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A CONCISE REVIEW ON THE ANTIMICROBIAL PEPTIDES AND THEIR CRITICAL ACTIVITY AGAINST INTRACELLULAR TARGETS OF BACTERIA

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ABSTRACT

Multi-drug resistance, which is the consequence of overusing antibiotics, has been shown to become a common problem in the medical environments. Accordingly, finding a substitute for daily used antibiotics is a topic of interest in medical microbiology and biotechnology. Antimicrobial peptides (AMPs) are among the main candidates for controlling this problem. These peptides are regarded as the critical defensive line in many organisms. These AMPs act as an innate immunity against pathogenic microorganisms; such as bacteria or fungi. AMPs could destroy their target via different methods; including membrane pore-formation or by targeting their intracellular targets and disrupting the normal cellular activity. Some AMPs have the property of targeting constructs like DNA, RNA, protein synthesis and folding and inhibiting cell life activities; such as normal metabolism or cell division. At this study, we reviewed more than 130 papers that were concerning the importance of intracellular targeting AMPs, by searching the valuable data sources such as PubMed, Scopus, and Web of Science. These AMPs can be considered as one of the possible options to improve the treatment of infected patients. In this review, it was aimed to discuss the activity of intracellular AMPs and provide an outlook for future studies.

Keywords: Antimicrobial peptides, Intracellular targets, Multi-drug resistance, bacterial infection

INTRODUCTION

The increased use of antibiotics for humans and animal husbandry has caused a cycle of resistance to be constantly rotating between other species and humans. Also, the indiscriminate use of antibiotics has made these therapeutic agents even less effective **(Dorado et al. , 2021, Besharati et al. , 2020, McCollum et al. , 2021)**. Bacterial pathogens have shown to become more resistant toward antibiotics; therefore, finding new antimicrobial compounds is necessary to provide an efficient therapy. Antimicrobial peptides (AMP) are one of the main candidates to be considered for therapeutics development against various pathogens **(Moghaddam et al. , 2015)**. It has been indicated that the activity and selectivity of AMPs could be influenced by the different factors; such as cell density and peptide entrapment in the target cells **(Schefter et al. , 2021, Talledo et al. , 2018)**.

Previous studies have shown that cationic and non-cationic peptides found in a variety of organisms, including bacteria, and could act synergistically to improve the immune responses toward infections **(Lei et al. , 2019, Seyfi et al. , 2020)**. AMPs are one of the most important defensive lines of the organisms' immunity and often protect them from microbial pathogens. These peptides have multifunctional influences on the innate immunity and provide antimicrobial effect on a wide range of pathogens; such as bacteria, fungi, and viruses. Their important role as a defensive mechanism has attracted the attention of many scientists who wish to find a more effective therapeutic and better outcome for the infection treatment.

Generally, AMPs are low molecular weight peptides with cationic (in most cases) and amphipathic properties **(Kardani and Bolhassani, 2021, Moravej et al. , 2018)**. So far, many of AMPs have been isolated from bacteria, animals, plants, various vertebrate and invertebrate species. Regarding the AMPs mode of actions, the membrane disruption and intracellular targeting have been investigated and discussed by previous studies **(Nayab et al. , 2022)**.

The activity of AMPs is very critical in a situation where the number and variety of antibiotic-resistant microorganisms has been increased **(Amani et al. , 2015)**. Initially, AMPs affect the cell membrane and afterward, they could also influence the components inside of the cell. Due to the amphipathic identity of AMPs, they first interact electrostatically with the LPS in Gram-negative and the teichoic acid in Gram-positive bacteria via their hydrophilic region, then they penetrate the membrane using the hydrophobic region and form pores that can lead to membrane permeability, which ultimately induces cell destruction. Also, AMPs can affect the intracellular components; such as RNA, DNA, ribosomes, proteins, and chaperones. It is known that some antimicrobial peptides could destroy their targets via different roles, meaning that some of them could affect internal targets and meanwhile cause membrane disruption. In the current review, we aimed to stay focused on AMPs with intracellular activity.

Moreover, it needs to be mentioned that some of these intracellular AMPs could act as multifunctional agents **(Le et al. , 2017b, Madani et al. , 2011, Nicolas, 2009)**. So far many studies have been performed to clarify the targets for AMPs, for example differential gene expression analysis of RNA-Seq data for detecting the internal targets of AMPs **(Mohammadi et al. , 2020)**, yet more in depth investigations are required.

Regarding the AMPs that have been suggested to target DNA, there are some controversy, since the binding of a cationic peptide to anionic nucleic acids is not surprising. Therefore, showing that some peptides associate with DNA is not sufficient to demonstrate that this interaction is responsible for bacterial killing, and it could be just a consequence of the accessibility of DNA **(Snoussi et al. , 2018)**. Accordingly, still far more information is required to exactly and completely make clear their exact activity that provides anti-microbial effect. In addition to affecting various components of the intracellular target, AMPs could inhibit a wide range of disorder causing pathogenic constructs, including the biofilms formation of bacteria, which can increase the drug resistance **(Davarzani et al. , 2021, Duan et al. , 2022, Yasir et al. , 2018)**.

Considering the importance of AMPs against infections, this field is an open area for research and practice. One of the important perspectives for future of AMPs is the application of bioinformatics and biotechnology methods to design and develop new AMPs. In this regard, the study by Madanchi et al., could be named as an example of designing and synthesis of an AMP for medical application. In that study, they introduced novel AMPs, based on truncated rabbit and human CAP18 peptides, and evaluated their action mechanism against Lipopolysaccharide **(Madanchi et al. , 2020a)**. Another study by the same author was focused on designing the novel truncated derivatives based on direct and reverse mirror repeats of first six residues of Caerin 4 antimicrobial peptide and investigated their activity

and toxicity. Their study showed that the site and arrangement of amino acids are crucial for a peptide function. Moreover, GLWQKI sequence is necessary for the antimicrobial role of Caerin 4 antimicrobial peptide family **(Madanchi et al. , 2020b)**.

In the current review, we tried to provide a brief outlook and discuss the importance of antimicrobial peptides and their crucial role to suppress the bacterial infection by disrupting the internal targets. **Figure 1** represents some antimicrobial peptides with their intracellular targets.

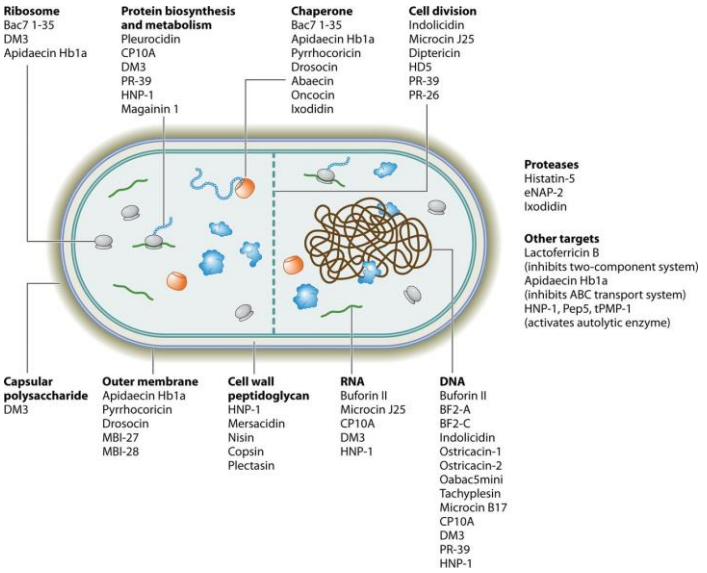

Figure 1. Schematic depiction of some intracellular targets in the bacterial cells which could be affected by AMPs. Taken with permission from Le et al., Intracellular Targeting Mechanisms by Antimicrobial Peptides, Antimicrobial Agents and Chemotherapy, American Society for Microbiology, doi.org/10.1128/AAC.02340-16 **(Le et al. , 2017a)**.

EVIDENCE ACQUISITION

To provide conclusive data for the current review, more than 130 papers were fetched from valuable scientific data resources including Web of Science, Scopus, and Pubmed by searching keywords such as multi-drug resistance, anti-microbial peptides, bacterial infection, and Intracellular targets.

RESULTS

AMPs can inhibit basic processes in the cells; such as nucleic acid synthesis, protein biosynthesis, and cell wall biosynthesis. For example, AMPs like DM3, CP 10A, and Microcin j25 are effective on RNA and DNA. Apidaecin Hb1a peptides are effective on ribosome; Pleurocidin, PR-39 and HNP-1 peptides are effective on protein biosynthesis and metabolism, and Indolicidin and Diptericin peptides are effective on cell division. In this paper, we tried to provide a brief overview of the AMPs that are capable of suppressing bacterial infection by targeting their intracellular components. **Table1** provides some examples regarding the AMPs that target intracellular components and activities.

AMPs with inhibitive effect on DNA, RNA and metabolism

AMPs could attach to the negative charge of the nucleic acids due to their positive charge. This way, they can target these component which eventually causes disrupting their activity. Some of these peptides are discussed in this section.

