Front. Biol. 2017, 12(2): 116–123
DOI 10.1007/s11515-017-1432-8

REVIEW

Cationic antimicrobial peptide: LL-37 and its role in periodontitis

Hansa Jain (✉)

Department of Pedodontics, Harsarn Dass Dental College, India

BACKGROUND: Periodontitis i.e. inflammation of the periodontium is a multifactorial disease. Antimicrobial peptides (AMPs) which demonstrate a broad-spectrum of activity against varied number of bacteria, fungi, viruses, and parasites, and cancerous cells have been linked to periodontitis. The AMPs even possess the caliber of immunomodulation, and are significantly responsive to innate immuno-stimulation and infections. LL-37 plays a salubrious role by preventing and in treatment of chronic forms of periodontitis.
OBJECTIVE: In the present work we will review the role of antimicrobial peptide LL-37 in periodontitis.
METHODS: A systematic search was carried out from the beginning till August, 2016 using the Pubmed search engine. The keywords included "LL-37," "periodontitis," "Papillon–Lefevre syndrome," "Morbus Kostmann," "Haim-Munk syndrome" along with use of Boolean operator "and."
RESULTS: The search resulted in identifying 67 articles which included articles linking LL-37 with periodontitis, articles on Papillon–Lefevre syndrome, Morbus Kostmann, Haim-Munk syndrome, LL-37 and periodontitis and articles on pathogenicity of periodontitis.
CONCLUSION: The literature search concluded that LL-37 plays a pivotal role in preventing and treatment of severe form of periodontitis.

Keywords LL-37, antimicrobial peptides, cathelicidin, periodontitis

Introduction

The immediate protection from a foreign invasion by body is called innate immunity. In response to pathogenic attack, there is production and response of a varied number of molecular factors enlisting pattern recognition receptors, scavenger receptors, lectins, pentraxin, Lipopolysaccharide binding protein, lysozyme, lactoferrin, cell adhesin molecules, chemokines, cytokines, components of complement system (Panteleev et al., 2015). The functions played by these cells include rapid and nonspecific response, epithelial barrier function, autophagy, and unfolded protein response, phagocytosis, antigen response thus facilitating T cell differentiation finally leading to activation of the adaptive immune systems (Oh and Koh, 2015). When a study was carried out in mice, it was concluded that attenuation of innate immune system after bacterial invasion results in dysregulated response drive disease (Godaly et al., 2015). Along with the above mentioned protein factors, endogenous antimicrobial peptides (AMPs) hold an eminent place in antibacterial attack by the body. AMPs are produced in most of the living organisms including vertebrates, invertebrates, plants, fungi and bacteria (Panteleev et al., 2015). Literature suggest that in plants they are produced in roots, seeds, stems, leaves and the flowers. In plants they play a pivotal role by inhibiting or killing phylogenetically related microorganisms that by transkingdom signaling afflict the growth and development of the plant (Lopez-Meza et al., 2015).

Peptides possessing antimicrobial activities were initially described in 1966 by Zeya and Spitznagel. They are synthesized on the ribosomes in the precursor proteins and they might undergo post-translational modifications during its' maturation process. AMPs are released by macrophages and granulocytes, numerous epithelial cells, small intestine, vaginal epithelium, respiratory epithelium, and oral cavity epithelium (Oyinloye et al., 2015). Later on it was observed that they act as a direct effector i.e. antibiotic agent; they have the ability to play as a regulator in immunomodulation and even actively participate in the functioning of both the innate and acquired immunity (Panteleev et al., 2015). Along with being part of innate immune response i.e. acting as defense

Received September 12, 2016; accepted November 2, 2016
Correspondence: Hansa Jain
E-mail: drhansajain25@gmail.com

peptides, their action also includes destructing and damaging the bacterial, viral or fungal membrane (Jenssen et al., 2006). Due to these activities they are termed as multifunctional peptides (Oyinloye et al., 2015). There is massive increase in the production of these peptides at sites of infection or inflammation and AMPs have been reported to have a broad spectrum antibacterial, antifungal, antisepsis, antiviral and antiprotozoan properties (Hancock and Diamond, 2000).

Classification of AMPs

Antimicrobial peptides can be classified considering various factors such as origin of the peptide, the type of charge the peptide possess i.e. cationic peptides and anionic peptides, amino acid content for example aspartic acid rich peptide and the most recent classification is based on solution structure of peptides. The last category can be further classified as linear α-helical peptides, disulphide bond within a loop peptides, two or more disulphide bonds containing peptides, linear peptides devoid of cysteine residue and AMPs resulting from larger proteins (Tables 1, 2) (Guzman-Rodriguez et al., 2015; Oyinloye et al., 2015).

