Infection and Drug Resistance

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REVIEW

Antimicrobial Peptides: Mechanisms, Applications, and Therapeutic Potential

Mohammed Alzain[1], Hussam Daghistani[2,3], Taghreed Shamrani[2,4], Yousef Almoghrabi[2,3], Yassir Daghistani[5], Ohood S Alharbi[6], Ahmad M Sait[3,7], Mohammed Mufrrih[7,8], Wafaa Alhazmi[7], Mona Abdulrahman Alqarni[9], Bandar Hasan Saleh[9], Manal A Zubair[9], Noha A Juma[9], Hatoon A Niyazi[9], Hanouf A Niyazi[9], Waiel S Halabi[10], Rawan Altalhi[11], Imran Kazmi[1], Hisham N Altayb[1], Karem Ibrahem[9], Abdelbagi Alfadil[9,12]

[1]Department of Biochemistry, faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia; [2]Department of Clinical Biochemistry, Faculty of Medicine, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [3]Regenerative Medicine Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [4]Food, Nutrition and Lifestyle Unit, King Fahd Medical Research Centre, King Abdulaziz University, Jeddah, 21551, Saudi Arabia; [5]Department of Medicine, Faculty of Medicine, University of Jeddah, Jeddah, Saudi Arabia; [6]Department of Microbiology and Parasitology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia; [7]Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [8]Special Infectious Agents Unit BSL-3, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia; [9]Department of Clinical Microbiology and Immunology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [10]Department of Optometry, Faculty of Applied Medical Sciences, University of Jeddah, Jeddah, Saudi Arabia; [11]Department of Biological Sciences, College of Science, University of Jeddah, Jeddah, 23445, Saudi Arabia; [12]Centre of Research Excellence for Drug Research and Pharmaceutical Industries, King Abdulaziz University, Jeddah, Saudi Arabia

Correspondence: Abdelbagi Alfadil, Department of Clinical Microbiology and Immunology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, Email aegmusa@kau.edu.sa

Abstract: Antimicrobial peptides (AMPs) are short protein fragments that function as an innate immune response across diverse life forms. Structurally, AMPs exhibit diverse configurations, including α-helical, β-sheet, mixed, and random-coil forms, enabling a variety of mechanisms to combat pathogens. The mechanisms of action of AMPs encompass membrane disruption and inhibition of critical cellular processes, highlighting their broad-spectrum activity against bacteria, fungi, viruses, and parasites. AMP activity extends to anti-tumor and anti-HIV activities, further emphasizing their therapeutic potential. Purifying AMPs from natural sources can be challenging due to posttranslational processing. Fortunately, chemical synthesis has the advantage of producing high yield and pure AMPs, but the reaction efficiency diminishes as the molecular weight of peptides increases. Advances in computational tools and curated databases have further accelerated AMP discovery and engineering. While commercially available AMP-based antibiotics and in vivo efficacy against multidrug-resistant bacteria demonstrate their clinical relevance, several limitations still hinder the widespread use of AMPs such as low stability and toxicity to human cells. This review provides a comprehensive overview of AMP origins, characteristics, mechanisms, applications, and future prospects in combating infectious diseases with a particular focus on the clinical applicability of AMPs and their prospects as potent alternative to traditional antibiotics.

Keywords: antimicrobial peptides, AMPs, AMP structure, anti-tumor peptides, anti-HIV peptides, peptide synthesis

Introduction

The discovery of penicillin around the turn of the century has greatly reduced the severity and mortality of infections and improved the safety of other therapies, including immunosuppressive medications and surgery. Unfortunately, antimicrobial resistance (AMR) has become more common in recent decades due to misuse of antifungals and antibiotics, even when they are not strictly required, as in the case of viral respiratory illnesses.[1] According to the World Health Organization (WHO), AMR is projected by 2050 to cause about ten million deaths every year, making it one of the top ten global public health threats.[2–4] Tracking antibiotic consumption patterns is vital, as studies indicate a clear correlation between antibiotic usage and resistance development. For example, a significant global increase has been documented in antibiotic consumption between 2000 and 2015, particularly pronounced in low- and middle-income

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countries.[5,6] This misuse extends to livestock, where antimicrobials are frequently employed as growth promoters, compounding the public health threat.[7] The ability of AMR bacteria to spread across geographic regions makes it a concern for global health.[8] The transmission pathways of AMR bacteria are multi-faceted, involving direct human-to-human contact, animal reservoirs, and environmental vectors.[9] The role of the environment is pivotal, as studies have shown that wastewater treatment plants serve as reservoirs for AMR bacteria and their genes.[9] Treated sewage from these plants, for example, often contains substantial concentrations of antibiotic-resistant genes (ARGs), enhancing the emergence and recirculation of AMR bacteria into aquatic systems, which pose a critical public health risk.[9,10]

One of the alarming implications of AMR is its impact on the management of severe infections like tuberculosis (TB). TB, particularly the multidrug-resistant (MDR) and extensively drug-resistant (XDR) forms, poses a staggering public health challenge. The global incidence of TB is compounded by the emergence of resistant strains, making its treatment increasingly complex and costly.[11,12] Effective control over these infections is pivotal not just for individual health but for societal well-being, as AMR can overwhelm healthcare systems.[13]

The period from 2011 to 2016, saw a decline in new antibiotic development with only eight new antibiotics approved by the US FDA.[14] This stagnation in antibiotic discovery is alarming, especially as the emergence of resistant strains outpaces the development of new treatments.[15] Currently, three main approaches are utilized in the quest for new antibiotics: (1) developing novel compounds from untapped chemical classes and targeting new biological pathways, (2) creating new compounds from existing classes that act on established targets, and (3) modifying existing compounds to circumvent resistance mechanisms.[16,17] Applying advanced technologies such as machine learning to predict microbial resistance and optimize drug design has become vital in the antibiotic discovery process.[15] In addition to novel chemical syntheses, natural products remain a significant source of new therapeutic agents. Studies highlight the potential of compounds derived from environmental microorganisms, such as a *Streptomyces* strain that showed activity against multi-resistant pathogens.[18] Similarly, the exploration of nonribosomal peptides and polyketides has been encouraged, as recent advancements in in silico strategies have facilitated the discovery of new antibiotic candidates.[19]

Antimicrobial peptides (AMPs) have emerged as a promising alternative to conventional antibiotics in the face of rising MDR bacteria.[20] AMPs are low molecular weight protein fragments (2–30 amino acids) that are released in vitro via enzymatic hydrolysis, fermentation, or food processing, or in vivo by digestive enzymes, AMPs possess improved antimicrobial activity compared to native proteins.[21–23] Various organisms produce AMPs in the course of their innate immune response to protect themselves against microbial infections. Cecropins, for example, are cationic peptides that serve as the first line of defense of insects against infectious agents.[24,25] These peptides have distinctive features, such as hydrophobicity and net positive charge, that allow them to adhere to and insert into membrane bilayers.[24,26,27] AMPs have many advantages over traditional antibiotics, including broad-spectrum antibacterial activity, a slower rate of resistance development, and the capacity to influence the host immunological response, making them a prospective alternative to conventional antibiotics.[28] Methicillin resistance, for instance, is caused by mutations in the penicillin-binding protein (PBP) of *Staphylococcus aureus*. AMPs, on the other hand, do not exhibit cross-resistance or overlap in their mechanisms of action since they act on the cell membrane, therefore, they can be utilized to treat the rising number of antibiotic-resistant infections.[29,30] Additionally, the capacity of a single AMP to act through various mechanisms and pathways enhances its potency and reduces resistance; a drug that functions through several pathways minimizes the possibility of bacteria acquiring multiple mutations at the same time. Moreover, because many AMPs target evolutionarily conserved cell membrane components, bacteria must entirely remodel their membranes, necessitating numerous mutations over an extended period.[31,32]

Because of these advantageous characteristics of AMPs, coadministration of antibiotics is one more possible use for AMPs. Antibiotic resistance may be weakened or prevented by combinational AMP and antibiotic therapy. For instance, combination therapy was used to eradicate vancomycin and azithromycin resistance in *Escherichia coli, Pseudomonas aeruginosa*, and *Staphylococcus aureus* employing the AMP DP7.[33] Additionally, several AMPs and antibiotics have been shown to work synergistically in vitro.[34,35]

Immune modulation is a notable advantage of AMPs beyond their antimicrobial activity, for instance, the AMP LL-37 has been shown to influence neutrophil functions by reducing the release of pro-inflammatory mediators while simultaneously enhancing antimicrobial activity.[36] This dual role can help prevent excessive inflammation during an

immune response, thereby providing a balanced approach to disease management in conditions such as infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[37]

Several limitations still hinder the widespread use of AMPs such as the toxicity of AMPs to eukaryotic cells.[38] Due in significant part to their high therapeutic dosage, a number of AMPs have been shown to be extremely nephrotoxic.[39,40] Another major limitation of AMPs is their susceptibility to enzymatic degradation by proteases, which shortens their half-life and bioavailability when administered in vivo.[41] Additionally, studies indicate that some bacteria can evolve resistance to various AMPs, which may limit their long-term effectiveness.[42] Large-scale production of AMPs also represents another challenge. In chemical synthesis, the reaction efficiency diminishes as the molecular weight of peptides increases[43] whereas the production of AMPs by recombinant expression is limited by the toxicity of AMPs toward the expression host cells.[44,45]

Addressing these limitations of efficacy, stability, toxicity, and resistance will be crucial in transitioning AMPs from the laboratory to the clinic.