Buforins are a class of DNA inhibitor peptides. Buforin II (Seq: TRSSRAGLQFPVGRVHRLLRK) is a 21 amino acid peptide with a strong antimicrobial effect on a wide variety of bacteria and fungi, without posing any considerable hemolytic activity. This peptide was initially isolated from the stomach of Asian toad (*Bufogargarizans*) **(Park et al. , 1996)**. These peptides could suppress the cellular activities of bacteria by attaching to their DNA and RNA content and inhibiting the cellular processes by disrupting DNA and RNA activity after penetrating the cell membrane, eventually causing an immediate cell death **(Cardoso et al. , 2019, Park et al. , 1998)**. Buforin II is more active than Buforin I. Buforin I has been shown to induce membrane penetration in *Escherichia coli*. Proline hinge plays an important role in the cellular penetration of Buforin II and determines the penetration efficiency of the peptides into their target bacterial cells. Its removal destroys the ability of a peptide to enter the cells. Degradation of four amino acids from the C-terminus of Buforin II can lead to complete degradation of the antimicrobial effect of these peptides **(Park, Yi, 2000)**. Buforin II can kill *E. coli* without losing the cell membrane and shows to decrease the number of viable cells **(Park, Kim, 1998)**.

Ostricacins are AMP, which could be isolated from ostrich leukocytes. These AMPs have bacteriostatic effect against Gram-negative bacteria via the interactions between the peptide and cytoplasmic processes; such as DNA and protein synthesis and enzymatic activities. These peptides are made of 36-42 amino acids. This class of AMPs cause minor abnormalities in the integrity of the cytoplasmic membranes, allowing them to cross the cytoplasmic membrane, enter the cytoplasm, and interact with the bacterial DNA **(Sugiarto and Yu, 2007)**. By binding to DNA, they could inhibit the activity of DNA in bacterial cells **(Ganz et al. , 1985)**. From this family, Ostricacin-1 (Seq: LFCRKGTCHFGGCPAHLVKVGSCFGFRACCKWPWDV) and Ostricacin-2 (Seq: APGNKAECEREKGYCGFLKCSFPFVVSGKCSRFFFCCKNIW) are two of the known members for their antibacterial effects.

Indolicidin (Seq: ILPWKWPWWPWRR) is a 13 amino acid peptide, derived from the cytoplasmic granules of bovine neutrophils **(Marchand et al. , 2006)**. This peptide belongs to the cathelicidin family, as a tryptophan/proline-rich AMP. This peptide has antibacterial properties against Gram-positive and -negative bacteria. In high concentrations, Indolicidin could increase the permeability of the bacterial cell and exclusively inhibits the DNA biosynthesis by reaching the cytosol **(Hsu et al. , 2005, Subbalakshmi and Sitaram, 1998)**. Earlier studies have shown that this peptide has a high affinity toward ds [AT], ds [CG], and ds [AG] and a low affinity to ds [GT]. Also, the binding affinity of peptides to DNA duplex is higher than to the single-strand DNA **(Fimland, Eijsink, 2002, Ghosh et al. , 2014, Subbalakshmi and Sitaram, 1998)**. Indolicidin is effective on *E. coli* (MIC 12.5 μM), but has a stronger effect on bacteria such as *Staphylococcus aureus* (MIC 0.2–0.4 μM) and *Bacillus cereus* (MIC 0.8 μM) **(Brahma et al. , 2015, Falla et al. , 1996)**.

CP10A (Seq: ILAWKWAWWAWRR**)** is a member of the cathelicidin family, a 13 amino acid peptide derived from indolicidin, which has alanine residues substituted for proline residues with the improvement of antibacterial activity against Gram-positive bacteria. CP10A Inhibits DNA and RNA biosynthesis **(Fimland, Eijsink, 2002, LUO, 2008)**. Studies have shown that in CP10A-treated bacteria, peptides affect thymidine, histidine, and uridine incorporation into DNA and RNA.

Tachyplesin (Seq: KWCFRVCYRGICYRRCR**)** is a cationic peptide, derived from the hemocytes of horseshoe crab (*Tachypleustridentatus*). Tachyplesin has a unique antiparallel β-sheet construct for binding to the DNA duplex. This peptide is made of 17 residues and provides broad-spectrum and potent antimicrobial activity against many bacterial pathogens, especially multidrug-resistant (MDR) isolates in low concentrations. However, the clinical application of this peptide is limited due to its highly hemolytic effects **(Nakamura et al. , 1988, Yonezawa et al. , 1992)**. Tachyplesin I is effective on Gram-positive and -negative bacteria, viruses, and yeasts **(Erdem Büyükkiraz and Kesmen, 2022)**.

As the first step, tachyplesin can interact with lipid membranes and enhance the permeability of bacterial membranes, contributing to bacteria death. In the second step and upon entering the cell and binding to DNA, it could even lead to cell death.

Microcins are very small bacteriocins, composed of relatively few amino acids, produced by bacteria such as *Enterobacteriaceae*. These peptides are secreted under the conditions of inadequate nutrients and have a strong antibacterial effect on closely related organisms. Seven types of microcins including A, B, C, D, E, H, and J are classified according to their cross-safety, genetic and biochemical criteria. Microcin B17 (MccB17, Seq: VGIGGGGGGGGGSCGGQGGGCGGCSNGCSGGNGGSGGSGSHI) is a peptide produced by *E. coli* ***(Novikova et al. , 2007b)***. Microcin B17 inhibits DNA topoisomerase II or gyrase (like quinolone antibiotics) **(Blond et al. , 2000)** and leads to the fragmentation of bacterial chromosomes **(Herrero and Moreno, 1986, Vizán et al. , 1991)**.

Microcin J25 (MccJ25, Seq: VGIGTPIFSYGGGAGHVPEYF) can inhibit transcription by affecting bacterial RNA polymerase. Previous studies have indicated that suppression of transcription is induced through NTP uptake or NTP attachment via RNA polymerase inhibition. Transcription suppression occurs by attachment of MccJ25 within the RNAP secondary channel **(Bayro et al. , 2003, Wang et al. , 2020)**. This peptide could act against a variety of gram-negative bacteria from the Enterobacteriaceae family; including *E. coli*, *Salmonella* sp. and *Shigella* sp. **(Salomon and Farías, 1992)**.

PR-39 (Seq: RRRPRPPYLPRPRPPPFFPPRLPPRIPPGFPPRFPPRFP) is a linear proline-rich cathelicidin, isolated from the porcine small intestine, which has an inhibitory effect on Gram-negative and -positive bacteria. This AMP not only promotes cell death via membrane disruption, but also could translocate across the cell membrane and disrupts some of the cellular activities; including synthesis of DNA and **protein (Agerberth et al. , 1991)**. PR-39 could affect various cellular processes like regulation of apoptosis, promoting the repair of the wound, inhibition of NADPH oxidase activity, induction of angiogenesis, and neutrophil chemotaxis **(Zanetti, 2004)**. All of these multiple actions indicate the active involvement of catalystidine peptides, such as PR-39, in regulation of the antimicrobial host defense **(Gallo et al. , 1994)**. Examination of PR-39 peptide proteomic microarrays has shown that this peptide can inhibit some metabolic pathways; such as coenzyme transport and metabolism, nucleotide transport, and metabolism **(Sang and Blecha, 2009, Zanetti, 2004)**. This peptide is structurally similar to the calcitonin (CGRP) and amylin gene peptides. Also, it has similarities with β-defensins and participates in the mechanisms of bacterial membrane

penetration. This peptide is present in various tissues; such as the adrenal medulla, brain, kidneys, and lungs. This peptide is involved in behavioral and biological reactions, like inhibition of drinking, nutrition, and appetite for salt **(Samson, 1999, Samson et al. , 1998)**.