Table 1 Classification of antimicrobial peptides on the basis of structure (Guzman-Rodriguez et al., 2015; Oyinloye et al., 2015)

Sr. No.	Structure of peptide	Antimicrobial peptide
1)	Linear α-helical peptide devoid of cysteine residue	Bombinins, cecropins, magainins
2)	Single disulphide bond packing into loop structure, with tail	Bactenecins, esculentins
3)	Two or more disulphide bonds with β-sheet	Defensins, protegrins
4)	Linear peptide devoid of cysteine residue	Histatins, indolicidin, temporins
5)	Large protein molecule or functional peptides	Lactoferrin, MUC7

Table 2 Classification of antimicrobial peptides on the basis of ionic charge (Guzman-Rodriguez et al., 2015; Oyinloye et al., 2015)

Sr. No.	Ionic charge	Antimicrobial peptide
1)	Cationic antimicrobial peptides	Defensins Cathelicidins Cecropins Thionins Amino acid enriched antimicrobial peptides Histone derived peptides
2)	Anionic antimicrobial peptides	Neuropeptide derived molecule Aspartic acid rich peptide

Cationic antimicrobial peptides (CAMPs) (Table 3)

Cationic antimicrobial peptides (CAMPs) can be described as positively charged peptides with a net charge of 12 to 17 due to an excess of basic amino acids having 2-50 amino acids

Table 3 Classification of cationic antimicrobial peptides on the basis of function (Hancock and Diamond, 2000)

Sr. No.	Function	Cationic antimicrobial peptide
1)	Broad-spectrum antibacterial	Defensins, indolicidin, protegrin and LL-37
2)	Synergy with other peptides	Defensins NP-1 and NP-5
3)	Antifungal	Protegrin, indolicidin and histatins
4)	Anti-endotoxin	LL-37
5)	Anti-enveloped virus (HIV,HSV,VSV)	Indolicidin, protegrin and defensins
6)	Anticancer	Indolicidin and defensins
7)	Wound healing	PR39 and defensins
8)	Antiparasite	Indolicidin and defensins

(Hancock and Diamond, 2000). Their genes are subjected to the positive selection and they are one of the most rapidly educing group of mammalian proteins. They have prominent differences even between the primate species with few CAMPs conserved throughout the copious mammalian lineages and few might have disappeared or expanded by gene multiplication in a group of mammals (Peschel and Sahl, 2006). They are a large and varied group of peptides and are produced by a large number of organisms. The organisms producing CAMPs range from prokaryotes to vertebrates and till date over 1200 have been reported (Band and Weiss, 2015). They are found in mucous membranes and skin and their antimicrobial activity depends on the existence of an ionic ambience which can be compared to the conditions of the body fluids and the ionic content. CAMPs even contributes to the competency of killing action of the phagocytic cells (Peschel and Sahl, 2006).

Cathelicidins are one of the families of antimicrobial peptides that are characterized by conserved propeptide sequences, they have been determined in a large number of species of the mammals (Koczulla et al., 2003). Literature suggest apparent variation among different numbers of cathelicidin genes between the varied mammalian species (Frohm et al., 1997). The distinct sequence identity at the N terminus prepro regions called cathelin domain is one the exclusive features of the cathelicidin peptides. The peptides are hoarded as inactive propeptide precursors that, are dealt into active peptides on stimulation (Scott et al., 2002). Till date the only human cathelicidin ascertained is prepro-LL-37 and the preproprotein of LL-37 was titled human CAP18 (hCAP18) by Larrick et al. in 1995. LL-37 is a cysteine-free peptide unlike defensins and readily gets adapted to an amphipathic α-helical conformation (Frohm et al., 1997). It is named so after the first two residues and the number of amino acids forming the peptide chain. The single letter abbreviation of the first two residues is used i.e. leucine, which are present at NH_2 terminus (McCrudden et al., 2013). The common nominator has been observed to be a well conserved proregion of cathelin type, whereas the C-terminal domain has been expressed by highly exceptionally divergent

antibacterial peptides (Frohm et al., 1997).

In mice also only one cathelicidin has been reported till date. It is called cathelicidin-related antimicrobial peptide (CRAMP). It has been observed that amino acid sequence alignment of CRAMP and LL-37 has 47% identity and 67% similarity (Nakamichi et al., 2014). hCAP18 is a protein allied to the family of cathelicidin proteins. It has 140 amino acid residues, with a highly conserved preproregion of ~128–143 residues, enlisting a putative ~29–30-residue signal peptide and a ~99–114-residue cathelin-like domain along with a COOH-terminal antimicrobial domain. The length of the COOH-terminal antimicrobial domain ranges from 12 to >100 amino acid residues and has the caliber to get bound and neutralize the bacterial LPS. Cleavage of hCAP18 was initially predicted by Ahuja et al. in the year 1996 and later on in the same year confirmed by Gudmundsson et al., they stated that hCAP18 occurs between Ala103 and Leu104 thus leading to production of LL-37 (Frohm et al., 1997; De Yang et al., 2000). Although highly charged with 16 charged residues, LL-37 has a neutral pH of + 6 (Henzler Wildman et al., 2003). It is found in saliva at 0.14-3 μg/mL (Gorr, 2012).

LL-37 has been witnessed in profuse number of sites including leukocytes like neutrophils, monocytes, NK cells, γδ T cells, and B cells, testis, myeloid cells (in the granules), keratinocytes, gastrointestinal tract, respiratory tract and inflamed sites. It is produced by bone marrow, testis, inflamed skin keratinocytes, lung epithelia, and squamous epithelia of human mouth, tongue, esophagus, cervix, and vagina; and has been detected in sweat and human milk (Frohm et al., 1997; Bals et al., 1998; Turner et al., 1998; De Yang et al., 2000; Davidopoulou et al., 2012). It was cloned from cDNA isolated from human bone marrow, and its gene was mapped and literature suggests that both purified and chemically synthesized LL-37 peptides possess compelling and comparable antimicrobial activities *in vitro* (Frohm et al., 1997; De Yang et al., 2000).