Antimicrobial Peptides (AMPs): An Introduction

Antimicrobial peptides (AMPs) are short protein fragments, typically made up of around 12 to 50 amino acids[28,46–48] and are generated as a component of the innate immune system in both prokaryotic and eukaryotic organisms.[49,50] The first two cationic AMPs, cecropins A and B, were identified in silk moth hemolymph in the early 1980s and they were considered to be the primary means of insect defense against invading pathogens. Subsequently, magainins were discovered in *Xenopus* frogs,[51,52] revealing that AMPs can be produced by higher organisms such as vertebrates. It has now been established that AMPs are expressed by most living organisms[24] and they function as the first line of defense from viral, fungal and bacterial infections.[53–56] Natural AMPs are secreted by epithelial cells in mammals and can be found in tissues, fluids, and body surfaces, including the mucosa. These areas are also frequently exposed to bacteria, both commensals and pathogens.[57] Furthermore, some immune system cells, particularly phagocytes, create AMPs, which are found in granules. At regions of infection or inflammation, these phagocytic cells release their AMPs at quantities that are probably strong enough to directly target bacterial cells in the near vicinity.[58]

Most AMPs share some common characteristics. In general, AMPs are ribosomally synthesized polypeptide sequences, usually produced as inactive pro-peptides requiring proteolytic cleavage to become active,[59,60] therefore, the regulation of AMPs depends not only on their own expression but also on the abundance of suitable proteases.[61,62] The primary amino acid sequences of AMPs are diverse, but they are abundant in cationic residues, such as Arg and Lys, which give these molecules a positive charge at neutral pH.[47,63,64] Furthermore, AMPs often contain a significant proportion (up to 50% or more) of hydrophobic amino acids.[50] These two features enable AMPs to fold (eg, following interaction with membranes) into amphipathic secondary structures, with hydrophobic residues on one side of the molecule and cationic and polar residues on the opposing face.[65,66]

AMPs have a wide range of activity against Gram-positive and Gram-negative bacteria, fungi, mycobacteria, and certain enveloped viruses.[24,67] Furthermore, it has been found that AMPs may have cytotoxic effects on cancer cells[20,68,69] as well as immunomodulatory functions,[70,71] such as immunostimulatory upregulation of cytokines[72,73] lactic acid formation control, causing casecidins to have immunostimulating action[70] stimulating lymphocyte proliferation[71] or inducing macrophages, and reducing expression of lipopolysaccharides.[74] For example, cytotoxic T cells and natural killer cells produce the peptide cNK-lysin, which is the chicken homolog of human granulysin. cNK-lysin and its synthetic variants have antimicrobial action against apicomplexan parasites by membrane disruption. The immune-modulatory effects of cNK-lysin derivatives entail the mitogen activated protein kinase-mediated signaling cascade, which includes p38, extracellular signal-regulated kinase 1, and c-Jun N-terminal kinases.[75]

Another aspect of AMP activity that has been extensively studied is their capacity to influence biofilm development.[76,77] Biofilms are microbial cells that adhere to surfaces and form their own matrix of polysaccharides, DNA, and proteins. These microorganisms can attach to any surface, including medical devices, and cause chronic infections that are challenging to treat.[78] The biofilm matrix actively participates in the development of antimicrobial resistance by shielding bacteria from the host immune system, harsh environmental conditions, and antimicrobial agents, including many antibiotics.[79] Biofilms are extremely difficult to treat because of their adaptive resistance to

antibiotics.[78,80] AMPs are promising candidates for developing antibiofilm medications by acting on a variety of molecular targets, at different phases of biofilm formation, and via a range of mechanisms. These include inhibiting biofilm development and adhesion, downregulating quorum sensing factors, and disrupting the pre-formed biofilm.[81,82] Examples of AMPs that can effectively inhibit biofilm growth are cationic AMPs, such as the viral-derived peptide pepR that have shown efficacy against *Staphylococcus aureus* biofilms.[83]

Structural and Physicochemical Properties of AMPs

Understanding the processes by which AMPs interact with biological targets requires an understanding of their structural organization and arrangement. Various experimental methods, including X-ray crystallography, NMR (nuclear magnetic resonance), cryo-EM (cryo-electron microscopy) and AFM (atomic force microscopy) have been combined with computational approaches, such as molecular modeling, docking, and dynamics to better understand the structures and biological functions of AMPs.[84] Based on their secondary structure, AMPs are classified as α-helical, β-sheet, mixed (α-helical/β-sheet),[85,86] or extended/random-coil peptides[87] (Figure 1).[50,65,88]

α-Helical Conformation of AMPs

The most abundant AMPs in nature are α-helical AMPs,[89,90] and they have been isolated from a wide range of species including fish, amphibians, plants, insects, and mammals.[59] Typically, the α-helices are abundant in Leu, Ala, Gly, and Lys. The way these AMPs interact with targeted membranes greatly influences their α-helical form, as numerous studies have revealed.[89,91,92] The conformational shift that happens upon interaction with the targeted membrane separates the hydrophilic and hydrophobic residues, and the peptide acquires an amphipathic shape, which is required for membrane-targeting activity.[93] With the hydrophilic part facing inward and forming a pore, and the hydrophobic part engaging with the membrane lipid core, α-helices form bundles in the membrane.[94,95] Some of the well-known AMPs that have an

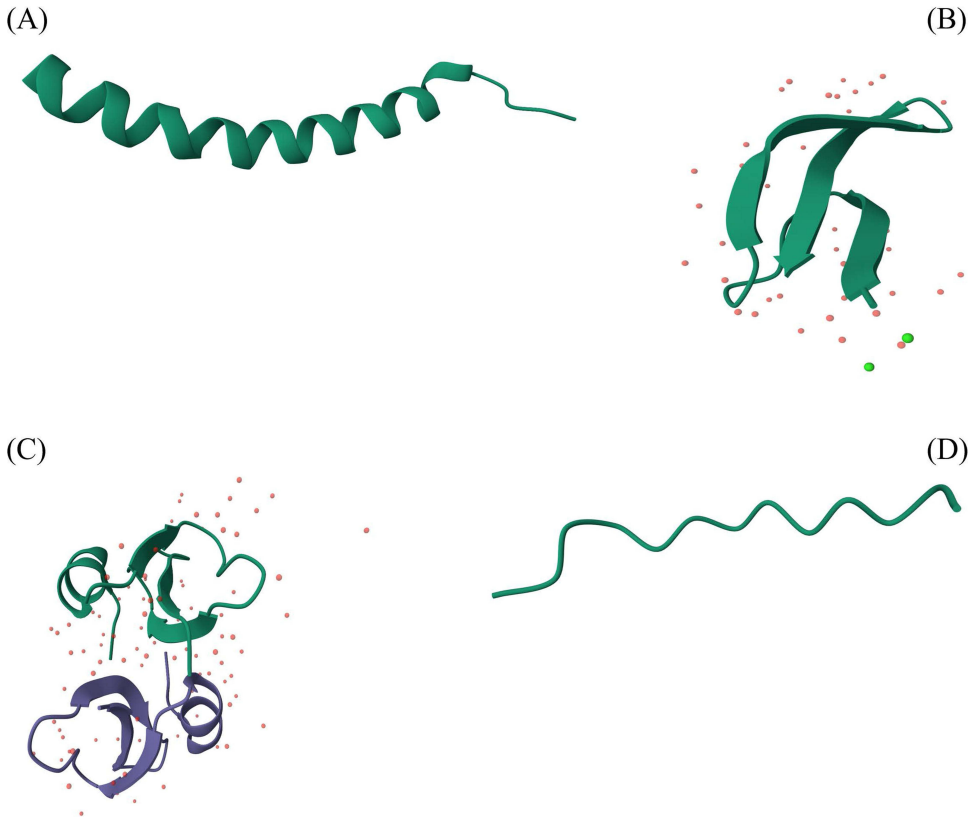

Figure 1 Four representative structural classes of AMPs. (**A**) α-helical peptide (human cathelicidin LL-37, PDB ID: 2K6O), (**B**) β-sheeted peptide (human α-defensin-6, PDB ID: 1ZMQ), (**C**) peptide containing both α-helix and β-sheet, (human β-defensin-2, PDB ID: 1FD3). (**D**) linear peptide (bovine indolicidin, PDB ID: 1G8C).

amphiphilic α-helix secondary structure in membrane-mimetic environments include: magainin from the skin of the frog *X. laevis*, melittin from the honey bee *Apis mellifera* venom, and LL-37-derived human cathelicidin.[65,96–98] The presence of α-helix motifs (helicity) enhances peptide interactions with target membranes and facilitates membrane rupture.[99] Disrupting the α-helix structure by substituting amino acids leads to decreased antibacterial activity.[100] Although the helical shape of AMPs has a major impact on their antibacterial efficacy,[101] it also has links to toxicity to mammalian cells and hemolytic activity.[102,103]

Key Takeaways:

- Abundance & Distribution: α-helical AMPs are the most common AMPs, found in various species including fish, amphibians, plants, insects, and mammals.
- Amino Acid Composition: Typically rich in Leu, Ala, Gly, and Lys.
- Membrane Interaction: Their α-helical conformation is influenced by interactions with target membranes, leading to an amphipathic structure that is essential for membrane-targeting activity.
- Mechanism of Action: The α-helices form bundles in membranes, with hydrophilic regions forming pores and hydrophobic regions interacting with lipid cores, facilitating membrane rupture.
- Notable Examples: Magainin (frog), melittin (bee venom), and LL-37 (human cathelicidin).
- Structure-Function Relationship: The α-helix structure enhances antibacterial activity, while disruptions reduce efficacy. However, this structure is also linked to toxicity and hemolytic activity in mammalian cells.

β-Sheet Conformation of AMPs

A number of linear structures take on a β-hairpin-like conformation, and the β-sheet conformation of AMPs is made up of at least two β-strands that are joined by disulphide bonds.[104] The conserved cysteine residues found in the majority of this family's members generate disulfide bridges, which are crucial for their conformation and function.[105,106] Defensins, for example, have disulfide bridges that improve structural stability and prevent protease degradation.[107] Head-to-tail cyclization and salt bridges are two other elements that support the stability of the secondary structure of the peptides. Because β-sheet AMPs have a more stable structure, they do not undergo significant conformational changes when interacting with phospholipid membranes.[20] β-sheet peptides are typically amphipathic, with polar and non-polar domains separated by β-strands.[27] The β-sheet AMPs include thanatin, gomesin, protegrin-1 (PG-1), tachyplesin, and polyphemusin I.[108–112] Protegrins (PG1-PG5) are antimicrobial peptides derived from porcine leukocytes. Protegrins' antimicrobial action is explained by a stepwise pore formation model that begins with antiparallel dimerization in a membrane, followed by oligomer formation and assembly into an octameric pore structure that acts as an uncontrolled ion transport channel.[113]

The most prevalent form of β-sheet AMPs is defensins, which are further classified into subfamilies based on disulfide bond position.[114,115] α-Defensins are primarily found in neutrophils, while β-defensins are released by epithelial cells in numerous organs.[116,117] θ-Defensins, the third class of defensins, were initially identified in leukocytes from rhesus macaques. The cyclic cysteine ladder confirmation, which has a cyclic peptide backbone joined by three parallel disulphides, is what defines the structure of θ-defensins.[118,119] The conformation of the cyclic cysteine ladder presumably contributes to the antibacterial action of θ-defensins by preserving the stability and structure of the cyclic backbone.[120] The disulphide bridges and circularity in human θ-defensin-1 (retrocyclin-1) were found to enhance receptor binding activity and block HIV-1 entrance.[121]

Key Takeaways:

- β-sheet Structure: AMPs with β-sheet conformations consist of at least two β-strands connected by disulfide bonds, forming a β-hairpin-like structure.
- Disulfide Bridges & Stability: Conserved cysteine residues form disulfide bridges, crucial for maintaining structural stability and resistance to protease degradation (eg, defensins).
- Structural Stability: β-Sheet AMPs are more rigid and do not undergo major conformational changes when interacting with membranes.

