Review Article

DOI: 10.7860/JCDR/2026/74591.22812

Dentistry Section

Antimicrobial Peptides in the Prevention and Management of Oral Diseases: A Narrative Review

JAYA AGALI RAMACHANDRAN[1], K SWETHA[2], MUHAMMED THAMEEM[3], GANAVI G NAYAK[4]

ABSTRACT

Antimicrobial Peptides (AMPs) are a diverse class of host-defence molecules that respond to microbial invasion and challenge. Owing to their broad spectrum of antimicrobial activity and the low rates of induced resistance resulting from the co-evolution of pathogens with host AMPs, these peptides play a crucial immunomodulatory role against microbes. This, in turn, contributes to effective defence against oral infections such as dental caries and periodontal diseases. Numerous studies and existing literature suggest that AMPs have a promising future in controlling the formation and growth of biofilms by oral pathogenic microorganisms, thereby helping to reduce the incidence and prevalence of dental caries, which commonly affects children, as well as other oral diseases. Consequently, researchers are actively developing synthetic AMPs with improved stability and biocompatibility that could potentially replace conventional antimicrobial therapies. The scope of the present review is to summarise AMPs, including their origin, structural characteristics, mechanisms of action and recent advances in their application for combating various oral diseases.

Keywords: Immunomodulatory, Dental caries, Pathogens

INTRODUCTION

A paradigm shift is emerging in the field of paediatric dentistry, with increasing emphasis on exploring non invasive and effective alternatives for the prevention and treatment of oral diseases such as dental caries, periodontal infections, mucosal diseases and oral cancer. To address the growing burden of oral health problems affecting children worldwide, AMPs represent a promising alternative. They are an ancient and widely distributed class of molecules, present in both prokaryotes and eukaryotes and are primarily involved in host defence against pathogenic invasion [1-3]. Research has demonstrated that AMPs can selectively target pathogenic microorganisms while preserving the healthy oral microflora [4].

The AMPs are naturally occurring immunomodulatory protein molecules that act directly on immune cells such as neutrophils, monocytes and T lymphocytes and indirectly by influencing B lymphocytes. Through these mechanisms, AMPs function as adjuncts in the induction of antigen-specific immunity, ultimately leading to activation of the adaptive immune response. In addition to their immunomodulatory effects, AMPs also exhibit potent antimicrobial properties, making them dual-acting molecules [5].

HISTORY

The discovery of gramicidin, a peptide derived from Bacillus species in soil that provides protection against pneumococcal infection, marked the beginning of AMP research in 1939 [6,7]. Subsequently, in 1956, animal-derived AMPs exhibiting lytic activity against Gram-negative bacteria were described.

In 1963, Zeya and Spitznagel isolated arginine-rich AMPs from the granules of rabbit and guinea pig neutrophils, which were named defensins [7-9]. In 1985, Ganz, Lehrer and their colleagues isolated AMPs from the azurophilic granules of human neutrophils for the first time and designated them as Human Neutrophil Peptide 1 (HNP-1), HNP-2 and HNP-3. Later, in-vitro studies demonstrated that a mixture of these three defensins at a concentration of 50 µg/mL exhibited lytic activity against *Staphylococcus aureus* and *Escherichia coli* [10].

Following Zasloff's M discovery of magainins—peptides isolated from the mucous membrane of the clawed frog Xenopus laevis in 1986—interest in AMPs increased substantially [11]. These peptides were found to be effective not only against bacteria but also against viruses, fungi and protozoa. By 1991, their pivotal role in establishing the first line of defence against infections was clearly recognised [12].

