Antimicrobial peptides: The miraculous biological molecules

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Abstract:
Antimicrobial peptides (AMPs) are biological molecules bridging the innate and acquired immune systems of the defense mechanism. They have been found to be effective against not only Gram-positive and -negative bacterial species but also fungi and viruses with their broad spectrum of activity. Among the various niches where they are found in the human body, in the oral cavity, the AMPs are secreted by the epithelial cells, defense cells, crevicular fluid, and in the salivary secretions and form the first line of defense against bacterial invasion. The present review gathers information from a number of literature reviews, systematic reviews articles, and original research work to come to a conclusion regarding the use of AMPs. AMPs are miraculous in that they either do not or develop resistance very slowly and hence are supposed to be great candidates for developing antibiotics. Their use in mouthwash formulations, topical applications, etc., as therapeutic modalities has found some success in the past but is still undergoing trials. In periodontal disease, their active role as biomarkers by the relative upregulations and downregulations during disease progression has also been recognized. The early recognition of these biomarker changes can help regulate the progression of periodontal diseases. They also control the development and progression of biofilm formation and might potentially contribute toward the development of therapeutic mimetics, probiotics, and antibiotics in the near future.

Key words:
Antimicrobial peptides, biomarkers and antibiotics, defense mechanism, innate immune system

INTRODUCTION

Periodontitis is supposed to be the leading cause of tooth loss in the adult population.[1] It is an inflammatory disease characterized by the formation of mixed biofilms on both the tooth surfaces and gingival tissues. Over 700 different species of microorganisms inhabit the oral cavity, of which 150–200 are found in most individuals and over 400 are found in the periodontal pocket.[2] This biofilm nature of the microorganisms involving quorum sensing (cell-to-cell communication), metabolic cooperation, and the ability to elude the host immune system make it highly resistant (up to 1,000 times) to antibiotics.[3]

The rapid innate immune system of the oral epithelia, gingival crevicular fluid (GCF), and saliva form the first line of defense against colonization by pathogenic microorganisms by secreting biological molecules called as antimicrobial peptides (AMPs).[4,5] Nearly 45 known AMP gene products are secreted by the salivary glands with some secreted in the GCF as well. The neutrophils being an important part of the innate defense also secrete AMPs. Resistance against AMPs is developed at a relatively slower pace and is a less common phenomenon.[6] Properties such as a net positive charge and the ability to adopt an amphipathic structure attract the AMP’s to the negatively charged phospholipids at the outer surfaces of bacterial membranes.[6] On disrupting the membrane integrity, they target the cytoplasmic elements ultimately causing bacterial cell death. Hence, they help maintain the complex ecological homeostasis between the host and bacteria in the oral environment.

A number of literature reviews, systematic reviews, articles, and original research works have been extensively studied to conclude the potential role of AMP’s in periodontal health and disease states and their implication in developing therapeutic modalities to fight periodontal diseases.

ANTIMICROBIAL PEPTIDES AND THE ORAL CAVITY

In 1950, the blood cells were discovered to have a broad spectrum of antimicrobial activity.[7] Later...
on, cationic AMP’s were found to be expressed by phagocytic cells in response to infection.[9] They have been evolutionarily conserved[9] and expressed by various organisms such as insects, pigs, frogs, rabbits, mice, and crabs.[10] The AMP’s are biological defense molecules encoded by specific genes expressed by the host cells as an active participant in the innate immune system. In humans, they are found in different niches such as skin, intestine, airway, and endocervix where they function mainly to keep the natural microbial flora in a steady state.[10]

In the oral cavity, the AMPs are produced by epithelial cells, neutrophils, and salivary gland secretions.[11] They are found chiefly in saliva and subset of it in GCF.[12] The mechanism of action of the AMPs involves a series of steps described as follows [Figure 1].[5]

1. Attraction – the electrostatic interaction between the cationic peptides and the anionic moieties on bacterial membrane (Gram-negative bacteria: lipopolysaccharide [LPS] phosphate group and anionic lipids; Gram-positive bacteria: teichoic acids) is presumed to cause attraction

2. Attachment – after getting bound to the bacterial membrane surface the AMPs get transformed into a secondary structure which causes them to orient either parallel or perpendicular to the membrane. The initial low and later high peptide/lipid ratios allow the bacterial membrane to stretch causing it to thin down. This is followed by subsequent pore formation with the peptides getting oriented in a perpendicular fashion to insert into the bilayer

3. Models of insertion – the penetration of the AMPs across the bacterial membrane takes place by either the carpet model, the barrel-stave model, or the toroidal pore model causing the ultimate bacterial cell death.