- Mechanism of Action: Typically amphipathic, β-sheet AMPs separate polar and non-polar domains through β-strands. Some, like protegrins, form pores in membranes, disrupting ion transport.
- Notable Examples: Thanatin, gomesin, protegrin-1 (PG-1), tachyplesin, polyphemusin I, and defensins.
- Defensins & Subtypes:
  - α-Defensins: Found in neutrophils.
  - β-Defensins: Secreted by epithelial cells.
  - θ-Defensins: Identified in rhesus macaques, featuring a cyclic cysteine ladder structure that enhances stability and antibacterial activity.
- Antiviral Activity: The cyclic structure of θ-defensin (eg, retrocyclin-1) enhances receptor binding and can block HIV-1 entry.

αβ-Conformation of AMPs

These AMPs are mostly found in membranes and have α-helices and β-sheets.[122] The α-helix/β-sheet mixed structure is stabilized by three or four disulphide bridges.[114] This cysteine-stabilized α/β (CSαβ) structural motif, was first identified in insect defensins and scorpion neurotoxins.[123–125] Defensins containing CSαβ are commonly found in plants and insects, and they mostly exhibit antimicrobial activity against bacteria and fungus.[126–128] Amphipathic structures often contain hydrophobic residues in the β-sheet of the motif and positively charged residues in the helix.[129] Due to these amphipathic structures, plectasin, a peptide antibiotic from a saprophytic fungus with a CSαβ pattern, can adhere to and damage bacterial cytoplasmic membranes.[130] Human β-defensins hBD1, hBD2, and hBD3 are examples of αβ-AMPs since they contain an αβββ fold.[107,131] Pisum sativum defensin 1 (Psd1), an antifungal plant-derived peptide, has a βαββ fold that disrupts *Neurospora crassa*'s cyclin F, impacting the cell cycle.[132–135]
Key Takeaways:

- Structural Composition: These AMPs contain both α-helices and β-sheets, stabilized by three or four disulfide bridges.
- CSαβ Motif: The cysteine-stabilized α/β (CSαβ) structural motif was first identified in insect defensins and scorpion neurotoxins.
- Distribution & Function: Found mainly in plants and insects, CSαβ-containing defensins exhibit antimicrobial activity against bacteria and fungi.
- Amphipathic Nature: Hydrophobic residues are present in the β-sheet, while positively charged residues are in the α-helix, aiding membrane interaction.
- Notable Examples:
  - Plectasin: A fungal peptide antibiotic that binds to and disrupts bacterial membranes.
  - Human β-Defensins (hBD1, hBD2, hBD3): Contain an αβββ fold.
  - Pisum sativum defensin 1 (Psd1): A plant-derived antifungal peptide that disrupts the fungal cell cycle by targeting cyclin F in *Neurospora crassa*.

Non-αβ AMPs

Tryptophan-rich, proline-rich, or glycine-rich peptides are examples of non-αβ AMPs, sometimes referred to as loop or extended peptides, which do not have α-helix or β-sheet structures.[136]

A common nonpolar amino acid is proline. In contrast to other AMPs, proline-rich AMPs do not kill bacteria by breaking down their membranes; instead, they reach the bacterial cytoplasm through SbmA (the inner membrane transporter).[137] Cytoplasmic proline-rich AMPs bind to ribosomes and stop aminoacyl-tRNA from attaching to peptidyl-transferase sites. Additionally, they impede protein synthesis by trapping decoding release components on the ribosome following translation termination.[138] Tur1A, an orthologous AMP of the bovine proline-rich AMP Bac7 discovered in *Tursiops truncatus*, attaches to ribosomes and inhibits the transition from the beginning to extension phase of protein synthesis. Proline-rich AMPs differ in sequence but share short motifs with repeated arginine and proline and residues,

such as PRPX in Bac7.[139,140] pPR-AMP1, a proline-rich AMP present in crabs (*Scylla paramamosain*), shows antibacterial action against both Gram-positive and Gram-negative bacteria, although proline-rich AMPs primarily kill Gram-positive bacteria.[141] Because of its non-αβ structure, the glycine-rich peptide KAMP-19 from the human eye can distort bacterial cell membranes and result in the formation of pores.[142]

Tryptophan is a non-polar amino acid that uses ion-pair-π interactions to naturally activate Arg-rich AMPs[143] improving the interactions between peptides and membranes.[144] Indolicidin and Triptricin are well-known AMPs rich in Tryptophan and Arginine residues. Octa 2 (RRWWRWWR) is an AMP high in tryptophan and arginine that inhibits Gram-positive *S. aureus, Pseudomonas aeruginosa*, and Gram-negative *E. coli*.[145]

Attacins and diptericins, two glycine-rich AMPs, are abundant in nature.[146,147] The percentage of glycine residues (14% to 22%) in these peptides significantly affects their tertiary structure. Salmonid cathelicidins produce glycine-rich AMP, which triggers phagocyte-mediated microbicidal processes.[148] Moreover, a promising commercial drug against clinical Gram-negative bacteria is the glycine-rich central-symmetrical GG3.[149]

Key Takeaways:

- Non-αβ AMPs: These antimicrobial peptides (AMPs) lack α-helix or β-sheet structures and include proline-rich, tryptophan-rich, and glycine-rich peptides.
- Proline-Rich AMPs:
  - Enter bacterial cytoplasm via SbmA transporter instead of disrupting membranes.
  - Inhibit protein synthesis by binding to ribosomes and blocking aminoacyl-tRNA attachment.
  - Examples: Tur1A (from *Tursiops truncatus*), Bac7 (bovine), and pPR-AMP1 (crab-derived).
- Glycine-Rich AMPs:
  - Distort bacterial membranes and form pores (eg, KAMP-19 from the human eye).
  - Found in nature as attacins and diptericins, with glycine content influencing structure.
  - Examples: Salmonid cathelicidins and GG3 (a potential commercial antimicrobial).
- Tryptophan-Rich AMPs:
  - Utilize ion-pair-π interactions to enhance peptide-membrane interactions.
  - Examples: Indolicidin, Triptricin, and Octa 2 (RRWWRWWR), which target Gram-positive and Gram-negative bacteria.

Cyclic and Unusual or Complex AMPs

Ribosomally generated peptides with an N-to-C-terminal covalent connection and no further linkages are known as cyclic bacteriocins.[150] Both enterocin NKR-5-3B from *Enterococcus faecium* NKR-5-3 and carbocyclin A from *Carnobacterium maltaromaticum* UAL307 have four α-helices, with the N-terminal connected to the C-terminal.[151,152] Thioether and disulfide bonds are used by other backbone-cyclized peptides to maintain their structural integrity. For example, cyclic AMPs, including plant cyclotide Kalata B1 and mammalian θ-defensin RTD-1, possess a cysteine-knotted structure formed by three disulfide bonds, which gives them more structural stability than linear peptides.[153,154] Kalata B1 exhibits anti-HIV action due to its intact cyclic backbone.[155] Three disulfide connections combine to form the structural motif known as the cysteine knot, which results in an embedded ring. Two disulfide links are joined by a third disulfide bond to form their backbone segments.[156] This cysteine knot framework is versatile and can handle many amino acid changes, making it a promising scaffold for drug design and protein engineering applications.[153] Circulin A and B are macrocyclic cyclotides from the bracelet sub-family.[157] The disulfide bond arrangement of Cys1-Cys17, Cys5-Cys19, and Cys10-Cys24 in Circulin A and B results in a compact structure and fold that are held up by a network of hydrogen bonds.[158] They have anti-viral action and could be used as anti-HIV medicines.[159,160] Cys4-Cys20, Cys11-Cys25, and Cys19-Cys37 are the three disulfide linkages found in the antimicrobial peptide tachystatin B. Together with two additional disulfide links and two backbone segments (Cys4-Cys11 and Cys20-Cys25), the Cys19-Cys37 disulfide

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bond creates a closed ring, forming an inhibitory cysteine-knot motif necessary for antibacterial action.[161] Subtilosin A is a distinct cyclic AMP that has three cross-links between the α-positions of Phe22, Thr28, and Phe31 and the sulfurs of Cys13, Cys7, and Cys4 as well as an amide bond between its N and C termini.[162]

Key Takeaways:

- Cyclic Bacteriocins: Ribosomally synthesized peptides with N-to-C-terminal covalent bonds, lacking additional linkages.
- Structural Stability: Maintained by thioether and disulfide bonds, which enhance resistance to degradation.
- Notable Examples:
  - Enterocin NKR-5-3B and Carbocyclin A: Feature four α-helices with N-to-C terminal cyclization.
  - Kalata B1 & RTD-1 (θ-defensin): Contain a cysteine-knotted structure, providing exceptional stability and potential anti-HIV activity.
  - Circulin A & B: Macrocyclic cyclotides with compact folds stabilized by hydrogen bonds, showing antiviral properties.
  - Tachystatin B: Forms an inhibitory cysteine-knot motif essential for antibacterial activity.
  - Subtilosin A: Features unique α-position cross-links and an N-to-C-terminal amide bond for added structural integrity.
- Potential Applications: The cysteine knot framework offers versatility for drug design and protein engineering.

A summary of structures, sources and mechanisms of action of AMPs discussed in this section can be found in Table 1.

Table 1 Structures, Sources and Mechanisms of Action of AMPs Discussed in Structural and Physicochemical Properties of AMPs

AMP	Source	Structure	Mechanism of Action	Ref
Magainin	Frog (*Xenopus laevis*)	α-helical peptide	Formation of pores in lipid bilayers	[163]
Melittin	Honeybee venom	α-helical peptide	Formation of pores in lipid bilayers	[164]
LL-37	Epithelial and immune cells of humans	α-helical peptide	Formation of pores in lipid bilayers	[165]
α-Defensins (HD5 and HD6)	Neutrophils of humans	β-sheet peptide	Membrane lysis	[166]
β-Defensins (hBD1 and hBD2)	Epithelial cells of humans	β-sheet peptide	Membrane lysis	[167]
θ-Defensins	Leukocytes of rhesus macaques	β-sheet peptide	Membrane lysis	[168]
Tur1A	Bovine	Linear peptide	Inhibition of protein synthesis	[139]
pPR-AMP1	Plants	Linear peptide	Formation of pores in lipid bilayers	[169]
KAMP-19	Human epithelial tissues	Linear peptide	Membrane lysis	[170]
Indolicidin	Bovine neutrophils	Linear peptide	Formation of pores in lipid bilayers	[171]
Triptricin	Fungi	Linear peptide	Membrane lysis	[172]
Attacins	Cecropia moth (*Hyalophora cecropia*)	Linear peptide	Membrane lysis	[173]
Diptericins	Insects (*Drosophila melanogaster*)	Linear peptide	Membrane lysis	[174]
NKR-5-3B	*Enterococcus faecium*	Cyclic peptide	Membrane permeation	[175]
Carbocyclin A	*Carnobacterium maltaromaticum*	Cyclic peptide	Formation of pores in lipid bilayers	[176]
Kalata B1	Plant (*Oldenlandia affinis*)	Cyclic peptide	Formation of pores in lipid bilayers	[177]

(*Continued*)

Table 1 (Continued).