Table 1 Cellular targets of AMPs and some of the peptides that affect these targets

Intracellular targets	Examples of AMPs	Reference
RNA	DM3 Buforin π HNP-1 CP 10A Microcin j25 BF2-C	**(Friedrich et al. , 2001, Le, Fang, 2017a, Le et al. , 2016, Pardi et al. , 1992, Park et al. , 2000, Yuzenkova et al. , 2002)**
DNA	DM3 CP 10A Microcin j25 Ostricacin-1 Ostricacin-2 PR-39 HNP-1 Buforin π BF2-A Indolicidin Oabac5mini Tachyplesin	**(Hao et al. , 2013, Le, Gudimella, 2016, Pardi, Zhang, 1992, Park, Yi, 2000, Polanco et al. , 2013, Subbalakshmi and Sitaram, 1998, Yuzenkova, Delgado, 2002)**
Ribosome	DM3 Bac7 1-35 Apidaecin Hb1a	**(Benincasa et al. , 2010, Le, Fang, 2017a, Le, Gudimella, 2016)**
Protein biosynthesis and metabolism	CP10A Pleurocidin PR-39 HNP-1 DM3 Magainin 1	**(Fimland et al. , 2002, Le, Gudimella, 2016, Matsuzaki et al. , 1996, Pardi, Zhang, 1992)**
Cell division	Indolicidin HD5 PR-26 PR-39 Diptericin Microcin J25	**(Feng et al. , 2020, Ishikawa et al. , 1992, Yuzenkova, Delgado, 2002)**
Cell wall biosynthesis	Mersacidin Nisin Plectasin	**(Mor et al. , 1991, Water et al. , 2015, Wiedemann et al. , 2001)**
Chaperone	Pyrrhocoricin Bac7 1-35 Drosocin Abaecin Oncocin Ixodidin ApidaecinHb 1a	**(Benincasa, Pelillo, 2010, Knappe et al. , 2011, Le, Fang, 2017a, Lele et al. , 2017)**

Seminalplasmin

(SPLN, Seq: SDEKASPDKTTRFSLSRYAKLANRLANPKLLETFLSKWIGDRGNRSV) is an AMP that inhibits RNA in *E. coli* and RNA polymerase I and II in yeast. This peptide is a 47 residues AMP isolated from bovine seminal fluid. Also, it is active against pathogens; such as bacteria, and fungi **(Shivaji, 1988)**.

AMPs with inhibitory effect on protein synthesis

Some AMPs can suppress protein synthesis in bacteria. For protein synthesis, DNA is first transcribed into mRNA, then mRNA is translated. AMPs can interfere with protein biosynthesis by inhibiting any of these stages. Several AMPs including Drosocin, Oncocin, Ixodidin could target protein synthesis. Some of these types of peptides are discussed below.

Oncocin is a class of proline-rich AMPs analogs from the *oncopeltus* antibacterial peptides that were initially isolated from *Oncopeltu sfasciatus*. This peptide (Seq: VDKPPYLPRPRPPRRIYNR) has a high antibacterial effect on Gram-negative bacteria at a minimal inhibitory concentration (around 1 µg/mL). Oncocin inhibits protein synthesis by binding to the bacterial ribosome **(Mattiuzzo et al. , 2007)**. Also, previous studies have shown that Oncocin can form a complex with DnaK, as a chaperone, and inhibit protein folding **(Agerberth, Lee, 1991)**.

Bactenecin 7 (Bac 7, Seq: RRIRPRPPRLPRPRPRPLPFPRPGPRPIPRPLPFPRPGPRPIPRPLPFPRPGPRPIPRPL**)** is an AMP with 60 residues that has been isolated from large granules of bovine neutrophils. This peptide is rich in proline and arginine. This peptide has been shown effective on Gram-negative bacteria by inhibiting DnaK and ribosomal proteins **(Schnapp et al. , 1996)**.

Microcin C7 (MccC7) is an anti-microbial peptide that suppresses protein expression without influencing DNA replication or RNA transcription **(Garcia-Bustos et al. , 1985, Guijarro et al. , 1995)**. Microscine C7 can enter bacterial cells with the help of membrane transducers; including YejABEF **(Novikova et al. , 2007a)**, then it would be processed by intracellular proteases. These actions eventually cause protein synthesis inhibition by releasing Asp-NH-adenosine monophosphate **(Metlitskaya et al. , 2006, Roush et al. , 2008)**.

AMPs with inhibitory effect on protein-folding and bacterial proteases

Chaperones are a group of proteins that promote the folding of newly expressed polypeptide chains and proteins in the cell, and support the refolding of misfolded proteins and protein trafficking. Chaperones play an important role in preventing the accumulation of proteins. Also, they are involved in the assembly and transport of newly synthesized polypeptides **(Georgopoulos and Welch, 1993)**. Previous studies have declared that some AMPs can interfere with chaperones, which leads to their inactivation and cell lysis. It has been indicated that a group of proline-rich AMPs; including pyrrhocoricin and apidaecin, could have inhibitory activity on bacterial chaperones. Also, some peptides can disrupt the pathogenesis of bacteria by inactivating some secreted proteases **(Le, Fang, 2017a)**.

Pyrrhocoricin is a proline-rich AMP with 20 residues that could be isolated from *Pyrrhocorisapterus* with an inhibitory effect on both Gram-negative and -positive bacteria by interacting with heat shock protein DnaK **(Cociancich et al. , 1994)**. Only the N-terminal region of pyrrhocoricin is required to suppress the ATPase activity of DnaK, while the C-terminal region of this peptide supports its cell entry and suppresses the ATPase activity of the chaperone, thus preventing the chaperone-assisted protein folding.

By inactivation of Dnak, this peptide causes the folding of newly synthesized proteins and refolding of the misfolded proteins **(Cociancich, Dupont, 1994)**. Pyrrhocoricin can also interact with the GroEL chaperone in a non-specific manner, while the interactions with DnaK is specific. The activity of this peptide against Gram-negative *P. aeruginosa*, *E. cloacae*, *E. coli* and some Gram-positive

ones like *B. megaterium* and *M. luteus* has been reported by earlier studies **(Bernini et al. , 1995, Kolda et al. , 2020, Rosetto et al. , 1996)**.

Apidaecins are a group of proline-rich AMPs with 18 to 20 residues expressed by insects **(Casteels and Tempst, 1994)**. They are effective against many Gram-negative bacteria without any significant toxicity on human cells **(Li et al. , 2006, Singh et al. , 2002)**. Apidaecin (Seq: GNNRPVYIPQPRPPHPRI) that could be harvested from lymph fluid of *Apismellifera*, has an inhibitory effect on Gram-negative and -positive bacteria by suppressing DnaK and GroEL **(Otvos et al. , 2000, Troxler et al. , 1990)**. From this family of AMPs, Apidaecins Ia,Ib and II are heat-stable and non-helical ones expressed by *A. mellifera* upon bacterial infection **(Casteels et al. , 1989)**.

Drosocin (Seq: GKPRPYSPRPTSHPRPIRV) is a glycosylated AMP with 19 residues, which is synthesized in the hemolymph of *Drosophila melanogaster* upon the bacterial challenge. Drosocin is an arginine and proline-rich AMP that contains an O-glycosylated threonine residue, with antibacterial effect on Gram-negative bacteria like *S. enterica* subsp. Enterica serovar Typhimurium and serovar Typhi, and *E. coli*, by entering the cells and inhibiting the DnaK chaperone, which could affect the protein folding **(Bulet et al. , 1993, Lele et al. , 2015)**.

Lipid II binding peptides

Despite many antibiotics that show their effect by binding and inhibiting enzymes involved in PGN synthesis, some AMPs attach to the peptidoglycan precursors and interfere with their enzymatic activities; leading to the suppression of peptide expression by sterically suppressing the activity of enzymes **(Mahapatra et al. , 2015)**. Among these targets, Lipid II, which is a membrane-anchored cell-wall precursor, is regarded as a critical target that has been mentioned to have a good potential for suppressing bacterial infection **(Breukink and de Kruijff, 2006)**. In this section, we provide a brief list of some peptides, such as members from lantibiotic, that have proven to be efficient against lipid II.

Mersacidin (Seq: CTFTLPGGGGVCTLTSECIC**)** is a lantibiotic AMP with 20 amino acids. This peptide is ribosomally expressed by *Bacillus* sp. strain HIL Y-85, 54728. Mersacidin is an uncharged molecule forming four intramolecular thioether bridges, which confer a globular shape. This peptide acts by complexing the sugar phosphate head group of lipid II as a peptidoglycan precursor. Accordingly, this peptide could inhibit the transglycosylation reaction of peptidoglycan biosynthesis **(Brötz et al. , 1998, Sass et al. , 2008)**.

Nisin (Seq: IOAIULAAPGAKAGALMGANMKAAAANASIHVUK**)** is a lantibiotic AMP, expressed by a group of bacteria. This compound belongs to *Lactococcus lactis* and suppresses a wide variety of Gram-positive bacteria **(Wiedemann, Breukink, 2001)**. This peptide contains several unusual amino acids, because of the post-translational modifications. Nisin could suppress bacterial growth by making pores on the cell membrane and interrupting cell-wall biosynthesis through specific interaction with lipid II. The N-region of Nisin is very important for attaching to the lipid II, as a cell wall precursor, by electrostatic interactions between negative and positive charges on the cell wall **(AlKhatib et al. , 2014, Najmi et al. , 2020, Yamauchi et al. , 2003).**

This peptide could act against a wide range of Gram-positive bacteria; such as *S.aureus*, *S.pyogenes*, *L. monocytogenes*, and *C.botulinum*, as well as, Gram-negative bacteria including *E.coli*, *Salmonella* enterica subsp. *Enterica* serovar Typhimurium, *Klebsiella* spp., *Aeromonas* spp., *Neisseria* spp., and *Yersinia enterocolitica* ***(Rodriguez, 1996)***.

