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REVIEW ARTICLE

Antimicrobial peptides (AMPs): A promising class of antimicrobial compounds

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Abstract

Antimicrobial peptides (AMPs) are compounds, which have inhibitory activity against microorganisms. In the last decades, AMPs have become powerful alternative agents that have met the need for novel anti-infectives to overcome increasing antibiotic resistance problems. Moreover, recent epidemics and pandemics are increasing the popularity of AMPs, due to the urgent necessity for effective antimicrobial agents in combating the new emergence of microbial diseases. AMPs inhibit a wide range of microorganisms through diverse and special mechanisms by targeting mainly cell membranes or specific intracellular components. In addition to extraction from natural sources, AMPs are produced in various hosts using recombinant methods. More recently, the synthetic analogues of AMPs, designed with some modifications, are predicted to overcome the limitations of stability, toxicity and activity associated with natural AMPs. AMPs have potential applications as antimicrobial agents in food, agriculture, environment, animal husbandry and pharmaceutical industries. In this review, we have provided an overview of the structure, classification and mechanism of action of AMPs, as well as discussed opportunities for their current and potential applications.

KEYWORDS

antibacterial, antimicrobial peptides, antiviral, applications of AMPs, mechanism of action, origins of AMPs

INTRODUCTION

The World Health Organization (WHO) reports that antibiotic resistance continues to increase worldwide and therefore warns that a period in which infections can no longer be treated with antibiotics is approaching (Xie et al., 2017). The increase in antibiotic-resistant bacterial strains has caused the need for the development of new antimicrobial agents that can be used in treatment (Neubauer et al., 2017). In recent years, epidemics and pandemics have revealed that public health is potentially under a global threat in terms of infectious diseases and the need for new and effective antimicrobial agents in combating new emerging microbial diseases continues.

Aquatic or terrestrial invertebrates can protect themselves against pathogenic microorganisms in their natural environment, although they do not have any adaptive immune system. These organisms overcome infections caused by pathogenic microorganism through antimicrobial peptides (AMPs) that are naturally produced by their innate immune defence system (Brogden, 2005; Gueguen et al., 2009).

AMPs are potential multifunctional therapeutic agents, which are effective for a broad spectrum of microorganisms. They are called 'natural antibiotics'. Some AMPs can cause rapid death in Gram-positive, Gram-negative, fungi, parasites, encapsulated viruses or tumour cells within a few minutes. AMPs have a

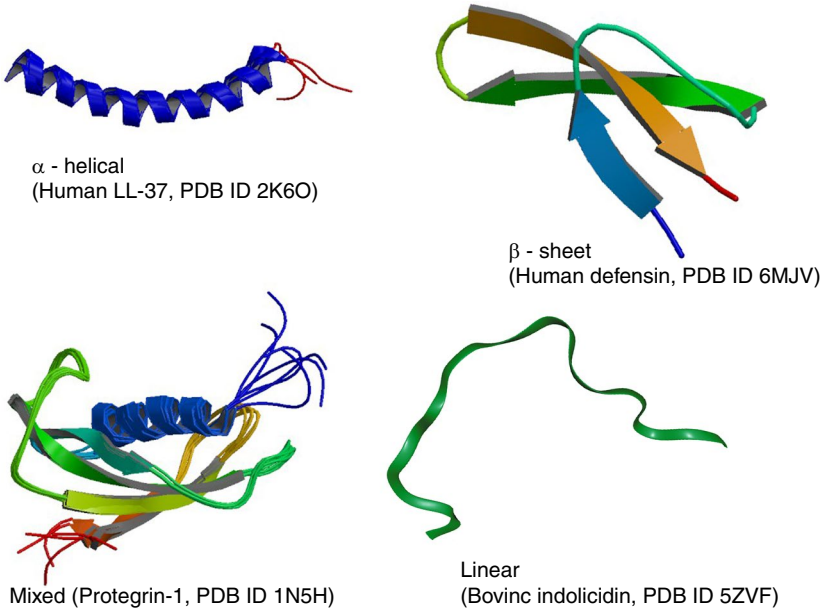

FIGURE 1 Examples for three-dimensional conformations of antimicrobial peptides (https://www.rscb.org)

low risk of resistance development and even they can inhibit antibiotic-resistant microorganisms (Hancock & Sahl, 2006; Mahlapuu et al., 2020). All these advantages make AMPs ideal candidates for pharmacological applications.

AMPs have been reported to be effective for microorganisms with resistance to conventional antibiotics (Miyoshi et al., 2016). It has been reported that persulcatusin, an AMP, which is isolated from the tick (*Ixodes persulcatus*), has an antimicrobial effect on methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA; Miyoshi et al., 2017).

The synergistic effect of AMPs with antibiotics or other AMPs can allow a more powerful inhibition (Döşler et al., 2006; Haney et al., 2009). For example, magainin 2 (MAG2) and PGLa from the skin of *Xenopus laevis* frogs are the most studied AMPs that show synergistic modes of action against bacterial strains by forming transmembrane pores (Tremouilhac et al., 2006; Zerweck et al., 2017). Similarly, combinations of jelleins and temporins have a synergistic effect against *S. aureus* A170 and *Listeria monocytogenes* (Romanelli et al., 2011). Yu et al. (2016) showed that various binary and triple combinations of six different AMPs (cecropin A, LL 19-27, melittin, pexiganan, indolicidin and apidaecin) have strong synergistic activity against *Escherichia coli*. In addition, it was demonstrated that the membrane lytic AMPs (e.g. protegrin 1, hBD-3) and intracellularly active antibiotics (e.g. gentamicin, rifampcin) showed synergistic effects against MRSA, *Micrococcus luteus*, *Acinetobacter baumannii*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *E. coli*, though they rarely exhibited synergistically cytotoxic effects on normal eukaryotic cells (Zharkova et al., 2019). Combinations of AMPs with antibiotics can be proposed as an effective strategy for the elimination of multidrug resistant bacterial strains and decreasing antibiotic doses in monotherapy.

Due to the increase in the number of AMPs discovered naturally or designed synthetically, the need for the creation of databases containing structure, activity, sequence, etc., information for AMPs has emerged. Among them, the 'antimicrobial activity and structure of peptides (DBAASP) database' contains information about more than 2000 ribosomal, 80 non-ribosomal and 5700 synthetic peptides; and includes their chemical structures and activities against more than 4200 specific target microorganisms (MIC, IC50, etc.; Pirtskhalava et al., 2015). In addition to efforts for exploring new AMPs, a large number of studies focusing on their structure, action mechanisms and proposed production methods were performed in the last years. This paper reviews the current and recent findings regarding the mentioned studies above and presents a detailed evaluation of known and proposed applications of AMPs different from previous works.

STRUCTURAL CLASSIFICATION OF AMPs

The structural organization/arrangement of AMPs is crucial to understand their interaction mechanisms with the biological targets. Many experimental methodologies, including magnetic resonance (NMR), x-ray crystallography, atomic force microscopy (AFM) and cryo-electron microscopy (cryo-EM) have been integrated with computational approaches, such as molecular modelling, docking and dynamics to deeply investigate the structures and biological functions of AMPs (Cardoso et al., 2018).

It is possible to classify AMPs according to a variety of properties but the classification based on their secondary structure is the most common. The AMP structures are generally classified into α-helical, β-sheet, mixed (α-helical/β-sheet) and cyclic structures (Figure 1). The α-helix peptides are the most studied AMP group. The magainin, from the skin of the African clawed frog *X. laevis*, melittin found in the venom of the honey bee *Apis mellifera*, and LL-37-derived human cathelicidin are the well-known peptides, which present an amphiphilic α-helix secondary structure in membrane mimetic environments (Nguyen et al., 2011; Vandamme et al., 2012; Yang et al., 2001; Zasloff, 1987). In this structure, the distance between the two adjacent amino acids is about 0.15 nm and the angle between them is approximately 100° (Bahar & Ren, 2013). The presence of the α-helix motifs (helicity) is a key factor that promotes interactions of peptides with target membranes and allows membrane disruption. When the a-helical structure disrupts via amino acid substitutions, antibacterial activity significantly decreases (Tossi et al., 1994). The facially amphiphilic conformation of α-helix structure, in which cationic and hydrophobic domains are arranged on opposite faces of the helix facilitates the interaction between AMPs and membranes. The electrostatic and hydrophobic interactions that cause the binding and insertion of peptides into biological membranes, respectively, are governed by these spatially segregated domains of the helix (Wiradharma et al., 2013). While the helical structure of AMPs significantly affects the antimicrobial potency it is also associated with haemolytic activity and toxicity to mammalian cells (Chen et al., 2005; Zhu et al., 2015). The strategies based on substitutions of some L-amino acids with their D-isomers to obtain stereoselectivity (Oren & Shai, 1997) or insertion of Lys residue into the nonpolar face of helical D-peptides (Chen et al., 2006) proposed to reduce haemolytic activity while maintaining antimicrobial activity. More recently, Mant et al. (2019) significantly eliminated haemolytic activity with the substitution of the two unusual amino acid residues, diaminobutyric acid and diaminopropionic acid on the polar face of de novo designed amphipathic α-helical peptides.