Defensins and cathelicidins are supposed to be the most abundant human AMP’s.[5] The defensins chiefly constituted two families: The alpha-defensins (α-defensins) predominantly found in neutrophils and the intestine, and the β-defensins predominantly found in epithelial cells.[12] In the oral cavity, saliva has been found to be associated with the expression of defensins alongside the oral, sulcular/pocket, junctional epithelia, as well as the dentogingival junction. The polymorphonuclear leukocytes found in discrete areas of the gingival connective tissue are also associated with the expression of defensins.[13] α-defensins isolated from neutrophils in the oral cavity include human neutrophil peptide (hNP)-1, hNP-2, hNP-3, and hNP-4. hNP-1–3 are abundantly expressed in saliva (90%) and hNP-4 are roughly 100-fold lower. hNP-5 and 6 are expressed in the enteric system and not the oral cavity.[14] Six members of the β-defensin family are expressed in humans, that is, human β-defensin (hBD)-1–6 principally by all epithelial surfaces (skin, oral mucosa, respiratory tract, gastrointestinal tract, genitourinary tract, and the kidney).[4,14] Studies reveal that only hBD-1–3 are expressed in the oral cavity (gingival epithelia, tongue, palate, and buccal mucosae, salivary glands/ducts, and saliva).[15] Cathelicidins are AMP’s belonging to the α-helical peptides without cysteine and located at the carboxyl terminus of a 15–18 kDa highly conserved cathespin-L-inhibitor (cathelin)-like domain.[11] LL-37 is the only cathelicidin expressed in humans. The number 37 denotes the length of the peptide and “LL” stands for the two amino acids formed by leucine. Other names such as human cathelicidin antimicrobial proprotein 18, CAMP, and FALL-39 have been used to describe LL-37.[16] They have also been found to be expressed in both steady state and disease state of the periodontium.

Other AMP’s expressed in the oral cavity include – adrenomedullin, histatins, statherin, C-C motif chemokine 28, and neuropeptides. Adrenomedullin is a cationic amphipathic peptide expressed in the GCF and saliva (in large concentrations).[17] Histatins are 7–38 amino acid long salivary proteins synthesized by the parotid and submandibular salivary glands.[18] The C-C motif chemokine 28 is a 128-amino acid peptide, primarily expressed by the epithelial cells, including salivary glands, and in saliva as well.[19] A 37 kDa cationic antimicrobial protein called Azurocidin is expressed in the azurophilic granules of neutrophils and has been found to have strong antibacterial properties.[14] Cysteine residues at positions 52 and 68 are held responsible for the antibacterial activity.[19] GCF is also rich in neuropeptides such as calcitonin gene-related peptide and substance P.[19] The salivary glands also express the vasoactive intestinal peptide and the neuropeptide Y.[14]

Figure 1: Mechanism of action of antimicrobial peptides. 1 – Attraction: Electrostatic interaction between Gram-positive and Gram-negative bacterial membranes with antimicrobial peptides; 2 – Attachment: Attachment of antimicrobial peptides to the bacterial membrane surface after transforming to a secondary structure; 3 – Insertion: Three modes. AMP – Antimicrobial peptides
### Table 1: Antimicrobial peptides expressed in saliva and gingival crevicular fluid and their role as biomarkers of periodontal disease