Plectasin (Seq: GFGCNGPWDEDDMQCHNHCKSIKGYKGGYCAKGGFVCKCY) is composed of 40 residues and is a member of the defensins. This peptide is the first defensin isolated from a fungus, the saprophytic ascomycete *Pseudoplectaniangrella*. This peptide exhibits strong bactericidal effects on several Gram-positive pathogens; such as *Staphylococcus*, *Streptococcus*, *Corynebacterium*, and *Enterococcus*. For example, MIC of this peptide against Gram-positive bacteria like *S. pyogenes* (MIC 0.015 lM), Corynebacterium jeikeium (MIC 0.2 lM), Corynebacterium diphtheriae (MIC 0.5 lM), and MRSA (MIC 0.9 lM) shows a good efficiency and high potential for therapeutic applications **(Mygind et al. , 2005)**.

This peptide acts by coalescing with the pyrophosphate moiety of the cell wall precursor, lipid II; therefore, it interferes with bacterial cell wall biosynthesis. However, plectasin derivatives can be effective on both cell membrane and cytoplasmic targets **(Li et al. , 2017)**.

hBD3 (Seq: GIINTLQKYYCRVRGGRCAVLSCLPKEEQIGKCSTRGRKCCRRKK) or Human β-defensin 3 is a highly charged (+11) cationic AMP, expressed by neutrophils and epithelial cells. This peptide has an antimicrobial effect on a broad range of pathogens; such as multidrug-resistant *S. aureus*. Based on the earlier studies, suppression of cell wall biosynthesis is a major activity of hBD3 by directly interfering with the membrane-bound cell wall precursor lipid II. Increased acylation reduces the bacterial membrane fluidity and inhibits resistance to CAMPs by preventing peptide insertion **(Escobar-Salom et al. , 2022)**.

Lipopolysaccharide-binding AMPs

Inflammation, which could be caused by LPS, is a critical issue along with the infection process **(Johari et al. , 2021, Maghsood et al. , 2020)**. In addition to the broad-spectrum antibacterial effect of AMPs, these peptides are also anti-inflammatory agents. Neutralization of LPS, an endotoxin from Gram-negative bacteria, is an important activity. Some AMPs can penetrate the cell wall barrier by neutralizing LPS to kill the Gram-negative bacteria that can cause infection. Conversely, AMPs could also reduce the inflammatory response by inhibiting the production of inflammatory cytokines by neutralization of LPS **(Sun and Shang, 2015)**. Increased acylation reduces bacterial membrane fluidity and increases the resistance toward cationic antimicrobial peptides (CAMPs) by preventing the peptide insertion. Changes in Lipid A could increase CAMP resistance in bacteria, which has been observed in some gram-negative bacteria, including *P. aeruginosa*. This has been shown to increase the CAMP resistance in a PhoP-dependent manner, in response to low levels of Mg^{2+} **(Ernst et al. , 1999, Guo et al. , 1998)**. PhoP-PhoQ virulence regulators in *Salmonella* bacteria could cause resistance to host cationic CAMP upon infection and Mg^{2+} or Ca^{2+} restriction **(Guo, Lim, 1998)**. CAMP resistance happens because of multifactorial factors. In *Legionella*, PgtE is an outer membrane CAMP protease and waaP is effective in altering the lipopolysaccharide core. In *Salmonella*, CAMP resistance is regulated by the pagP gene with PhoPQ. The PmrAB gene is a two-component system that regulates PmB resistance which increases amino arabinosis **(Guina et al. , 2000, Gunn and Miller, 1996)**.

Cecropins (A, B, and D**)** are linearly positive peptides. Cecropins A and B are isolated from Boman's group from the hemolymph of the giant silk moth. They can lead to cell lysis by forming membrane channels. These AMPs are more effective on Gram-negative bacteria. Cecropin B is 40 times more effective against *E. coli* (MIC 1.7–3.3 μM) than *S. aureus* **(Hancock, 2001, Moore et al. , 1996)**.

MBI-27 (formerly CEME, Seq: KWKLFKKIGIGAVLKVLTTGLPALIS) and **MBI-28** (Seq: KWKLFKKIGIGAVLKVLTTGLPALKLTK) are peptides harvested from parts of silk moth cecropin and bee melittin. They have both anti-endotoxic and anti-bacterial effects against Gram-negative bacteria. However, peptide MBI-28 is more powerful than MBI-27 (Piers et al. , 1994). The binding of AMP to endotoxin and its neutralization prevents the uncontrollable activation of inflammatory responses by reducing the related cytokines; such as IL-1 and TNF **(Crittenden et al. , 2005, Sun and Shang, 2015).**

CAP18 is 18-kDa cationic antimicrobial protein that was originally identified from rabbit leukocytes due to its capacity to bind and inhibit various activities of lipopolysaccharide (LPS). CAP18 (Sun and Shang, 2015) has been reported to have therapeutic potential for conditions related to increased levels of LPS. hCAP18 is found in humans, and its carboxyl-terminal antibacterial peptide, which is known as LL-37, (Seq: L1LGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES37) has been identified to bind LPS and neutralize its biological activities **(Nagaoka et al. , 2002).**

Inhibition of cell-division

FtsZ is one of the main factors of the cell division process in bacteria. This factor is necessary for Z-ring formation in the bacterial cell division. Accordingly, it is regarded as an attractive target for the development of new antibacterial drugs. Suppression of Z-ring and septum formation could lead to bacterial filaments disruption and eventual cell death **(Lutkenhaus, 1990)**. Earlier studies have demonstrated that a series of peptides could cause bacterial cell death via binding to FtsZ. Some of these types of peptides are discussed below:

MciZ is a 40 residues AMP, which acts during spore formation in *B. subtilis*, as an endogenous inhibitor for Z-ring formation in the mother cells, by perturbing the assembly of FtsZ. This peptide binds to the C-terminal polymerization interface of FtsZ and inhibits its polymerization **(Han et al. , 2021, Ray et al. , 2013).**

CRAMP or cathelin-related antimicrobial peptide is a biological construct with 37 amino acid residues, necessary for the host defense response in mammals. CRAMP (16-33) with the sequence GEKLKKIGQKIKNFFQKL could inhibit the bacterial growth of *B. subtilis* and *E. coli* by targeting FtsZ and blocking the formation of Z-ring and FtsZ polymerization **(Ray et al. , 2014)**.

Edeine are polypeptide AMPs that have been harvested from *B. brevis*. Edeine could suppress the growth of *B. subtilis* bacteria by blocking Z-ring formation. Edeine has two subtypes; including edeine A and edeine B as biologically active (A1 and B1), and inactive ones (A2 and B2) **(Shimotohno et al. , 2010)**.

Kil is an AMP composed of 47 amino acid residues. This peptide could be isolated from phage λ, which can prevent cell division in *E. coli* by filamentation of bacterial cells. This peptide interacts with FtsZ-GDP and inhibits the overall GTPase activity, and could block the Z-ring formation **(Chen et al. , 2012, Hernández-Rocamora et al. , 2015)**.

Resistance toward AMPs

Despite the effect of AMPs on microorganisms, some cases indicate resistance to peptides in bacteria, which could happen via various routes such as sensing systems, resistance by proteases, production of external AMP-binding molecules (trapping), modification of membrane and cell wall (surface remolding), capsule

production (exopolymers), modulation of host AMP gene expression and the other possible ways **(Moravej, Moravej, 2018)**.

In this regard, integration of molecules with positive charge on the surface of bacterial cells to reduce the interaction and binding of cationic AMPs is one of the common routes of resistance toward AMPs. Resistance to AMP in Gram-positive bacteria can occur due to the concatenation of positively charged molecules on the cell wall teichoic acids (TA). One example of such a defense is the activity of pagP gene in *Salmonella* that increases resistance toward the antibacterial activity of CAMPs. As an example of such a resistance, the rcp gene in *L. pneumophila* has been determined by Robey et al. **(Robey et al. , 2001)**.

Regarding to quorum sensing methods against AMPs, PhoP-PhoQ virulence regulators in *Salmonella* bacteria causes resistance toward host cationic CAMP **(Guo, Lim, 1998)**. Outer membrane (OM) changes and lipopolysaccharide (LPS) are mechanisms of resistance of gram-negative bacteria to CAMPs **(Madanchi, Ebrahimi Kiasari, 2020a)**. A RosA and RosB proteins efflux pump/potassium antiporter system is a recently discovered mechanism of resistance toward CAMPs in *Yersinia* bacteria **(Bengoechea and Skurnik, 2000)**.

In spite of all the probable microbial defensive mechanisms against AMPs, they seem to be more effective than the regular antibiotics due to their broad-spectrum activity. Another advantage of these AMPs compared to the conventional antibiotics is their immediate onset of killing the targets, along with respectively lower levels of resistance than regular antimicrobial agents **(Moravej, Moravej, 2018)**. In recent years, so many studies have been performed regarding the mechanisms by which the pathogens act against AMPs, and increased knowledge about these activities have been of a great help to the scientists to find a solution for this issue. To overcome such a problem, scientists have come up with solutions; such as insertion or deletion or change of amino acids in the structure of AMPs, modifying biochemical characteristics; such as cationicity, hydrophobicity, and amphipathicity. Also, co-therapy using AMPs and regular antibiotics has showed promising results to reduce the resistance via their synergic effect **(Amani, A Barjini, 2015, Mohammadi Azad et al. , 2017, Mojsoska and Jenssen, 2015, Moravej et al. , 2019)**.