Oudhoff et al. (2010) stated that LL-37 cause fibroblasts migration and proliferation in a wound thus promoting wound healing. Another study by Gronberg et al. tested the safety and efficacy of LL-37 on healing of venous leg ulcers. It was observed that the topical treatment with LL-37 was well tolerated with marked healing (Gronberg et al., 2014). Leszczynska and colleagues (2010) tested the antibacterial activity of amoxicillin with clavulanic acid, tetracycline, erythromycin and amikacin against various isolates of *Staphyloccocus aureus* along with synthetic LL-37. It was observed that there was increase in potency of amoxicillin with clavulanic acid due to addition of LL-37 but not much difference was observed in other groups.

Role of LL-37 in oral cavity

Periodontitis is an inflammation of the periodontium, which includes gingiva, periodontal ligament, cementum and alveolar bone. The major clinical features of periodontitis include gingival inflammation, periodontal pocketing, alveolar bone loss and clinical attachment loss. Periodontitis is the result of interaction between dental microbial plaque and the host response (Hatipoglu et al., 2015). There are over 500 bacterial species residing in the oral cavity. Among them *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* forming the red complex are strongly related with periodontal inflammation (Mysak et al., 2014). Other complexes include orange complex, green complex and purple complex. The red and orange complexes microflora are associated with subgingival plaque whereas green and purple complexes microflora are related with supragingival plaque (Ximenez-Fyvie et al., 2000).

The microbial attack results in an increase in host response in the periodontium. This leads to severe increase in the production of inflammatory cytokines for example interleukins, tumor necrosis factor-α, enzymes including the matrix metalloproteinases (MMPs) and prostanoids like prostaglandin E2 (Hatipoglu et al., 2015; Silva et al., 2015). Thus leading to increase in inflammation, destruction of tooth supporting structures and formation of periodontal pocket. The progression of destruction in periodontitis is observed to be dependent on abnormal host response to sub-gingival plaque biofilm (Dahiya et al., 2013). Although periodontitis includes a complex interplay of cytokines and cell types, it is majorly a neutrophil-mediated disease. The build-up of plaque nurtures the growth of anaerobic bacteria, which through a series of mechanisms results in enrollment and activation of neutrophils. The excessive or unimpeded exposure of the connective tissue to the enzymes released by neutrophils leads to destruction of the tissue (Usher and Stockley, 2013). The untreated disease begets bone resorption and gingival recession. Chronic periodontitis can also evoke other inflammatory diseases such as type 2 diabetes (Inomata et al., 2010), rheumatoid arthritis (RA) and cardiovascular diseases (Roberts et al., 2015).

A conglomerate of over 45 antimicrobial proteins and peptides has been observed in oral fluids. Like other AMPs, LL-37 is considered a major component of the mucosal antimicrobial defense. It is induced by bacterial stimulation of gingival epithelial cells and by peripheral blood neutrophils (Chung et al., 2007). LL-37 has been found in inflamed epithelia and in saliva. It was observed that both the mRNA and protein for cathelicidin peptides are found in salivary glands, specifically in acinar cells of the submandibular gland and palatine minor glands. LL-37 is also observed in lingual epithelium and palatal mucosa in mice and submandibular duct cells in humans (Tao et al., 2005).

Literature suggests a positive relationship between levels of LL-37 and probing depth, clinical attachment level, bleeding on probing, plaque index and papilla bleeding index at sampled sites (Turkoglu et al., 2009). Serine proteinases including elastase, cathepsin G, and proteinase 3 along with LL-37 forms the basis of the oxygen-

independent machinery PMNs which are bactericidal. As there is reduced oxygen tension in periodontal pocket, the dependency of defense against the periodontopathogens in this environment might be on oxygen-independent means (Gorr and Abdolhosseini, 2011).

It has been observed that in the innate immune defense there is direct killing of microbes which leads to release of LPS and membrane lipoproteins by destructed microbes. These may in return enable the host recognition of components like molecular patterns by Toll like receptors (TLRs), and induction of varied number of genes which function for initiation of proinflammatory immune defense. Into et al. stated that LL-37 reduced LPS-induced gene expression of interleukin (IL)-6, IL8 and CXCL10 and intracellular signaling events, degradation of Interleukin 1 Receptor Associated Kinase 1 (IRAK-1) and IjBa and phosphorylation of p38 mitogen-activated protein kinases (MAPK) and Interferon regulatory factor 3 (IRF3). LL-37 even reduced the expression of IL6, IL8 and CXCL10 which was induced by the TLR3 ligand poly(I:C) (Gorr and Abdolhosseini, 2011).

Yilmaz et al. in 2015 carried out an experiment to test the levels of antimicrobial peptides including LL-37 in patients suffering from diabetes mellitus type 2 and generalized periodontitis. They divided subjects into three groups, diabetics with periodontitis, systemically healthy patients with periodontitis and systematically healthy subjects with healthy periodontium (control). It was observed that the expression of LL-37 was highest in diabetics with periodontitis followed by systemically healthy patients with periodontitis and then the control. It can be concluded that both periodontitis and diabetes causes increase in the level of LL-37. In a study by Turkoglu et al. (2015) stated that there is increase in levels of LL-37 in gingival crevicular fluid following cyclosporine treatment at the gingival overgrowth sites. Takeuchi et al. carried out a study to relate effect of smoking on level of LL-37 in patients with chronic periodontitis. Salivary concentration of LL-37 and cotinine were measured using enzyme-linked immunosorbent assay. The results presented that smoking decreased the level of LL-37 in saliva (Takeuchi et al., 2012). When caries index was related to level of LL-37 in saliva, it was observed that caries index is inversely proportional to concentration of LL-37 i.e. higher the index lower the concentration (Davidopoulou et al., 2012).

