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Endogenous antimicrobial factors in the treatment of infectious diseases

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Abstract

Nowadays, a number of antibiotic-resistant bacteria strains is increasing. It is a serious clinical problem and poses a threat to the effectiveness of conventional antibiotic therapy. Thus, scientists are constantly seeking new alternatives for treatment of infectious diseases. There are some natural endogenous factors, which possess antimicrobial activities against a large number of microorganisms, including both Gram-positive and Gram-negative bacteria, viruses and fungi. These factors are present in all eukaryotic organisms and constitute an essential element of their immune system. A large number of in vitro and in vivo models have been used to show the activity of antimicrobial factors, and only few studies have been conducted on people. Results indicate that administration of these molecules is therapeutically beneficial. This review summarizes knowledge of selected endogenous antimicrobial agents, such as cathelicidins, defensins, histatins, lysozyme and lactoferrin. We also discuss potential uses of these factors in the treatment of infectious diseases.

Key words: *lactoferrin (LTF), antimicrobial peptides, histatins, lysozyme, treatment of infectious disease.*

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Introduction

The search for new alternatives to antibiotics becomes unavoidable when we bear in mind the fact that resistance of pathogens towards conventional antibiotics is constantly on the increase. More and more data indicate that there are natural endogenous factors, possessing antimicrobial properties that play an important role in the host defence against pathogens. These factors demonstrate direct activity against microorganisms such as bacteria, viruses, or fungi, and they are able to kill invading microbes. Furthermore, they show a number of immunomodulatory functions that might be involved in the clearance of infection. These factors are found in many cells and tissues and may be produced constitutively or synthesised in response to the presence of pathogens or their products. Hence, the exploration of new solutions with the application of antimicrobial agents for clinical use is still in progress.

Most endogenous factors, characterised by antimicrobial activity, constitute a group of relatively small-sized peptides (antimicrobial peptides – AMPs). Antimicrobial peptides are found in both prokaryotes and eukaryotes, and they are produced by bacteria, invertebrates, and vertebrates. To date, 2706 AMPs have been identified (based on the Antimicrobial Peptide Database). Generally, they consist of 12-50 amino acid residues and they have a positive charge, which is a result of the presence of arginine and lysine residues. For this reason, AMPs are often called cationic peptides. Antimicrobial peptides have an amphipathic structure, enabling them to interact with membranes of a pathogen cell. These peptides are able to destroy the pathogen cell by counteracting with the negatively charged membrane elements of microorganisms. Consequently, it leads to pore formation and membrane permeabilization. Antimicrobial peptides are also capable of penetrating into the pathogen cell. In this way they may inhibit DNA, RNA, and cell wall component synthesis. Nowadays, AMPs are classified into two major and well known groups: cathelicidins and defensins. Apart from cathelicidins and defensins, there are some other important endogenous antimicrobial agents, e.g. histatins, lysozyme, and lactoferrin.

Characteristics of antimicrobial endogenous factors

Cathelicidins are a group of highly differential peptides, which are found in many mammalian species, including rabbits (18-kDa cationic antimicrobial protein, CAP18), cattle (bactenecin), sheep (cyclic dodecapeptide), mice (mCRAMP), rats (rCRAMP), pigs (protegrins), monkeys (rhLL-37), and humans. All cathelicidins have an α-helix linear structure. These peptides show direct antimicrobial activity against a broad spectrum of Gram-positive

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and Gram-negative bacteria, viruses, and fungi. Cathelicidins are synthesised as inactive precursors. The precursor form of cathelicidins consists of highly conserved N-terminal region, catelin domain, and variable C-terminal region. The C-terminal domain is a mature peptide released from the precursor by different serine proteases. So far, the only one human cathelicidin has been identified. It is LL-37 (leucin-leucin 37), which consists of 37 amino acid residues. The gene coding human cathelicidin is located on chromosome 3. This gene is responsible for cathelicidin synthesis and it involves four exons and three introns. It is characterised by average weight of a base pair, which is about 2000. The precursor of LL-37 is called human CAP18 (hCAP18). The cathelicidin LL-37 is expressed in many cell types, and therefore it is present in different tissues and bodily fluids, such as gastric juices, saliva, plasma, and semen. Cathelicidin LL-37 is constitutively produced by mast cells, NK cells, monocytes, and neutrophils, where it is stored within cytoplasmic granules as an inactive pre-pro-peptide. It has been confirmed that induced expression occurs in enterocytes of the intestine, epithelial cells, and keratinocytes. Recent studies imply that LL-37 expression can be regulated by many endogenous factors, including inflammatory cytokines, growth factors, and active form of vitamin D [1, 2].