The second group of antimicrobial peptides exhibits β-sheet conformation that consists of at least a pair of two β-strands, binding with disulphide bonds. The presence of disulphide bridges are required for the stabilization of the structure and fulfil the biological function of peptides. The salt bridges and head-to-tail cyclization are additional factors that support the overall stability of the secondary structure of the peptides. Because the β-sheet AMPs possess a more stable structure, they do not undergo essential conformational changes upon interaction with phospholipid membranes (Kumar et al., 2018). The β-sheet peptides usually exhibit an amphipathic character conferred with β-strands spatially segregated as polar and non-polar domains (Lee et al., 2016). The β-sheet AMPs include β-hairpin peptides and cyclic α-, β- and θ-defensins. β-Hairpin antimicrobial peptides are characterized with antiparallel β-sheets forming a hairpin shape that is stabilized by interstrand disulphide bridges (Edwards et al., 2016). Protegrins (PG1–PG5) are antibacterial peptides isolated from porcine leukocytes. A stepwise pore formation model, starting with antiparallel dimerization in a membrane environment, followed by oligomer formation and then assembling of oligomers into an octameric pore structure that acts as an uncontrolled ion transport channel in the biological membranes, was proposed to explain the antimicrobial mode of action of protegrins (Usachev et al., 2017). The tachyplesin-1, polyphemusin-1, gomesin, arenicin-3 are other important AMPs that adopt a β-hairpin structure.

Defensins are one of the well-described groups of AMPs with a broad spectrum of antimicrobial activity against bacteria, fungi and viruses. α-Defensins are mainly present in neutrophils while β-defensins are largely secreted in epithelial cells in various tissues (Dong et al., 2016). Defensins contain three to six disulphide bridges and the position intramolecular disulphide linkages determine the class of the defensin. The disulphide-bridge linkages that stabilized the triple-stranded β-sheet structure are found in the positions Cys1–Cys6, Cys2–Cys4 and Cys3–Cys5 for α-defensins and C1–C5, C2–C4 and C3-C6 for β-defensins. The third class of defensins is the θ-defensins, which were first isolated in rhesus macaque leukocytes. The structure of θ-defensins is characterized by the cyclic cysteine ladder confirmation containing a cyclic peptide backbone cross-connected by three parallel disulphides (Conibear et al., 2012). The cyclic cysteine ladder conformation probably supports the antimicrobial activity of θ-defensins by maintaining the structure and stability of the cyclic backbone (Conibear et al., 2013). In addition, the highly stabile, cyclic peptides have a large surface area and restricted conformational flexibility, which improves binding ability and selectivity (Falanga et al., 2017). It was indicated that the disulphide bridges and circularity in human θ-defensin-1 (retrocyclin-1) increased the receptor binding activity and inhibited entry of HIV-1 (Wang et al., 2003).

A group of antimicrobial polypeptides adopts an α-helix/β-sheet mixed structure that stabilizes three or four disulphide bridges. This cysteine-stabilized α/β (CSαβ) structural motif, which is composed of a single α-helix and one β-sheet of two or three anti-parallel strands, was first recognized in antibacterial insect defensins and scorpion neurotoxins (Bontems et al., 1991; Zhu et al., 2005). CSαβ-containing defensins are commonly present in plants and insects and they have mainly shown antimicrobial activity

against fungi and bacteria, respectively (de Oliveira Dias & Franco, 2015). In an amphipathic structure, the positively charged residues are usually located in the helix while the β-sheet of the motif consists of hydrophobic amino acid residues (Yang, 2012). These amphipathic structures make possible the binding and disruption of bacterial cytoplasmic membranes of plectasin, which is a peptide antibiotic containing CSαβ motif from a saprophytic fungus *Pseudoplectania nigrella* (Schneider et al., 2010). Plectasin contains a conserved CSαβ motif sequenced as C..... CXXXC.....GXC.....CXC (X, any amino acid), and it is potently active against drug-resistant Gram-positive bacteria especially streptococci (Zhu, 2008).

The majority of AMPs are an unstructured form in aqueous solutions but they undergo conformational change and adopt a well-defined conformation depending on the environmental conditions. For example, a cationic, amphipathic, model peptide, GL13K is in the disordered state in water, exhibits an α-helical structure in the presence of zwitterionic model membranes (DOPC) and transits to predominantly β-sheet conformation in anionic membranes (DOPG; Harmouche et al., 2017).

NMR spectroscopy is a highly reliable approach for the determination of the structure of peptides in aqueous solution or membrane mimetic environments. Deuterated trifluoroethanol (TFE)/water mixture has been commonly used in solution NMR as a membrane-mimetic solvent for determining the solution structure of peptides. However, it has been found that deuterated detergent micelles better simulate biological membrane environments than aqueous TFE. Negatively charged sodium dodecylsulphate (SDS) molecules represent the bacterial cell membranes while zwitterionic dodecylphosphocholine (DPC) molecules mimic the eukaryotic cell membranes (Haney et al., 2009).

NMR spectroscopy has been employed to investigate the structure of the magainin, transiting from random coil structure in an aqueous environment to α-helix in a variety of model membrane environments. Experimental data based on solution NMR analysis showed that 23-residue magainin-2 formed α-helical between residues 2 and 22 in DPC and residues 3 and 22 in TFE/water solution (Gesell et al., 1997). Similarly, solution NMR studies have revealed that other amphibian antimicrobial peptide families such as caerin, aurein, dermaseptin and temporin exhibit amphipathic α-helical structures in the presence of membrane-mimetic environments or organic solvent mixtures (Haney et al., 2009). Human cathelicidin (LL-37) displays a salt-dependent antiparallel dimer structure, including two amphipathic helices stabilized by backbone H-bonds and salt bridges (Giangaspero et al., 2001; Zelezetsky & Tossi, 2006). Recently, Sancho-Vaello et al. (2017) studied the atomic structure of LL-37 in solution and determined the presence of *in vivo* lipid-binding sites between dimer interface inducing supramolecular fibre-like oligomerization that probably represent the active form of the peptide interacted with membranes of bacteria. Circular dichroism (CD) studies indicated that cecropins mainly form the α-helix structure in the presence of various membrane-mimetic environments (Sato & Feix, 2006).

ACTION MECHANISMS OF AMPs

AMPs exert their antimicrobial effects mainly through two different mechanisms. The membrane-targeting AMPs impair the structural integrity of the cell membrane while the AMPs that use non-membrane targeting mechanisms mainly inhibit the synthesis of nucleic acids, essential enzymes and other functional proteins (Figure 2).

Membrane active mechanisms

The membrane-active peptides can interact with microbial cell surfaces via receptor-mediated or non-receptor-mediated interactions. The first defined receptor-mediated AMP is nisin, a bacteriocin that specifically binds to lipid II in the initial step of the mechanism of action. This interaction blocks peptidoglycan synthesis and leads to pore formation that results in membrane permeabilization, at even nanomolar concentrations. The most known AMPs establish initial interaction with general targets on a cell surface without the need for any specific receptor. Physicochemical properties of AMPs, such as net charge, hydrophobicity, amphipathicity, membrane curvature and the self-aggregation tendency, have essential roles in the administration of peptide–membrane interactions resulting in disruption of the membrane integrity (Pirtskhalava et al., 2020). The peptide–membrane interactions occur by the collective effects of many of the physicochemical parameters of AMPs. Therefore, it is possible to predict the antimicrobial activity of AMPs based on the structure-activity relationship and to design certain types of peptides with specific properties (Kumar et al., 2018).

The mechanism of action of membrane-active AMPs is explained mainly with cationic and hydrophobic interactions. Especially, electrostatic attraction is the major driving force in the initial binding of the positively charged residues of AMPs to the negatively charged bacterial cell surface (Bahar & Ren, 2013; Kumar et al., 2018). The bacterial cytoplasmic membranes are characterized by the high content of anionic lipids, including phospholipids phosphatidylglycerol (PG), cardiolipin and phosphatidylserine, which is highly attractive for cationic AMPs,