The AMPs play a pivotal role as defense molecules in oral environment. This is due to the fact that oral epithelia are exposed to a varied number of microbial pathogens. LL-37 is expressed in high quantity in the epithelium of tongue, buccal mucosa and saliva after inflammatory stimuli though research states that gingival epithelium cells express LL-37 even in absence of inflammation (Turkoglu et al., 2011). There is high level of LL-37 in neutrophils that migrate to gingival sulcus through the junctional epithelium during the inflammatory attack. This protects junctional epithelium and action of AMPs is a pivotal antimicrobial property in the gingival sulcus (Dale, 2003). In the year 2001 Dale et al. stated that the antimicrobial peptides had area specific function and LL-37 was observed to act in the junctional epithelium (Dale et al., 2001). Here it serves as a route for migration of neutrophil from the connective tissue into the gingival crevice (Nakamichi et al., 2014).

Literature suggests that LL-37 has been observed to have bactericidal effects on *Aggregatibacter actinomycetemcomitans* which is an important pathogen in causation of aggressive periodontitis and decrease in the level of LL-37 leads to severe form of periodontitis (Turkoglu et al., 2011). Makeudom et al. claimed that levels of LL-37 are elevated in both chronic as well as aggressive periodontitis but there is not much difference between the levels of LL-37 in both the forms (Makeudom et al., 2014). Puklo et al. (2008) observed elevated levels of LL-37 in patients with aggressive periodontitis and chronic periodontitis when compared to healthy subjects. It was also observed that higher levels of LL-37 was related to periodontopathogens. Turkoglu et al. carried out an experiment in which they evaluated the mutation of CAMP gene encoding LL-37 in patients suffering from different forms of periodontal inflammations. It was noted that there was a significant difference between mutation in the CAMP gene i.e. p.S34N mutation in different forms of periodontitis. The prevalence of p.S34N was much higher in case of aggressive periodontitis than chronic periodontitis or the control group (Turkoglu et al., 2011). These studies suggest that LL-37 has different roles in different forms of periodontitis. Makeudom et al. carried out a study to relate levels of LL-37 and chondroitin sulfate in patients with two forms of periodontitis i.e. aggressive and chronic. It was noticed that the levels of chondroitin sulfate were elevated in both types of periodontitis with no significant difference between the groups. It was also observed that the levels of chondroitin sulfate were correlated with levels of LL-37 in gingival crevicular fluid of patients with chronic periodontitis but not in case of aggressive periodontitis. Thus suggesting that measurement of these two biomarkers might be helpful in differentiating between chronic and aggressive forms of periodontitis (Makeudom et al., 2014).

In 2010, Inomata et al. examined regulatory activity of LL-37 immune responses of human gingival fibroblasts triggered by *Porphyromonas gingivalis* and its components. It was observed that LL-37 exerts a suppressive effect on fibroblasts responses to components of *P. gingivalis* enlisting phenol, water extracts, LPS, lipid A, and fimbriae thus stimulating TLRs (Inomata et al., 2010). TLRs on the other hand initiates intracellular signaling cascade thus resulting in inflammation in the host (Mahanonda and Pichyangkul, 2007). Therefore, it can be suggested that LL-37 exerts an immune-suppressive effect in a paracrine manner on inflammatory responses by *P. gingivalis*. This indicates that *in vivo* excess inflammatory responses induced by *P. gingivalis* in components of periodontium are suppressed by LL-37 (Inomata et al., 2010). Along

with *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* LL-37 has been observed to downregulate the growth of a number of periodontopathogens including *Fusobacterium nucleatum*, *Treponema denticola, Streptococcus gordinii, Streptococcus sanguinis* and *Capnocytophaga* sp.(Greer et al., 2013; Nakamichi et al., 2014).

LL-37 and treatment of periodontitis

In a study synergistic effect of LL-37 and human-beta-defensin-3 as anti-inflammatory was analyzed. The effect was tested on coculture model of gingival epithelial cells and fibroblasts. It was concluded that human-beta-defensin-3 acted in synergy with LL-37 and reduced the secretion of cytokines by LPS stimulated model of gingival epithelial cells and fibroblast. Thus, claiming the use of antimicrobial peptide as an adjunctive therapy for the treatment of periodontitis, especially in the era of antibiotic resistance (Bedran et al., 2014). Bedran et al. in 2015 tested the efficacy of green tea polyphenol epigallocatechin-3-gallate and cranberry proanthocyanidins to act in a synergistic relationship with LL-37 to reduce inflammatory response induced by *A. actinomycetemcomitans* LPS in a coculture model of gingival epithelial cells and fibroblasts. The findings suggested that the combination might be a favorable option as a novel adjunctive therapy for the treatment of periodontitis (Lombardo Bedran et al., 2015). Beves et al. (2008) published a patent for use of LL-37 as a therapeutic agent in the treatment or prophylaxis of cancer, autoimmune diseases, fibrotic diseases, inflammatory diseases including periodontitis, lung diseases, heart and vascular diseases and metabolic diseases. The invention was in the form of a lyophilisate or liquid buffer solution or artificial human milk. The invention was prepared with the idea of balancing over or under activity of biological pathway.

