Review

Istanbul J Pharm 47 (2): 72-76
DOI: 10.5152/IstanbulJPharm.2017.0012

Antimicrobial peptides: Coming to the end of antibiotic era, the most promising agents

Sibel Döşler
Department of Pharmaceutical Microbiology, Faculty of Pharmacy, İstanbul University, 34116, İstanbul-Turkey

Cite this article as: Döşler S (2017). Antimicrobial peptides: Coming to the end of antibiotic era, the most promising agents. Istanbul J Pharm 47 (2): 72-76.

ABSTRACT

Recently, because of the rising in multidrug resistance from infectious agents, there is a prompted interest for the development of new antimicrobial agents and new therapeutic strategies to combat the infections caused by the resistant bacteria. Among them, the natural bactericidal compounds, such as antimicrobial cationic peptides (AMPs) seems very promising agents. AMPs are the important component of the innate immune response to the surrounding microorganisms. This substances which can be isolated from most of the living organisms, have various activity like broad spectrum antibacterial, antifungal, antiviral, and antiprotozoal. However there are some resistance mechanisms that affects the AMPs, because of the rapid action and existing more than one mechanism of action, development of resistance to AMPs is quite rare. Due to their many advantages and characteristics, AMPs looks like a good candidate for being a new generation, active antimicrobial agent for antimicrobial chemotherapy against especially multi drug resistant bacteria and biofilms, either alone or in combination.

Keywords: Antimicrobial peptides, antibiotic, resistance

INTRODUCTION

The misuse of antibiotics which are the main forces in antimicrobial therapy has led to the development of widespread resistance in microorganisms. Especially the nosocomial infections are caused by the Gram positive or Gram negative pathogens which have increased antibiotic resistance in intensive care units (Akova 2016; Rosenrhal et al. 2016). While some microorganisms are resistant to only one antimicrobial agent, many of them developed the resistance to multiple antimicrobials, so they called multidrug-resistant (MDR) strains. Infections caused by the MDR bacteria are generally not respond to antimicrobial therapy and they comprises a major risk for the mortality. Worse still, sometimes MDR microorganisms become resistant to all available antibiotics, named "pan-resistant organisms", and they could not treated with any single agent (Giamarellon 2010; Naim et al. 2016).

World Health Organization (WHO), had taken an extensive interest for that problem and published a report named "Antimicrobial resistance: Global report on surveillance 2014" to capture the attractions for antimicrobial resistance (WHO 2014). Then the "global action plan on antimicrobial resistance" was composed in 2015, by WHO as a World Health Assembly documents. That document outlines five objectives including improving the awareness and understandings, strengthening the knowledges and evidences, reducing the incidence of infections, optimizing the antimicrobial usage, and increasing the investment in new medicines (WHO 2015).

While combating the infectious diseases, there is conspicuous decrease in existing antibiotics, and as indicated by the WHO, finding of the alternative antimicrobial agents which have a new mechanism of action is very crucial. Antimicrobial activities of natural substances are always known, and there is a reinterest for their potential usages due to the rise of multidrug resistance in a variety of bacteria. Among them antimicrobial cationic peptides (AMPs) seems very promising antibacterial agents to controlling the resistant bacterial infections Donadio et al. 2010).

Address for Correspondence :
Sibel Döşler, e-mail: sibel.dosler@istanbul.edu.tr

Received: 07.08.2017
Accepted: 22.08.2017

This substances which, have AMPs are very prevalent in nature as important component of the innate immune response to the surrounding microorganisms, and they can be isolated from most of the living organisms such as insects, plants, microorganisms, mammals or non-mammalian vertebrates. AMPs have rapid action and various activity like broad spectrum antibacterial, antifungal, antiviral, and antiprotozoal (Hancock and Chapple 1999; Otvos 2005).