To date, there is not much data about LL-37 concentration under physiological conditions (Table 1). It is known that in healthy subjects LL-37 concentrations are the following: 30.5 ng/ml in saliva, 27.2 ng/ml in plasma, and 0.039 ng/ml in sputum [3-5]. LL-37 levels in sweat and bronchoalveolar lavage fluid (BAL) of healthy infants are notably higher: 4.47 μg/ml and 4.8 μg/ml, respectively [6]. The sputum LL-37 level in asthmatic patients is estimated to be 0.136 ng/ml, whereas the LL-37 concentration in sputum, obtained from cystic fibrosis patients, is 79.6 pg/ml [5]. The LL-37 concentration in patients with active pulmonary tuberculosis is 49.5 ng/ml [7]. In systemic sclerosis, patients with interstitial lung disease serum demonstrated lower concentration of LL-37 (1.36 mg/ml) than healthy subjects (5.53 ng/ml) [8].

Defensins constitute quite a large and differential group of AMPs, with 3.5-4.5 kDa molecular weight. Defensins contain six cysteine residues, which form three disulphide bridges responsible for stabilisation of the β-sheet structure of the chain. Defensins are classified into three groups: α-defensins, β-defensins, and θ-defensins. This classification is based on the structure of defensin precursors, the length of the amino acids chain, and the location of disulphide bonds. In humans, defensins are present in many cells, such as neutrophils, thrombocytes,

Table 1. Concentrations of antimicrobial factors

Factor	Material	Concentration	
		physiological condition	pathological condition
LL-37	blood	27.2 ng/ml	systemic sclerosis – 1.36 mg/ml [8] tuberculosis – 49.5 ng/ml [7]
	sputum	0.039 ng/ml	asthma – 0.136 ng/ml chronic obstructive pulmonary disease – 0.753 ng/ml cystic fibrosis – 0.79 ng/ml [5]
α-defensin	blood	0.91 ng/ml	atopic dermatitis – 1.41 ng/ml [49] type 1 diabetes – 28.8 ng/ml type 2 diabetes – 29.8 ng/ml [50]
	saliva	246 pg/ml	moderate periodontitis – 628 pg/ml severe periodontitis – 784 pg/ml [51]
	urine	15.7 ng/ml	glomerulonephritis – 21 ng/ml [17]
hBD-2	sputum	69.2 pg/ml	pneumonia – 178 pg/ml [52] diffuse panbronchiolitis – 264 pg/ml [53]
histatin	saliva	50-425 mg/ml	dental caries – 66.8 mg/ml [54] HIV – 7.3 μg/ml [55]
lysozyme	serum	0.5-2.0 μg/ml	ankylosing spondylitis – 14.1 μg/ml Behcet's disease – 14.4 μg/ml syphilis – 13.98 μg/ml tuberculosis – 14.99 μg/ml [56]
lactoferrin	blood	176 ng/ml	neutropenic sepsis – 20 ng/ml non-neutropaenic sepsis – 332 ng/ml [57]
	saliva	51 ng/ml	early childhood caries – 37.9 ng/ml [58]