MECHANISM OF ACTION

Antimicrobial Peptides (AMPs) are dual-acting molecules that exhibit both antimicrobial (bactericidal) and immunomodulatory properties. Amphipathic AMPs, possessing both hydrophilic and hydrophobic regions, incorporate into the lipid bilayer of the microbial cell membrane and create pores, a process that is crucial for their antimicrobial activity. Bacterial cell surfaces are negatively charged due to the presence of phospholipids, teichoic acids and lipopolysaccharides, which promotes electrostatic attraction to cationic AMPs. The specificity of cationic AMPs is ensured by their preferential affinity for bacterial membranes rather than host cell membranes.

The bactericidal action of AMPs occurs through both extracellular and intracellular mechanisms. The extracellular mechanism is primarily explained by four hypothetical models of membrane pore formation:

Barrel Steve model: In this model, membrane thinning occurs as a result of conformational changes induced by an increasing number of AMPs binding to and aggregating on the bacterial surface, ultimately leading to pore formation [13].

Toroidal pore model: The toroidal pore model differs from the barrel-stave model in that peptide helices insert into the membrane and interact with lipid molecules to form toroidal pore complexes. At high local concentrations, AMPs cause lipid molecules to bend and curve, allowing peptide and lipid head groups to line the pore, with the hydrophobic regions oriented toward the membrane interior [14].

Carpet model: In this model, AMPs cover the bacterial membrane in a carpet-like manner and, at sufficiently high concentrations, cause complete membrane disruption through micelle formation. Although electrostatic interactions between the anionic bacterial membrane and cationic AMPs are essential, pore formation does not occur. Instead, when a threshold concentration is reached, AMPs induce surfactant-like membrane rupture without inserting into the hydrophobic core of the membrane [13].

Aggregate model: Unlike the carpet model, in the aggregate model AMPs bind to the anionic cytoplasmic membrane and form peptide-lipid complexes that create micelle-like aggregates. These structures may facilitate AMP entry into the cytoplasm, allowing interaction with intracellular targets while also permitting the leakage of ions and intracellular contents. This mechanism explains how AMPs can exert both membrane-disruptive and intracellular antimicrobial effects [15].

Intracellular Mechanisms of Action

AMPs can also penetrate the cytoplasm and interact with intracellular components by inhibiting Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA) and protein synthesis; interfering with protein folding; suppressing enzyme activity and cell wall synthesis; and accelerating the release of lyases that degrade the cell wall. In addition to directly inducing DNA damage, AMPs can indirectly inhibit DNA replication and transcription. PR-39, a proline- and arginine-rich AMP isolated from the small intestine of pigs, disrupts DNA synthesis by inhibiting protein synthesis and promoting the degradation of proteins essential for DNA replication. Proline-rich AMPs typically bind to ribosomes and obstruct protein synthesis [16].

Immunomodulatory Role of AMPs in Oral Health

AMPs, also referred to as host defence peptides, play a vital immunomodulatory role in the innate immune system. They are rapidly produced by host cells, requiring less time and energy compared with antibody production in acquired immunity. Pathogen invasion triggers a cascade of immunological responses, with neutrophils serving as a primary source of defensins and cathelicidins. AMPs help maintain immune homeostasis by regulating Tumour Necrosis Factors (TNFs), Interferons (IFNs), chemokines and the activity of immune cells such as mast cells, dendritic cells, monocytes, macrophages, granulocytes and lymphocytes. For instance, LL-37 induces the release of proinflammatory cytokines and chemokines, triggering an inflammatory response, while defensins also exhibit strong proinflammatory effects [16].

Classification and Advances in Synthetic AMPs

The AMPs are classified based on their origin into natural and synthetic peptides. Natural AMPs are produced by multicellular organisms as a first line of host defence and are found in epithelial linings, blood and lymphocytes [17]. Defensins and cathelicidins are the two major classes of AMPs present in most animals. Defensins, the first AMPs to be identified, are further subdivided into α-defensins and β-defensins based on the arrangement of disulphide bonds [18]. Cathelicidins possess a unique structure characterised by diverse amino acid sequences and peptide lengths, along with a highly conserved cathelin domain. They are synthesised and stored in an inactive form within the secretory granules of neutrophils and macrophages and are released upon leukocyte activation.