| Protein                                      | Concentration in saliva (µg/mL) | Concentration in GCF (µg/mL) | Change in periodontal disease                                      |
|----------------------------------------------|----------------------------------|------------------------------|------------------------------------------------------------------|
| Adrenomedullin                               | 0.06                             | 1.8                          | Two-fold rise                                                    |
| hNP-1                                        | 8.6                              | 0.0012                       | Upregulated 15-fold in aggressive periodontitis and 60-fold in chronic periodontitis, respectively |
| hNP-2                                        | 5.6                              | 0.0012                       |                                                                   |
| hNP-3                                        | 0-2.7                            | 0.0012                       |                                                                   |
| hNP-4                                        | MS                               |                              |                                                                   |
| hBD-1                                        | 0.15                             | +                            |                                                                   |
| hBD-2                                        | 0.15                             | +                            |                                                                   |
| hBD-3                                        | 0.31                             |                              |                                                                   |
| Cathelicidin/LL-37                           | 1.6                              | +                            | Upregulated in aggressive periodontitis and chronic periodontitis  |
| Histatin 1                                   | 10.1 (parotid); 34.7 (SM/SL)     |                              |                                                                   |
| Histatin 3                                   | 7.3 (parotid); 10.2 (SM/SL)      |                              |                                                                   |
| Statherin                                    | 26.5                             | MS                           |                                                                   |
| CCL28                                        | 0.9                              |                              |                                                                   |
| Azurocidin/CAP37/heparin-binding protein SP  | 7.5x10⁻⁶                         | 0.061-0.11                   | SP concentration was similar in healthy gingivitis or periodontitis. Others found that concentration was decreased 7-fold postperiodontal treatment |
| Calcitonin gene-related peptide              | 23.5x10⁻⁶                        | 0.013-0.7                    | Concentration 20-fold lower in gingivitis, not detected in periodontitis |
| Neuropeptide Y                               | 41.4x10⁻⁶                        |                              |                                                                   |
| Vasoactive intestinal peptide                | 39.9x10⁻⁶                        |                              |                                                                   |
| Mucin 7                                       | 40                               |                              |                                                                   |
| GP340/salivary agglutinin/DMBT1               | MS                               |                              |                                                                   |
| Surfactant protein-A                          | 0.9                              |                              |                                                                   |
| Beta-2-microglobulin                          | 0.38                             | 9.4                          | Increased 3-fold in mild periodontitis and 10-fold in severe periodontitis, respectively |
| Proline-rich proteins                         | MS                               | MS                           | Decreased 2-fold in periodontitis and 30-fold in gingivitis. Less intact FN is found in periodontitis than in healthy control or treated sites |
| FN                                           | 1.2-0.13                         | 106                          | Increased 2-3-fold in periodontitis, decreased 2-3-fold after periodontal therapy |
| Calgranulin A                                 | 1.93                             | 204                          | Increased in periodontitis, decreased 2-3-fold after periodontal therapy |
| Calgranulin B                                 | 1.93                             | +                            | Calprotectin concentration increased with the gingival index; 3-5-fold increase in periodontitis (>4 mm pocket depth); 70 ng/µL detected in children |
| Calprotectin                                  | 570                              |                              |                                                                   |
| Psoriasin                                     | MS                               |                              | Concentration highly variable. No consistent change with disease |
| Lactoferrin                                   | 20                               | 600                          |                                                                   |
| Cystatin A                                    | MS                               | MS                           | Main cystatin activity in gingival crevicular fluid of periodontal patients |
| Cystatin B                                    | MS                               |                              | No change in children with gingivitis                             |
| Cystatin C                                    | 0.9                              | 1.15 (children)              |                                                                   |
| Cystatin D                                    | 3.8                              |                              |                                                                   |
| Cystatin S                                    | 53-116                           |                              |                                                                   |
| Cystatin SA                                   | 78                               |                              |                                                                   |
| Cystatin SN                                   | 39                               |                              |                                                                    |
| Secretory leukocyte protease inhibitor SKALP/Elafin | 2.9                          | No data                      | 79.7 pg/µL in periodontitis, increased 3-4-fold at 2 and 4 weeks posttreatment |
| Lactoperoxidase (salivary peroxidase)          | 0.02                             |                              | Peroxidase identified in gingival crevicular fluid is most likely myeloperoxidase |
| Myeloperoxidase                               | 1.9                              | +                            | No change in aggressive or chronic periodontitis. 660 µg/mL in >5 mm pockets. Concentration decreased 2-fold after therapy |
| Lysozyme C                                    | 3                               | 0.3-5.5                      | Increased in juvenile periodontitis                                |
| Peptidoglycan recognition protein 1           | 40                               | +                            |                                                                   |

+ – Present; MS – Mass spectroscopy detection of proteins in unstimulated whole saliva; SM – Submandibular; SL – Sublingual; GCF – Gingival crevicular fluid; FN – Fibronectin; SP – Substance P; hNP – human neutrophil peptide; hBD – human β-defensin; CCL28 – Chemokine (C-C motif) ligand 28; CAP37 – Cationic antimicrobial protein of 37kDa; SP – Substance P; GP340 – Glycoprotein 340; DMBT1 – Deleted in Malignant Brain Tumors-1 protein; FN – Fibronectin; SKALP – Skin-derived antileukoproteinase
These AMPs are expressed in the periodontium in both health and disease and help maintain homeostasis of the periodontal environment at all times. This role of AMPs has been discussed in detail in the section that follows.