monocytes, macrophages, mast cells, NK cells, and epithelial cells. α-defensin pre-pro-peptides consist of 90-100 amino acid residues and the precursor containing signal sequence, consisting of 19 amino acid residues, anionic pro-peptide, consisting of five amino acid residues, and the cationic C-terminus domain, which encodes the mature peptide. In humans, α-defensins are subdivided into six different types. Four of them are identified in human neutrophils (HNP-1, HNP-2, HNP-3, and HNP-4). Human neutrophil peptides are synthesised as precursors, activated by proteolytic cleavage. During neutrophil differentiation and maturation, HNP 1-4 precursors are excised by neutrophil elastase or proteinase 3, and then stored in azurophilic granules. α-defensin (or cryptidin) expression has also been found in Paneth cells of the intestinal mucosa (HD-5 and HD-6). Modification of HD-5 occurs in the extracellular space, and it is mediated by a trypsin isoform. It has also been confirmed that α-defensins are found in urogenital epithelial cells. Well-known human β-defensins include hBD-1, hBD-2, hBD-3, and hBD-4. hBD-1 is constitutively expressed by keratinocytes and epithelial cells, but it can also be synthesised by monocytes and dendritic cells in response to activation by lipopolysaccharide (LPS) or pro-inflammatory cytokines. The synthesis of defensins hBD-2-4 in keratinocytes, epithelial cells, monocytes, mast cells, and dendritic cells is induced by pro-inflammatory cytokines, such as tumour necrosis factor (TNF) and interleukin (IL)-1 [9]. Cyclic θ-defensins RTD-1 (rhesus theta defensin 1), RTD-2, and RTD-3 were identified during a study of defensin expression in neutrophils and monocytes of the rhesus monkey (*Macacca mulata*). The θ-defensins are formed by cyclisation of two 76-amino-acid α-defensins in post-translational splicing [10].

The physiological serum concentration of hBD-1 in infants is 18 μg/ml [11], whereas the serum concentration of hBD-1 in adults is 8.85 ng/ml. It should be pointed out that hBD-1 serum concentration is higher in cirrhosis (18.26 ng/ml) [12]. The serum hBD-2 level is 0.67 ng/ml [13]. It is known that in healthy subjects, the sputum hBD-1 concentration is 18.2 ng/ml [14]. HNP 1-3 concentrations in saliva and BAL are 0.8 μg/ml and 268.3 pg/ml, respectively. The level of HNP-1 in the saliva of patients with oral diseases are found to be significantly higher than the physiological level. The concentration of HNP-1 in the saliva of patients with oral lichen planus, leukoplakia, and glossitis, caused by iron deficiency are 8.3 μg/ml, 13.2 μg/ml, and 11.4 μg/ml, respectively [15, 16]. Interestingly, it has been shown that the concentration of defensins in urine is 15.7 ng/ml, but the concentration of defensins in urine of patients with glomerulonephritis is slightly higher (21 ng/ml) [17].

It has been confirmed that histidine-rich peptides in primary structure, known as histatins, also possess antibacterial properties. They contain from 7 to 38 amino acid residues in length. Histatins are produced by cells of parotid and submaxillary glands. To date, several peptides belonging to the histatin group have been identified. But the histatin group consists predominantly of the following: histatin 1 (HST1), histatin 3 (HST3), and histatin 5 (HST5). HST1 and HST3 are products of various genes, but HST5 is a proteolytic cleavage product of HST3. What is more, histatins demonstrate antifungal properties. HST5 is the most active histatin against the yeast *Candida albicans*. Histatins play an important role in the local immune response in the oral cavity. They are found in saliva at a concentration ranging between 50 and 425 mg/ml. Antimicrobial activity is manifested by a reduction of the intracellular ATP by reactive oxygen species, which may induce cell death [18].

Lysozyme is another example of an interesting and widespread AMP, which is one of the better-known natural factors inhibiting bacterial growth. Furthermore, it demonstrates antiviral and antifungal activity. Lysozyme is a hydrolytic enzyme, which is a single peptide chain composed of 129 amino acid residues with a molecular weight of 14.4 kDa. It is found not only in cells such as neutrophils, macrophages, or monocytes, but also in bodily fluids, including serum, saliva, gastric juice, milk, airway mucus secretions, and tears. Human serum lysozyme concentration is about 0.5-2.0 μg/ml, whereas its concentration in tears is 2.0-5.0 μg/ml. Lysozyme mainly destroys Gram-positive bacteria and, to a lesser extent, Gram-negative bacteria. This AMP causes bacterial death by catalytic hydrolysis of their peptidoglycans (PGN). The bond consisting of β-(1,4)-linked N-acetylglucosamine and N-acetylmuramic acid is broken by lysozyme. Disulphide bonds in spatial lysozyme conformation are responsible for its high thermostability [19].

