systems maintaining therapeutic concentration without killing host cells, so that careful release kinetics and dosing protocols can be established.

Innovative strategies that are addressing the above challenges include nanocarrier-based delivery systems that shield AMPs from degradation while allowing for controlled release, or peptidomimetics—protease-resistant AMP mimetics created with non-natural amino acids or structural changes that preserve their antimicrobial activity, but have improved stability. Therapies around gene transfer are also considered via delivering plasmids encoding β-defensins or cathelicidin transfer directly to gingival tissues for local AMP expression, hence restoring innate antimicrobial balance. Finally, randomized controlled clinical trails will be required to confirm safety and efficacy, to determine the best dosage, and dosing process, to identify the effiacy of AMPs via delivery methods or regimen for multiple populations **[57]**.

CONCLUSION

Antimicrobial peptides are an essential part of periodontal defence at the interface of microorganisms and immune host responses. Their collective actions as antimicrobial, immunomodulatory, and tissue repair peptides support periodontal homeostasis and halt disease progression. Dysregulation and proteolytic degradation of key peptides such as defensins and LL-37 have been associated with disease severity, demonstrating their pathophysiological importance and therapeutic relevance.

Emerging peptide engineering, biomaterial use, and gene modulating methods will likely further position AMPs at the forefront of new diagnostics and therapeutic approaches to periodontitis, targeting microbial balance and periodontal health.

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