**ANTIMICROBIAL PEPTIDES IN PERIODONTAL HEALTH AND DISEASE**

The oral cavity is unique in that the microorganisms and pathogens have an easy access to it and the rest of the body through the epithelium and the gastrointestinal tract. The gingival epithelial cells on exposure to bacteria related to periodontitis actively express AMPs. Nearly twenty genetic disorders connected to periodontal disease have been identified so far and are associated with the expression of AMPs.

GCF analysis for the content of LL-37 was carried out by Puklo et al. in 2008. They concluded that LL-37 was chiefly produced by neutrophils in the healthy periodontium and helped maintain it in a steady state. In patients with chronic or aggressive periodontitis cells other than neutrophils were responsible for the production of LL-37. Therefore, in case of a state of deficiency in LL-37 secretion, as noted in morbus Kostmann syndrome and Papillon–Lefèvre syndrome, the propensity to infection including chronic periodontal infections increases. In addition, LL-37 could also modulate neutrophil response to bacterial challenge, especially in aggressive forms of disease.

LL-37 possesses a broad spectrum of activity against both Gram-positive and Gram-negative bacteria including periodontopathogens such as Porphyromonas gingivalis, Prevotella intermedia, and Aggregatibacter actinomycetemcomitans alongside fungi and viruses. It miraculously neutralizes the activity of LPS and thus help protect the tissues from their harmful effects. They maintain a balance between pro- and anti-inflammatory mediators at the time of LPS attack. The LL-37 peptides possess a direct bactericidal action against LPS of Gram-negative and teichoic acid of Gram-positive bacteria. Using either the barrel stave, tripodal or the carpet model the LL-37 cathelicidin is inserted into the bacterial cell membrane causing cell rupture and leakage of cytoplasm causing bacterial cell death. However, the erythrocyte membrane contains sialic acid making them vulnerable to an unwanted attack by the LL-37. The only nonhemolytic variety of cathelicidin derived from LL-7 to LL-27.

LL-37 has also emerged as having novel antibiotic properties at low concentration as well helping fight the biofilm bacteria such as Pseudomonas aeruginosa, Burkholderia pseudomallei, Streptococcus mutans, and Staphylococcus epidermidis. It prevents the adherence of bacteria to the tooth surface by controlling the genes responsible for quorum sensing, which are necessary for the formation of biofilm. It also increases the surface motility of bacteria (twitching) atop the biofilm thus interfering with its thickness.

LL-37 acts as an opsonin rendering Aa susceptible to clearance by neutrophils and monocytes by their phagocytic action. However, Pg possesses a unique LPS composition rendering it resistance against LL-37.

A metalloprotease, karilysin found to be released by the red complex bacteria such as Tannerella forsythia, downregulates the antibacterial and anti-inflammatory properties of LL-37. The maximum inhibitory effect of LL-37 has been exerted against primary colonizers belonging to the yellow-orange complex.

hBD-1 and 2 are found in the suprabasal layer of the normal gingival epithelium, whereas hBD-3 peptide is expressed by the undifferentiated epithelial cells within the basal layer. It has been found that hBD-1 is continuously expressed and plays a pivotal role in maintaining the homeostasis of the oral environment, whereas hBD-2 and 3 are induced in response to bacterial LPS, pro-inflammatory mediators (interleukins-1), tumor necrosis factors-α, interferon-γ and are thought to be effective against almost all pathogens. α-defensins are markedly reduced in number in (≤30% of normal) patients suffering from neutrophil deficiency disorders, whereas HNP-1–3 have shown a 15-fold raise in expression in patients suffering from aggressive periodontitis.

It has been observed that the quantity of adrenomedullin is almost twice the amount in periodontally compromised areas than in healthy areas. Histatins not only inhibit the growth of Candida species but also regulate the oral hemostasis. Children with Down’s syndrome commonly suffer from periodontal disease as well and are related to LL-37 deficiency. In periodontitis associated with A. actinomycetemcomitans the mucin-7 levels have been found to be decreased by 3 fold. Lactoferrin, however, remains within normal range. Beta-2-microglobulin, calgranulin-A and B, calprotectin, secretory leukocyte protease inhibitor, and lysozyme C usually increase by 2–4 fold in periodontitis, whereas substance P, calcitonin gene-related peptide, and fibronectin show a decrease in concentration.