Structure of AMPs

AMPs are generally relatively short molecules, including 10–100 amino-acid residues display an positive net charge ranging from +2 to +11, and containing an amphiphilic and hydrophobic residues (in general 50%) (Hancock and Sahl 2006). Due to the increasing number of natural, semi-synthetic or synthetic AMPs, there are several databases are exist for today, which manage information and conduct peptide analysis (Wang 2015). As shown in Figure 1, despite their similar general physical properties, AMPs are classified based on the composition of their amino-acid, size and conformational secondary structures into major groups including peptides with β-strands, amphipathic α-helices, loop structure, and extended structures. Most of the AMPs are belongs to the first two categories (Hancock 2001; Jenssen et al. 2006).

Among AMPs, the most studied ones are colistin, melittin, indolicidin, nisin, CAMA, defensins, protegrins, magainins, etc. Colistin is a non-ribosomally synthesized AMP which is used as a prodrug as the methanesulfonic acid derivative of polymyxin E from ***Bacillus polymyxa*** var ***colistinus,*** and it's bactericidal to Gram negative bacteria especially ***Pseudomonas aeruginosa*** due to a detergent-like mechanism (Bechinger and Lohner 2006). Indolicidin is a haemolytic and antimicrobial peptide isolated from bovine neutrophils. It has a 13 tridecapeptide amide and an extremely high tryptophan content corresponding to its wide range of antimicrobial activities (Selsted et al. 1992). Nisin is an important bacteriocin AMP and one of the most studied lantibiotic which has a 34 amino acid including lanthionine and methyl-lanthionine. It is isolated from the bacteria ***Lactococcus lactis***, and shows rapid bactericidal effects against Gram-positive bacteria with no discrimination between multidrug resistant or sensitive pathogens due to its' dual mode of action against bacterial cell membranes (Willey and Van der Donk 2007). Melittin is a main toxic element of the honey bee venom, and an active AMP against Gram positive and Gram negative bacteria. It is known as a hemolytic peptide which have 26 amino acid and amphipathic α-helices (Raghuraman and Chattopadyay 2007). Because of the toxic characters of some effective AMPs, hybride peptides such as CAMA (Cecropin (1-7)-melittin A (2-9) amide) are designed for increasing the antimicrobial activity while decreasing toxicity. CAMA included the some amino acid regions of cecropin-A and melittin and is very active against Gram-positive bacteria, forming the ion-permeable channels in lipid membranes (Cao et al. 2010).

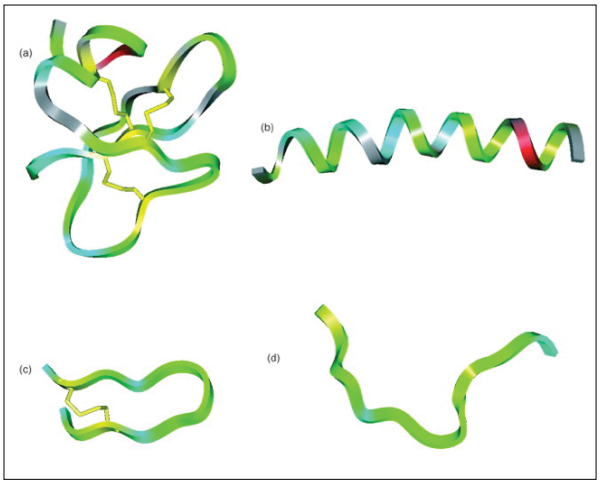

Figure 1. a-d. Structural classes of AMPs. (a) amphiphilic peptides with β-strands, (b) amphipathic α-helices, (c) loop structure, (d) extended structure

AMPs' mechanisms of actions

Most of the active AMPs interact with bacterial membranes, especially the Gram negative's lipopolysaccharide (LPS) layer. They create an ion-permeable channels, and increase membrane permeability to developing the cleavages. While crossing the small molecules into the bacterial cells from that cracks, some antimicrobial agents including the AMPs' are passing through the membrane. To explain how AMPs damages the membranes, as shown in Figure 2, a variety of possible membrane-weakening mechanisms such as toroidal, barrel-stave or carpet models have been maintained. As a result of this interactions, AMPs are taken up by "self-promoted uptake" pathway and they also affect many intracellular mechanisms to toward the bacterial cell death. The explanation both how AMPs bind to and inhibit endotoxins and how they shown the synergistic interactions with conventional antibiotics are existing by this pathway (Steinberg et al. 1997; Yeaman and Yount 2003; Wang et al. 2015).