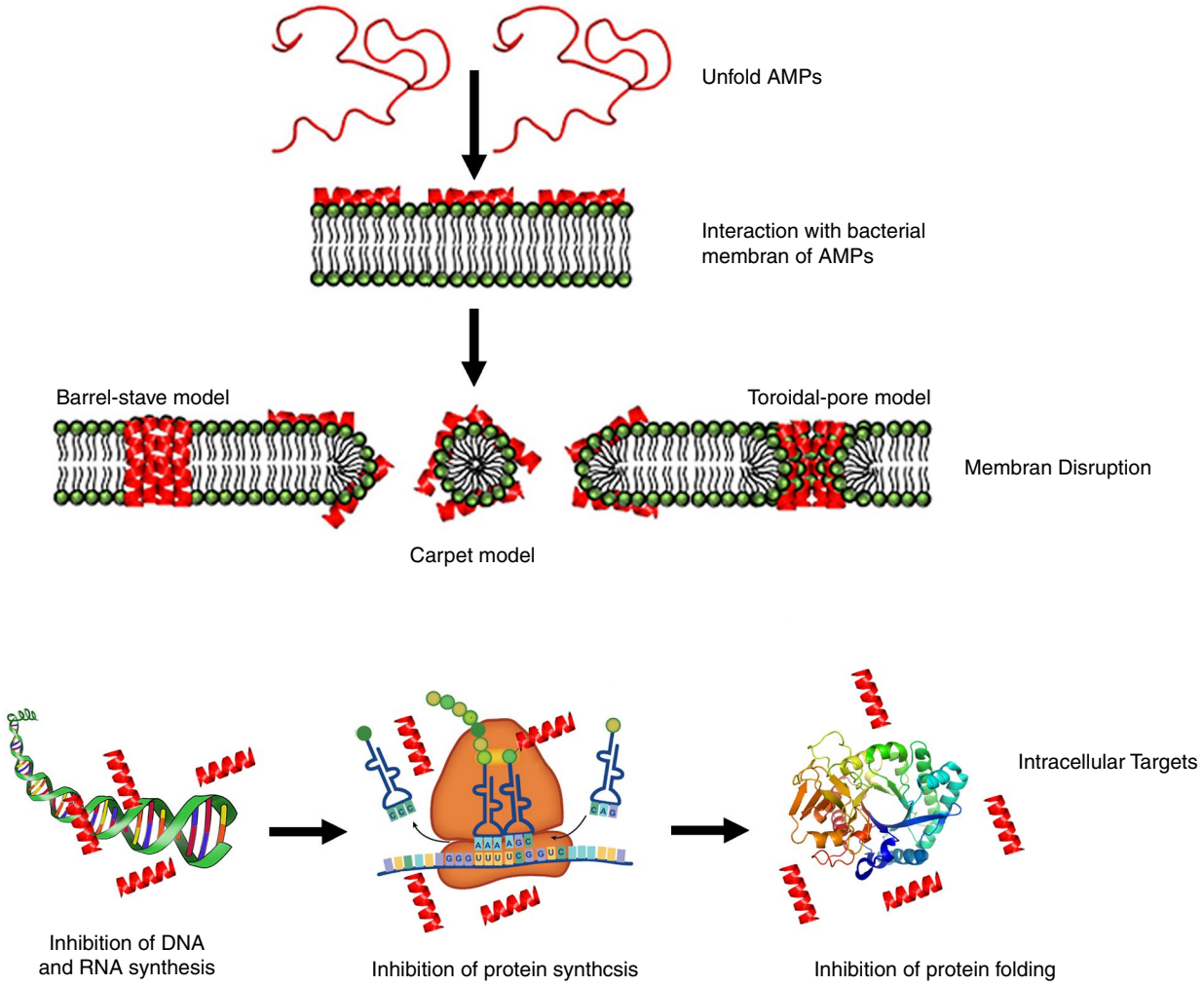

FIGURE 2 Action mechanism of AMPs

while animal membranes possess zwitterionic phospholipids, such as phosphatidylcholine (PC) and sphingomyelin. Furthermore, teichoic acid, lipoteichoic acid and lipopolysaccharides (LPS) are the other negatively charged bacterial cell surface components considered as potential targets for AMPs. Therefore, electrostatic interactions between AMPs and mammalian cell membranes are relatively weak when compared to the interactions, occurring between AMPs and bacterial membranes. Additionally, mammalian cell membranes contain cholesterol, which enhances membrane stability and blocks the insertion of AMPs (Gaspar et al., 2013).

Hydrophobicity is the main feature of peptides, governing the interactions of hydrophobic residues with the fatty acyl chains of membrane lipids and thus the insertion and partition of transmembrane segments of the peptides into the hydrophobic core of the bilayer (Pirtskhalava et al., 2013). The hydrophobicity reflects the percentage of hydrophobic residues within a peptide sequence. AMPs achieve high antimicrobial activity at threshold hydrophobicity levels. In general, moderately hydrophobic peptides have optimal activity while highly hydrophobic peptides exhibit strong haemolytic activity and decreased antimicrobial activity (Chen et al., 2007; Teixeira et al., 2012).

Amphipathicity, describing the relative quantity of hydrophilic and hydrophobic residues located in the opposing face of peptides, contribute to the binding affinity of α-helix AMPs to membranes. The hydrophobic residues of amphipathic AMPs bind to a lipid bilayer while their hydrophilic residues interact with phospholipid groups (Bahar & Ren, 2013; Kumar et al., 2018; Li et al., 2012).

Membrane topography is an important parameter to describe the membrane adsorption properties of the peptides. Chemically distinct lipid components of biological membranes cause spontaneous curvatures in the membrane. The orientation of peptides closely related to the lipid composition constituting membrane curvatures. The peptides generally prefer to stay on a surface-bound state in the membranes with negative spontaneous curvature while they tend to embed in membranes with positive spontaneous curvature. Additionally, the cationic peptides have an increased electrostatic affinity for the domains of

the bacterial membrane where the accumulation of anionic lipids causes negative charge abundance (Strandberg et al., 2012). Indeed, under most conditions, membrane curvature and lipid composition have cumulative effects on the membrane adsorption of proteins through hydrophobic interactions (Vanni et al., 2014).

As the concentration of AMPs binding to the membrane increases, they create peptide–peptide or lipid–peptide complexes. Upon the accumulation of AMPs in the membrane reaches critical aggregation concentration, AMPs penetrate into the hydrophobic core of the bilayer and form transmembrane pores in the cytoplasmic membrane (Figure 2; Sato & Feix, 2006).

I. In the barrel-stave model, AMP molecules adsorb on the membrane surface by the interaction of the hydrophilic regions of peptides and self-assemble. When the laterally accumulated peptide monomers reach a certain density on the membrane, the peptide bulks perpendicularly rotate to the plasma membrane. Finally, the peptide bulks are located along the hydrophobic region of the bilayer and construct a channel with the hydrophilic surface directed inwards (López-Meza et al., 2011).
II. According to the action mechanism of the toroidal model, peptides are inserted perpendicularly in the bilayer, similar to the barrel-stave model but form a peptide–lipid complex instead of peptide–peptide interactions. This conformation of peptides promotes a local membrane curvature surrounded partly by peptides and partly by phospholipid head groups, resulting in the formation of a 'toroidal pore' (Hazam et al., 2018).
III. In the carpet model, antimicrobial peptides are bound parallel to the membrane surface, thanks to an interaction between the positively charged cationic peptides and negatively charged polar phospholipid heads. After accumulation, the peptides reach a critical concentration and then they reorient towards the inside of the membranes and form micelles with a hydrophobic core, causing membrane disintegration (Hazam et al., 2018).

Non-membrane active mechanisms

Although bactericidal effects of AMPs were initially described by membrane-active mechanisms, lately, it has been understood that many AMPs target essential cell components and cellular functions resulting in bacterial death. These AMPs first translocate into the cell membrane without perturbing it and then prevent critical cellular processes by interacting with intracellular targets. To date, many mechanisms have been described, such as the inhibition of protein and nucleic acid synthesis and degradation of enzyme and protein (Brogden, 2005). The proline-rich antimicrobial peptides (PrAMPs) are peptides characterized by a generally high content of proline and arginine residues, which mostly display intracellular activity by inhibiting bacterial protein synthesis. Studies showed that PrAMPs, bactenecin 7 (Bac7) and Tur1A from bovine and bottlenose dolphin (*Tursiops truncatus*), respectively display an inhibitor effect by interacting with the ribosome and inhibit translation by blocking the transition from the initiation to the elongation phase (Gagnon et al., 2016; Mardirossian et al., 2018). In another study, it was shown that Api137, a derivative of the insect-produced AMP apidaecin, inhibits translation by arresting the release factor on the ribosome (Florin et al., 2017). Several transmembrane AMPs display an antimicrobial effect by interacting with nucleic acids (DNA and/or RNA). For example, it has been found that buforin II, a derivative of histone obtained from frogs, passes across the bacterial membrane and binds to the DNA and RNA of *E. coli* (Park et al., 1998). The cell wall is essential for bacterial viability as it is the main protective barrier against osmotic lysis. Several AMPs such as copsin, a defensin from *Coprinopsis cinerea*, plectasin a fungal-originated peptide and a bacteriocin nisin inhibit the bacterial cell wall biosynthesis by binding to the precursor lipid II, which is an essential component in peptidoglycan synthesis (Essig et al., 2014; Hsu et al., 2004; Schneider et al., 2010). Chaperone proteins, which drive the proper folding and assembly of newly synthesized proteins are other targets of AMPs showing intracellular activity. A number of AMPs have been demonstrated to block the important components in *E. coli* chaperone pathways. Otvos et al. (2000) proved that the insect-originated PrAMPs, pyrrhocoricin, apidaecin and drosocin, block the protein-folding pathway by binding specifically to the DnaK, a 70-kDa heat shock protein, and non-specifically to the GroEL, which is a 60-kDa bacterial chaperonin.

Approximately 80% of chronic infections in the human are associated with microbial biofilm formation (Jamal et al., 2018). Pathogenic biofilms comprise microbial cells covered by a self-produced extracellular polymeric matrix and are protected against conventional antimicrobial agents (Flemming et al., 2016). In recent years, the antibiofilm effects of AMPs have been investigated and the proficiency of a group of AMPs as antibiofilm agents was demonstrated for the prevention of biofilm-related infections (Di Luca et al., 2014; Pletzer et al., 2016; Pompilio et al., 2012). Batoni et al. (2016) suggested two modes of action, namely classical and non-classical mechanisms, to explain the antibiofilm activity of AMPs. The classical mode of action is based mainly on the prevention of biofilm formation by known bactericidal effects on planktonic

bacteria (Gonzalez Moreno et al., 2017). The non-classical mechanism is associated with an AMP action of targeting the essential attributes of the biofilm mode of life. According to the non-classical model, AMPs may inhibit cell–cell interaction by binding the bacterial surface, prevent bacterial adhesion by attaching to the biomaterial surface, interfere with cell communication signals, or cause downregulation of the genes essential for biofilm formation (Batoni et al., 2016; Brackman & Coenye, 2015; de la Fuente-Nunez et al., 2012; Pletzer et al., 2016).