AMP	Source	Structure	Mechanism of Action	Ref
Circulin A and B	Plant (*Chassalia parvifolia*)	Cyclic peptide	Inhibition of replication of HIV	[178]
Tachystatin B	Horseshoe crab (*Tachypleus tridentatus*)	Cyclic peptide	Membrane lysis	[179]
Subtilosin A	*Bacillus subtilis*	Cyclic peptide	Formation of pores in lipid bilayers	[180]

Physicochemical Characteristics of AMPs

Natural AMPs span between 10 and 100 amino acid residues in length, with the majority having fewer than 50 amino acids (Figure 2).[181] The two amino acid-only peptides F3 and Gageotetrin A are the shortest in the Antimicrobial Peptide Database (APD).[182,183] For antibacterial and membrane-lytic activity, AMP length is essential,[184–186] because as the peptide length decreases, there is a decreased likelihood of generating secondary structures like α-helices and β-sheets, which are essential for antibacterial activity. AMPs are often amphipathic, meaning they comprise hydrophilic and hydrophobic residues on both ends of positively charged cationic peptides.[20] Gram-positive bacteria have a thick cell wall (15–30 nm) that contains peptidoglycans, polymers, neutral polysaccharides, lipoteichoic acids, and glycolipids. Gram-negative bacteria have a more complex structure, with an outer membrane containing lipopolysaccharide, phospholipids, and protein, and a peptidoglycan layer between the outer and inner membranes made of phospholipids and proteins. Bacterial membranes feature a high concentration of negatively charged molecules,[187] therefore positively charged AMPs bond to them by electrostatic interactions, initiating their bactericidal effect.[188]

Natural AMPs range in cationicity from 0 to over 20 positive charges, with most active peptides falling in an intermediate range of +3 to +6 net charge (Figure 2). Some studies suggest a correlation between charge and potency. However, no ideal structure-function profiles have been identified, perhaps due to the need for additional parameters to improve prediction sensitivity. Secondary interactions, solvation, and amino acid composition determine how these

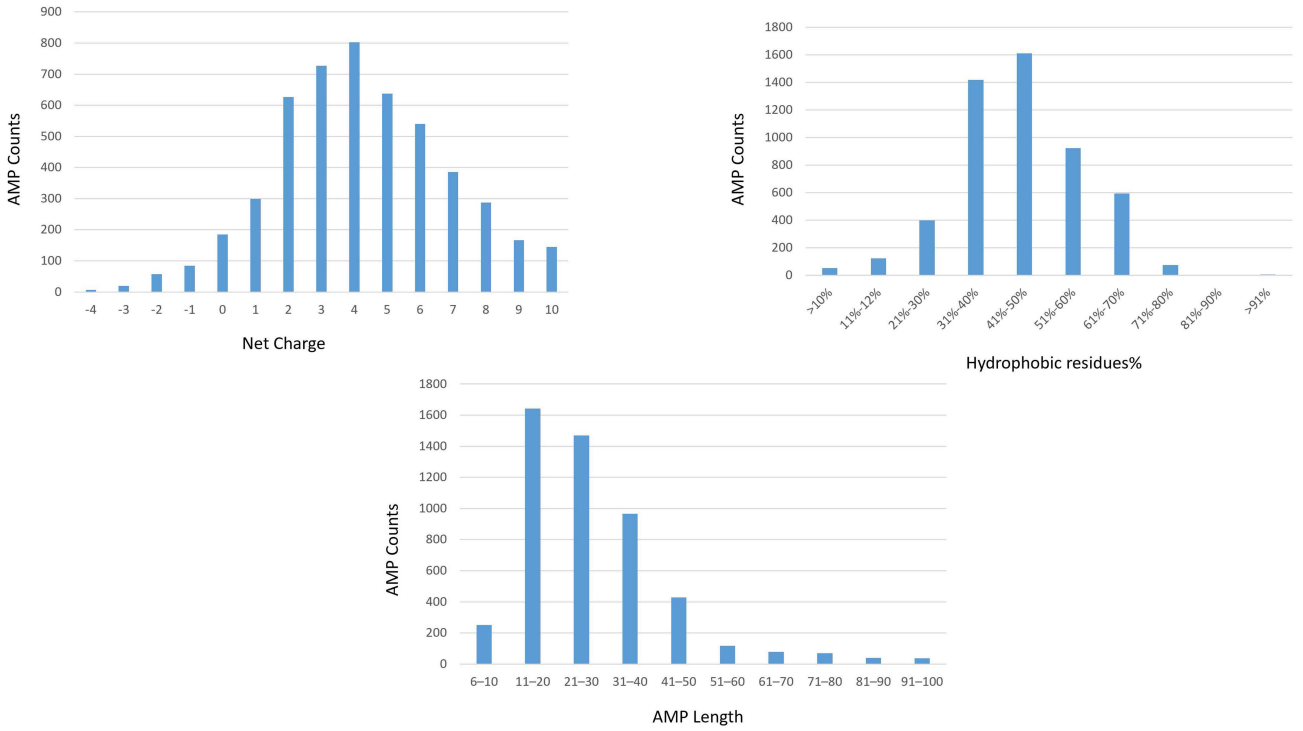

Figure 2 Statistics of the main features of AMPs. This figure was obtained from a total of 5099 peptides available on the APD3 database (available at https://aps.unmc.edu/ [accessed on 25 March 2025]).

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molecules interact and whether they exhibit broad-spectrum or specialized activity. For example,[189] examined the impact of net charge and positively charged residues on the biological activity and biophysical features of the amphipathic helical AMP L-V13K, including hydrophobicity, amphipathicity, helicity, and peptide self-association. The net charge of V13K analogs ranged from +5 to +10, with 1–10 positively charged residues. The study found that the alterations produced antibacterial as well as hemolytic action against six Pseudomonas aeruginosa strains: adding an additional positive charge to the polar face of peptide V13K (from +8 to +9) increased hemolytic activity (>32-fold).

The AMPs, Oabac11 and Oncorhyncin II, are the most positively charged peptides with a net charge of +30,[190,191] while the most negatively charged AMP is cattle chrombacin with a net charge of −12.[192] When Zn2+ and Ca2+ ions are present, anionic AMPs form oligomers, permitting them to enter membranes with their lipid tails.[193,194] In addition to negatively charged molecules, lipids make up most of the bacterial membrane. Therefore, hydrophobicity is a key factor in the antibacterial action of peptides. The number of hydrophobic residues in naturally occurring AMPs fluctuates between 40% and 60% (Figure 2), indicating the need for energetically stable amphipathic structures for antibacterial action.[195] Amino acid residues are classed based on their side chain groups: hydrophobic, hydrophilic charged, or hydrophilic uncharged. Hydrophobicity scales are used to quantitatively classify amino acids in certain environments. Hydrophobicity scales vary in approach but all of them aim to compare side chain hydrophobicity[196] classified these approaches based on the similarities of their parameter and value approximations. A set of short amphipathic helical peptides consisting of the backbone sequence LLKK2[197] were reported as inhibitors of both susceptible and drug-resistant *Mycobacterium tuberculosis*. The authors investigated how essential physicochemical characteristics, such as hydrophobicity, affect anti-mycobacterial efficacy. W(LLKK)2W, the most hydrophobic homolog, was selective against mycobacteria, while intermediate hydrophobic peptides were equally active but much less toxic.

Amphipathicity, a key characteristic of AMPs, has a direct impact on their mechanism of action and antibacterial properties. Although AMP amphipathicity is often associated with peptide helicity, it can also refer to β-turn or β-sheet structures, which can exhibit high amphipathicity depending on their sequence.[198] Amphipathic compounds typically have cationic charges and hydrophobic moieties. The cationic moiety initiates peptide-membrane electrostatic interactions with lipid anionic or zwitterionic head groups. Hydrophobic moiety interacts directly with the hydrocarbon chains in lipids. Peptides are often unstructured until hydrophobic interactions occur. Intramolecular contacts then strengthen, resulting in the lowest-energy conformations. Amphipathicity is linked to hydrophobicity, which is determined by the peptide's secondary structure. Amphipathicity was initially defined as the resulting vector from the hydrophobic moment vectors of each residue.[199] Additionally, the structural distribution of hydrophobicity and the effects of nearby residues on the scalar value of these vectors have been linked to amphipathicity.[200]

The Susceptibility of AMPs to Enzymatic Degradation by Proteases

AMPs can be differentially affected by proteolytic enzymes based on their structural features and the presence of specific amino acid residues. For instance, studies suggest that substituting L-amino acids with D-amino acids can enhance stability against proteolytic degradation, as proteases typically target L-amino acids more effectively.[201,202] Furthermore, the development of peptides that incorporate unnatural amino acids or modified structures revealed that the addition of cationic or amphiphilic properties to peptide designs can also improve their resistance to proteolytic cleavage while maintaining antimicrobial activity.[203,204] Mechanisms such as binding to host proteins like actin have also been noted to protect AMPs from degradation, thereby prolonging their effective lifespan during immune responses.[205]

Mechanisms of Action of AMPs

AMPs work against bacteria in two different ways: membrane-targeted AMPs damage the integrity of cell membranes, whereas non-membrane targeting AMPs primarily prevent the production of enzymes, functional proteins, and nucleic acids.[63]