Challenges of AMPs application

Prior to clinical application of AMPs, issues such as toxicity, hemolytic activity, immunogenicity, resistance, and the other potential downsides need to be considered **(Moravej, Moravej, 2018)**. Some peptides could have toxic side effects on mammalian cells in the long-term application, or causing hemolytic activity **(Lei, Sun, 2019, Starr et al. , 2018)**. For example, Indolicidin indicates a broad spectrum of antimicrobial, but has shown some hemolytic activity which rstricts its clinical use **(Mirski et al. , 2018)**. Considering these limitions, scientists have been working on modifying the structure of AMPs through bioinformatics and biotechnology methods, which has indicated to be helpful for both increasing their efficacy and reducing the undesired side effects.

CONCLUSION

The growing resistance toward several antibiotics, including extensively Drug-Resistant (XDR) and MDR, among various bacteria has become a concern in medical society, and this has made the treatment process very difficult. Increased drug resistance is faster than the discovery and approval of new antimicrobial agents. All of these issues has increased the need for the international community to find a new group of antimicrobials. AMPs are a group of the main candidates in the design of the new generation of antimicrobial agents. This has led to an increased proposal to study peptides and discovery of natural AMPs and designing effective treatments for patients. In this review, AMPs with intracellular targets were briefly discussed. These targets include DNA, RNA, protein biosynthesis, cell wall, and some other intracellular components. AMPs usually have several targets, rather than a single target. Despite the efforts to investigate AMPs with intracellularly targets, still more studies are required to be carried out.

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REFERENCES

Agerberth B, Lee JY, Bergman T, Carlquist M, Boman HG, Mutt V, et al. Amino acid sequence of PR-39. Isolation from pig intestine of a new member of the family of proline-arginine-rich antibacterial peptides. Eur J Biochem. 1991;202:849-54. DOI: 10.1111/j.1432-1033.1991.tb16442.x

AlKhatib Z, Lagedroste M, Fey I, Kleinschrodt D, Abts A, Smits SH. Lantibiotic immunity: inhibition of nisin mediated pore formation by NisI. PloS one. 2014;9:e102246. DOI: 10.1371/journal.pone.0102246

Amani J, A Barjini K, M Moghaddam M, Asadi A. In vitro synergistic effect of the CM11 antimicrobial peptide in combination with common antibiotics against clinical isolates of six species of multidrug-resistant pathogenic bacteria. Protein and peptide letters. 2015;22:940-51. DOI: 10.2174/0929866522666150728115439

Bayro MJ, Mukhopadhyay J, Swapna G, Huang JY, Ma L-C, Sineva E, et al. Structure of antibacterial peptide microcin J25: a 21-residue lariat protoknot. Journal of the American Chemical Society. 2003;125:12382-3. DOI: 10.1021/ja036677e

Bengoechea JA, Skurnik M. Temperature-regulated efflux pump/potassium antiporter system mediates resistance to cationic antimicrobial peptides in Yersinia. Molecular microbiology. 2000;37:67-80. DOI: 10.1046/j.1365-2958.2000.01956.x

Benincasa M, Pelillo C, Zorzet S, Garrovo C, Biffi S, Gennaro R, et al. The proline-rich peptide Bac7 (1-35) reduces mortality from Salmonella typhimurium in a mouse model of infection. BMC microbiology. 2010;10:1-8. DOI: 10.1186/1471-2180-10-178

Bernini LF, Telford JL, Marchini D, Manetti AG, Rosetto M, Baldari CT, et al. cDNA Sequence and Expression of the Ceratotoxin Gene Encoding an Antibacterial Sex-specific Peptide from the Medfly Ceratitis capitata (diptera)(∗). Journal of Biological Chemistry. 1995;270:6199-204. DOI: 10.1074/jbc.270.11.6199

Besharati S, Sadeghi A, Ahmadi F, Tajeddin E, Mohammad Salehi R, Fani F, et al. Serogroups, and drug resistance of nontyphoidal Salmonella in symptomatic patients with community-acquired diarrhea and chicken meat samples in Tehran. Iranian journal of veterinary research. 2020;21:269-78.

Blond A, Peduzzi J, Goulard C, Chiuchiolo M, Prigent Y, Barthélémy M, et al. Microcin J25, a 21-residue peptide antibiotic from Escherichia coli. Peptides 1998 Proceedings of the 25th European Peptide Symposium2000. DOI: 10.1046/j.1432-1327.1999.00085.x

Brahma B, Patra MC, Karri S, Chopra M, Mishra P, De BC, et al. Diversity, antimicrobial action and structure-activity relationship of buffalo cathelicidins. PloS one. 2015;10:e0144741. DOI: 10.1371/journal.pone.0144741

Breukink E, de Kruijff B. Lipid II as a target for antibiotics. Nature reviews Drug discovery. 2006;5:321-3. DOI: 10.1038/nrd2004

Brötz H, Bierbaum G, Leopold K, Reynolds PE, Sahl H-G. The lantibiotic mersacidin inhibits peptidoglycan synthesis by targeting lipid II. Antimicrobial agents and chemotherapy. 1998;42:154-60. DOI: 10.1128/AAC.42.1.154

Bulet P, Dimarcq J-L, Hetru C, Lagueux M, Charlet M, Hegy G, et al. A novel inducible antibacterial peptide of Drosophila carries an O-glycosylated substitution. Journal of Biological Chemistry. 1993;268:14893-7.

Cardoso MH, Meneguetti BT, Costa BO, Buccini DF, Oshiro KG, Preza SL, et al. Non-lytic antibacterial peptides that translocate through bacterial membranes to act on intracellular targets. International Journal of Molecular Sciences. 2019;20:4877. DOI: 10.3390/ijms20194877

Casteels P, Ampe C, Jacobs F, Vaeck M, Tempst P. Apidaecins: antibacterial peptides from honeybees. The EMBO journal. 1989;8:2387-91. DOI: 10.1002/j.1460-2075.1989.tb08368.x

Casteels P, Tempst P. Apidaecin-type peptide antibiotics function through a nonporeforming mechanism involving stereospecificity. Biochemical and biophysical research communications. 1994;199:339-45. DOI: 10.1006/bbrc.1994.1234

Chen Y, Milam SL, Erickson HP. SulA inhibits assembly of FtsZ by a simple sequestration mechanism. Biochemistry. 2012;51:3100-9. DOI: 10.1021/bi201669d

Cociancich S, Dupont A, Hegy G, Lanot R, Holder F, Hetru C, et al. Novel inducible antibacterial peptides from a hemipteran insect, the sap-sucking bug Pyrrhocoris apterus. Biochemical Journal. 1994;300:567-75. DOI: 10.1042/bj3000567

Crittenden MR, Thanarajasingam U, Vile RG, Gough MJ. Intratumoral immunotherapy: using the tumour against itself. Immunology. 2005;114:11-22. DOI: 10.1111/j.1365-2567.2004.02001.x

Davarzani F, Saidi N, Besharati S, Saderi H, Rasooli I, Owlia P. Evaluation of antibiotic resistance pattern, alginate and biofilm production in clinical isolates of Pseudomonas aeruginosa. Iranian Journal of Public Health. 2021;50:341. DOI: 10.18502/ijph.v50i2.5349

Dorado G, Gálvez S, Rosales TE, Vásquez VF, Hernández P. Analyzing Modern Biomolecules: The Revolution of Nucleic-Acid Sequencing - Review. Biomolecules. 2021;11. DOI: 10.3390/biom11081111

Duan S, Wu R, Xiong Y-H, Ren H-M, Lei C, Zhao Y-Q, et al. Multifunctional antimicrobial materials: From rational design to biomedical applications. Progress in Materials Science. 2022;125:100887. DOI: 10.1016/j.pmatsci.2021.100887

Erdem Büyükkiraz M, Kesmen Z. Antimicrobial peptides (AMPs): A promising class of antimicrobial compounds. Journal of Applied Microbiology. 2022;132:1573-96. DOI: 10.1111/jam.15314

Ernst R, Yi E, Guo L, Lim K, Burns J, Hackett M, et al. Specific Pseudomonas aeruginosa lipopolysaccharide found in cystic fibrosis airway. Science. 1999;286:1561-5. DOI: 10.1126/science.286.5444.1561

Escobar-Salom M, Torrens G, Jordana-Lluch E, Oliver A, Juan C. Mammals' humoral immune proteins and peptides targeting the bacterial envelope: from natural protection to therapeutic applications against multidrug-resistant Gram-negatives. Biological Reviews. 2022. DOI: 10.1111/brv.12830