As it was previously defined, lactoferrin is not classified to AMPs, but is instead one of the glycosylated proteins belonging to the transferrin family, with a molecular weight of 80 kDa. Lactoferrin is composed of a single polypeptide chain, which consists of 700 amino acid residues, and it has two homologous lobes: N and C. Each of them has only one binding site, which may bind one Fe^{3+} ion. Lactoferrin plays a crucial role in maintaining iron levels in body cells and fluids, especially in milk. Lactoferrin is synthesised by epithelial cells so it is also detected in other secretions of mucosa, including saliva, tears, and semen as well as nasal, bronchial, and vaginal secretions. In milk and colostrum the lactoferrin concentration can reach a value of 7 mg/ml. Currently, it is known that lactoferrin has bacteriostatic activity by blocking iron sources for microorganisms through storing the iron in tissues. By coming into direct interaction with bacterial surfaces, lactoferrin demonstrates its bactericidal function. With regards to Gram-negative bacteria, lactoferrin interacts with bacterial LPS. The destruction of Gram-positive bacteria starts when fragments of the protein possessing a positive charge combine with the bacterial cell membrane [20].

Endogenous antimicrobial peptides and their analogues as therapeutic agents

It is becoming increasingly evident that natural AMPs, as well as their synthetic analogues, can be effective enough to eliminate pathogens. However, it should be emphasised that the available data concerning the therapeutic capabilities of AMPs are limited and ambiguous. A large number of *in vitro* and *in vivo* models have been used to characterise the activity of AMPs, and only few studies have been conducted on people. AMPs are still being sought and tested, and currently several clinical trials using these peptides are being conducted or have recently been completed.

In the past few years the significance of cathelicidins in pathogen defence was confirmed in clinical studies. Omiganan pentahydrochloride (MBI 226) is a recently described synthetic analogue of bovine cathelicidin, i.e. indolicidin, a peptide originally purified from the cytoplasmic granules of bovine neutrophils. Extensive *in vitro* studies conducted on antimicrobial activity of omiganan show that it is active against many Gram-positive species, such as *Staphylococcus aureus, Enterococcus faecium, Bacillus* sp. and Gram-negative species, e.g. *Escherichia coli* [21], and fungi, e.g. *Candida* sp., too [22]. This peptide has just undergone phase III of clinical trials for the prevention of venous catheter-related bloodstream infections. An application of omiganan 1% gel in an *in vivo* guinea pig skin colonisation model has revealed that the drug has bactericidal and fungicidal properties and is characterised by important activity against a broad spectrum of pathogens, including *S. aureus, Staphylococcus epidermidis*, and *C. albicans.* Moreover, a significant dose-dependent omiganan activity against *S. epidermidis* was confirmed in an *ex vivo* pig skin colonisation model [23], and *in vitro* studies conducted by Dawgul *et al.* demonstrate destruction of *S. epidermidis* biofilm and, to a lesser extent, *E. coli* biofilm, by omiganan [24]. The other synthetic analogue of indolicidin, i.e. MBI 594AN, demonstrates the ability to eradicate *Propionibacterium acnes* strains. Topical administration of 2.5% MBI 594AN diminishes the severity of acne lesions, both of inflammatory and non-inflammatory origin [25].

Pexiganan is a synthetic analogue of an African frog-derived peptide – magainin 2. Pexiganan is the first AMP which was introduced on the market as an anti-infective topical drug for the therapy of diabetic foot ulcers. In phase III of clinical trials, involving 835 patients with infected foot diabetic ulcers, application of topical pexiganan contributed to an improvement in 90% of the patients. Pexiganan demonstrates *in vitro* antibacterial activity against a lot of Gram-positive and Gram-negative bacteria, isolated from an infected foot, such as *Morganella* sp., *Serratia* sp., *Enterococcus faecalis, Proteus mirabilis,* methicillin-resistant *S. aureus* (MRSA) [26]. Moreover, a double-blind randomised controlled trial has demonstrated that pexiganan acetate cream may be as effective as oral ofloxacin, a fluoroquinolone antibiotic class, in promoting clinical improvement, pathogen eradication, and wound healing in mildly infected diabetic ulcers [27]. Interestingly, it has been proven that pexiganan is a valuable factor against parasitic protozoan *Leishmania* sp. An arginine-rich type of pexiganan shows *in vitro* enhanced action against *Leishmania* sp. because it proved to be protease-resistant and it induces apoptosis of promastigote forms [28].