Membrane Targeting Mechanism

Membrane-active peptides can interact with microbial cell surfaces through receptor-mediated or non-receptor-mediated interactions. Nisin, a bacteriocin, is the first known receptor-mediated AMP. It binds to lipid II in the first phase of its

mode of action. Even at nanomolar quantities, this interaction inhibits peptidoglycan synthesis and causes membrane permeability through pore formation. AMPs usually interact with cell surface targets without requiring a particular receptor. AMPs' physicochemical features, including net charge, hydrophobicity, amphipathicity, membrane curvature, and self-aggregation, play a crucial role in disrupting membrane integrity through peptide-membrane interactions.[206] The peptide-membrane interactions are caused by the combined effects of several of the physicochemical properties of AMPs. The structure-activity relationship of AMPs can predict their antimicrobial activity, allowing for the design of peptides with desired features.[20]

Membrane-active AMPs function through cationic and hydrophobic interactions. Electrostatic attraction is the primary factor that binds positively charged AMP residues to the negatively charged bacterial cell surface.[207] Bacterial membranes are rich in anionic lipids such as phosphatidylglycerol (PG), cardiolipin, and phosphatidylserine, which attract cationic AMPs, whereas animal membranes contain zwitterionic phospholipids such as phosphatidylcholine (PC) and sphingomyelin. Moreover, lipopolysaccharides (LPS), teichoic acid, and lipoteichoic acid are the additional negatively charged components of bacterial cell surfaces that are thought to be possible AMP targets. The electrostatic interactions that occur between AMPs and bacterial membranes are therefore relatively stronger than those between AMPs and mammalian cell membranes. Furthermore, the presence of cholesterol in mammalian cell membranes improves membrane stability and prevents the insertion of AMPs.[208]

Hydrophobicity, a primary characteristic of peptides, controls how hydrophobic residues interact with the fatty acyl chains of membrane lipids, and in turn how transmembrane portions of the peptides insert and partition into the hydrophobic core of the bilayer.[209] Hydrophobicity refers to the percentage of hydrophobic residues in a peptide sequence. AMPs exhibit significant antibacterial activity at certain hydrophobic levels. Moderately hydrophobic peptides are most effective, while very hydrophobic peptides have significant hemolytic action but low antibacterial activity.[210,211]

The binding affinity of α-helix AMPs to membranes is affected by their amphipathicity, which refers to the ratio of hydrophilic and hydrophobic residues on the opposing face of peptides. Amphipathic AMPs attach to lipid bilayers through hydrophobic residues and interact with phospholipid groups via hydrophilic residues.[212]

Membrane topography is crucial for understanding the adsorption properties of peptides on membranes. Chemically different lipid components in biological membranes result in spontaneous curvatures. Membrane curvatures are determined by the orientation of peptides and their lipid content. Peptides prefer to remain surface-bound in membranes with negative spontaneous curvature, while embedding in membranes with positive curvature. Furthermore, cationic peptides have a higher electrostatic attraction for bacterial membrane domains with an accumulation of anionic lipids, resulting in negative charge abundance.[213] In fact, under most circumstances, hydrophobic interactions between the membrane's curvature and lipid composition contribute to the membrane adsorption of proteins.[214] Peptide–peptide or lipid–peptide complexes are formed as the concentration of AMPs binding to the membrane increases. When the concentration of AMPs in the membrane reaches a critical point, the AMPs enter the hydrophobic bilayer's core and create transmembrane pores in the cytoplasmic membrane.[215] A number of models, such as the pole and carpet models—the pole model of which is further subdivided into the toroidal pore and barrel-stave models—have been put forth to explain the mechanisms at the bacterial cytoplasmic membrane that result in membrane permeabilization (Figure 3).[47]

i. The barrel-stave model describes how AMP molecules adsorb on the membrane surface and self-assemble due to interactions with hydrophilic peptide sequences. When peptide monomers accumulate to a certain density on the membrane, they rotate perpendicularly towards the plasma membrane. The peptide bulks are positioned along the hydrophobic part of the bilayer, creating a channel with the hydrophilic surface facing inwards.[216] Under extreme conditions, AMPs can result in the collapse and death of cell membranes.[217] This model explains how alamethicin forms pores. Both implicit and explicit tetrameric arcs (half barrels) and stable octameric β-barrels can be formed in membranes by hairpin AMP protegrin-1, according to simulations.[218]
ii. The toroidal model inserts peptides perpendicularly into the bilayer, analogous to the barrel-stave model, resulting in a peptide-lipid complex rather than peptide-peptide interactions. The conformation of peptides creates a small membrane curvature surrounded by peptides and phospholipid head groups, forming

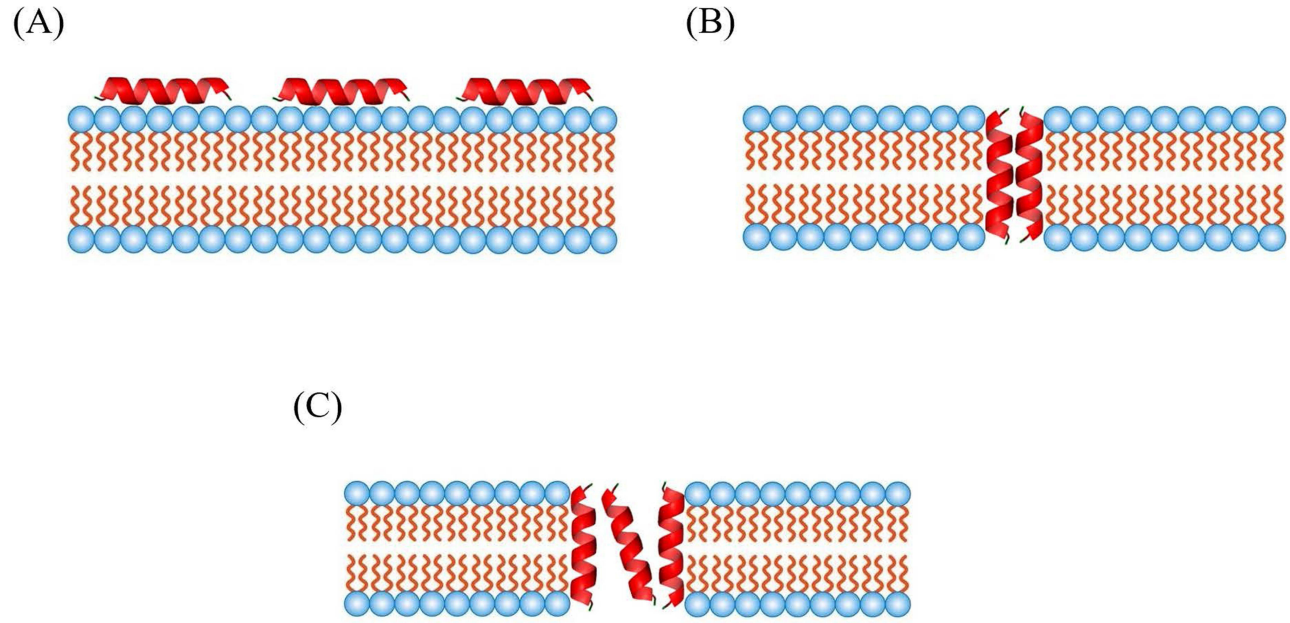

Figure 3 Membrane targeting mechanism of action of AMPs. (**A**) Carpet model: the surface of the membrane is covered with AMPs without forming pores. (**B**) Toroidal pore model: AMPs insert perpendicularly into the lipid bilayer forming a channel, this is a membrane adsorption model (**C**) Barrel stave model: AMPs insert perpendicularly into the lipid bilayer forming a channel, unlike the toroidal pore model, this model involves a conformational change.

a "toroidal pore".[219] Arenicin, lacticin Q, and magainin 2 are a few examples of this paradigm. By creating fluid domains, cationic peptides like TC19, TC84, and BP2 break down the membrane barrier.[220]

iii. In the carpet model, the arrangement of antimicrobial peptides is parallel to the membrane of the cell. Their hydrophobic end is facing the phospholipid bilayer, and their hydrophilic end is facing the solvent. AMPs will act as a "detergent" to break down the cell membrane and cover the membrane surface like a carpet.[94] AMP concentrations must be high for this pore-forming mechanism to function, and there is a required concentration threshold. This method is how human cathelicidin LL-37 works, and AMPs with a β-sheet structure also play a role in this scenario.[221,222] Fourier transform infrared spectroscopy (ATR-FTIR) with polarized light-attenuated total reflection was used to examine the impact of AMP cecropin P1 on bacterial cell membranes. When applied directly to the pathogen's cell membrane, it was found to destabilize and ultimately disintegrate the membrane.[223]

Membrane targeting strategies can be refined further to account for the significant changes in lipid content across fungi, bacteria and humans. Sterols, glycerophospholipids (GPLs), lysolipids, and sphingolipids are the main lipids present in cell membranes. In bacteria, the most prevalent anionic lipids are phosphatidylethanolamine (PE), phosphatidylglycerol (PG), and cardiolipin (CL), but in fungal cell membranes, The primary GPLs are phosphatidic acid, phosphatidylcholine, and phosphatidylinositol.[224,225] Comparing fungal cell membranes to those of mammals, the former are more anionic and contain more phosphatidylcholine. Lower eukaryotic organisms, such as fungi, have ergosterol in their plasma membranes, whereas animal membranes include cholesterol.[226]

As anti-biofilm agents, AMPs are potential candidates. They differ from cell-penetrating peptides (CPPs), which may penetrate cell membranes and have 5–30 amino acids. Based on their physicochemical characteristics, CPPs can be divided into three categories: hydrophobic, amphipathic, and cationic. For these physicochemical characteristics, anti-biofilm peptides must adhere to stricter specifications. EPS production modulation, membrane permeabilization, and signal degradation are just a few of the ways anti-biofilm peptides target biofilms. Chronic, multi-resistant bacterial infections can be successfully treated by them.[227–230] For instance, SAAP-148, which is generated from LL-37, successfully prevents *S. aureus* and *A. baumannii* from forming biofilms.[231] Similarly, it has been found that fragments

of the human cathelicidin LL-37 could inhibit biofilm formation by *Pseudomonas aeruginosa*, demonstrating the clinical relevance of these peptides with low concentrations.[232]

Non-Membrane Targeting Mechanism

The bactericidal actions of AMPs were first attributed to membrane-active mechanisms. However, it is now recognized that many AMPs target key cell components and functions, causing bacterial death. AMPs enter cells either by direct penetration or endocytosis. AMPs enter the cytoplasm and identify and act on their target. AMPs can be categorized based on their target as follows (Figure 4),

i. Inhibition of protein biosynthesis, antimicrobial peptides interfere with enzymes and effector molecules during molecular chaperone folding, affecting transcription, translation, and peptide assembly.[233,234] For example, Bac7 1–35 inhibits protein translation by targeting ribosomes,[235] whereas Tur1A hinders the transition from the initial phase to the extension phase, which in turn inhibits the synthesis of proteins in *E. Coli* and *Thermus thermophilus*. But variations between Tur1A and Bac7 result in different mechanisms of interacting with the ribosomal peptide exit tunnel and binding to ribosomes.[139] Different targets are used by some AMPs. One example is the effect of AMP DM3 on several important intracellular protein synthesis pathways, as demonstrated by genome-wide transcription.[236] Chaperones play an essential role in the proper folding and assembly of newly synthesized proteins, resulting in stereoisomerism, cell selectivity, and reduced cytotoxicity. According to a previous review, by permanently blocking the peptide-binding cavity,