Falla TJ, Karunaratne DN, Hancock RE. Mode of action of the antimicrobial peptide indolicidin. Journal of Biological Chemistry. 1996;271:19298-303. DOI: 10.1074/jbc.271.32.19298
Feng S, Zhong Z, Fan J, Li X, Shi D, Jiang L. Upregulated Expression of Intestinal Antimicrobial Peptide HD5 Associated with Renal Function in IgA Nephropathy. Disease markers. 2020;2020. DOI: 10.1155/2020/2078279
Fimland G, Eijsink VG, Nissen-Meyer J. Comparative studies of immunity proteins of pediocin-like bacteriocins. Microbiology. 2002;148:3661-70. DOI: 10.1099/00221287-148-11-3661
Friedrich CL, Rozek A, Patrzykat A, Hancock RE. Structure and mechanism of action of an indolicidin peptide derivative with improved activity against gram-positive bacteria. The Journal of biological chemistry. 2001;276:24015-22. DOI: 10.1074/jbc.M009691200
Gallo RL, Ono M, Povsic T, Page C, Eriksson E, Klagsbrun M, et al. Syndecans, cell surface heparan sulfate proteoglycans, are induced by a proline-rich antimicrobial peptide from wounds. Proceedings of the National Academy of Sciences. 1994;91:11035-9. DOI: 10.1073/pnas.91.23.11035
Ganz T, Selsted ME, Szklarek D, Harwig SS, Daher K, Bainton DF, et al. Defensins. Natural peptide antibiotics of human neutrophils. J Clin Invest. 1985;76:1427-35. DOI: 10.1172/JCI112120
Garcia-Bustos J, Pezzi N, Mendez E. Structure and mode of action of microcin 7, an antibacterial peptide produced by Escherichia coli. Antimicrobial agents and chemotherapy. 1985;27:791-7. DOI: 10.1128/AAC.27.5.791
Georgopoulos C, Welch W. Role of the major heat shock proteins as molecular chaperones. Annual review of cell biology. 1993;9:601-34. DOI: 10.1146/annurev.cb.09.110193.003125
Ghosh A, Kar RK, Jana J, Saha A, Jana B, Krishnamoorthy J, et al. Indolicidin targets duplex DNA: structural and mechanistic insight through a combination of spectroscopy and microscopy. ChemMedChem. 2014;9:2052-8. DOI: 10.1002/cmdc.201402215
Guijarro JI, González-Pastor JE, Baleux F, San Millán JL, Castilla MA, Rico M, et al. Chemical Structure and Translation Inhibition Studies of the Antibiotic Microcin C7 (∗). Journal of Biological Chemistry. 1995;270:23520-32. DOI: 10.1074/jbc.270.40.23520
Guina T, Yi EC, Wang H, Hackett M, Miller SI. A PhoP-regulated outer membrane protease of Salmonella enterica serovar Typhimurium promotes resistance to alpha-helical antimicrobial peptides. Journal of bacteriology. 2000;182:4077-86. DOI: 10.1128/JB.182.14.4077-4086.2000
Gunn JS, Miller SI. PhoP-PhoQ activates transcription of pmrAB, encoding a two-component regulatory system involved in Salmonella typhimurium antimicrobial peptide resistance. Journal of bacteriology. 1996;178:6857-64. DOI: 10.1128/jb.178.23.6857-6864.1996
Guo L, Lim KB, Poduje CM, Daniel M, Gunn JS, Hackett M, et al. Lipid A acylation and bacterial resistance against vertebrate antimicrobial peptides. Cell. 1998;95:189-98. DOI: 10.1016/s0092-8674(00)81750-x
Han H, Wang Z, Li T, Teng D, Mao R, Hao Y, et al. Recent progress of bacterial FtsZ inhibitors with a focus on peptides. The FEBS Journal. 2021;288:1091-106. DOI: 10.1111/febs.15489
Hancock RE. Cationic peptides: effectors in innate immunity and novel antimicrobials. Lancet Infect Dis. 2001;1:156-64. DOI: 10.1016/S1473-3099(01)00092-5
Hao G, Shi Y-H, Tang Y-L, Le G-W. The intracellular mechanism of action on Escherichia coli of BF2-A/C, two analogues of the antimicrobial peptide Buforin 2. Journal of microbiology. 2013;51:200-6. DOI: 10.1007/s12275-013-2441-1
Hernández-Rocamora VM, Alfonso C, Margolin W, Zorrilla S, Rivas G. Evidence that bacteriophage λ Kil peptide inhibits bacterial cell division by disrupting FtsZ protofilaments and sequestering protein subunits. Journal of Biological Chemistry. 2015;290:20325-35. DOI: 10.1074/jbc.M115.653329
Herrero M, Moreno F. Microcin B17 blocks DNA replication and induces the SOS system in Escherichia coli. Microbiology. 1986;132:393-402. DOI: 10.1099/00221287-132-2-393
Hsu C-H, Chen C, Jou M-L, Lee AY-L, Lin Y-C, Yu Y-P, et al. Structural and DNA-binding studies on the bovine antimicrobial peptide, indolicidin: evidence for multiple conformations involved in binding to membranes and DNA. Nucleic acids research. 2005;33:4053-64. DOI: 10.1093/nar/gki725
Ishikawa M, Kubo T, Natori S. Purification and characterization of a diptericin homologue from Sarcophaga peregrina (flesh fly). Biochemical journal. 1992;287:573-8. DOI: 10.1042/bj2870573
Johari B, Maghsood F, Madanchi H, Moradi M, Kadivar M. Investigating the anti-inflammatory effects of high molecular weight secretions from Limosilactobacillus reuteri PTCC 1655 on LPS-stimulated PMA-differentiated THP-1 cells. Journal of applied microbiology. 2021;131:938-48. DOI: 10.1111/jam.14984
Kardani K, Bolhassani A. Antimicrobial/anticancer peptides: Bioactive molecules and therapeutic agents. Immunotherapy. 2021;13:669-84. DOI: 10.2217/imt-2020-0312
Knappe D, Zahn M, Sauer U, Schiffer G, Sträter N, Hoffmann R. Rational design of oncocin derivatives with superior protease stabilities and antibacterial activities based on the high-resolution structure of the oncocin-DnaK complex. ChemBioChem. 2011;12:874-6. DOI: 10.1002/cbic.201000792
Kolda A, Mujakić I, Perić L, Vardić Smrzlić I, Kapetanović D. Microbiological quality assessment of water and fish from Karst Rivers of the Southeast Black Sea Basin (Croatia), and antimicrobial susceptibility of Aeromonas isolates. Current Microbiology. 2020;77:2322-32. DOI: 10.1007/s00284-020-02081-5
Le C-F, Fang C-M, Sekaran SD. Intracellular targeting mechanisms by antimicrobial peptides. Antimicrobial agents and chemotherapy. 2017a;61:e02340-16. DOI: 10.1128/AAC.02340-16
Le C-F, Gudimella R, Razali R, Manikam R, Sekaran SD. Transcriptome analysis of Streptococcus pneumoniae treated with the designed antimicrobial peptides, DM3. Scientific reports. 2016;6:1-9. DOI: 10.1038/srep26828
Lei J, Sun L, Huang S, Zhu C, Li P, He J, et al. The antimicrobial peptides and their potential clinical applications. American journal of translational research. 2019;11:3919.
Lele DS, Kaur G, Thiruvikraman M, Kaur KJ. Comparing naturally occurring glycosylated forms of proline rich antibacterial peptide, Drosocin. Glycoconjugate Journal. 2017;34:613-24. DOI: 10.1007/s10719-017-9781-8
Lele DS, Talat S, Kumari S, Srivastava N, Kaur KJ. Understanding the importance of glycosylated threonine and stereospecific action of Drosocin, a Proline rich antimicrobial peptide. Eur J Med Chem. 2015;92:637-47. DOI: 10.1016/j.ejmech.2015.01.032
Li W-F, Ma G-X, Zhou X-X. Apidaecin-type peptides: biodiversity, structure–function relationships and mode of action. Peptides. 2006;27:2350-9. DOI: 10.1016/j.peptides.2006.03.016
Li Z, Wang X, Wang X, Teng D, Mao R, Hao Y, et al. Research advances on plectasin and its derivatives as new potential antimicrobial candidates. Process Biochemistry. 2017;56:62-70. DOI:10.1016/j.procbio.2017.02.006
LUO Y-PH-w. Fusion Expression of Antimicrobial Peptide CP10A in E. coli. China Biotechnology. 2008;28:105-9.
Lutkenhaus J. Regulation of cell division in E. coli. Trends in Genetics. 1990;6:22-5. DOI: 10.1016/0168-9525(90)90045-8
Madanchi H, Ebrahimi Kiasari R, Seyed Mousavi SJ, Johari B, Shabani AA, Sardari S. Design and synthesis of lipopolysaccharide-binding antimicrobial peptides based on truncated rabbit and human CAP18 peptides and evaluation of their action mechanism. Probiotics and antimicrobial proteins. 2020a;12:1582-93. DOI: 10.1007/s12602-020-09648-5
Madanchi H, Sardari S, Shajiee H, Taherian S, Ashkar M, Johari B, et al. Design of new truncated derivatives based on direct and reverse mirror repeats of first six residues of Caerin 4 antimicrobial peptide and evaluation of their activity and cytotoxicity. Chemical Biology & Drug Design. 2020b;96:801-11. DOI: 10.1111/cbdd.13689
Madani F, Lindberg S, Langel U, Futaki S, Gräslund A. Mechanisms of cellular uptake of cell-penetrating peptides. Journal of biophysics (Hindawi Publishing Corporation : Online). 2011;2011:414729. DOI: 10.1155/2011/414729
Maghsood F, Johari B, Ghahhari NM, Moradi M, Kadivar M. Conditioned medium of lipopolysaccharide-treated embryonic stem cell-derived mesenchymal stem cells modulates in vitro secretion of inflammatory cytokines. Thai Journal of Pharmaceutical Sciences. 2020;44:152-8.
Mahapatra DK, Asati V, Bharti SK. Chalcones and their therapeutic targets for the management of diabetes: structural and pharmacological perspectives. European journal of medicinal chemistry. 2015;92:839-65. DOI: 10.1016/j.ejmech.2015.01.051
Marchand C, Krajewski K, Lee H-F, Antony S, Johnson AA, Amin R, et al. Covalent binding of the natural antimicrobial peptide indolicidin to DNA abasic sites. Nucleic acids research. 2006;34:5157-65. DOI: 10.1093/nar/gkl667
Matsuzaki K, Murase O, Fujii N, Miyajima K. An antimicrobial peptide, magainin 2, induced rapid flip-flop of phospholipids coupled with pore formation and peptide translocation. Biochemistry. 1996;35:11361-8. DOI: 10.1021/bi960016v
Mattiuzzo M, Bandiera A, Gennaro R, Benincasa M, Pacor S, Antcheva N, et al. Role of the Escherichia coli SbmA in the antimicrobial activity of proline-rich peptides. Molecular microbiology. 2007;66:151-63. DOI: 10.1111/j.1365-2958.2007.05903.x
McCollum CR, Levy M, Bertram JR, Nagpal P, Chatterjee A. Photoexcited Quantum Dots as Efficacious and Nontoxic Antibiotics in an Animal Model. ACS Biomaterials Science & Engineering. 2021;7:1863-75. DOI: 10.1021/acsbiomaterials.0c01406
Metlitskaya A, Kazakov T, Kommer A, Pavlova O, Praetorius-Ibba M, Ibba M, et al. Aspartyl-tRNA synthetase is the target of peptide nucleotide antibiotic microcin C. Journal of Biological Chemistry. 2006;281:18033-42. DOI: 10.1074/jbc.M513174200
Mirski T, Niemcewicz M, Bartoszcze M, Gryko R, Michalski A. Utilisation of peptides against microbial infections–a review. Annals of Agricultural and Environmental Medicine. 2018;25. DOI: 10.26444/aaem/74471
Moghaddam MM, Aghamollaei H, Kooshki H, Barjini KA, Mirnejad R, Choopani A. The development of antimicrobial peptides as an approach to prevention of antibiotic resistance. Reviews in Medical Microbiology. 2015;26:98-110. DOI: 10.1097/MRM.0000000000000032
Mohammadi Azad Z, Moravej H, Fasihi-Ramandi M, Masjedian F, Nazari R, Mirnejad R, et al. In vitro synergistic effects of a short cationic peptide and clinically used antibiotics against drug-resistant isolates of Brucella melitensis. J Med Microbiol. 2017;66:919-26. DOI: 10.1099/jmm.0.000524