ORIGINS OF AMPs

AMPs from natural sources

AMPs from many species, including amphibians, insects, mammals and fish, account for 75.65% of total AMPs, while the remaining originate from mostly plants and bacteria and represent 13.5% and 8.53% of total AMPs, respectively (Hazam et al., 2018).

AMPs from bacteria

Bacterial AMPs are often called bacteriocins. Although their mechanism of action and other characteristics are similar to those of eukaryotic AMPs, there are many differences between them. Bacteriocins are effective at lower concentrations than that of eukaryotic AMPs. In addition, bacteriocins have limited effect on a few species or genera, whereas eukaryotic AMPs can target a greater variety of bacterial groups (Nissen-Meyer & Nes, 1997).

Bacteriocins are classified depending on size, origin, structure and mechanisms of action. The bacteriocins obtained from Gram-negative bacteria such as *E. coli* and/or other enterobacteria are grouped as small peptide-structured microcins and/or larger protein-structured colisins (Duquesne et al., 2007). Bacteriocins produced by Gram-positive bacteria are divided into two main groups: lantibiotics (Class I) containing thioether-based ring structures called lanthionine or β-methyllanthionine and non-lantibiotics (Class II) containing unmodified antimicrobial peptides (Hassan et al., 2012).

Actinomycetes are an important microbial group that are well adapted to the soil ecosystem, and they are rich sources of peptide antibiotics (Kalyani & Rajina, 2017). In addition to the well-known natural antibiotics such as vancomycin and daptomycin produced by different actinomycetes species, pargamicins B, C and D produced by *Amycolatopsis* sp. ML1-hF4 (Hashizume et al., 2017), ohmyungsamycins A and B isolated from *Streptomyces* sp. (Um et al., 2013) and a lipopeptide arylomycin A6 from *Streptomyces parvus* HCCB10043 (Rao et al., 2013) are novel AMPs that are obtained from soil-derived actinomycetes strains.

AMPs from marine sources

The marine environment is known to be one of the richest sources of antimicrobial peptides. Oceans cover just over 70% of the Earth and are tremendous sources for the discovery of potential AMPs (Charlet et al., 1996; Cheung et al., 2015). Unlike the terrestrial environment, usually, the marine environment is characterized by low temperatures, high pressure, absolute darkness and high salinity (Lauro & Bartlett, 2008). Therefore, it has been stated that marine AMPs are structurally different from terrestrial AMPs and are more adaptive to stringent environmental conditions such as high salinity (Falanga et al., 2016).

Marine AMPs are isolated from microorganisms and marine organisms. Usually, the marine AMPs are classified into four basic categories, depending on their structural and biochemical properties, without consideration of their mechanism of action. According to this classification, even if some peptides are in the same structural class, their mode of action can vary considerably. Linear α-helical AMPs (I) have hydrophobic and hydrophilic regions in a linear and short-chain structure that acquire a helical conformation after interaction with the membrane. Clavanins, hedistin, piscidin, myxinidin, pleurocidin and styelins are marine AMPs included in this group (Lehrer et al., 2001; Pundir et al., 2014). Proline- and arginine-rich callinectin (Khoo et al., 1999; Noga et al., 2011), histidine-rich chrysophsin (Iijima et al., 2003; Mason et al., 2007), and proline- and glycine-rich collagencin (Ennaas et al., 2016) are linear or helical peptides with an abundance of one amino acid (II). The third group is peptides forming a hairpin-like β-sheet or α-helical/β-sheet mixed structures stabilized by intramolecular disulphide bonding (III). The most well-known example of this group is defensins, characterized by multiple disulphide bonds, which provide further stability and compactness in high salt concentrations (Scudiero et al., 2010, 2013). While cyclic peptides (IV) are isolated from the marine ecosystem in large amounts, they generally show antimycotic activity and their antibacterial activities have not been investigated in detail (Falanga et al., 2016). Discodermin A, isolated from the sea sponge, is the most well-known example of cyclic marine AMPs (Matsunaga et al., 1985).

AMPs from plants

Plant-derived AMPs are peptides that exhibit strong and broad-spectrum antimicrobial activity. The first reported

plant AMP was purothionin from wheat flour (*Triticum aestivum*; De Caleya et al., 1972). Most plant AMPs are naturally basic with a molecular weight ranging from 2 to 10 kDa and contain 4–12 cysteine residues that improve structural and thermodynamic stability (García Olmedo et al., 2001). Generally, plant AMPs are classified according to peptide chain length as well as the number and location of cysteines that form disulphide bonds (de Souza Cândido et al., 2011; Marcus et al., 1997). Numerous plant-derived AMP groups, including defensins, snakins, puroindolines, glycine-rich proteins, cyclotides, hevein-type proteins, thionins, knottins and lipid transfer proteins have been purified, identified and characterized (Nawrot et al., 2014; Stotz et al., 2013; Tang et al., 2018). These AMPs were isolated from various plant organs such as stems, roots, seeds, flowers and leaves (Montesinos, 2007). In addition to the strong microbiocidal activity of plant AMPs against viruses, bacteria, fungi, parasites and protozoa, they also have anti-insect activity against oomycetes and herbivorous pests, and anticancer activity against some cancer cells (Allen et al., 2008; Koike et al., 2002; Kong et al., 2004; Nawrot et al., 2014).

AMPs originated from insects

Insect antimicrobial peptides play an important role in the humoral immune system. Insect AMPs are synthesized in an insect's body fat and stored in haemolymph (Brown et al., 2009; Bulet & Stocklin, 2005). More than 200 AMPs have been identified from insects to date. These peptides are classified under five major groups: cecropins, insect defensins, glycine-rich peptides, proline-rich peptides and lysozymes (Hwang et al., 2009).

Synthetic AMPs

The AMPs extracted from natural sources possess a number of problems including low stability, salt tolerance and high toxicity that hurdle their widespread therapeutic use. Many studies associated with the structure-activity relationship of AMPs have shown that the antimicrobial activity of peptides can be affected by changes in the structural and physicochemical parameters (e.g. net charge, secondary structure, hydrophobicity and amphipathicity; Cytryńska & Zdybicka-Barabas, 2015; Huang et al., 2010). The studies investigating the structure–activity relationship (SAR) of AMPs proved the relationship between the physicochemical and structural properties and biological activities of natural and de novo designed synthetic peptides. This made it possible to design peptides with broad-spectrum activity and good stability (Porto et al., 2012; Zelezetsky & Tossi, 2006).

Several methods have been developed to design new synthetic antimicrobial peptides by modifying the sequences of the naturally found antimicrobial peptides from various organisms. It was demonstrated that small changes in amino acid composition can lead to changes in all conformational and physicochemical properties of a peptide. The modifications on the template peptide were usually performed via truncation, amino acid substitution, hybridization and/or cyclization. Obtaining short peptides by truncating the AMP sequence provides a cost-reduction advantage in the large-scale production of synthetic AMPs. Cyclization of AMPs leads to higher membrane permeability compared to linear peptides. Hybridization is another effective strategy in synthetic peptide design (Cardoso et al., 2021; Ong et al., 2014).

The hybrid peptides produced by combining fragments cut from naturally occurring AMP sequences allow the exploits of the different desirable properties of template peptides. For instance, the combination of AMPs that have low toxicity and activity, with AMPs that exhibit high activity but relatively higher toxicity enables the development of new chimeric AMPs with high antimicrobial activity and low toxicity (Ong et al., 2014). De novo AMP design makes it possible to generate peptides with limited similarity to natural AMPs in amino acid frequency and location. In this context, an AMP rational design algorithm called Joker has been developed to perform modifications based on the introduction of antimicrobial motifs into the known AMP sequence (Porto et al., 2018). These AMPs show modular character. Therefore, it has been suggested that if a new antimicrobial motif is added to an AMP sequence, the antimicrobial effect of this AMP will be strengthened. Studies have shown that amino acid residues, which are frequently encountered in AMP databases, can be used to design peptides. For example; KL-12 was designed by using KR-12 which is the smallest antibacterial peptide derived from human LL-37 by turning all hydrophobic residues to leucines and all charged and hydrophilic residues to lysine. Another approach based on combining 'database-derived peptide motifs', comprising of frequently used residues. For instance; a new peptide, GLK-19 was designed using motifs consisting only of glycine (Gly), leucine (Leu) and lysine (Lys) residues and found to be more active *against E. coli* than human LL-37 (Wang, Li, et al., 2009). A number of computational approaches such as machine learning methods, linguistic model, motif addition methods and genetic algorithms were used to design AMPs. These methodologies combine important information about biochemical parameters and bioactivities of AMP sequences (Boone et al., 2021; Porto et al., 2012). Thus, it is possible to predict the antibacterial potential of a candidate sequence prior to synthesis.

PRODUCTION OF AMP's

Extraction of AMPs from natural sources

AMPs are obtained from natural living forms such as plants, frogs, insects, fungi, bacteria and other organisms by applying a series of steps of an extraction and purification process. Although AMPs are generally isolated directly from raw materials by following basic extraction procedures, in some cases the further purification of AMPs from crude extracts is performed by sophisticated techniques (Moreira et al., 2011; Tang et al., 2018). Odintsova et al. (2009) suggested an efficient method to purify and characterize potential new AMPs from plant materials including amino acid sequencing and a similarity search in databases.