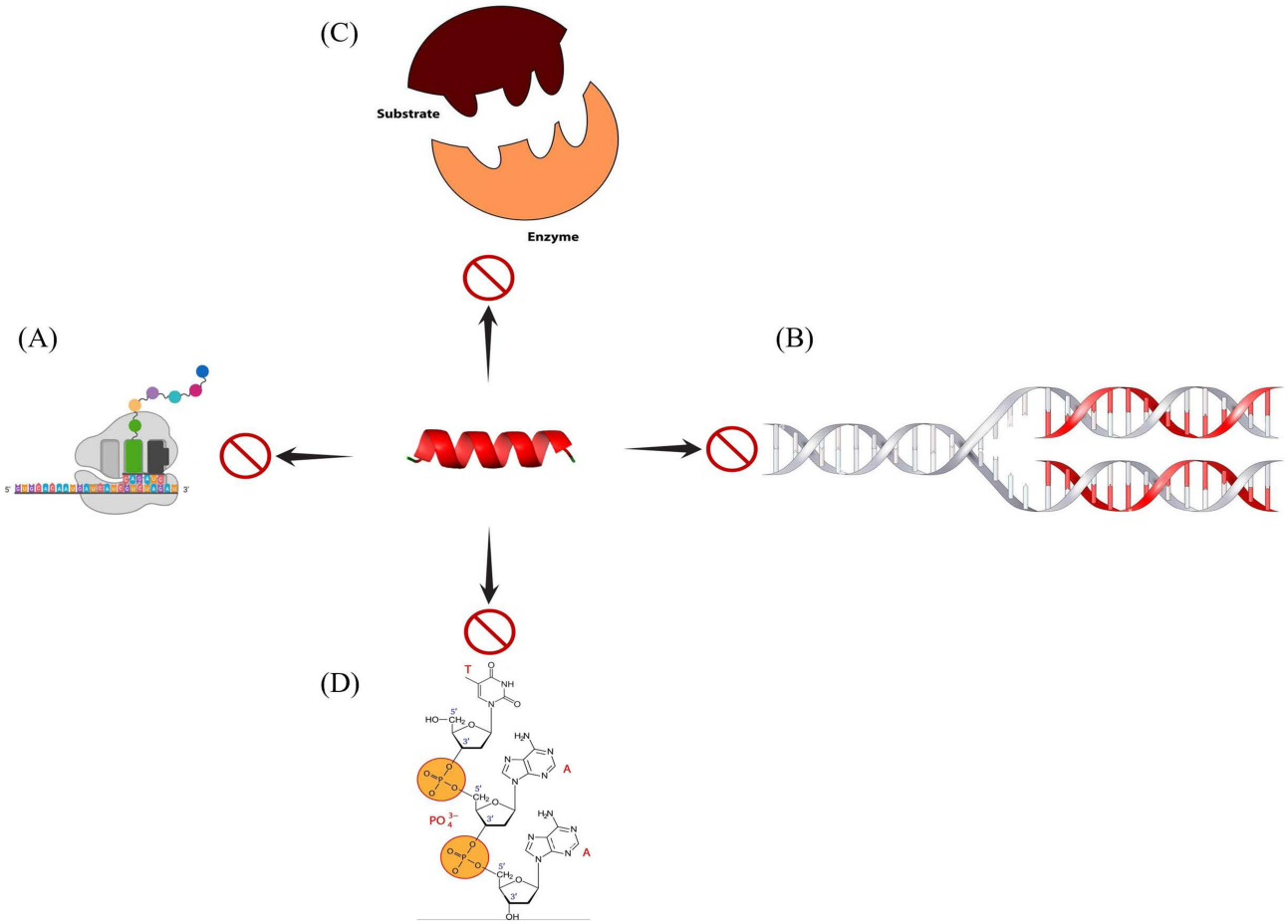

Figure 4 Non-membrane targeting mechanism of action of AMPs. (**A**) Inhibition of protein biosynthesis. (**B**) Inhibition of DNA replication. (**C**) Inhibition of protease activity. (**D**) Inhibition of nucleic acid biosynthesis.

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pyrhocoricin and drosocin can prevent DnaK from refolding misfolded proteins.[237–239] By utilizing the toroidal pore model to create ion channels, pleurocidin can prevent *E. coli* from synthesizing proteins.[240] Through interference with transcription, ribosome assembly, DNA replication, and amino acid synthesis, the hybrid peptide DM3 inhibits bacteria.[241] Recent research has shown that apidecin inhibits the translation termination process by competitively binding to release factors on the ribosome A-site.[59] Human neutrophil peptide defensin (HNP)-1 suppresses transcription, protein synthesis, and DNA replication in *E. Coli* by successively causing the outer and inner membranes to permeabilize.[242] A number of proteins, including arginine decarboxylase, were inhibited when Lactoferrin B, PR39, P-Der, and Bac7 were incubated with *E. coli*.[243] Some proline-rich, insect-derived peptides have been shown to interfere with protein folding, hence preventing bacterial DNA replication.[244,245] By inhibiting competition, pyrrhocoricin can decrease DnaK ATPase activity and disrupt the molecular chaperones DnaK and GroEL.[237,246] Gram-negative bacteria including *E. coli, P. aeruginosa*, and *A. baumannii* are inhibited by oncocin, a 19-residue proline-rich peptide, which enters the cell membrane and interacts with DnaK to stop protein folding.[247,248]

ii. Inhibition of nucleic acid biosynthesis, AMPs could block nucleic acid production by affecting important enzymes or causing the breakdown of nucleic acid molecules.[249] A 13 amino acid cationic Trp-rich AMP with a C-terminal amide, indolicidin specifically targets the abasic region of DNA to crosslink single- or double-stranded DNA. DNA topoisomerase I can also be blocked by it.[250] After membrane rupture, the tongue-derived AMP TFP (Tissue Factor Pathway Inhibitor)1–1TC24 reaches the cytoplasm of target cells and breaks down DNA and RNA.[251]

iii. Protease activity inhibition: By specifically targeting protease activity, AMPs can interfere with metabolic processes.[252] Proteases generated by the bacterium and the host are efficiently inhibited by histatin 5.[253] Elastase and chymotrypsin are examples of microbial serine proteases that are blocked by AMPs eNAP-2 and indolicidin.[238] The venom of Bungarus fasciatus contains a peptide called cathelicidin-BF, which blocks protease-activated receptor 4 and prevents thrombin-induced platelet aggregation.[254] Tick hematocytes contain ixodidin, a cysteine-rich, 65-residue AMP that inhibits chymotrypsin and elastase to slow down cellular metabolism.[255] Histatin 5, a histidine-rich cationic AMP that is a member of the histatin family, is present in the salivary secretions of human parotid and submandibular glands. Histatin 5 works well against *S. mutans*, which is a major contributor to tooth cavities, it targets trypsin-like proteases and inhibits both bacterial and host proteases.[256]

iv. AMPs inhibit the division of cells by interfering with DNA replication and damage response, interfering with the cell cycle, and preventing chromosome separation.[257] A 20-amino acid AMP called APP (GLARALTRLLRQLTRQLTRA), for instance, effectively eliminates Candida albicans because of its ability to enter cells, attach to DNA.[258] With its 40 amino acid residues, MciZ efficiently prevents the formation of Z-rings, bacterial cell proliferation, and localization.[259] Moreover, it has been demonstrated that AFPs harm fungal organelles. Cell death may result from interactions between histintin 5 and mitochondria.[260]

Biological Functions of AMPs

All life forms, from prokaryotes to humans, produce AMPs, which have been preserved throughout evolution.[261] In higher organisms, AMPs play a crucial role in innate immunity, defending against infections. Bacteria synthesize AMPs to eliminate competitors in their ecological niche.[262] AMPs can influence the host's innate immune responses in addition to their direct antimicrobial effect, which indirectly promotes pathogen clearance.[263] Their significance is further supported by the fact that humans with diseases linked to decreased AMP synthesis, such as atopic dermatitis, and Mice who have had their genes changed to exclude the gene that codes for the mouse counterpart of the human AMP LL-37 are more prone to infection.[264] AMPs are naturally generated through two processes: nonribosomal peptide synthesis and ribosomal translation of mRNA. While bacteria are the primary producers of nonribosomally manufactured peptides, all life forms, including bacteria, produce genetically encoded ribosomally synthesized AMPs.[265] As opposed to nonribosomal peptides, which have been recognized for several decades and many of which are employed as antibiotics

(eg, polymyxins and gramicidin S), ribosomally produced AMPs have been recognized for their therapeutic potential and crucial role in innate immunity.

AMP's biological activity is categorized into 18 groups by the Antimicrobial Peptide Database (ADP3). These classifications can be summarized as anti-tumor, anti-parasitic, anti-viral, antifungal, antibacterial, and anti-HIV.