Besides of the antimicrobial activities, AMPs also has an "enhancer" activity for classical antibiotics. That enhancement in activities of the antibiotics with appropriate AMPs, especially for MDR strains, caused by not only a permeability-increasing, but also the result of an increased access to the intracellular targets. Thus AMPs could be serve as anti-resistance compounds against planktonic cells (Sawyer et al. 1998; McCafferty et al. 1999).

On the other hand, when the planktonic forms of bacteria generally causes an acute infections, biofilm-associated forms cause persistent and chronic infections. A biofilm is a clusters of microorganisms in their extracellular matrix (EPS), on the biotic or abiotic surfaces. The cells growing in a biofilms are physiologically different from their planktonic forms. The bacteria in biofilms become more resistant to antimicrobial agents up to 1000-fold and the host's immune responses. That increased resistance in biofilm forming bacteria, could be explained by the decreased diffusion of antimicrobials, increased activity of multidrug efflux pumps, quorum-sensing systems, antimicrobial tolerance, and slow-growing cells, … etc (Donlan 2001; Høiby et al. 2010).

To prevent or delay the emergence of resistance caused by the biofilm, AMPs might be use in the antimicrobial combi-

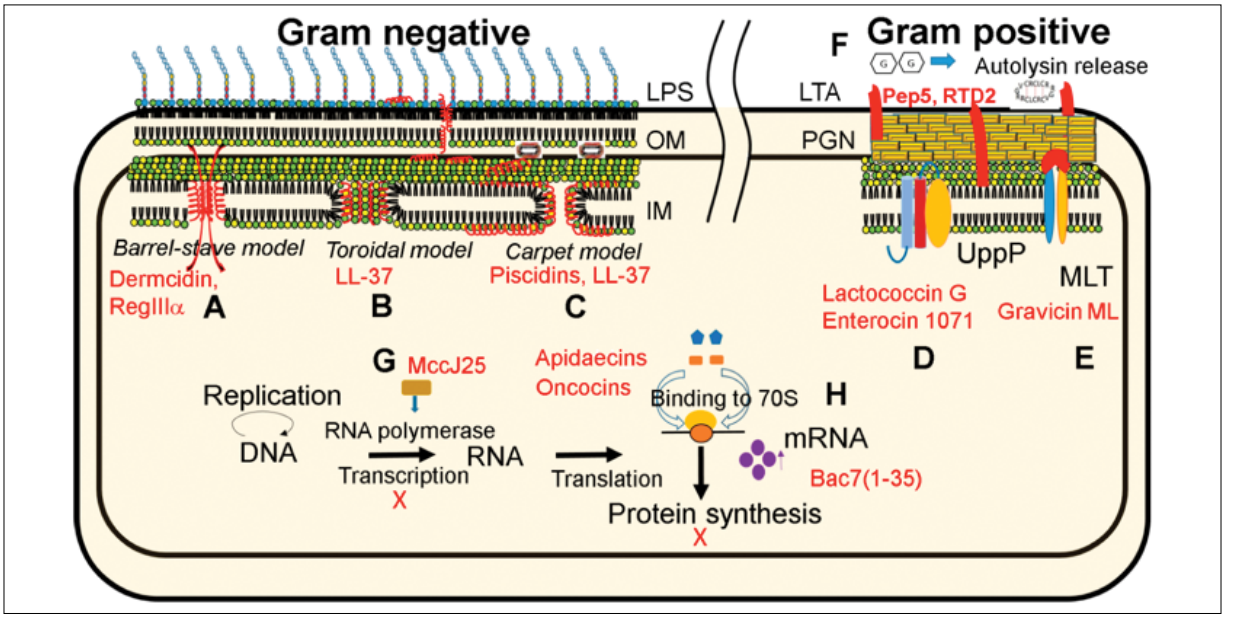

Figure 2. Mechanisms of action of AMPs (Wang et al. 2015).

nations to providing the synergistic interactions. There are many kind of AMPs were found active against bacterial biofilms in that way (Dosler and Mataracı 2013; Dosler and Karaaslan 2014). However, the anti-biofilm activities of AMPs are not completely understood, there are some possible explanations provided by some limited studies. That explanations includes matrix disruption; inhibition of some biofilm-related genes in DNA, blocking the quorum sensing systems, and AMPs dual mode of actioss on both the cytoplasmic membrane and intracellular targets (Hancock and Sahl 2006; Jorge et al. 2012).