However, natural AMPs have certain limitations, including structural instability, long peptide sequences, short half-lives and reduced activity within the variable oral microenvironment. Advances in research and technology have led to the development of synthetic AMPs with structural modifications designed to overcome these limitations. These synthetic peptides exhibit improved pharmacokinetics, enhanced stability and broad-spectrum antimicrobial activity. Numerous synthetic analogues have been developed for the prevention and management of dental caries and other oral diseases [17]. To date, more than 40 synthetic AMPs have demonstrated activity against cariogenic species, including Variable Segment Length-2 (VSL2), D-enantiomer of Glycine-Leucine-13-Lysine peptide (D-GL13K), Proline-Arginine-rich peptide with 39 amino acids (PR-39), Human Beta-Defensin-3 C-terminal 15-amino-acid fragment (hBD-3-C15), and Palmitoyl (C16) di-glycine peptide (C16-G2) have demonstrated activity against cariogenic species.

Based on their structure, AMPs are classified into α-helical, β-sheet, extended and mixed peptides.

Applications of AMP's to Dentistry

Role of AMPs in dental caries: Several studies have demonstrated that human β-defensins (hBD-1, hBD-2 and hBD-3) are active against various oral pathogens, particularly key cariogenic organisms such as *Streptococcus mutans* and *Enterococcus faecalis*. The primary mechanism of action of AMPs involves the prevention of biofilm adhesion to the tooth surface, thereby inhibiting bacterial growth and colonisation. In addition to their antimicrobial properties, AMPs have also been reported to promote pulpal healing.

The hBD-2 has been shown to significantly increase Dentin Sialophosphoprotein (DSPP) mRNA expression in human pulp cells, suggesting its potential role in stimulating odontoblast differentiation [19-21]. Similarly, hBD-4 promotes the differentiation of mesenchymal stem cells into osteoblasts and odontoblasts within the dental pulp, indicating its potential application in indirect pulp capping procedures [20].

Extensive research has been conducted to develop synthetic analogues of naturally occurring AMPs. Synthetic peptides such as hBD-3-C1-15 and D1-23, derived from hBD-3, have demonstrated inhibitory effects against *Streptococcus mutans*, thereby contributing to the prevention of dental caries [21].

Composite restoration failure is frequently attributed to secondary caries caused by bacterial adhesion and proliferation at the composite-adhesive-tooth interface. To address this challenge, researchers have explored the use of non specific peptide adsorption in antimicrobial adhesive copolymer systems. Currently, AMPs are conjugated with monomers, such as Methacrylate-Modified AMPs (MA-AMPs), for incorporation into dental adhesives.

Sullivan R et al., evaluated the effectiveness of a C16-G2 mouthwash in selectively eliminating *Streptococcus mutans* from both saliva and dental plaque. Although numerous AMPs have shown promising results in preclinical and in-vitro studies, only a limited number have progressed to clinical evaluation to date [22].

Role of AMP's in periodontal diseases: Periodontal disease is an inflammatory condition caused by microbial biofilms that form on the periodontal supporting tissues. Anaerobic microorganisms such as *Porphyromonas gingivalis*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum* are strongly associated with the initiation and progression of periodontal diseases. In addition, biofilm adhesion-induced peri-implantitis accounts for a significant proportion of dental implant failures.

Research on Antimicrobial Peptides (AMPs) in periodontal disease has primarily focused on two key aspects: their antibacterial activity and their ability to modulate immune responses. As host defence peptides, AMPs possess inherent antimicrobial properties that can aid in controlling periodontal pathogens. It has been reported that LL-37 suppresses Toll-Like Receptor-4 (TLR-4)-induced secretion of Interleukin-6 (IL-6) and Tumour Necrosis Factor-α (TNF-α) and plays a critical role in recruiting neutrophils to sites of periodontal infection [23]. Furthermore, coating metal-based dental implants with AMPs has shown promise in preventing peri-implantitis by inhibiting microbial colonisation.