Antibacterial Peptides

Antibacterial peptides account for the larger part of AMPs. These are cationic peptides; the net positive charge allows them to interact with the negatively charged bacterial membranes.[266] Gram-negative and Gram-positive bacteria have negatively charged outer membrane components that interact electrostatically with cationic peptides. AMPs aggregate on the bacterial membrane after first accumulating at its surface.[234] Antibacterial peptides broadly inhibit common harmful bacteria, including *listeria monocytogenes, S. aureus, E. coli, Salmonella*, and Vibrio parahaemolyticus in aquatic products, as well as VRE, *Acinetobacter baumannii*, and MRSA in clinical treatment. Numerous synthetic and natural AMPs, such as defensins, cecropins, and nisins, have demonstrated effective suppression of both Gram-positive and Gram-negative bacteria. According to recent studies, the *Aristicluthys nobilia* interferon-I-based AMPs P5 (YIRKIRRFFKKLKKILKK-NH2) and P9 (SYERKINRHFKTLKKNLKKK-NH2) can inhibit MRSA and have minimal cytotoxicity.[267] Stability is a critical challenge in the clinical application of antibacterial peptides; nisin, for example, exhibits optimal stability only under specific acidic conditions (pH 3).[268]

Antifungal Peptides

Antifungal peptides can be classified into two groups based on their origin and mode of action: non-membrane-traversing peptides that interact with the cell membrane and cause cell lysis, and membrane-traversing peptides that can affect β-glucan or chitin synthesis.[269] Antifungal peptides can cause fungal death via a variety of mechanisms. These mechanisms may include permeabilization of membranes, induction of apoptotic mechanisms, inhibition of DNA, RNA, and protein synthesis, inhibition of cell wall synthesis and enzyme activity, or repression of protein folding and metabolic turnover.[270] Excellent anti-fungal activity has been demonstrated by many antifungal peptides against common pathogenic fungi, including yeast, filamentous fungi (such *Aspergillus flavus*), mold in food and agriculture, and *Aspergillus* and *Candida albicans* in clinical care.[271] Examples of antifungal peptides includes; brevinin, ranatuerin, and cecropins, in addition to many synthetic peptides that have strong antifungal properties.[272] For instance, *C. albicans* infections, which have a 40% fatality rate, can be successfully treated with AurH1, which is produced from aurein 1.2.[273] *A. flavus* produces aflatoxin, a carcinogen that is detrimental to human health. *A. flavus* growth can be inhibited by several antifungal peptides. For instance, *A. flavus* MD3 development can be inhibited by an antifungal peptide containing the sequence FPSHTGMSVPPP. A mixture of 37 antifungal peptides isolated from *Lactobacillus plantarum* TE10 can inhibit the growth of *A. flavus* spores in fresh maize seeds. Two chemically produced radish AMPs are capable of efficiently inhibiting *Zygosaccharomyces bailii* and *Zygosaccharomyces rouxii*.[274] One significant challenge in the clinical application of antifungal peptides is their toxicity to human cells, for example, the peptide LL-37 exhibited efficacy against various fungal pathogens, but also disrupted mammalian cell membranes at elevated doses, leading to potential side effects.[275]

Antiviral Peptides

Since viruses are becoming more resistant and existing treatments are ineffective, antiviral peptides are prospective therapeutic agents. Antiviral drugs can inhibit viral reverse transcriptase, the pre-integration complex, or prevent circular viral DNA from reaching the nucleus. Alternatively, they can inhibit viral integrase, preventing viral DNA from integrating into the cellular chromosome. Furthermore, antiviral drugs can inhibit viral proteases by preventing retroviral morphogenesis. After transcription, proviral DNA is translated into a polyprotein that requires viral proteases to construct the viral capsid.[276] Antiviral peptides effectively target both encapsulated RNA and DNA viruses. AMPs can create membrane instability by integrating into viral envelopes, which prevents viruses from entering host cells.[277] Melittin has anticancer properties and inhibits enveloped viruses like Junin virus (JV), HIV-1, and HSV-2. It was suggested that Melittin may reduce HSV-1 syncytial mutant-mediated cell fusion by inhibiting the activity of Na+ K+ ATPase, a cellular

enzyme involved in membrane fusion.[278] By attaching particular receptors on mammalian cells, antiviral AMPs can prevent viruses from entering host cells. Lactoferrin, an α-helical cationic peptide, can prevent HSV infections by binding to heparan sulfate molecules and inhibiting virus-receptor interactions.[279,280]

A subclass of antiviral peptides are anti-HIV peptides; These peptides include, maximin 3, magainin 2, dermaseptin-S1, dermaseptin-S4, LL-37, gramicidin D, and defensins. Fuzeon, also known as enfuvirtide, is an antiviral peptide that has been marketed as an anti-HIV drug.[281] Although many antiviral peptides exhibit low toxicity profiles against human cells compared to conventional antiviral drugs, the potential for cytotoxicity still exists.[282]

Antiparasitic Peptides

Parasitic protozoa can transmit diseases to humans and animals through several routes, such as person-to-person or animal-to-person contact, water, soil, and food.[283] As parasites become more resistant to drugs, the demand for new therapies grows. Antiparasitic peptides effectively eliminate parasites responsible for disorders including malaria and leishmaniasis.[284] The first known antimicrobial peptides with antiparasitic activity were magainins and cecropins.[285] According to recent studies, Trichomonas vaginalis can be successfully inhibited by the marine produced AMP Epi-1, which damages its membrane.[286] The peptide, scorbine, which is derived from the venom of the *Pandinus imperator* scorpion, can prevent *Plasmodium berghei* from developing its ookinete or gamete.[287] It has been discovered that jellein, a peptide made from bee royal jelly and the four amino acid AMP KDEL, significantly affects Leishmania parasites.[288] The mechanics are different, though. The antiparasitic action of cyanobacterial peptides targets particular proteins, which sets them apart from higher-eukaryotic AMPs. Even if they are members of the same genus or family, these target parasites can be correctly recognized.[289] A major challenge in the clinical application of antiparasitic peptides is establishing their toxicity profile. It has been found that assessing cytotoxicity of antiparasitic peptides solely through fish cell lines is inadequate, as the tested peptides showed no adverse effects on viability in those models, which does not guarantee safety in human cells.[290]

Anticancer Peptides

Anticancer peptides function by recruiting immune cells to kill tumor cells, causing necrosis or apoptosis, inhibiting angiogenesis to prevent metastasis, and activating regulatory proteins to disrupt gene transcription and translation.[291] In vitro, tricrpticin and its derivatives are hazardous to Jurkat cells, although puroindoline A and indolicidin have anticancer properties.[292] It should be noted that hydrophobicity and net charge can both affect and inhibit one another, and that they both play significant roles in optimizing the anticancer activity of anticancer peptides. Therefore, for improved anticancer action, striking a balance between net charge and hydrophobicity is crucial.

Peptides toxic to bacteria and both cancer and normal cells, include the human LL-37 peptide, insect defensins, and melittin from bee venom.[293] Anticancer peptides can kill cancer cells through membranolytic or non-membranolytic methods, depending on the peptide properties and target membrane features. Cancer cells have a net negative charge on their membrane, which is caused by anionic substances such phosphatidylserine (PS), heparin sulfate, O-glycosylated mucins, and sialylated gangliosides. This suggests that AMPs and anticancer peptides may have comparable basic principles for selectivity and action. Human prostate, mammary, and lymphoma cancer cell proliferation has been shown to be inhibited by dermaseptin B2 and B3.[294,295]

Toxicity remains a critical concern in the clinical use of anticancer peptides. While these peptides are generally designed to target cancer cells selectively, their interactions with normal cells can result in cytotoxicity, leading to adverse effects.[296] For instance, peptides that disrupt cellular membranes may cause necrosis or apoptosis not only in cancer cells but also in healthy cells, raising the concern of dose-dependent toxicity.[297] It has been observed that hydrophobic peptides, which exhibit stronger anticancer activity, also pose higher risks of hemolysis and damage to healthy tissues.[298] Thus, achieving a balance between efficacy and safety is vital for the clinical translation of anticancer peptides.[299] Stability is another significant challenge in the clinical applicability of anticancer peptides, some studies have indicated that the anticancer peptides P8 peptide and P10 lipopeptide lose their effectiveness when exposed to serum due to proteolytic degradation.[300]

Immunomodulatory Function of AMPs

Some AMPs perform both bactericidal and immunomodulatory functions. Numerous immunomodulatory processes, including chemotaxis stimulation, immune cell differentiation modulation, and adaptive immunity initiation, are facilitated by AMPs and aid in the host's ability to eradicate microorganisms. Furthermore, the immunomodulatory activities decrease the generation of proinflammatory cytokines and/or toll-like receptors (TLRs) as well as anti-endotoxin activity, which together prevent excessive and harmful proinflammatory reactions, such as sepsis.[263,301] For example, defensins, including hBD2 and hBD3, as well as their mouse orthologs mBD4 and mBD14, can chemoattract leukocytes migration (dendritic cells, macrophages, and monotypes) through chemokine receptors CCR6 and CCR2.[302] Furthermore, hBD3 can inhibit Toll-like receptor 4 (TLR4)-mediated pro-inflammatory cytokine expression on activated macrophages in myeloid differentiation factor 88 (MyD88) and Toll/interleukin-1 receptor-domain-containing adapter-inducing interferon-β (TRIF)-dependent signaling pathways.[303] DEFB126, a human β-defensin, effectively inhibits LPS-induced inflammatory cytokines such as IL-1β, IL-6, and TNF-α in macrophages, and showed highly binding and neutralizing LPS ability.[303] Human cathelicidin LL-37 affects the differentiation of T cells during inflammation, promoting Th17 and inhibiting Th1 development, which plays a significant part in autoimmune disorders.[304]

Sources of AMPs

The majority of AMPs—75.65%—come from a variety of species, including fish, amphibians, invertebrates, and mammals. Approximately 13.5% and 8.53% of all AMPs are generated from bacteria and plants, respectively.[219]

AMPs from Mammals

Humans, sheep, cattle, and other animals all include mammalian AMPs. The two main families of AMPs are defensins and cathelicidins.[305] AMPs that are not a part of these two groups include dermcidin, hepcidins, and platelet antimicrobial proteins.[306] All mammalian cathelicidin peptides that have matured possess an amphipathic structure that can take on elongated, β-helical, or β-hairpin conformations, despite the fact that their sequences differ greatly.[307,308]

The expression of HDPs (human host defense peptides) varies during human development. For example, cathelicidin LL-37, is the only cathelicidin found in humans and is usually found in newborn infants' skin, whereas human beta-defensin 2 (hBD-2) is more commonly expressed in the elderly than in the young.[309,310] HDPs can be found in several body parts, including the skin, eyes, ears, mouth, respiratory tract, lung, intestine, and urethra. The peptide Casein201, which is generated from β-Casein 201–220 amino acids, can be found in both term and preterm human colostrums.[311]

The 13-residue peptide known as cathelicidin 4 (indolicidin) is produced by bovine neutrophils. It has been discovered that water buffalo carry seven different forms of cathelicidin 4 (buCATH4 A-G). The most potent of them is buCATH4C, which shows efficacy against both *S. aureus* and *B. cereus*.[312] Porcine white blood cells (WBCs) generate protegrins (PG), which are cationic amino acid polymers (AMPs) rich in arginine and cysteine with a β-hairpin structure and two disulfide connections.[313] There are five members of the protegrin family (PG1–5). The most well-studied protegrin, PG1, isolated from caprine, bovine, and ovine neutrophilic granules. There are three known equine cathelicidins (eCATHs): eCATH1–3. The broadest spectrum of action and the most potent antibacterial efficiency are possessed by eCATH1, whereas eCATH-2 exhibits a more restricted range of activity.[314]