AMPs produced by chemical synthesis

The chemical synthesis of AMPs is performed by solid-phase peptide synthesis (SPPS; Bray, 2003). The growing chain (peptide or oligomer) is attached to a solid support such as a resin or bead and remains adhered to this support during synthesis. To minimize racemization, the peptide synthesis starts from the C-terminus. The peptide growth takes place by applying a selective coupling based on the 'Fmoc strategy' between the carboxylic acid group of the added amino acid and the amino-terminal group of the amino acid attached to the solid phase. High concentrations of reagents are used during the synthesis and excess reagents can be easily removed by the washing and filtering steps after each binding step. The disadvantages of solid-phase peptide synthesis are the cost of the solid support, the limited number of the 'linker' groups on the surface of the bead and the use of toxic reagents that lead to adverse environmental effects. Although, peptides shorter than 30 amino acids can be synthesized using this method, longer peptides only have a 55% correct sequence rate of the target peptide (Chan & White, 2000; Fields & Noble, 1990).

AMPs produced from genetically modified organisms

Traditional production methods of AMPs are associated with some limitations. For example, the purification of AMPs from natural sources such as bacteria, plants, frogs, insects, or fungi is expensive and time-consuming (Ingham & Moore, 2007). Moreover, production of AMPs with standard activity and high purity is generally difficult and a specific extraction method is required for the purification of AMPs from each source (Parachin et al., 2012). However, in the chemical synthesis of AMPs, which is another conventional method, the cost is quite high, and therefore, peptide synthesis is suitable for only small-scale production, such as laboratory applications.

Therefore, the recombinant production of AMPs based on the expression of AMP genes from natural sources in host organisms has become a more attractive method in recent years. Furthermore, in recombinant production, it may be possible to make modifications in the peptide sequence or to produce fully synthetic analogous peptides for specific purposes such as increasing peptide stability or/and production of hybrid AMPs with high antimicrobial activity (Bahar & Ren, 2013; Piers et al., 1993; Ramos et al., 2013; Wade et al., 2012).

Many bacterial host cells have been used for the expression of AMPs. However, *E. coli* is the most preferred recombinant bioreactor because of its rapid growth and well-known genetic, physiological and biochemical features (Ingham & Moore, 2007). In the expression of AMPs in bacterial hosts, combining the antibacterial peptide with a carrier protein reduces the lethal effect of the peptide on the host organism and provides resistance to proteolytic degradation (Vassilevski et al., 2008). Several recombinant AMPs such as dermsidin (DCD), ABP-CM4 peptide, LfcinB-W10 (a derivative bovine lactoferricin), protegrin-1 (PG-1), cathelicidin LL-37 and some beta-defensins have been produced by fusion protein strategy in *E. coli*. In addition, hybrid AMPs with different properties have been designed and expressed by the combination of multiple AMP genes to increase antimicrobial activities of heterologous products and obtain a high yield (Rodriguez-Cabello et al., 2012).

Pichia pastoris (Komagataella phaffii) is the most widely used and studied yeast expression system for the production of eukaryotic heterologous proteins (Balamurugan et al., 2007). Successful expression of AMPs, including cecropins (Jin et al., 2006; Wang et al., 2011), defensins (Hsu et al., 2009), ABP-CM4 peptide (Zhang et al., 2006) and human CAP18/LL37 AMP (Kim et al., 2009), was performed in the *P. pastoris* expression system. In addition, the expression of hybrid AMPs has been successful in *P. pastoris* (Jin et al., 2009). The *P. pastoris* expression system was considered an ideal heterologous host because it allowed numerous eukaryotic post-translational modifications such as glycosylation, signal sequencing processing and disulphide bond formation, which are required for cysteine-rich cationic AMPs (Cereghino & Cregg, 2000). For example, this system was used for the expression of HD5, a cationic peptide with six cysteine residues forming three intramolecular disulphide bonds (Hsu et al., 2009).

Various diseases caused by viruses, bacteria or fungi negatively affect agricultural production and cause

economic losses. Product losses caused by phytopathogens and pests have been reported to reach 30%–40% per year in developing countries (Flood, 2010). AMPs are considered a good candidate for the control of plant diseases (Holaskova et al., 2015). AMPs, expressed in model plants provided varying degrees of protection against plant pathogens (Montesinos, 2007).

Plant bioreactors are also alternative recombinant expression systems that have been widely used to produce pharmaceuticals and therapeutics. High yield expression of AMPs in plant bioreactors offers an excellent option for large-scale production of medical products due to the increasing demand (da Cunha et al., 2017; Tregoning et al., 2005). Plant bioreactors are low-cost production systems for the synthesis of large quantities of heterologous polypeptides in various organs of plants since they only require soil, water and light (Davies, 2010; Obembe et al., 2011). Cn-AMP1, clavanin A, Cm AMP-5 and parigidina-br1, which have antimicrobial and insecticidal activities, were expressed in high yields in the leaves of the tobacco plant (*Nicotiana benthamiana*; Leite et al., 2018).

APPLICATIONS OF AMPs

In recent decades, antibiotic-resistant bacterial infections are an alarmingly and increasing worldwide problem not only in the medical industry but also in animal husbandry and aquaculture. The urgent need for developing alternative agents to control microbial diseases has been the major driving force in the development of peptide antibiotics, which could become the most potent solution in cases where current antibiotics are insufficient (Global Peptide Antibiotics Market & Clinical Pipeline Insight, 2023). However, AMPs are multi-functional agents that have also several therapeutic functions such as anti-inflammatory, immunomodulatory, endotoxin-neutralizing activities and cytotoxic effects on cancer cells, which make them good candidates for pharmacological practices, besides their direct antimicrobial effects (Gordon et al., 2005; Kang et al., 2017). Rapid and broad-spectrum activities, multipurposes use opportunities and low resistance development potentials of AMPs are the main factors increasing their appeal in the biopharmaceutical industry and investment in the peptide antibiotics market. The Global Antimicrobial Peptides market was valued at 5 million USD in 2020 and will reach 6 million USD by the end of 2027 at a compound annual growth rate (CAGR) of 5.4% between 2022 and 2027 (Global Antimicrobial Peptides Sales Market Report, 2021). Currently, more than 60 peptides are approved by the US Food and Drug Administration (FDA) and over 400 peptides are under clinical phase trials (Agarwal & Gabrani, 2021).

Pharmaceutical practices

AMPs are one of the most promising antibiotic candidates to overcome challenges regarding multidrug resistance. They can be used alone or in combination with conventional antibiotics, antivirals or other antimicrobial components to obtain a synergistic effect (Gordon et al., 2005). Although only a few AMPs have been approved by the FDA up to now, there are numerous AMPs under preclinical stages or clinical trials (Koo & Seo, 2019). Daptomycin is a cyclic lipopeptide that exhibits a fast bactericidal effect against various drug-resistant Gram-positive bacteria. It was approved by the FDA in 2003, for the treatment of complicated skin and skin structure infections (Carpenter & Chambers, 2004). Another peptide antibiotic, vancomycin is a tricyclic glycopeptide that shows a killer effect against Gram-positive bacteria by inhibiting the synthesis of the peptidoglycan layer of the bacterial cell wall. Vancomycin was approved by the FDA for clinical uses of *Clostridium difficile*-associated diarrhoea, pseudomembranous colitis and *S. enterocolitis*, and infections (Patel et al., 2020). Dalbavancin, oritavancin and telavancin are semisynthetic lipoglycopeptide derivatives of vancomycin, which were approved by the FDA between 2009 and 2014 for the treatment of complicated skin and skin structure infections. Their antibacterial activity has been improved through liposaccharide elements attached to the peptide, which increase the binding ability with bacterial cells (Bambeke, 2015). The polymyxins (colistin and polymyxin B) are well-characterized cyclic lipopeptide antibiotics that have been used clinically for the treatment of multidrug Gram-negative bacterial infections since the late 1950s. Polymyxin B and colistin possess similar action mechanisms, attributed to their similar chemical structures and they act on Gram-negative bacteria with minor differences. Colistin is mainly marketed as its inactive prodrug form, colistin methanesulphonate (CMS), and is administered intravenously or intramuscularly. However, polymyxin B is infused parenterally in its active sulphate form (Tran et al., 2016; Vardakas & Falagas, 2017).

Histatin is a histidine-rich cationic salivary peptide with strong anticandidal activity. The phase I and II clinical trials of PAC113, which is a derivative histatin, have been shown to be a promising drug for the treatment and prevention of oral candidiasis (Koo & Seo, 2019). Omiganen pentahydrochloride (MBI-226) is a synthetic analogue of indolicidine, which is a cationic peptide that originated from bovine neutrophils. In vitro activity of MBI-226 has been demonstrated against 1437 clinical bacterial isolates and 214 clinical yeasts (Sader et al., 2004) and its phase III clinical trial has been completed for the treatment of rosacea (Table 1). Human lactoferrin and its variety of derivatives were evaluated to produce drugs

effective against bacterial, fungal and viral infections. For instance, human lactoferrin 1-11 (hLF1-11) is a derivative with broad-spectrum antibacterial and antifungal activity, which has been developed for intravenous treatment of bacterial and fungal infections in immune-compromised stem cell transplant recipients (van der Velden et al., 2009). Novexatin (NP213) is a cyclic fungicidal peptide, which effectively penetrates the human nail, has been proposed for the topical treatment of onychomycosis (fungal nail infection; Mercer et al., 2020).