Literature suggests that cathelicidins suppresses osteoclastogenesis induced by receptor activator of NF-κB ligand (RANKL) in humans. It also inhibits osteoclastogenesis in cocultures of mouse osteoblast and bone marrow cells which have been treated with LPS and flagellin (both which promote osteoclastogenesis). They inhibit LPS and flagellin-induced RANKL expression in osteoblasts, LPS and flagellin-induced expression of tumor necrosis factor α thus downturning osteoclastogenesis in alveolar bone of patients suffering from periodontitis (Nakamichi et al., 2014; Guzman-Rodriguez et al., 2015; Oyinloye et al., 2015). Greer et al. (2013) stated that LL-37 contribute to wound healing in the periodontium as well. It promotes epithelial cell migration and epithelial cell differentiation; it shows involvement in keratinocyte migration and proliferation by the induction of Signal Transducer and Activator of Transcription protein.

Degradation of LL-37

Gutner et al. (2009) in a study stated that cysteine proteases Arg-gingipains and Lys-gingipain degrades LL-37 thus protecting *P. gingivalis* in a dose-dependent and heat resistant manner. In a study degradation of LL-37 by proteinases was studied. They added synthetic LL-37 to healthy as well as periodontitis affected gingival crevicular fluid (GCF). The sites were divided into *P. gingivalis* absence (Pg^-) and *P. gingivalis* presence (Pg^+). This was done to clearly distinguish between the effect of presence or absence of *P. gingivalis* on the levels of LL-37. It was concluded that LL-37 present in GCF from Pg^+ sites were degraded much more rapidly than Pg^- sites whereas there was no degradation in the healthy GCF samples (McCrudden et al., 2013). In a study stated that *Tannerella forsythia* expresses karilysin, a metalloprotease. This metalloprotease can inactivate the bactericidal activity of LL-37 in a time- and concentration-dependent manner thus leaving LL-37 inactive (Koziel et al., 2010). Another protease, Mirolase, a subtilisin-like serine protease from *Tannerella forsythia* causes hydrolysis of LL-37. It synergistically with karilysin and gingipain degrades LL-37 thus eliminating it from infected site, thereby disturbing the regulation of inflammation during periodontitis by rendering LL-37 inactive (Carlsson et al., 2006).

LL-37 and syndromes

Papillon–Lefevre syndrome (PLS) is a disease in which features like hyperkeratosis of hands and feet and generalized aggressive periodontitis are observed. This form of periodontitis is present both in the primary as well as the permanent dentition. It is a rare autosomal recessive trait in which 20%-40% cases have parental consanguinity. Other features include calcification of the falx cerebri and the choroid plexus, and retardation of somatic development. There is genetic defect in PLS which has been mapped to chromosome 11q14–q21 involving mutations of cathepsin C thus resulting in 90% reduction in cathepsin C activity (Khan et al., 2012; Shah et al., 2014). In a case report a female patient of PLS, there was lack of LL-37 along with other proteins including serine proteases, elastase, cathepsin G, and proteinase 3 (Sorensen et al., 2014). PLS patients even lack serine protease activity in their neutrophil which is necessary for cathelicidin LL-37 generation from hCAP18 precursor. In a study the mentioned activity and absence of LL-37 in the PLS patients contributing to periodontitis was examined. It was observed that along with absence of LL-37 in PLS patients, there was deficiency of cathepsin C and protease 3 activities. The three reasons all together lead to infection with *A. actinomycetemcomitans* in the patients thus resulting in the development of severe periodontitis (Eick et al., 2014).

Morbus Kostmann is a severe congenital neutropenia which was first observed and defined in descendants of the Kostmann family belonging to northern Sweden. It is an autosomal recessive disorder caused by mutation of a number of genes but one of it's subtype is a dominant disorder. It affects myelopoiesis and leads to severe congenital neutro-

penia. This disorder is different from most of other inherited neutropenias in the sense that they have dominant mutations in the gene for elastase (Putsep et al., 2002). These patients suffer from symptoms of recurrent bacterial infections in the first months of life. The initial bacterial infections observed are of skin, respiratory infections or mucous membrane and may also suffer from septic infections (Carlsson et al., 2006). In a study levels of defensins and LL-37 in patients suffering from morbus Kostmann syndrome were investigated and it was observed that there was complete absence of LL-37 in plasma as well as saliva whereas there was reduction in the level of defensins (Putsep et al., 2002). It was also stated that even after treatment of the disease, periodontitis prevails, even though neutrophil count was normalized. Zetterstrom in 2002 mentioned that the defect in the anti-infectious peptides which prevails even post-treament was the cause of oral inflammation caused by *A. actinomycetescomitans* thus giving rise to imbalance between different oral bacterium and the etiological factors of chronic periodontitis. He even concluded on the fact that in LL-37 and defensins absence skin is unable to degrade *Staphylococcus aureus* (Zetterstrom, 2002).

Haim-Munk syndrome (HMS) has been named after a professor Salim Haim who was a renowned dermatologist. It was observed in a Jewish family in Cochin City in India. HMS is also called keratosis palmoplantaris along with periodontopathia and onychogryposis. The disorder is caused by mutation in the cathepsin C gene mapped to 11q14.2. It is allelic to PLS and juvenile periodontitis, also known as prepubertal periodontitis (Al Aboud and Al Aboud D, 2011). HMS along with PLS is classified as type IV palmoplantar keratoderma (Aswath et al., 2014). The major clinical characteristics are palmoplantar hyperkeratosis, arachnodactyly, severe early onset periodontitis, pes planus, onychogryphosis, and acro-osteolysis (Pahwa et al., 2010). Literature suggest role of LL-37 in occurrence of periodontitis (Chapple, 2009).