Thus, this wide range of AMPs expressed in the oral cavity can successfully be used as potential biomarkers for understanding the periodontal disease activity by estimation of their relative GCF and salivary levels from time to time.

**CLINICAL APPLICATIONS/FUTURE PERSPECTIVES**

In the use of AMPs as biomarkers for periodontal disease assessment, the ratios between up- and downregulated proteins from individual patients may overcome individual variation and potentiate the observed differences to allow prospective assignment of any given sample as “healthy” or “diseased.” Thus, treatment outcomes may be monitored by changes in AMP levels pre- and post-treatment. Systems which specifically target the AMPs to the bacteria are being developed. Their antimicrobial activity and selectivity help kill bacteria in mixed cultures. To overcome the problems of toxicity, peptide mimetics with the ability to retain their properties as AMPs are being developed with a favorable therapeutic index and stability; one such mimetic being XOMA 629. Topical and local applications under the names of Pexiganan (MSI-78), Iseganan (IB-367), P113, and KSL have successfully been used as adjunct to standard oral hygiene care, mouthrinse for oral candidiasis in HIV patients, prevention of plaque-mediated dental diseases, and control of biofilms. Furthermore, coated AMPs are used to prevent the biofilm formation on implants.
Additional studies into new biological activities of AMPs are needed and will be beneficial for us to better understand and gain deep insight into the importance of these multifunctional molecules in maintaining tissue homeostasis during the healthy and diseased states of the periodontium.