Hou *et al.* [29], in their *in vivo* studies, showed that LL-37 can be effective in the treatment of MRSA-induced pneumonia. A single administration of LL-37 improved histological images of infected mice lungs. Furthermore, expression levels of pro-inflammatory cytokines in the plasma – IL-6 and TNF – were significantly lower in infected mice treated with LL-37 than in untreated ones. Also, Beaumont *et al.* [30] conducted *in vivo* studies that revealed that human cathelicidin may reduce the number of *Pseudomonas aeruginosa* in BAL of infected mice. In turn, Xia *et al*. [31] demonstrated that cathelicidin-BF, isolated from the venom of *Bungarus fasciatus,* is effective in the treatment of *Salmonella enterica* serovar typhimurium infection. Studies with the use of a mouse model revealed that an application of cathelicidin-BF reduces the spread of bacteria to the spleen and liver, as compared with the untreated control group.

So far, there are some data about defensin therapeutic application. α-defensins are shown to be potent particularly against *Clostridium difficile* strains. To be more precise, HNP-1 and HD-5 inhibit *C. difficile* growth *in vitro* [32]. The defensin from the bedbug *Cimex lectularius* is demonstrated to be efficacious against Gram-positive bacteria commonly found on the human skin, such as *S. aureus*, *S. epidermidis*, *Micrococcus luteus*, and *Corynebacterium renale* [33]. Plectasin, the first antimicrobial defensin peptide, isolated from the fungus *Pseudoplectania nigrella*, has potent *in vitro* antimicrobial activity against Gram-positive bacteria, including *Streptococcus pneumoniae* strains resistant to conventional antibiotics. What is more, it is tolerated in high doses and it has appeared to be useful in the treatment of peritonitis and pneumonia in mice [34]. Results of studies on a murine model indicate that the combination of hBD-1 and hBD-2 may be therapeutically effective against salmonellosis [35]. What is interesting, a combination of plant-derived β-defensins, phBD-1, and phBD-2, demonstrates great efficacy with regards to salmonellosis, which was documented in a mouse model [36].

The results of many *in vitro* and *in vivo* studies indicate that lactoferrin acts against a lot of Gram-positive bacteria, such as *Clostridium* sp. and *Bacillus subtilis*, and Gram-negative bacteria, such as *Haemophilus influenzae*, *Listeria monocytogenes, Helicobacter pylori, Legionella pneumophila,* and *P. aeruginosa.* Moreover, lactoferrin is also known for having antifungal and antiparasitic ac-

tivities [20]. A clinical trial conducted on a mouse model showed an antimicrobial effect of human lactoferrin, which decreases bacteraemia generated by *Streptococcus mutans*. Lactoferrin exerts an anti-inflammatory effect as it decreases plasma levels of pro-inflammatory cytokines, interferon (IFN)-γ, and TNF and C-reactive protein (CRP), too [37].

It should be emphasised that lactoferrin shows antiviral activity, which is demonstrated in the inhibition of poliovirus type 1, cytomegalovirus, rotavirus viral replication, and blockage of viral access to the host cells. What is important, the proteolytic cleavage of lactoferrin by pepsin leads to production of its derivative – lactoferricin, which is also known as an antiviral factor. *In vivo* studies on mice showed that this antimicrobial agent is effective in inhibition of *Herpes simplex* virus type 2 (HSV-2) infection. The *in vitro* antiviral properties of lactoferrin and lactoferricin have been also documented in the treatment of HSV-2 infection [38]. The prophylactic effect of lactoferrin was also tested. Namely, it has been used as an effective adjuvant for the BCG vaccine. Lactoferrin enhances the efficacy of this vaccine through induction of Th1 immune responses [39].

Remarkably interesting *in vivo* studies have been conducted by Teenback *et al.* [40]. They showed a positive effect of lysozyme in the treatment of experimentally generated *P. aeruginosa* lung infection. Treatment with lysozyme decreases levels of cytokine KC (keratinocyte-derived cytokine) and TNF in BAL. It has been confirmed in *in vivo* studies that lysozome is an antimicrobial agent against *L. monocytogenes*. It appears to reduce levels of inflammatory markers, such as CRP and fibrinogen, and the levels of pro-inflammatory cytokines: IL-6, IL-8, IFN-γ, and TNF. It should be emphasised that lysozyme exhibits efficient bactericidal activity at the time of bacterial inoculation or five days later [41].