Role of AMPs in oral mucosal and fungal infections: Several autoimmune and inflammatory diseases affecting the oral mucosa are caused by viral or fungal infections. As key components of innate immunity, AMPs play an important role in preventing infections such as oral candidiasis by inhibiting fungal growth and modulating host immune responses.

Role of AMP's as tumour suppressor: There is increasing interest in exploring the potential role of AMPs as anticancer agents. Certain cationic peptides have demonstrated selective cytotoxicity toward cancer cells due to the negatively charged nature of tumour cell

membranes. However, the precise relationship between AMPs and tumour cells remains incompletely understood. Human β-defensin-1 (hBD-1) has been reported to exhibit tumour suppressor activity [24].

CONCLUSION(S)

By combining potent immunomodulatory functions with broad-spectrum antimicrobial activity, AMPs represent a promising therapeutic approach for the prevention and management of various oral disorders. The development of synthesised AMPs further enhances their clinical potential. Additionally, AMPs may serve as preventive adjuncts to routine oral hygiene practices through their incorporation into toothpastes, mouth rinses and other oral care products. Encouraging their use, particularly in children, may contribute significantly to improved oral health outcomes.

REFERENCES

[1] Hancock RE. Cationic peptides: Effectors in innate immunity and novel antimicrobials. Lancet Infect Dis. 2001;1:156-64.
[2] Pazgier M, Hoover DM, Yang D, Lu W, Lubkowski J. Human beta-defensins. Cell Mol Life Sci. 2006;63:1294-313.
[3] Stotz HU, Thomson J, Wang Y. Plant defensins. Plant Signal Behav. 2009;4:1010-12.
[4] Niu JY, Yin IX, Mei ML, Wu WKK, Li QL, Chu CH. The multifaceted roles of antimicrobial peptides in oral diseases. Mol Oral Microbiol. 2021;36(3):159-71.
[5] Guryanova SV, Ovchinnikova TV. Immunomodulatory and allergenic properties of antimicrobial peptides. Int J Mol Sci. 2022;23(5):2499.
[6] Hirsch JG. Phagocytin: A bactericidal substance from polymorphonuclear leucocytes. J Exp Med. 1956;103:589-611.
[7] Zeya HI, Spitznagel JK. Antibacterial and enzymic basic proteins from leukocyte lysosomes: Separation and identification. Science. 1963;142:1085-87.
[8] Zeya HI, Spitznagel JK. Cationic proteins of polymorphonuclear leukocyte lysosomes. I.I. Composition, properties, and mechanism of antibacterial action. J Bacteriol. 1966;91:755-62.
[9] Zeya HI, Spitznagel JK. Arginine-rich proteins of polymorphonuclear leukocyte lysosomes. Antimicrobial specificity and biochemical heterogeneity. J Exp Med. 1968;127:927-41.
[10] Ganz T, Selsted ME, Szklarek D, Harwig SS, Daher K, Bainton DF, et al. Defensins. Natural peptide antibiotics of human neutrophils. J Clin Investig. 1985;76:1427-35.
[11] Zasloff M. Magainins, a class of antimicrobial peptides from Xenopus skin: Isolation, characterization of two active forms, and partial cDNA sequence of a precursor. Proc Natl Acad Sci USA. 1987;84:5449-53.
[12] Lehrer RI, Ganz T, Selsted ME. Defensins: Endogenous antibiotic peptides of animal cells. Cell. 1991;64:229-30.
[13] Lee TH, Hall KN, Aguilar MI. Antimicrobial peptide structure and mecha nism of action: A focus on the role of membrane structure. Curr Top Med Chem. 2016;16(1):25-39.