AMPs' resistance mechanisms

AMPs are generally not affected by many resistance mechanisms that influenced the antibiotics. Also, there are a few number of resistance mechanisms which can effect antimicrobial cationic peptides and these mechanisms perform independently from others that effect antibiotics. A general mechanism causing resistance bacteria is the association of positively charged molecules onto the cell surface which reduces the interaction and binding of AMPs. The most important resistance mechanisms against AMPs are decreased permeability towards the cells, secretion of proteases, release of AMP degrading enzymes, down-regulation of host responses, active efflux, and alteration of the membrane physiology. In addition, evolutionary changes like mutations that allow innate expression of intrinsic resistance genes, also help for the bacteria to protecting from AMPs,. However there were some mechanisms that affects the AMPs, development of resistance to cationic peptides is quite rare because of the substantial theories such as "the death of the organisms occurs rapidly, hence, it does not leave much time for the bacteria to mutate and divide" and "AMPs possess multiple targets, hence, even if one fails, others remain to take the task forward" (Guilhelmelli et al. 2013; Nawrocki et al. 2014; Yeung et al. 2011).

AMPs' therapeutic potentials

Nowadays, there is a rising interest in potential therapeutic uses of AMPs. Especially linear and circular AMPs are preferable classes, because of the simple molecular structure and easy synthesis, and inherent stability to degrading by proteases, respectively. However the AMPs have desirable facilities for their therapeutic uses, there is some limitations especially lability depends on the environment including the presence of protease, pH change, and etc. for drug development. There are many ongoing studies to overcome the disadvantages that limits the potential clinical applications of AMPs. They generally focused on using the unusual amino acids such as D-forms, acetylation or amidation of the terminal regions, increasing the peptide stability against proteases, immobilization of AMPs on solid materials, using the modern drug delivery systems, such as liposome encapsulation or nanoparticles (Seo et al. 2012; Wang et al. 2015; Mendez-Samperio 2013). Some AMPs in clinical trials for therapeutic usage, are summarized in Table 1.

In conclusion, AMPs have attracted attention as alternative antibiotics due to their desirable properties such as potency, rapid and multiple mechanisms of action, broad spectrum activities, and low potential to induce novel resistance mechanisms, make them excellent prospects. There are a lot of clinical study which about local or systemic infections, showed that the AMPs can contribute to the rapid clearance of microorganisms through direct killing, inhibition of pro-inflammatory mediators such as lipopolysaccharide, and by modulating the inflammatory response to infection. However, in addition to ongoing phase II and phase III clinical trials, major concerns surrounding cationic peptides such as stability, toxicity, immunogenity, pharmacokinetic and pharmacodynamic parameters and antimicrobial activity will prove resolvability and they have to be formulated properly to develop into a drug form. According to those clinical trials,

Table 1. AMPs in commercial development

Peptide	Medical usage	Clinical trials
Pexiganan (MSI-78)	Diabetic foot ulcers	Phase III
Iseganan (IB-367)	Ulcerative oral mucositis	Phase III
Omiganan (MBI-226)	Bloodstream infections	Phase III
RDP58	Inflammatory bowel diseases	Post phase II
MBI-594 AN	Acne infections	Phase II
P113	Oral candidiasis	Phase II
P113D	Lung infections	Phase II
D2A21	Skin infections, burn wounds	Phase II
Neuprex (rBPI21)	Meningococcemia	Phase II
XMP 629	Topical dermal therapy	Phase II
hLF-1-11	Transplantation infections	Phase II
CZEN-002	Vulvo-vaginal candidiasis	Phase II
MX-226	Dermatological infections	Phase II
Glutoxim	Tuberculosis	Phase II
IMX-942	Immunomodulation, fevers in chemotherapy	Phase IA
HB-1345	Acne	Pre Phase I
Plectasin	Systemic anti Gram positive	Preclinical
HB-107	Wound healing	Preclinical

AMPs seems to be the new and active group of antimicrobial agent, not only as a single agent but also an adjuvant for the treatment of serious infections without a significant resistance problem in the near future (Hancock and Sahl 2006; Yeung et al. 2011; Findlay et al. 2016; Felício et al. 2017; Griffith et al. 2017).