Lysozyme complexes with other components may also be a great alternative for antibiotic therapy against various bacteria. *In vitro* studies show that such complexes possess antimicrobial activity, which is aimed against some Gram-positive and Gram-negative bacteria. For example, a synthetic complex consists of equine lysozyme and oleic acid (ELOA). It shows a bactericidal effect by accumulating at the cell membrane of *S. pneumoniae*. Such accumulation leads to irreparable depolarisation of membranes and subsequent cell bursting. ELOA is produced from two, easily accessible constituents, so there is a strong likelihood that it will be a novel drug against *S. pneumoniae* infection, which, importantly, will not cause any side-effects [42]. Lysozyme attached to ZnO nanoparticle is another complex. The synergistic effect of lysozyme and ZnO conjugate increases antimicrobial activity against *E. coli* and *S. aureus* [43].

Polysaccharides of *Porphyromonas gingivalis* are able to induce fibroblast apoptosis. Hence, *P. gingivalis* infection is responsible for tissue destruction in periodontitis. *In vitro* studies conducted by Imatani *et al.* [44] indicate that salivary histatin is an important agent that protects against virulence factors of periodontopathic bacteria. Thus, HST5 decreases induction of fibroblast apoptosis caused by *P. gingivalis*. In *in vivo* studies, Cirioni *et al.* [45] showed the effectiveness of treatment of *P. aeruginosa* infection with P-113D, a human histatin-derived synthetic peptide. The studies demonstrate the therapeutic efficacy in various rat models of *P. aeruginosa* infection, caecal ligation, and puncture. The studies also confirmed a decrease in endotoxin levels and a considerable reduction of plasma concentration of TNF after a single application of P-113D. Furthermore, shorter peptide derived from HST5 exhibits significant bactericidal activity as well. Homodimerisation of histatin-derived peptides improves *in vitro* activity against *S. aureus* [46].

Extensive studies were conducted to analyse the antifungal activity of histatin. Genetically engineered HST3 constructs with one, two, three, or four antifungal domain copies show more important, amplified activity against *C. albicans* than normal HST3. These observations indicate a biological advantage and potential effectiveness of HST3 variants in the treatment of cumbersome and hard-to-treat candidiasis [47]. Tati *et al.* stated that conjugate consisting of polyamine spermidine, linked to the active fragment of HST5 (Hst 5_{4-15}-Spd), is more effective *in vitro* than HST5 itself in killing *C. albicans* and *Candida glabrata* in both biofilm and planktonic cells. Furthermore, the effect of Hst 5_{4-15}-Spd for topical application was tested on an immunocompromised mouse model with oropharyngeal candidiasis. The *in vivo* studies point out that Hst 5_{4-15}-Spd causes considerable reduction of white lesions caused by *C. albicans* in tongue tissues [48].

Conclusions

The increasing number of antibiotic-resistant bacteria strains is a serious clinical problem, which poses a threat to the effectiveness of conventional therapy. In most cases this antibiotic resistance is as a result of overuse and improper use of this drug class. It should be emphasised that antibiotics can cause many side effects, such as hepatotoxicity and nephrotoxicity symptoms, as well as allergic reactions. The above problems have encouraged researchers to seek new alternatives that could be used in the therapies of infectious diseases. Undoubtedly, natural antimicrobial factors, including AMPs, can be promising substitutes. Endogenous antimicrobial factors have a lot of potential applications against pathogens, which was confirmed in *in vitro* and *in vivo* studies. More and more data indicate that they can also be used in clinical practice. It should be stressed that AMPs are considered safer than antibiotics, because they are natural molecules found in all eukaryotic organisms. Moreover, a lack of bacterial resistance

to AMPs is also an advantage. Therefore, knowledge of the biological aspects of AMP may contribute to effective treatment of many diseases and also to their prevention. Potential alternative for antibiotics may be human cathelicidin LL-37, α-defensins: HNP-1 and HD-5, and β-defensins: hBD-1 and hBD-2. Histatins, lysozyme, and lactoferrin are also promising agents in treating infectious diseases. Although many studies indicate that administration of AMPs is therapeutically beneficial, further studies on the application potential in humans are required.

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