[14] Kumar P, Kizhakkedathu JN, Straus SK. Antimicrobial peptides: Diversity, mechanism of action and strategies to improve the activity and bio compatibility in vivo. Biomolecules. 2018;8(1):04.
[15] Hale JD, Hancock RE. Alternative mechanisms of action of cationic antimicrobial peptides on bacteria. Expert Rev Anti Infect Ther. 2007;5(6):951-59.
[16] Zhang QY, Yan ZB, Meng YM, Hong XY, Shao G, Ma JJ, et al. Antimicrobial peptides: Mechanism of action, activity and clinical potential. Mil Med Res. 2021;8(1):48.
[17] Kaplan CW, Sim JH, Shah KR, Kolesnikova-Kaplan A, Shi W, Eckert R. Selective membrane disruption: Mode of action of C16G2, a specifically targeted antimicrobial peptide. Antimicrob Agents Chemother. 2011;55(7):3446-52.
[18] Dommisch H, Winter J, Acil Y, Dunsche A, Tiemann M, Jepsen S. Human beta-defensin (hBD-1, -2) expression in dental pulp. Oral Microbiology and Immunology. 2005;20(3):163-66.
[19] Shiba H, Mouri Y, Komatsuzawa H, Ouhara K, Takeda K, Sugai M, et al. Macrophage inflammatory protein-3alpha and beta-defensin-2 stimulate dentin sialophospho protein gene expression in human pulp cells. Biochemical and Biophysical Research Communications. 2003;306(4):867-71.
[20] Zhai Y, Yuan X, Zhao Y, Ge L, Wang Y. Potential application of human beta-defensin 4 in dental pulp repair. Frontiers in Physiology. 2020;11:1077.
[21] Ahn KB, Kim AR, Kum KY, Yun CH, Han SH. The synthetic human beta-defensin-3 C15 peptide exhibits antimicrobial activity against Streptococcus mutans, both alone and in combination with dental disinfectants. J Microbiol. 2017;55(10):830-36.
[22] Sullivan R, Santarpia P, Lavender S, Gittins E, Liu Z, Anderson MH, et al. Clinical efficacy of a specifically targeted antimicrobial peptide mouth rinse: Targeted elimination of Streptococcus mutans and prevention of demineralization. Caries Res. 2011;45(5):415-28. Doi: 10.1159/000330510.
[23] Montreekachon P, Nongparn S, Sastraruji T, Khongkhunthian S, Chruewkamlow N, Kasinrerk W, et al. Favorable interleukin-8 induction in human gingival epithelial cells by the antimicrobial peptide LL-37. Asian Pac J Allergy Immunol. 2014;32(3):251-60.
[24] Hoskin DW, Ramamoorthy A. Studies on anticancer activities of antimicrobial peptides. Biochim Biophys Acta. 2008;1778(2):357-75. Doi: 10.1016/j.bbamem.2007.11.008.

PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of Paediatric and Preventive Dentistry, Rajarajeswari Dental College and Hospital, Bengaluru, Karnataka, India.
2. Postgraduate Student, Department of Paediatric and Preventive Dentistry, Rajarajeswari Dental College and Hospital, Bengaluru, Karnataka, India.
3. Postgraduate Student, Department of Paediatric and Preventive Dentistry, Rajarajeswari Dental College and Hospital, Bengaluru, Karnataka, India.
4. Postgraduate Student, Department of Paediatric and Preventive Dentistry, Rajarajeswari Dental College and Hospital, Bengaluru, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. K Swetha,
Postgraduate Student, Department of Paediatric and Preventive Dentistry,
Rajarajeswari Dental College and Hospital, Bengaluru-560074, Karnataka, India.
E-mail: saiswethasankar@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 01, 2024
- Manual Googling: Jun 09, 2025
- iThenticate Software: Jun 11, 2025 (27%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 31, 2024**
Date of Peer Review: **Nov 01, 2024**
Date of Acceptance: **Jun 13, 2025**
Date of Publishing: **Apr 01, 2026**