REFERENCES

- Akova M (2016) Epidemiology of antimicrobial resistance in bloodstream infections, *Virulence*, **7:** 252-266. [CrossRef]
- Bechinger B, Lohner K (2006) Detergent-like actions of linear amphipathic cationic antimicrobial peptides, *Biochim Biophys Acta*., **1758:** 1529-1539. [CrossRef]
- Cao Y, Yu RQ, Liu Y, Zhou HX, Song LL, Cao Y, Qiao DR (2010) Design, recombinant expression, and antibacterial activity of the cecropins-melittin hybrid antimicrobial peptides, *Curr. Microbiol.*, **61:** 169-175. [CrossRef]
- Donadio S, Maffioli S, Monciardini P, Sosio M, Jabes D (2010) Antibiotic discovery in the twenty-first century: current trends and future perspectives, *J Antibiot.*, **63:** 423-430. [CrossRef]
- Donlan RM (2001) Biofilm formation: a clinically relevant microbiological process, *Clin Infect Dis.*, **33:** 1387–1392. [CrossRef]
- Dosler S, Karaaslan E (2014) Inhibition and destruction of *Pseudomonas aeruginosa* biofilms by antibiotics and antimicrobial peptides, *Peptides*, **63:** 32-37. [CrossRef]
- Dosler S, Mataraci E (2013) In vitro pharmacokinetics of antimicrobial cationic peptides alone and in combination with antibiotics against methicillin resistant *Staphylococcus aureus* biofilms, *Peptides*, **49:** 53-58. [CrossRef]
- Felício MR, Silva ON, Gonçalves S, Santos NC, Franco OL (2017) Peptides with dual antimicrobial and anticancer activities, *Front Chem*, **5:** 1-9. [CrossRef]
- Findlay F, Proudfoot L, Stevens C, Barlow PG (2016) Cationic host defense peptides; novel antimicrobial therapeutics against Category A pathogens and emerging infections, *Pathog Glob Health*, **110:** 137-147. [CrossRef]
- Giamarellou H (2010) Multidrug-resistant gram-negative bacteria: how to treat and for how long, *International Journal of Antimicrobial Agents*, **36:** S50–S54. [CrossRef]
- Griffith GL, Kasus-Jacobi A, Pereira HA (2017) Bioactive antimicrobial peptides as therapeutics for corneal wounds and infections, *Adv Wound Care (New Rochelle)*, **6:** 175-190. [CrossRef]
- Guilhelmelli F, Vilela N, Albuquerque P, Derengowski Lda S, Silva-Pereira I, Kyaw CM (2013) Antibiotic development challenges: the various mechanisms of action of antimicrobial peptides of bacterial resistance, *Front Microbiol*, **4:** 1-12. [CrossRef]
- Hancock RE (2001) Cationic peptides: effectors in innate immunity and novel antimicrobials, *Lancet Infect Dis*, **1:** 156-164. [CrossRef]
- Hancock RE, Sahl HG (2006) Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies, *Nat. Biotechnol*, **24:** 1551-1557. [CrossRef]
- Hancock RE., Chapple DS (1999) Peptide antibiotics, *Antimicrob Agents Chemother.*, **43:** 1317-1323.
- Høiby N, Bjarnsholt T, Givskov M (2010) Antibiotic resistance of bacterial biofilms, *Int L Antimicrob Agents*, **35:** 322-332. [CrossRef]
- Jenssen H, Hamill P, Hancock RE (2006) Peptide antimicrobial agents, *Clin Microbiol Rev*, **19:** 491-511. [CrossRef]
- Jorge P, Lourenço A, Pereira MO (2012) New trends in peptide-based anti-biofilm strategies: a review of recent achievements and bioinformatic approaches, *Biofouling*, **28:** 1033-1061. [CrossRef]
- McCafferty DG, Cudic P, Yu MK, Behenna DC, Kruger R (1999) Synergy and duality in peptide antibiotic mechanisms, *Curr Opin Chem Biol*, **3:** 672-680. [CrossRef]
- Mendez-Samperio P (2013) Recent advances in the field of antimicrobial peptides in inflammatory diseases, *Adv Biomed Res*, **2**:50-55. [CrossRef]
- Naim H, Rizvi M, Azam M, Gupta R, Taneja N, Shukla I, Khan HM (2017) Alarming emergence, molecular characterization, and outcome of blaNDM-1 in patients infected with multidrug-resistant Gram-negative bacilli in a tertiary care hospital, *J Lab Physicians*, **9:** 170-176. [CrossRef]