Mohammadi S, Prokopczuk F, Li X, Taheri-Araghi S. Differential Gene Expression Analysis of RNA-Seq Data for Detecting Internal Targets of Antimicrobial Peptides. Biophysical Journal. 2020;118:383a. DOI: 10.1016/j.bpj.2019.11.2185
Mojsoska B, Jenssen H. Peptides and peptidomimetics for antimicrobial drug design. Pharmaceuticals. 2015;8:366-415. DOI: 10.3390/ph8030366
Moore AJ, Beazley WD, Bibby MC, Devine DA. Antimicrobial activity of cecropins. Journal of Antimicrobial Chemotherapy. 1996;37:1077-89. DOI: 10.1093/jac/37.6.1077
Mor A, Van Huong N, Delfour A, Migliore-Samour D, Nicolas P. Isolation, amino acid sequence and synthesis of dermaseptin, a novel antimicrobial peptide of amphibian skin. Biochemistry. 1991;30:8824-30. DOI: 10.1021/bi00100a014
Moravej H, Fasihi-Ramandi M, Moghaddam MM, Mirnejad R. Cytotoxicity and antibacterial effect of Trp-substituted CM11 cationic peptide against drug-resistant isolates of Brucella melitensis alone and in combination with recommended antibiotics. International Journal of Peptide Research and Therapeutics. 2019;25:235-45. DOI: 10.1007/s10989-017-9658-5
Moravej H, Moravej Z, Yazdanparast M, Heiat M, Mirhosseini A, Moosazadeh Moghaddam M, et al. Antimicrobial peptides: features, action, and their resistance mechanisms in bacteria. Microbial Drug Resistance. 2018;24:747-67. DOI: 10.1089/mdr.2017.0392
Mygind PH, Fischer RL, Schnorr KM, Hansen MT, Sönksen CP, Ludvigsen S, et al. Plectasin is a peptide antibiotic with therapeutic potential from a saprophytic fungus. Nature. 2005;437:975-80. DOI: 10.1038/nature04051
Nagaoka I, Hirota S, Niyonsaba F, Hirata M, Adachi Y, Tamura H, et al. Augmentation of the lipopolysaccharide-neutralizing activities of human cathelicidin CAP18/LL-37-derived antimicrobial peptides by replacement with hydrophobic and cationic amino acid residues. Clinical and Vaccine Immunology. 2002;9:972-82. DOI: 10.1128/cdli.9.5.972-982.2002
Najmi Z, Kumar A, Scalia AC, Cochis A, Obradovic B, Grassi FA, et al. Evaluation of Nisin and LL-37 antimicrobial peptides as tool to preserve articular cartilage healing in a septic environment. Frontiers in Bioengineering and Biotechnology. 2020;8:561. DOI: 10.3389/fbioe.2020.00561
Nakamura T, Furunaka H, Miyata T, Tokunaga F, Muta T, Iwanaga S, et al. Tachyplesin, a class of antimicrobial peptide from the hemocytes of the horseshoe crab (Tachypleus tridentatus). Isolation and chemical structure. The Journal of biological chemistry. 1988;263:16709-13.
Nayab S, Aslam MA, Sajid S, Zafar N, Razaq M, Kanwar R. A Review of Antimicrobial Peptides: Its Function, Mode of Action and Therapeutic Potential. International Journal of Peptide Research and Therapeutics. 2022;28:1-15. DOI: 10.1007/s10989-021-10325-6
Nicolas P. Multifunctional host defense peptides: intracellular-targeting antimicrobial peptides. The FEBS journal. 2009;276:6483-96. DOI: 10.1111/j.1742-4658.2009.07359.x
Novikova M, Metlitskaya A, Datsenko K, Kazakov T, Kazakov A, Wanner B, et al. The Escherichia coli Yej transporter is required for the uptake of translation inhibitor microcin C. Journal of bacteriology. 2007a;189:8361-5. DOI: 10.1128/JB.01028-07
Otvos L, O I, Rogers ME, Consolvo PJ, Condie BA, Lovas S, et al. Interaction between heat shock proteins and antimicrobial peptides. Biochemistry. 2000;39:14150-9. DOI: 10.1021/bi0012843
Pardi A, Zhang XL, Selsted ME, Skalicky JJ, Yip PF. NMR studies of defensin antimicrobial peptides. 2. Three-dimensional structures of rabbit NP-2 and human HNP-1. Biochemistry. 1992;31:11357-64. DOI: 10.1021/bi00161a013
Park CB, Kim HS, Kim SC. Mechanism of action of the antimicrobial peptide buforin II: buforin II kills microorganisms by penetrating the cell membrane and inhibiting cellular functions. Biochemical and biophysical research communications. 1998;244:253-7. DOI: 10.1006/bbrc.1998.8159
Park CB, Kim MS, Kim SC. A novel antimicrobial peptide frombufo bufo gargarizans. Biochemical and biophysical research communications. 1996;218:408-13. DOI: 10.1006/bbrc.1996.0071
Park CB, Yi K-S, Matsuzaki K, Kim MS, Kim SC. Structure–activity analysis of buforin II, a histone H2A-derived antimicrobial peptide: the proline hinge is responsible for the cell-penetrating ability of buforin II. Proceedings of the National Academy of Sciences. 2000;97:8245-50. DOI: 10.1073/pnas.150518097
Piers KL, Brown MH, Hancock R. Improvement of outer membrane-permeabilizing and lipopolysaccharide-binding activities of an antimicrobial cationic peptide by C-terminal modification. Antimicrobial agents and chemotherapy. 1994;38:2311-6. DOI: 10.1128/aac.38.10.2311
Polanco C, Buhse T, Samaniego JL, Castañón-González JA. Detection of selective antibacterial peptides by the Polarity Profile method. Acta Biochim Pol. 2013;60:183-9.
Ray S, Dhaked HPS, Panda D. Antimicrobial peptide CRAMP (16–33) stalls bacterial cytokinesis by inhibiting FtsZ assembly. Biochemistry. 2014;53:6426-9. DOI: 10.1021/bi501115p
Ray S, Kumar A, Panda D. GTP regulates the interaction between MciZ and FtsZ: a possible role of MciZ in bacterial cell division. Biochemistry. 2013;52:392-401. DOI: 10.1021/bi301237m
Robey M, O'Connell W, Cianciotto NP. Identification of Legionella pneumophila rcp, a pagP-like gene that confers resistance to cationic antimicrobial peptides and promotes intracellular infection. Infection and Immunity. 2001;69:4276-86. DOI: 10.1128/IAI.69.7.4276-4286.2001
Rodriguez J. Review: Antimicrobial spectrum, structure, properties and mode of action of nisin, a bacteriocin produced by Lactococcus lactis. Food Science and Technology International. 1996;2:61-8. DOI: 10.1177/10820132960020020
Rosetto M, Manetti AG, Giordano PC, Marri L, Amons R, Baldari CT, et al. Molecular characterization of ceratotoxin C, a novel antibacterial female-specific peptide of the ceratotoxin family from the medfly Ceratitis capitata. European journal of biochemistry. 1996;241:330-7. DOI: 10.1111/j.1432-1033.1996.00330.x
Roush RF, Nolan EM, Löhr F, Walsh CT. Maturation of an Escherichia coli ribosomal peptide antibiotic by ATP-consuming N− P bond formation in microcin C7. Journal of the American Chemical Society. 2008;130:3603-9. DOI: 10.1021/ja7101949
Salomon R, Farías RN. Microcin 25, a novel antimicrobial peptide produced by Escherichia coli. Journal of bacteriology. 1992;174:7428-35. DOI: 10.1128/jb.174.22.7428-7435.1992
Samson WK. ADRENOMEDULLIN AND THE CONTROL OF FLUID AND ELECTROLYTE HOMEOSTASIS. Annual Review of Physiology. 1999;61:363-89. DOI: 10.1146/annurev.physiol.61.1.363
Samson WK, Murphy TC, Resch ZT. Central mechanisms for the hypertensive effects of preproadrenomedullin-derived peptides in conscious rats. The American journal of physiology. 1998;274:R1505-9. DOI: 10.1152/ajpregu.1998.274.5.R1505
Sang Y, Blecha F. Porcine host defense peptides: expanding repertoire and functions. Developmental & Comparative Immunology. 2009;33:334-43. DOI: 10.1016/j.dci.2008.05.006
Sass P, Jansen A, Szekat C, Sass V, Sahl H-G, Bierbaum G. The lantibiotic mersacidin is a strong inducer of the cell wall stress response of Staphylococcus aureus. BMC Microbiology. 2008;8:186. DOI: 10.1186/1471-2180-8-186
Schefter BR, Nourbakhsh S, Taheri-Araghi S, Ha B-Y. Modeling Cell Selectivity of Antimicrobial Peptides: How Is the Selectivity Influenced by Intracellular Peptide Uptake and Cell Density. Frontiers in Medical Technology. 2021;3:626481. DOI: 10.3389/fmedt.2021.626481
Schnapp D, Kemp GD, Smith VJ. Purification and characterization of a proline-rich antibacterial peptide, with sequence similarity to bactenecin-7, from the haemocytes of the shore crab, Carcinus maenas. European Journal of biochemistry. 1996;240:532-9. DOI: 10.1111/j.1432-1033.1996.0532h.x
Seyfi R, Kahaki FA, Ebrahimi T, Montazersaheb S, Eyvazi S, Babaeipour V, et al. Antimicrobial peptides (AMPs): roles, functions and mechanism of action. International Journal of Peptide Research and Therapeutics. 2020;26:1451-63. DOI: 10.1007/s10989-019-09946-9
Shimotohno KW, Kawamura F, Natori Y, Nanamiya H, Magae J, Ogata H, et al. Inhibition of septation in Bacillus subtilis by a peptide antibiotic, edeine B1. Biological and Pharmaceutical Bulletin. 2010;33:568-71. DOI: 10.1248/bpb.33.568
Shivaji S. Seminalplasmin: a protein with many biological properties. Bioscience reports. 1988;8:609-18. DOI: 10.1007/BF01117340
Singh PK, Parsek MR, Greenberg EP, Welsh MJ. A component of innate immunity prevents bacterial biofilm development. Nature. 2002;417:552-5. DOI: 10.1038/417552a
Snoussi M, Talledo JP, Del Rosario N-A, Mohammadi S, Ha B-Y, Košmrlj A, et al. Heterogeneous absorption of antimicrobial peptide LL37 in Escherichia coli cells enhances population survivability. Elife. 2018;7. DOI: 10.7554/eLife.38174
Starr CG, Maderdrut JL, He J, Coy DH, Wimley WC. Pituitary adenylate cyclase-activating polypeptide is a potent broad-spectrum antimicrobial peptide: Structure-activity relationships. Peptides. 2018;104:35-40. DOI: 10.1016/j.peptides.2018.04.006
Subbalakshmi C, Sitaram N. Mechanism of antimicrobial action of indolicidin. FEMS microbiology letters. 1998;160:91-6. DOI: 10.1111/j.1574-6968.1998.tb12896.x
Sugiarto H, Yu P-L. Mechanisms of action of ostrich β-defensins against Escherichia coli. FEMS microbiology letters. 2007;270:195-200. DOI: 10.1111/j.1574-6968.2007.00642.x
Sun Y, Shang D. Inhibitory effects of antimicrobial peptides on lipopolysaccharide-induced inflammation. Mediators of inflammation. 2015;2015. DOI: 10.1155/2015/167572
Talledo P, Snoussi M, Del Rosario N, Ha B-Y, Košmrlj A, Taheri-Araghi S. Population Dynamics of Antimicrobial Peptides and Bacteria. Biophysical Journal. 2018;114:455a. DOI:10.1016/j.bpj.2017.11.2516
Troxler RF, Offner GD, Xu T, Vanderspek JC, Oppenheim FG. Structural relationship between human salivary histatins. Journal of dental research. 1990;69:2-6. DOI: 10.1177/00220345900690010101
Vizán JL, Hernández-Chico C, del Castillo I, Moreno F. The peptide antibiotic microcin B17 induces double-strand cleavage of DNA mediated by E. coli DNA gyrase. Embo j. 1991;10:467-76. DOI: 10.1002/j.1460-2075.1991.tb07969.x
Wang G, Song Q, Huang S, Wang Y, Cai S, Yu H, et al. Effect of antimicrobial peptide microcin J25 on growth performance, immune regulation, and intestinal microbiota in broiler chickens challenged with Escherichia coli and Salmonella. Animals. 2020;10:345. DOI: 10.3390/ani10020345