Conclusion

From the above discussion, it can be stated that LL-37 plays a crucial role in preventing and treatment of severe form of periodontitis. I would suggest use LL-37 in synergy with other molecules or alone to carry out these functions. I would even propound more *in vivo* and *in vitro* studies so that LL-37 can be used in prevention and treatment of all forms of periodontitis.

Acknowledgments

It was self-funded research and the authors reported no conflict of interest. The author would like to thank Mr. Salil Jain and Mrs. Parul Jain.

Compliance with ethics guidelines

As it is a narrative review there was no requirement of ethical approval or consent letter. There was no reported conflict of interest.

References

Al Aboud K, Al Aboud D (2011). Salim Haim and the syndrome that bears his name. Dermatol Online J, 17: 15

Aswath N, Swamikannu B, Ramakrishnan S N, Shanmugam R, Thomas J, Ramanathan A (2014). Heterozygous Ile453Val codon mutation in exon 7, homozygous single nucleotide polymorphisms in intron 2 and 5 of cathepsin C are associated with Haim-Munk syndrome. Eur J Dent, 8(1): 79–84

Bals R, Wang X, Zasloff M, Wilson J M (1998). The peptide antibiotic LL-37/hCAP-18 is expressed in epithelia of the human lung where it has broadantimicrobial activity at the airway surface. Proc Natl Acad Sci USA, 95(16): 9541–9546

Band V I, Weiss D S (2015). Mechanisms of antimicrobial peptide resistance in Gram-negative bacteria. Antibiotics (Basel), 4(1): 18–41

Bedran T B, Mayer M P, Spolidorio D P, Grenier D (2014). Synergistic anti-inflammatory activity of the antimicrobial peptides human beta-defensin-3 (hBD-3) and cathelicidin (LL-37) in a three-dimensional co-culture model of gingival epithelial cells and fibroblasts. PLoS One, 9(9): e106766

Bevec D, Cavalli F, Cavalli V, Bacher G (2008). Use of peptide ll-37 as a therapeutic agent. U.S. Patent Application 12/677,802, filed September 9

Carlsson G, Andersson M, Putsep K, Garwicz D, Nordenskjold M, Henter J I, Palmblad J, Fadeel B (2006). Kostmann syndrome or infantile genetic agranulocytosis, part one: celebrating 50 years of clinical and basic research on severe congenital neutropenia. Acta Paediatr, 95(12): 1526–1532

Chapple I L (2009). Periodontal diagnosis and treatment–where does the future lie? Periodontol 2000, 51(1): 9–24

Chung W O, Dommisch H, Yin L, Dale B A (2007). Expression of defensins in gingiva and their role in periodontal health and disease. Curr Pharm Des, 13(30): 3073–3083

Dahiya P, Kamal R, Gupta R, Bhardwaj R, Chaudhary K, Kaur S (2013). Reactive oxygen species in periodontitis. J Indian Soc Periodontol, 17(4): 411–416

Dale B A (2003). Periodontal epithelium: a newly recognized role in health and disease. Periodontol 2000, 30(1): 70–78

Dale B A, Kimball J R, Krisanaprakornkit S, Roberts F, Robinovitch M, O'Neal R, Valore E V, Ganz T, Anderson G M, Weinberg A (2001). Localized antimicrobial peptide expression in human gingiva. J Periodontal Res, 36(5): 285–294

Davidopoulou S, Diza E, Menexes G, Kalfas S (2012). Salivary concentration of the antimicrobial peptide LL-37 in children. Arch Oral Biol, 57(7): 865–869

De Yang C Q, Chen Q, Schmidt A P, Anderson G M, Wang J M, Wooters J, Oppenheim J J, Chertov O (2000). LL-37, the neutrophil granule- and epithelial cell-derived cathelicidin, utilizes formyl peptide receptor-like 1(FPRL1) as a receptor to chemoattract human peripheral blood neutrophils, monocytes, and T cells. J Exp Med, 192(7): 1069–1074

Eick S, Puklo M, Adamowicz K, Kantyka T, Hiemstra P, Stennicke H, Guentsch A, Schacher B, Eickholz P, Potempa J (2014). Lack of cathelicidin processing in Papillon-Lefèvre syndrome patients reveals essential role of LL-37 inperiodontal homeostasis. Orphanet J Rare Dis, 9(1): 148

Frohm M, Agerberth B, Ahangari G, Stahle-Backdahl M, Liden S, Wigzell H, Gudmundsson G H (1997). The expression of the gene coding for the antibacterial peptide LL-37 is induced in human keratinocytes duringinflammatory disorders. J Biol Chem, 272(24): 15258–15263

Godaly G, Ambite I, Svanborg C (2015). Innate immunity and genetic determinants of urinary tract infection susceptibility. See comment in PubMed Commons below. Curr Opin Infect Dis, 28: 88–96

Gorr S U (2012). Antimicrobial peptides in periodontal innate defense. Front Oral Biol, 15: 84–98

Gorr S U, Abdolhosseini M (2011). Antimicrobial peptides and periodontal disease. J Clin Periodontol, 38(Suppl. 11): 126–141

Greer A, Zenobia C, Darveau R P (2013). Defensins and LL-37: a review of function in the gingival epithelium. Periodontol 2000, 63(1): 67–79

Gronberg A, Mahlapuu M, Stahle M, Whately-Smith C, Rollman O (2014). Treatment with LL-37 is safe and effective in enhancing healing of hard-to-heal venous leg ulcers: a randomized, placebo-controlled clinical trial. Wound Repair Regen, 22(5): 613–621