CONCLUSION

A wide range of AMPs has been discovered to be expressed in various niches in the oral cavity. Their potential roles in regulating the oral environment in both health and disease have also been successfully described in literature. They have been conserved in evolution and show relatively lower potential to resistance against microbes as they co-evolve with these pathogens thus potentially help regulate the biofilm environment and progressing gingival and periodontal diseases. Not just this but the role of AMPs in controlling the spread of caries has also been documented. Challenges such as their design, synthesis, and function at molecular level need to be overcome in the near future so as to open doors toward the design of potentially effective oral microbial antibiotics.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bartold PM, Van Dyke TE. Periodontitis: A host-mediated disruption of microbial homeostasis. Unlearning learned concepts. Periodontol 2000 2013;62:203-17.
2. Gorr SU. Antimicrobial peptides of the oral cavity. Periodontol 2000 2009;51:152-80.
3. Li YH, Tian X. Quorum sensing and bacterial social interactions in biofilms. Sensors (Basel) 2012;12:2519-38.
4. Gorr SU, Abdolhosseini M. Antimicrobial peptides and periodontal disease. J Clin Periodontol 2011;38 Suppl 11:126-41.
5. Diamond G, Beckloff N, Weinberg A, Kisich KO. The roles of antimicrobial peptides in innate host defense. Curr Pharm Des 2009;15:2377-92.
6. Altman H, Steinberg D, Porat Y, Mor A, Fridman D, Friedman M, et al. In vitro assessment of antimicrobial peptides as potential agents against several oral bacteria. J Antimicrob Chemother 2006;58:198-201.
7. Skarnes RC, Watson DW. Antimicrobial factors of normal tissues and fluids. Bacteriol Rev 1957;21:273-94.
8. Zeya HI, Spitznagel JK. Antibacterial and enzymic basic proteins from leukocyte lysosomes: separation and identification. Science 1963;142:1085-7.
9. Pasupuleti M, Schmidtchen A, Malmsten M. Antimicrobial peptide: Key components of the innate immune system. Crit Rev Biotechnol 2012;32:143-71.
10. Weinberg A, Krisanaprakornkit S, Dale BA. Epithelial antimicrobial peptides: Review and significance for oral applications. Crit Rev Oral Biol Med 1998;9:399-414.
11. Dale BA, Fredericks LP. Antimicrobial peptides in the oral environment: Expression and function in health and disease. Curr Issues Mol Biol 2005;7:119-33.
12. Diamond G, Ryan L. Beta-defensins: What are they really doing in the oral cavity? Oral Dis 2011;17:628-35.
13. Bedi T, Mahendra J, Ambalavanan N. Defensins in periodontal health. Indian J Dent Res 2015;26:340-4.
14. Khurshid Z, Naseem M, Sheikh Z, Najeeb S, Shahab S, Zafar MS, et al. Oral antimicrobial peptides: Types and role in the oral cavity. Saudi Pharm J 2016;24:513-24.
15. Krisanaprakornkit S, Weinberg A, Perez CN, Dale BA. Expression of the peptide antibiotic human beta-defensin 1 in cultured gingival epithelial cells and gingival tissue. Infect Immun 1998;66:4222-8.
16. Fuko M, Guentsch A, Hiemstra PS, Eick S, Potempa J. Analysis of neutrophil-derived antimicrobial peptides in gingival crevicular fluid suggests importance of cathelicidin LL-37 in the innate immune response against periodontogenic bacteria. Oral Microbiol Immunol 2008;23:328-35.
17. de Sousa-Pereira P, Amado F, Abrantes J, Ferreira R, Esteses PJ, Vitorino R, et al. An evolutionary perspective of mammal salivary peptide families: Cystatins, histatins, statherin and PRPs. Arch Oral Biol 2013;58:451-8.
18. Soehnlein O, Lindbom L. Neutrophil-derived azurocidin alarms the immune system. J Leukoc Biol 2009;85:344-51.
19. Awadbeh I, Lundy FT, Shaw C, Lamey PJ, Linden GJ, Kennedy JG, et al. Quantitative analysis of substance P, neurokinin A and calcitonin gene-related peptide in pulp tissue from painful and healthy human teeth. Int Endod J 2002;35:30-60.
20. Okumura K. Cathelicidins-therapeutic antimicrobial and antitumor host defense peptides for oral diseases. Jpn Dent Sci Rev 2011;47:67-81.
21. Ouhara K, Komatsuawaha Y, Yamada S, Shiba H, Fujiwara T, Ohara M, et al. Susceptibilities of periodontopathogenic and cariogenic bacteria to antibacterial peptides, [beta]-defensins and LL37, produced by human epithelial cells. J Antimicrob Chemother 2005;55:888-96.
22. Vallaban CG, Sivaranjan S, Ahamed M, Chandramohan S, Thomas BR, Geetha S. A comprehensive review of LL-37 in periodontal disease. J Int Oral Health 2016;8:147-52.
23. Vandamme D, Landuyt B, Luyten W, Schools L. A comprehensive summary of LL-37, the factotum human cathelicidin peptide. Cell Immunol 2012;280:22-35.
24. Thennarasu S, Tan A, Penumatchu R, Shelburne CE, Heyl DL, Ramamoorthy A, et al. Antimicrobial and membrane disrupting activities of a peptide derived from the human cathelicidin antimicrobial peptide LL37. Biophys J 2010;98:248-57.
25. Bai LL, Takagi S, Guo YK, Kuroda K, Ando T, Yoneyama H, et al. Inhibition of Streptococcus mutans biofilm by LL-37. Int J Med Sci Biotech 2013;1:56-64.
26. Kanthawong S, Bölscher JG, Veerman EC, van Marle J, de Soet HJ, Kazmi K, et al. Antimicrobial and antibiofilm activity of LL-37 and its truncated variants against Burkholderia pseudomallei. Int J Antimicrob Agents 2012;39:39-44.
27. Sol A, Ginesin O, Chauush S, Karra L, Coppenhagen-Glazer S, Ginsburg I, et al. LL-37 opsonizes and inhibits biofilm formation of Aggregatibacter actinomycetemcomitans at subbactericidal concentrations. Infect Immun 2013;81:3577-85.
28. Pisano E, Cabras T, Montaldo C, Piras V, Inzitari R, Olmi C, et al. Peptides of human gingival crevicular fluid determined by HPLC-ESI-MS. Eur J Oral Sci 2005;113:462-8.
29. Gorr SU. Antimicrobial peptides in periodontal innate defense. Front Oral Biol 2012;15:84-98.
30. Tew GN, Clements D, Tang H, Arnt L, Scott RW. Antimicrobial activity of an abiotic host defense peptide mimic. Biochim Biophys Acta 2006;1758:1387-92.
31. Leung KP, Crowe TD, Abercrombie JJ, Molina CM, Bradshaw CJ, Jensen CL, et al. Control of oral biofilm formation by an antimicrobial decapeptide. J Dent Res 2005;84:1172-7.
32. Brandenburg LO, Mieres J, Albrecht LJ, Varoga D, Pufe T. Antimicrobial peptides: Multifunctional drugs for different applications. Polymers 2012;4:539-60.