- Nawrocki KL, Crispell EK, McBride SM (2014) Antimicrobial Peptide Resistance Mechanisms of Gram-Positive Bacteria, *Antibiotics (Basel)*, **3:** 461–492. [CrossRef]
- Otvos L. Jr (2005) Antibacterial peptides and proteins with multiple cellular targets, *J Peptide Sci*, **11:** 697–706. [CrossRef]
- Raghuraman H, Chattopadyay A (2007) Melittin: a membrane-active peptide with diverse function, *Biosci Rep*, **27:** 189-223. [CrossRef]
- Rosenthal VD, Al-Abdely HM, El-Kholy AA, AlKhawaja SA, Leblebicioglu H, Mehta Y, Rai V, et al (2016) International Nosocomial Infection Control Consortium report, data summary of 50 countries for 2010-2015: Device-associated modüle, *Am J Infect Control*, **44:** 1495-1504. [CrossRef]
- Sawyer JG, Martin NL, Hancock REW (1988) Interaction of macrophage cationic proteins with the outer membrane of *Pseudomonas aeruginosa, Infect Immun*, **56:** 693-698.
- Selsted ME, Novotny MJ, Morris WL, Tang YQ, Smith W, Cullor JS (1992) Indolicidin, a novel bactericidal tridecapeptide amide from neutrophils, *J. Biol. Chem*, **267:** 4292-4295.
- Seo MD, Won HS, Kim JH, Mishig-Ochir T, Lee BJ (2012) Antimicrobial peptides for therapeutic applications: a review, *Molecules*. **17:** 12276-12286. [CrossRef]
- Steinberg DA, Hurst MA, Fujii CA, Kung AH, Ho JF, Cheng FC et al (1997) Protegrin-1: a broad- spectrum, rapidly microbicidal peptide with in vivo activity, *Antimicrob Agents Chemother*, **41:** 1738-1742.
- Wang G, Mishra B, Lau K, Lushnikova T, Golla R, Wang X (2015) Antimicrobial Peptides in 2014, *Pharmaceuticals*, **8:** 123-150. [CrossRef]
- Wang G (2015) Improved methods for classification, prediction, and design of antimicrobial peptides, *Methods Mol Biol*, **1268:** 43-66. [CrossRef]
- Willey JM, Van der Donk WA (2007) Lantibiotics: peptides of diverse structure and function, *Annu. Rev. Microbiol*, **61:** 477–501. [CrossRef]
- World Health Organization (2014) Antimicrobial resistance: global report on surveillance 2014, Geneva, Switzerland: WHO.
- World Health Organization (2015) Antimicrobial resistance. Draft global action plan on antimicrobial resistance, Geneva, Switzerland: WHO.
- Yeaman MR, Yount NY (2003) Mechanisms of antimicrobial peptide action and resistance, *Pharmacol Rev*, **55:** 27-55. [CrossRef]
- Yeung AT, Gellatly SL, Hancock RE (2011) Multifunctional cationic host defence peptides and their clinical applications, *Cell Mol Life Sci*, **68:** 2161-2176. [CrossRef]