Gutner M, Chaushu S, Balter D, Bachrach G (2009). Saliva enables the antimicrobial activity of LL-37 in the presence of proteases of *Porphyromonas gingivalis*. Infect Immun, 77(12): 5558–5563

Guzman-Rodriguez J J, Ochoa-Zarzosa A, Lopez-Gomez R, Lopez-Meza J E (2015). Plant antimicrobial peptides as potential anticancer agents. BioMed Res Int, 735087

Guzman-Rodriguez J J, Ochoa-Zarzosa A, Lopez-Gomez R, Lopez-Meza J E (2015). Plant antimicrobial peptides as potential anticancer agents. BioMed Res Int, 735087

Hancock R E, Diamond G (2000). The role of cationic antimicrobial peptides in innate host defences. Trends Microbiol, 8(9): 402–410

Hatipoglu M, Saglam M, Koseoglu S, Koksal E, Keleş A, Esen H H (2015). The effectiveness of *Crataegus orientalis* M Bieber. (Hawthorn) extract administration in preventing alveolar bone loss in rats with experimental periodontitis. PLoS One, 10(6): e0128134

Henzler Wildman K A, Lee D K, Ramamoorthy A (2003). Mechanism of lipid bilayer disruption by human antimicrobial peptide, LL-37. Biochemistry, 42(21): 6545–6558

Inomata M, Into T, Murakami Y (2010). Suppressive effect of the antimicrobial peptide LL-37 on expression of IL-6, IL-8 and CXCL10 induced by *Porphyromonas gingivalis* cells and extracts in human gingival fibroblasts. Eur J Oral Sci, 118(6): 574–581

Into T, Inomata M, Shibata K, Murakami Y (2010). Effect of the antimicrobial peptide LL-37 on Toll-like receptors 2-, 3- and 4-triggered expression of IL-6, IL-8 andCXCL10 in human gingival fibroblasts. Cell Immunol, 264(1): 104–109

Jenssen H, Hamill P, Hancock R E (2006). Peptide antimicrobial agents. Clin Microbiol Rev, 19(3): 491–511

Khan F Y, Jan S M, Mushtaq M (2012). Papillon-Lefèvre syndrome: Case report and review of the literature. J Indian Soc Periodontol, 16 (2): 261–265

Koczulla R, von Degenfeld G, Kupatt C, Krotz F, Zahler S, Gloe T, Issbrucker K, Unterberger P, Zaiou M, Lebherz C, Karl A, Raake P, Pfosser A, Boekstegers P, Welsch U, Hiemstra P S, Vogelmeier C, Gallo R L, Clauss M, Bals R (2003). An angiogenic role for the human peptide antibiotic LL-37/hCAP-18. J Clin Invest, 111(11): 1665–1672

Koziel J, Karim A Y, Przybyszewska K, Ksiazek M, Rapala-Kozik M, Nguyen K A, Potempa J (2010). Proteolytic inactivation of LL-37 by karilysin, a novel virulence mechanism of *Tannerella forsythia*. J Innate Immun, 2(3): 288–293

Leszczynska K, Namiot A, Janmey P A, Bucki R (2010). Modulation of exogenous antibiotic activity by host cathelicidin LL-37. APMIS, 118(11): 830–836

Leszczynska K, Namiot D, Byfield F J, Cruz K, Zendzian-Piotrowska M, Fein D E, Savage P B, Diamond S, McCulloch C A, Janmey P A, Bucki R (2013). Antibacterial activity of the human host defence peptide LL-37 and selected synthetic cationic lipids against bacteria associated with oral and upper respiratory tract infections. J Antimicrob Chemother, 68(3): 610–618

Lombardo Bedran T B, Palomari Spolidorio D, Grenier D (2015). Green tea polyphenol epigallocatechin-3-gallate and cranberry proanthocyanidins act in synergy withcathelicidin (LL-37) to reduce the LPS-induced inflammatory response in a three-dimensional co-culture model ofgingival epithelial cells and fibroblasts. Arch Oral Biol, 60 (6): 845–853

Lopez-Meza J E, Ochoa-Zarzosa A, Barboza-Corona J E, Bideshi D K (2015). Antimicrobial peptides: current and potential applications in biomedical therapies. BioMed Res Int, 367243 doi:10.1155/2015/367243

Mahanonda R, Pichyangkul S (2007). Toll-like receptors and their role in periodontal health and disease. Periodontol 2000, 43(1): 41–55

Makeudom A, Kulpawaropas S, Montreekachon P, Khongkhunthian S, Sastraruji T, Pothacharoen P, Kongtawelert P, Krisanaprakornkit S (2014). Positive correlations between hCAP18/LL-37 and chondroitin sulphate levels in chronic periodontitis. J Clin Periodontol, 41(3): 252–261

McCrudden M T, Orr D F, Yu Y, Coulter W A, Manning G, Irwin C R, Lundy F T (2013). LL-37 in periodontal health and disease and its susceptibility to degradation by proteinases present in gingival crevicular fluid. J Clin Periodontol, 40(10): 933–941

Mysak J, Podzimek S, Sommerova P, Lyuya-Mi Y, Bartova J, Janatova T, Prochazkova J, Duskova J (2014). *Porphyromonas gingivalis*: major periodontopathic pathogen overview. J Immunol Res, 476068

Nakamichi Y, Horibe K, Takahashi N, Udagawa N (2014). Roles of cathelicidins in inflammation and bone loss. Odontology, 102(2): 137–146