In globalized world, epidemic and pandemic infections caused by the emergence or re-emergence of virus strains are a growing threat to the world population. AMPs exhibit antiviral activity by virus-targeting or host-targeting action mechanisms. The virucidal mechanism of action describes the direct effect of AMPs against viral particles, based on lysis of envelope or inhibition of essential viral components. In contrast, the host-focused mechanism is related with interfering the viral binding site in the host cell membrane and blocking of adsorption (Boas et al., 2019). Up to now several natural or rationally designed AMP's were tested against human immunodeficiency virus (HIV), zika virus (ZIKV), respiratory syncytial virus (RSV; He et al., 2018), hepatitis C virus (HCV; El-Bitar et al., 2015), severe acute respiratory syndrome coronavirus (SARS-CoV), influenza A (H5N1, H1N1; Li et al., 2011), herpes simplex virus (HSV), hepatitis B virus (HBV; Zeng et al., 2018), vaccinia virus (VV; Howell et al., 2004), etc. An HIV fusion inhibitor Enfuvirtide (trade name Fuzeon) is a synthetic 36-amino acid peptide that is FDA approved for combination therapy of HIV-1 infection. A more efficient HIV fusion inhibitor peptide, sifuvirtide, which can effectively inhibit HIV replication and exhibit high activity against ENF-resistant HIV-1 strains, is under phase II clinical trial (Wang, Yang, 2009; Yao et al., 2012). Other FDA-approved peptides are boceprevir and telaprivir, used in the treatment of chronic hepatitis C (HCV), genotype 1. They are selective protease inhibitors blocking the activity of the viral HCV nonstructural [NS] region 3/4 serine protease that is essential for viral replication (Agarwal & Gabrani, 2021). Anti-SARS-CoV activities of heptad repeat (HR)-based peptides were demonstrated against coronaviruses in several studies (Outlaw et al., 2020; Ujike et al., 2008; Xia et al., 2020; Yuan et al., 2004). For example, EK1 is a modified form of the OC43-HR2P peptide, which exhibited broad fusion inhibitory activity against multiple human coronaviruses (HCoVs). A cholesterol-conjugated derivative of the EK1, EK1C4 was tested against SARS-CoV-2. The EK1C4 exhibited 240-fold more potent inhibitory activity against SARS-CoV-2 spike protein-mediated membrane fusion than the EK1 peptide (Xia et al., 2020). In another study, Outlaw et al. (2020) described a derivative lipopeptide from the C-terminal heptad repeat (HRC) domain of SARS-CoV-2 S conjugated with tetra-ethylene glycol-cholesterol, which inhibits cell-cell fusion mediated by SARS-CoV-2 S and blocks infection.

Since AMPs are one of the most promising antimicrobial drug candidates, understanding the bacterial resistance mechanisms that are developed against AMPs is a critical issue (Bechinger & Gorr, 2017). AMPs act on diverse bacterial cellular targets through multiple mechanisms, therefore resistance development is less common compared to conventional antibiotics (Browne et al., 2020). However, various bacterial resistance mechanisms have been reported acquired against AMPs. Many defence strategies are based on modification cell surface components since the cell membrane is the main target of attack of AMPs. The changes in the charge and fluidity of external cell structures often contribute to the resistance by reducing the attachment and insertion of AMPs to the bacterial cell surface (Joo et al., 2016). Proteolytic degradation of the peptides is another potential resistance mechanism and strongly depends on the peptide structure since many secreted proteases are nonspecific for AMPs (Pfalzgraff et al., 2018). The efflux pumps expelling the harmful substances and capsular polysaccharides serving as a barrier that protects the bacteria are other important bacterial defence mechanisms that contribute to the resistance against AMPs (Abdi et al., 2019). Compared to antibiotics, the resistance to AMPs occurs through nonspecific and intrinsic mechanisms, and horizontal transfer of resistance genes generally occurs at a lower frequency (Joo et al., 2016). This may be considered a factor, increasing the medical importance of AMPs and stimulating their applications as substitutes for antibiotics.

Food applications

AMPs can be used as food additives in the food industry or they can also be included in the composition of packaging materials. Nisin, an antimicrobial peptide produced naturally by *Lactococcus lactis*, is a bacteriocin in the group of lantibiotics. Nisin is the only bacteriocin licensed in more than 50 countries. Although nisin can inhibit Gram-positive food-borne pathogenic and spoilage bacteria, it is ineffective on yeast and Gram-negative bacteria. An iron-binding glycoprotein, lactoferrin is an effective antimicrobial peptide founding in milk and colostrum. Lactoferrin has been approved for use as an antimicrobial agent in meat products in the USA (USDA-FSIS 2008 FSIS Directive 7120.1 Amendment 15). Pepsin digested lactoferrin derivative lactoferricin is a more potent antimicrobial peptide and offers a potential advantage in food preservation due to its relative heat resistance (Villalobos-Delgado

TABLE 1 Peptide-based antimicrobial compounds in clinical trials (http://dramp.cpu-bioinfor.org/)

DRAMP ID	NAME	Description
DRAMP18062	Histatin	Using a variant of histatins, which are naturally occurring cationic peptides in saliva
DRAMP18061	Histatin	Using a variant of histatins, which are naturally occurring cationic peptides in saliva
DRAMP18068	hLF1-11	An 11-mer peptide from the N terminus of human lactoferrin
DRAMP18178	IDR-1	Derivative of bactenecin from bovine neutrophils
DRAMP18080	Plectasin	A fungal defensin (*Pseudoplectania nigrella*)
DRAMP18166	Vasoactive intestinal peptide (VIP)	A peptide hormon
DRAMP18153	Opebacan	21-amino-acid peptide derivative of bactericidal/permeability-increasing protein
DRAMP20761	LTX-109	A chemically synthesized, peptide-mimetic bactericidal antimicrobial drug
DRAMP18164	AP-214	Synthetic derivative from α-melanocyte-stimulating hormone
DRAMP20760	C16G2	A synthetic AMP
DRAMP18083	CZEN-002	Synthetic 8-mer derived from α-melanocyte-stimulating hormone
DRAMP18088	EA-230	A derivative peptide from the human pregnancy hormone
DRAMP18163	Ghrelin	Endogenous host-defence peptide, synthetic construct
DRAMP18152	IMX942	Synthetic cationic host defence peptide, derivative of IDR-1 and indolicidin
DRAMP18067	MX-594AN	Indolicidin based antimicrobial peptide variant
DRAMP18157	Novexatin (NP213)	Cyclic cationic peptide derived from NovaBiotics arginine peptide platform
DRAMP18161	OP-145	Synthetic 24-mer peptide derived from LL-37
DRAMP18063	P113	A 12 amino acid fragment of histatin 5
DRAMP18081	PAC113	A 12 amino-acid antimicrobial peptide derived from histatin
DRAMP28983	PL-5	An α-helical AMP developed by ProteLight Pharmaceuticals
DRAMP18158	PMX-30063 (brilacidin)	Defensin structural mimetic, non-peptide, small molecule/copolymer
DRAMP18182	Sifuvirtide (SFT)	Designed based on the 3D structure of the HIV-1 gp41 fusogenic core conformation
DRAMP18154	XOMA-629	9-amino-acid peptide derivative of bactericidal/permeability-increasing protein
DRAMP18070	XMP 629	A 9-amino-acid peptide derived from bactericidal/permeability-increasing protein (BPI)
DRAMP18071	Mycoprex	Extracted from insects
DRAMP20774	Murepavadin (POL7080)	A synthetic analogue of protegrin I
DRAMP18160	Omiganan (MBI-226)	A synthetic analogue of indolicidine

et al., 2019). ε-Polylysine is a homopolymer of L-lysine originated by *Streptomyces albulus*, which has broad-spectrum antimicrobial activity in Gram-positive and Gram-negative bacteria, yeast, mould and viruses. It has been approved by FDA as a food preservative in generally recognized as safe (GRAS) status (Luz et al., 2018). Natamycin, produced by *Streptomyces* species, is an effective bacteriocin against almost all food-borne yeasts and

Activity	Medical use	Development Stage
Antifungal	Chronic *Pseudomonas aeruginosa* infections	Phase I
Antifungal	Antimicrobial-peptide-containing mouth wash for the treatment of oral candidiasis (gingivitis and periodontal diseases)	Phase II-III
Antibacterial, Antifungal	LPS-mediated diseases and fungal infections	Phase I (completed)
Chemokine induction and reduction of pro-inflammatory cytokines	Prevention of infections in the immune compromised	Phase I
Antibacterial	Systemic anti-Gram positive, especially pneumococcal and streptococcal infections	Phase I
Antibacterial	Acute respiratory distress syndrome and sepsis	Phase I
Antibacterial, Antiviral	Endotoxaemia in haematopoetic, stem cell transplant, recipients	Phase I/II
Antibacterial	Treatment of nasal carriers MRSA	Phase I/IIa
Antibacterial	Sepsis and post-surgical organ failure	Phase II (completed)
Antibacterial	Treatment of adult and adolescent dental subjects	Phase II
Anticandidal	Vulvovaginal candidiasis	Phase IIb
Anti-inflammatories; Antiseptics	Sepsis	Phase II
Anti-inflammatory	Airway inflammation, chronic respiratory infection and cystic fibrosis	Phase II (completed)
Antibacterial	Nosocomial infections, febrile, neutropenia	Phase II
Antibacterial, Antifungal	The treatment of catheter-related infections and acne	Phase IIb (completed)
Antifugal	Treatment of dermatophyte fungal infections such as onychomycosis	Phase IIb
Antibacterial	Chronic bacterial middle ear infection.	Phase II (completed)
Antifungal	HIV	Phase II (completed)
Antifungal	Oral candidiasis	Phase IIb
Antibacterial	Skin wound infection	Phase II
Antibacterial	Acute bacterial skin infections caused by *Staphylococcus* spp.	Phase II
Anti-HIV	HIV fusion inhibitor; AIDS	Phase II
Antibacterial	Impetigo	Phase IIA
Antibacterial	Acne	Phase III
Antifungal	Fungal infections	Phase III
Antibacterial	Treatment of nosocomial pneumonia and ventilator-associated bacterial pneumonia (VABP)	Phase III
Antibacterial	Treatment of rosacea	Phase III (completed)

moulds, although it is not effective in bacteria or viruses. To inhibit fungal growth natamycin is applied on the surface of cheese and salami-type sausages (Elsser-Gravesen & Elsser-Gravesen, 2014). Spheniscin is an avian-defensin defined in king penguins (*Aptenodytes patagonicus*), which preserves undigested food in their stomach for the last part of the egg incubation period. This event gave researchers a good idea that sphenicin may be used in the

long-term preservation of foods (Thouzeau et al., 2003). Pediocins, other bacteriocins synthesized by *Pediococcus acidilactici* and *Pediococcus pentosaceus* have been suggested to be used for the preservation of vegetable and meat products (Papagianni & Anastasiadou, 2009; Figure 3).