Water JJ, Smart S, Franzyk H, Foged C, Nielsen HM. Nanoparticle-mediated delivery of the antimicrobial peptide plectasin against Staphylococcus aureus in infected epithelial cells. European Journal of Pharmaceutics and Biopharmaceutics. 2015;92:65-73. DOI: 10.1016/j.ejpb.2015.02.009
Wiedemann I, Breukink E, van Kraaij C, Kuipers OP, Bierbaum G, de Kruijff B, et al. Specific binding of nisin to the peptidoglycan precursor lipid II combines pore formation and inhibition of cell wall biosynthesis for potent antibiotic activity. Journal of Biological Chemistry. 2001;276:1772-9. DOI: 10.1074/jbc.M006770200
Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, et al. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. Journal of Biological Chemistry. 2003;278:2461-8. DOI: 10.1074/jbc.M209033200
Yasir M, Willcox MDP, Dutta D. Action of antimicrobial peptides against bacterial biofilms. Materials. 2018;11:2468. DOI: 10.3390/ma11122468
Yonezawa A, Kuwahara J, Fujii N, Sugiura Y. Binding of tachyplesin I to DNA revealed by footprinting analysis: significant contribution of secondary structure to DNA binding and implication for biological action. Biochemistry. 1992;31:2998-3004. DOI: 10.1021/bi00126a022
Yuzenkova J, Delgado M, Nechaev S, Savalia D, Epshtein V, Artsimovitch I, et al. Mutations of bacterial RNA polymerase leading to resistance to microcin J25. Journal of Biological Chemistry. 2002;277:50867-75. DOI: 10.1074/jbc.M209425200
Zanetti M. Cathelicidins, multifunctional peptides of the innate immunity. Journal of leukocyte biology. 2004;75:39-48. DOI: 10.1189/jlb.0403147