Oh D Y, Koh S J (2015). Cross-regulation of innate and adaptive immunity: a new perspective for the pathogenesis of inflammatory bowel disease. Gut Liver, 9(3): 263–264

Oudhoff M J, Blaauboer M E, Nazmi K, Scheres N, Bolscher J G, Veerman E C (2010). The role of salivary histatin and the human cathelicidin LL-37 in wound healing and innate immunity. Biol Chem, 391(5): 541–548

Oyinloye B E, Adenowo A F, Kappo A P (2015). Reactive oxygen species, apoptosis, antimicrobial peptides and human inflammatory diseases. Pharmaceuticals (Basel), 8(2): 151–175

Oyinloye B E, Adenowo A F, Kappo A P (2015). Reactive oxygen species, apoptosis, antimicrobial peptides and human inflammatory diseases. Pharmaceuticals (Basel), 8(2): 151–175

Pahwa P, Lamba A K, Faraz F, Tandon S (2010). Haim-Munk syndrome. J Indian Soc Periodontol, 14(3): 201–203

Panteleev P V, Bolosov I A, Balandin S V, Ovchinnikova T V (2015). Structure and biological functions of β-hairpin antimicrobial Peptides. Acta Naturae, 7: 37–47

Peschel A, Sahl H G (2006). The co-evolution of host cationic antimicrobial peptides and microbial resistance. Nat Rev Microbiol, 4(7): 529–536

Puklo M, Guentsch A, Hiemstra P S, Eick S, Potempa J (2008). 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, 23(4): 328–335

Putsep K, Carlsson G, Boman H G, Andersson M (2002). Deficiency of antibacterial peptides in patients with morbus Kostmann: an observation study. Lancet, 360(9340): 1144–1149

Roberts H M, Ling M R, Insall R, Kalna G, Spengler J, Grant M M, Chapple I L (2015). Impaired neutrophil directional chemotactic accuracy in chronic periodontitis patients. J Clin Periodontol, 42(1): 1–11

Scott M G, Davidson D J, Gold M R, Bowdish D, Hancock R E (2002). The human antimicrobial peptide LL-37 is a multifunctional modulator of innate immune responses. J Immunol, 169(7): 3883–3891

Shah A F, Tangade P, Agarwal S (2014). Papillon-Lefevre syndrome: Reporting consanguinity as a risk factor. Saudi Dent J, 26(3): 126–131

Silva N, Abusleme L, Bravo D, Dutzan N, Garcia-Sesnich J, Vernal R, Hernandez M, Gamonal J (2015). Host response mechanisms in periodontal diseases. J Appl Oral Sci, 23(3): 329–355

Sorensen O E, Clemmensen S N, Dahl S L, Ostergaard O, Heegaard N H, Glenthoj A, Nielsen F C, Borregaard N (2014). Papillon-Lefèvre syndrome patient reveals species-dependent requirements for neutrophil defenses. J Clin Invest, 124(10): 4539–4548

Takeuchi Y, Nagasawa T, Katagiri S, Kitagawara S, Kobayashi H, Koyanagi T, Izumi Y (2012). Salivary levels of antibacterial peptide (LL-37/hCAP-18) and cotinine in patients with chronic periodontitis. J Periodontol, 83(6): 766–772

Tao R, Jurevic R J, Coulton K K, Tsutsui M T, Roberts M C, Kimball J R, Wells N, Berndt J, Dale B A (2005). Salivary antimicrobial peptide expression and dental caries experience in children. Antimicrob Agents Chemother, 49(9): 3883–3888

Turkoglu O, Berdeli A, Emingil G, Atilla G (2011). A novel p.S34N mutation of CAMP gene in patients with periodontal disease. Arch Oral Biol, 56(6): 573–579

Turkoglu O, Emingil G, Kutukçuler N, Atilla G (2009). Gingival crevicular fluid levels of cathelicidin LL-37 and interleukin-18 in patients with chronic periodontitis. J Periodontol, 80(6): 969–976

Turkoglu O, Gurkan A, Emingil G, Afacan B, Toz H, Kutukçuler N, Atilla G (2015). Are antimicrobial peptides related to cyclosporine A-induced gingival overgrowth? Arch Oral Biol, 60(3): 508–515

Turkoglu O, Kandiloglu G, Berdeli A, Emingil G, Atilla G (2011). Antimicrobial peptide hCAP-18/LL-37 protein and mRNA expressions in different periodontal diseases. Oral Dis, 17(1): 60–67

Turner J, Cho Y, Dinh N N, Waring A J, Lehrer R I (1998). Activities of LL-37, a cathelin-associated antimicrobial peptide of human neutrophils. Antimicrob Agents Chemother, 42: 2206–2214

Usher A K, Stockley R A (2013). The link between chronic periodontitis and COPD: a common role for the neutrophil? BMC Med, 11(1): 241

Ximenez-Fyvie L A, Haffajee A D, Socransky S S (2000). Microbial composition of supra- and subgingival plaque in subjects with adult periodontitis. J Clin Periodontol, 27(10): 722–732

Yılmaz D, Guncu GN, Kononen E, Barış E, Çaglayan F, Gursoy UK (2015). Overexpressions of hBD-2, hBD-3, and hCAP18/LL-37 in gingiva of diabetics with periodontitis. Immunobiology, pii: S0171–2985: 30010–3

Zetterstrom R (2002). Kostmann disease-infantile genetic agranulocytosis: historical views and new aspects. Acta Paediatr, 91(12): 1279–1281