The integration of volatile or non-volatile antimicrobial agents with packing materials is one of the most interesting issues in active packaging. In the development of antimicrobial packaging, AMPs were coated on polymer surfaces by adsorption or immobilization (Appendini & Hotchkiss, 2002). Many AMPs, including cecropins, defensin and magainins may be coupled to polymers alone or in combination with antibiotics, certain organic acid and enzymes, such as lactoperoxidase and lysozyme (Suppakul et al., 2003). Dermaseptin K4K20-S4, which shows antimicrobial activity against a wide range of pathogenic microorganisms, has been incorporated into different food coatings and showed significant inhibition effect against mould and aerobic bacteria (Miltz et al., 2006). The incorporation of AMPs with food packaging material instead of antimicrobial additives directly added to bulk food provides a significant reduction of microbial load that occurs on the surface of foods. This application may increase the protection efficiency by allowing only the required amount of peptide to be released. The gradual release of an antimicrobial from packaging material to the food surface may contribute an advantage over other applications, such as dipping and spraying. In current applications, the activity of antimicrobial agents may rapidly reduce due to their interaction with food components (Appendini & Hotchkiss, 2002; Gennadios et al., 1997). In a study on non-degradable films incorporated with antimicrobial peptide Gramicidin A, a partial release of the peptide from the film was demonstrated with partial inhibition of the bacterial growth, and consequently strong antibacterial activity was observed (Guyomard et al., 2008).

Animal husbandry applications

The emergence of antibiotic-resistant bacteria in animal products has become a serious threat to public health and food security because of the potential risk related to antibiotic resistance genes that may be transferred from bacteria to humans. Antimicrobial peptides, which have strong therapeutic effects and weak resistance developmental ability represent one of the most favourable alternatives for the management of crises concerning antibiotic-resistant microbes and achieving sustainable livestock production.

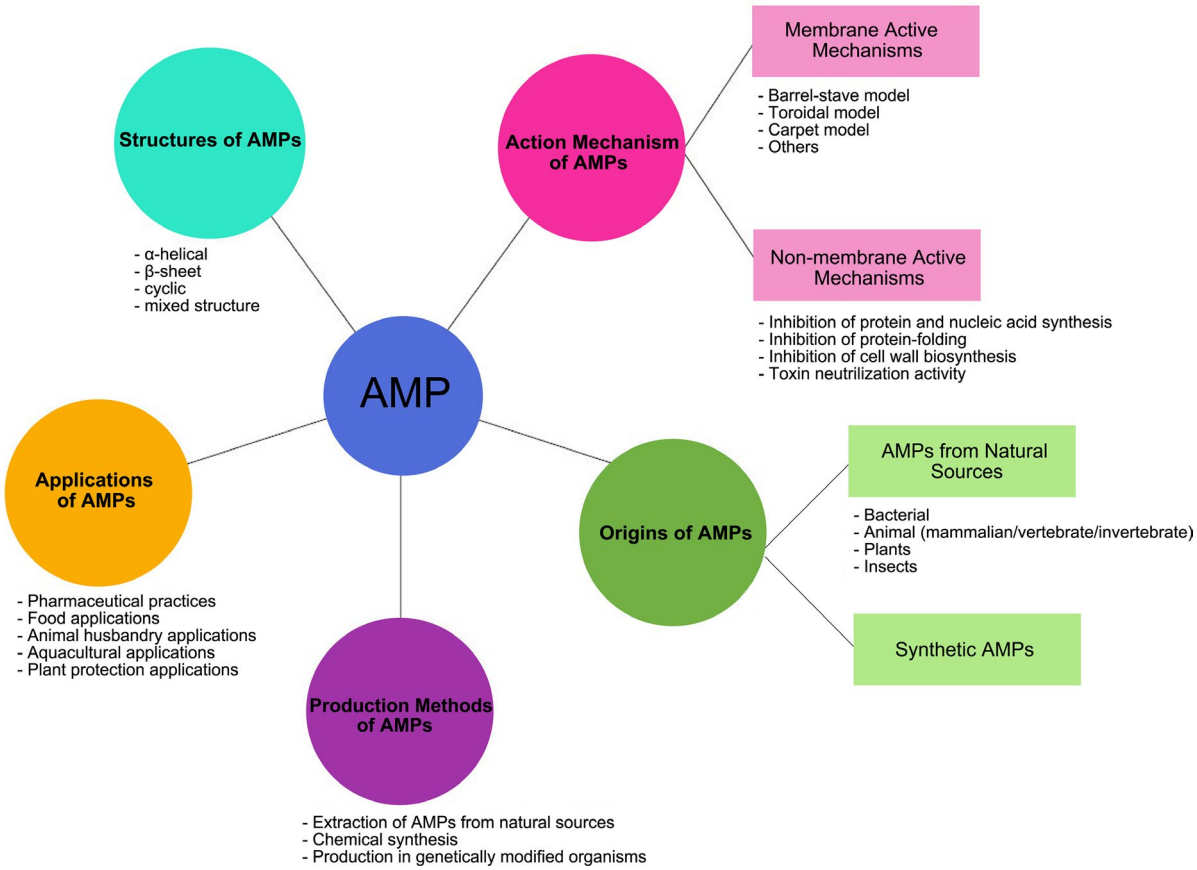

FIGURE 3 Classification of AMPs according to their different properties

The potential of AMPs to treat microbial infections was evaluated for many critical diseases in livestock. It has been reported that the dietary supplementation of broiler chickens with nisin exerted a clearly modulating effect on the gut microbial ecology and significantly decreased counts of *Bacteroides* and Enterobacteriaceae in ileum digesta (Józefiak et al., 2013).

Transgenic expression of AMPs can be an effective strategy to overcome some important problems of animal husbandry that directly affect both animal health and milk yield, such as mammary gland infection (mastitis; Donovan et al., 2005). For example, mammary gland expression of bovine lactoferricin and human lactoferrin in transgenic goats conferred a wide spectrum of antimicrobial activity against several pathogens (Zhang et al., 2007, 2008).

Dietary supplementation of antibiotics was a common practice to prevent disease outbreaks and improve feed efficiency until banned by the EU in 2006 (Hao et al., 2014). Recently, AMPs have been proposed as an alternative to conventional antibiotic feed additives for improving the growth performance and health of the animals. Several studies indicated that the addition of the AMPs to weanling pig diets beneficially affects the host by improving growth performance, health condition and immune functions and reducing harmful gut microflora. For example, antimicrobial peptide colisin E1 (Cutler et al., 2007), cipB-lactoferricin-lactoferrampin (Tang et al., 2008), and Cecropin AD (Wu et al., 2012) increased immune function and reduced intestinal pathogens. In another experiment, the positive effects on the growth performance, and coefficient of total tract apparent digestibility and intestinal morphology of weanling pigs fed a diet supplemented with synthetic antimicrobial peptide-A3 (AMP-A3) were observed. It was also reported that the dietary supplementation of increasing levels of the AMP-A3 linearly reduced the faecal and intestinal TAB, coliforms and *Clostridium* spp. in weanling pigs (Yoon et al., 2012). In a recent study, the antimicrobial peptide, *Epinephelus lanceolatus* piscidin (EP) was expressed in *Pichia pastoris* host cell and recombinant EP (rEP) was then used as a dietary supplement for *Gallus gallus domesticus*. The rEP supplementation increased body weight, feed efficiency and the levels of interleukin-10 and interferon-γ in the supplemented group *Gallus gallus domesticus* more than in the control (Tai et al., 2020).

AMPs have been demonstrated as promising antiviral agents in the fight against animal infecting viruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV; Elnagdy & AlKhazindar, 2020), porcine epidemic diarrhea virus (PEDV; Guo et al., 2018), porcine transmissible gastroenteritis virus (TGEV; Liang at al., 2020), infectious bronchitis virus (IBV; Sun et al., 2010) and influenza A (Hsieh & Hartshorn, 2016). The antiviral activity of swine intestine antimicrobial peptides (SIAMP) was assessed against infectious bronchitis virus (IBV) in chick embryos. The mortality caused by IBV was reduced remarkably in the SIAMP-treated chick embryos. This result was attributed to the interaction of SIAMP with IBV, which blocked the binding of IBV to host epithelial cells and thus, inhibited virus replication (Sun et al., 2010). In another study, the inhibitory effect of porcine leukocytes originated protegrin-1 (PG-1) against porcine reproductive and respiratory syndrome virus (PRRSV) was investigated in PRRSV infected Marc-145 cells or porcine alveolar macrophages (PAMs). The PG-1 treatment specifically blocked the viral attachment stage, probably due to the presence of specific virus receptor molecules in Marc-145 cells and thus inhibited viral replication but a similar inhibition effect was not observed in PAMs (Guo et al., 2015).

Applications in aquaculture

Fish and other aquatic products are important sources of animal proteins and other essential nutrients needed in the human diet. Although aquaculture is one of the fastest-growing animal food production sectors in the world (FAO, 2020), microbial disease outbreaks are considered the major sectoral problem that leads to significant economic losses (Paria et al., 2018). The use of AMPs can also eliminate detrimental microorganisms in an aquaculture environment, where antibiotic usage is limited due to increasing resistance. For instance, in earlier studies, synthetic AMP epinecidin-1 demonstrated antimicrobial activity against a group of bacteria such as *E. coli*, *Pasturella multocida*, *Aeromonas sobrio*, *A. hydrophila*, *Morganella morganii*, *Flavobacterium meningosepticum* and *Vibrio* species, including *V. parahaemolyticus*, *V. vulnificus*, *V. alginolyticus*, *which are* considered detrimental to aquacultural organisms (Yin et al., 2006). Furthermore, it was found that co-incubation of native cecropin B and a synthetic analogue CF17 with some important fish viral pathogens (infectious hematopoietic necrosis virus, viral haemorrhagic septicaemia virus, snakehead rhabdovirus and infectious pancreatic necrosis virus) decreased viral titres up to 10^4-fold (Chiou et al., 2002).

A recent study by León et al. (2020) demonstrated that the *in vitro* antibacterial and antiviral activity of several synthetic peptides, such as frog caerin1.1, dicentracin (Dic) and NK-lysin peptides (NKLPs) and sole NKLP27. The majority of peptides exhibited strong antibacterial activity against all tested human and fish pathogenic bacteria except *Aeromonas salmonicida*, and inhibits a wide spectrum of fish viruses that are considered the most devastating viruses for aquaculture. It was demonstrated that

the NKL-24, a truncated peptide derived from zebrafish NK-lysin had a potent antibacterial effect against *V. parahaemolyticus* via disruption of the membrane permeabilization (Shan et al., 2020). Recently, antibiotic-resistant *V. parahaemolyticus* was detected from aquatic farmed products such as scallops (De Silva et al., 2019), shrimps (Letchumanan et al., 2019) and shellfish (Lopatek et al., 2015). Hu et al. (2019) proposed Malabar grouper piscidin 1 (EmPis-1) as a safe and efficient agent for eliminating the viable but non-culturable (VBNC)-state cells of ampicillin and kanamycin-resistant pathogenic bacteria. They demonstrated that full-length and truncated forms of EmPis-1 could effectively kill the antibiotic- resistant *E. coli* Top10, *S. aureus* and *V. parahaemolyticus* OS4 by membrane disruption and cell lysis at a concentration of less than 10 μmol/L.

Plant protection applications

Every year around the world, high amounts of pesticides are used to prevent yield losses caused by plant pathogens and insects. However, long-term usage of chemical pesticides is one of the most important reasons for environmental pollution and leads to human health problems (Naik et al., 2006). AMPs are good candidates, which can be used against phytopathogens in various fields of agriculture, without any side effects for the environment, humans or animals (Zasloff, 2002). In vitro, experimental studies reported useful results to evaluate the potency of many candidate peptides to be used in plant protection. For instance, antibacterial activities of the three synthetic peptides including iseganan, pexiganan, and the cecropin-melittin hybrid peptide CAMEL, were demonstrated to inhibit in vitro growth of phytopathogenic bacteria *Pectobacterium carotovorum* and *Pectobacterium chrysanthemi* (Kamysz et al., 2005). In several studies, the antifungal and antibacterial activities of synthetic cecropin A-melittin hybrid peptides were tested against important plant pathogens. Ferré et al. (2006) synthesized short cecropin-A melittin hybrid peptides and proved the activity against fire blight agent *Erwinia amylovora*, halo blight agent *Pseudomonas syringae* and bacterial spot agent *Xanthomonas vesicatoria*. Recently, it was determined that five AMPs, including RW-BP100, CA-M, 3.1, D4E1 and Dhvar-5 were good candidates against *E. amylovora* (Mendes et al., 2021). Vila-Perelló et al. (2003) reported the antimicrobial activity of D32R, an analog of *Pyrularia pubera* thionin, against the pathogenic fungi *Fusarium oxysporum*, *Plectosphaerella cucumerina* and *Botrytis cinerea*, and bacteria *Xanthomonas campestris* pv. *translucens* and *Clavibacter michiganensis*.

The recombinant expression of AMPs in plant bodies has been demonstrated as a successful approach that provided a certain degree of resistance to phytopathogens in various transgenic plants. For example, Alf-AFP defensin and a dermaseptin B1 derivative MsrA2 were expressed in the potato against *Verticullum dahliae* and *Pectobacterium carotovorum*, respectively (Gao et al., 2000; Osusky et al., 2005). Mj-AMP1 jalapa defensin provided certain protection against *Alternaria solani* in transgenic tomatoes (Schaefer et al., 2005). The expression of horseshoe crab-derived tachyplesin I, in tobacco plants provided resistance to the fungal pathogen *Verticullum dahliae* and the phytopathogen *Erwinia carotovora* (Allefs et al., 1996). Similarly, a synthetic polyphemusin variant PV5 showed broad-spectrum enhanced resistance against a variety of bacteria (*E. carotovora*, *Staphylococcus epidermidis*, *Bacillus subtilis* and *E. coli*), fungi (*Fusarium oxysporum* and *Botrytis cineria*) and virus (Tobacco Mosaic Virus) in the transgenic tobacco plant (Bhargava et al., 2007). The expression of cecropin P1, a mammalian antimicrobial peptide, in transgenic tobacco provided an increased resistance towards the pathogenic bacteria *P. syringae*, *Pseudomonas marginata* and *E. carotovora* (Zakharchenko et al., 2005). In several studies focused on MSI-99, an analogue of magainin was expressed in different plants, such as tobacco, banana, tomato and grapevine, which demonstrated effective protection against a variety of fungal and bacterial phytopathogens (Alan et al., 2004; Chakrabarti et al., 2003; Vidal et al., 2006). In another study, Dm-AMP1, a defensin from *Dahlia merckii*, was expressed in the aubergine plant to protect against *B. cinerea* and *V. alboatrum* (Turrini et al., 2004).

In recent years, AMPs have drawn attention as a good alternative for controlling post-harvest decay as well as controlling plant diseases. The phytopathogens are important reasons for postharvest decays, resulting in significant economic losses by declining quality or leading deterioration in agricultural products (Keymanesh et al., 2009). For instance, it was reported that the derived peptide KYE28 from heparin cofactor II successfully inhibited symptoms of spot disease caused by *Xanthomonas vesicatoria* and *Xanthomonas oryzae* in separated tomato leaves (Datta et al., 2016). In another study, the antifungal effects of O_3TR (H-OOWW-NH_2) and its lipopeptide derivative $C_{12}O_3$TR (C_{12}-OOWW-NH_2) were evaluated against the green mould agent *Penicillium digitatum*, one of the main post-harvest pathogens in citrus. Both *in vitro* and *in vivo* studies showed that the O_3TR and $C_{12}O_3$TR peptides successfully controlled *P. digitatum* in citrus plants (Li et al., 2019). Vase water contains various spoilage bacteria, shorting the vase life of roses after harvest. In a study performed by Florack et al. (1996), it was found that tachyplesin I and cecropin B were highly effective against the

pure cultures of *Bacillus*, *Enterobacter* and *Pseudomonas* species typically found in vase water. Datta et al. (2015) showed that the external application of de novo designed VG16KRKP peptide in both rice and cabbage plants could effectively prevent the Gram-negative plant pathogens, *X. oryzae* and *X. campestris* that cause bacterial diseases. These last experiments show the potential of AMPs in the control of important pathogens in the postharvest stage. However, further studies are needed to examine the stability and economic feasibility of various peptides in delaying post-harvest decay and inhibition of plant diseases.

CONCLUSION

AMPs are basic elements of innate immunity in living organisms, which act rapidly and are multifunctional. Today, studies for the detection of new AMPs from various sources are increasingly continuing. Intensive research is being carried out in order to convert the discovered AMPs into commercial products and find new application areas. All living organisms, particularly marine organisms are infinite sources of AMPs. AMPs emerged as promising agents to be able to meet the need for new antimicrobial compounds. Although studies to date have indicated that AMPs have a lower tendency to resist than antibiotics, it should not be forgotten that this evolution is an inevitable consequence. The limitations such as efficacy, stability and toxicity associated with natural AMPs are well-known drawbacks that restrict the comprehensive utilization of AMPs. The synthetic AMPs produced by de novo design offer promising progress at a certain level to eliminate these challenges. Even though it is easy to change the characteristics of AMPs with minor modifications, the results of these changes are still difficult to predict. Therefore, recently, computational approaches have been introduced to AMP research to understand the effects of structural modifications on the physicochemical properties, stability and activity of AMPs. These approaches also help to understand the action mechanism of AMPs better and accurately predict their activities. Apart from this, it is clear that the legal regulations of AMPs should proceed in line with all this effort.

CONFLICT OF INTEREST

None of the authors declare a conflict of interest.

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