α-Defensins are produced by intestinal Paneth cells, promyelocytes, and neutrophil precursor cells. The two α-defensins found in guinea pig neutrophils, GNCP1 and GNCP2, have three intramolecular disulfide linkages and 31 residues, respectively. A number of rabbit α-defensins, such as NP-1 and NP-2, have been identified.[315–318] Neutrophils secrete human α-defensins HNP1-4, while Paneth cells in the intestinal epithelium secrete HD-5 and HD-6.[319,320] Humans and new-world primates do not express θ-defensins, but some old-world monkeys and orangutans do.[321,322]

Dairy is high in AMPs, which are formed by milk's enzymatic hydrolysis. Casein fractions, α-lactalbumin, β-lactoglobulin, and lactoferrin all include AMPs, the most well-known of which is lactoferricin B (LfcinB).[323]

AMPs from Amphibians

The AMPs found in amphibians are critical for protecting them against the infections responsible for the worldwide fall in amphibian populations.[324] Frogs are the main source of amphibian AMPs, and magainin is the most well-known AMP present in frogs. Skin secretions of frogs belonging to the Pipidae family's genera *Xenopus, Silurana, Hymenochirus*, and *Pseudhymenochirus* are rich in AMPs.[325]

AMPs from Insects

Insects produce AMPs in fat and store them in haemolymph.[326,327] The most well-known family of insect AMPs, cecropin, is present in Drosophila, bees, and guppy silkworms.[328] Depending on the species, invasive harlequin ladybirds (*Harmonia axyridis*), black army flies (*Hermetia illucens*), and pea aphids (*Acyrthosiphon pisum*) can have up to 50 AMPs.[329]

AMPs from Bacteria

Bacterial AMPs are commonly known as bacteriocins.[330] Bacteriocins are classified based on size, origin, structure, and mechanism of action, they can be derived from Gram-negative bacteria, including *E. coli* and other enterobacteria, and are classified as small peptide-structured microcins or larger protein-structured colisins.[331] Gram-positive bacteria produce bacteriocins that are classified into four groups: lantibiotics (Class I), Bacteriocins are classified into three types: non-lantibiotics (Class II), large-sized bacteriocins (Class III), and those with distinctive structures (Class IV).[332]

Lantibiotics, or class I bacteriocins, are composed of tiny peptides (less than 5 kDa; 19–38 amino acids) that are resistant to proteolysis, heat, and pH. They typically target Gram-positive bacteria. Post-translational modifications (PTMs) such as lysinoalanine bridges, thioether synthesis, dehydration, and oxidative decarboxylation are used to add lanthionine and β-methyllanthionine to lantibiotics in order to increase structural stability.[332–335] Examples of lantibiotics include; nisin, epidermin, and lacticin 481.[332,336]

Class II bacteriocins are those that do not contain lanthionine and have a limited PTM (eg, pediocin AcH and PA-1 bisulfide bridge formation). They lack unique amino acids. These small (<10 kDa) heat-stable peptides function as bacteriocins that generate pores, destabilize membranes, and increase permeability.[337,338] Examples of Class II comprises lactacin F, lactococcin G and Q, pediocin PA-1, leucocin A, and acidocin A.[339]

Class III bacteriocins, also known as bacteriolysins, are heat-labile peptides with a molecular weight greater than 30 kDa. Examples of this class include heleveticin M, J, and V, enterolysin A, lysostaphin, and zoocin A and they function as endopeptidases that break cell walls by targeting peptidoglycans.[340,341]

Class IV bacteriocins are AMPs with distinctive structures that incorporate amino acids, lipids, or carbohydrates, making them susceptible to lipolytic and glycolytic enzymes. Plantaricin S, leuconocin S, lactocin 27, and pediocin SJ-1 are examples of this class and they have membrane-disrupting activity.[342,343]

Although *E. coli* is the primary source of bacteriocins from Gram-negative bacteria, other species such as *Klebsiella* and *Pseudomonas* also produce AMPs.[344] *E. coli* produces most colicins (MW > 10 kDa) which bind to cell surface receptors and move across the outer, periplasm, and inner membranes to the cytoplasm.[345,346] Microcins are small peptides (<10 kDa) produced by *Enterobacteriaceae* and are active against phylogenetically close species.[347]

AMPs from Fungi

Peptaibols and fungal defensins are two categories for fungal AMPs. The primary source of peptidaibols is the soil fungus *Trichoderma*; these small peptides range in length from 5 to 21 amino acids. Three essential elements—peptide, Aib, and amino alcohol—are the source of their name.[348,349] Alamethicin, derived from *T. viridea*, is the most studied peptaibol. The first known fungal defensin is plectasin, which is produced from *Pseudoplectania nigrella*.[130]

AMPs from Plant

Based on disulfide bridge configurations, sequence similarity, and cysteine motifs, plant AMPs are divided into groups; these groups include thionins, lipid transfer proteins, defensins, α-hairpinin, and unclassified cysteine-rich AMPs.[350] Purothionin was the first reported plant AMP isolated from wheat flour *Triticum aestivum*.[351]

Synthesis of AMPs

Early investigations of AMPs focused on extracting peptides from natural sources and testing their antibacterial effectiveness. The downside of this process is that it requires a significant amount of raw biological samples to get little amounts of peptide. For example, to extract dermaseptin from the skin of *Phyllomedusa sauvagii* frogs, 1 g of dried skin yielded 40 μg of pure peptide.[352] Furthermore, natural AMPs are synthesized as larger precursor proteins, which are then proteolytically cleaved to produce the active AMPs, for example, Human cathelicidin hCAP-18 is produced and stored intracellularly as a larger preprotein.[353] During secretion, it is processed by protease-3 to release the active form of the LL-37 peptide.[354] LL-37 can be degraded by proteases at various locations in the body, resulting in different active forms of the peptide.[355,356] Therefore, purifying AMPs from natural sources can be challenging due to posttranslational processing, as the necessary peptide may not be present in a unique or active form. Fortunately, chemical synthesis of peptides is now the preferred method for producing high yield and pure AMPs.

AMPs Produced by Chemical Synthesis

The chemical synthesis of AMPs is performed by solid-phase peptide synthesis.[357] During synthesis, the expanding chain (peptide or oligomer) is connected to a solid support (eg, resin or bead) and remains there. To minimize racemization, peptide synthesis begins at the C-terminus. Peptide growth occurs through selective coupling using the "Fmoc strategy" between the carboxylic acid group of an additional amino acid and the amino-terminal group of an amino acid linked to a solid phase. Solid-phase peptide synthesis produces pure and large amounts of the desired AMP fast and at a reasonable cost.[358] Following cleavage from the solid-phase support, the AMP of interest is purified using reversed phase liquid chromatography, and its identity is verified using mass spectrometry. This method can manufacture peptides shorter than 30 amino acids, however, larger peptides only have a 55% correct sequence rate (target peptide).[359]

The selection of a production system in solid-phase synthesis significantly influences yield, activity, and overall cost.[360] Automated synthesis techniques reduce human error and labor costs while increasing throughput, which is especially vital in high-demand scenarios such as pharmaceutical production.[361] Recent studies emphasize the importance of automation and the transition towards continuous flow synthesis techniques to enhance scalability and cost efficiency further. Additionally, the economics of alternatives to traditional solvents, alongside the mitigation of common side reactions, showcases a significant interest in reducing operational costs through innovative method adaptation.[362]

Chemical synthesis of peptides has various advantages over purification from natural sources. Researchers can change AMP sequences to regulate antibacterial efficacy and study structure-activity relationships by adding amino acids sequentially. Synthetic peptides can incorporate non-natural amino acids to enhance biological activity and stability, extending beyond the 20 naturally occurring amino acids. For example, substituting ornithines for two Arg residues in oncocin (an AMP produced from Oncopeltus antibacterial peptide-4) boosted serum half-life and antibacterial effectiveness against Gram-negative infections.[363]

One notable limitation of solid-phase synthesis is the difficulty associated with synthesizing longer or complex biomolecules; the reaction efficiency diminishes as the molecular weight of the target increases, leading to prolonged synthesis times and lower yields.[43] Another substantial barrier to large-scale solid-phase synthesis is the necessity for a large excess of reagents. Due to the inherent limitations in access and diffusion within solid support matrices, achieving complete reactions often requires using a surplus of reactants, which complicates purification and increases costs.[364]

AMPs Produced from Genetically Modified Organisms

In addition to synthetic peptides, AMPs can be expressed and purified by molecular cloning techniques. Many bacterial host cells have been employed to express AMPs; however, *E. coli* is the preferred recombinant bioreactor due to its rapid growth and well-defined genetic, physiological, and biochemical characteristics.[365] In the expression of AMPs, combining the antibacterial peptide with a carrier protein decreases its fatal effect on the host organism and gives resistance to proteolytic breakdown when expressed in bacteria.[366] *E. coli* has been used to produce several recombinant AMPs such as dermsidin (DCD), ABP-CM4 peptide, LfcinB-W10 (a bovine lactoferricin derivative), protegrin-1 (PG-1), cathelicidin LL-37, and some beta-defensins by fusion protein strategies.[367]

The eukaryotic yeast cell *Pichia pastoris* (*Komagataella phaffii*) is the most used yeast expression system for producing eukaryotic heterologous proteins.[368,369] The *P. pastoris* expression system successfully expressed many AMPs, such as cecropins,[370,371] defensins,[372] ABP-CM4 peptide,[373] and human CAP18/LL37 AMP[374] and also hybrid AMPs.[375] The *P. pastoris* expression system allows many eukaryotic post-translational modifications like glycosylation, signal sequencing processing, and disulphide bond formation. These modifications are necessary to produce cysteine-rich cationic AMPs,[376] such as HD5 a cationic peptide with six cysteine residues forming three intramolecular disulphide bonds.[372]

Plant bioreactors are a popular recombinant expression technique for producing medicines and treatments. High-yield expression of AMPs in plant bioreactors is a promising solution for large-scale manufacture of medical pharmaceuticals, meeting growing demand.[377] The leaves of the tobacco plant *Nicotiana benthamiana* were used for a high yield production of the recombinant AMPs; Cn-AMP1, clavanin A, Cm AMP-5 and parigidina-br1.[378]

However, several limitations and challenges complicate the production of AMPs through recombinant methods, one prominent challenge is the inherent toxicity of AMPs toward the expression host cells making it difficult to maintain viable host cell populations during expression. For instance, in bacterial expression systems such as *Escherichia coli*, the induction time must be carefully optimized to mitigate the effects of these toxic peptides on host cell survival and productivity.[44,45] The lack of proper post-translational modifications in prokaryotic expression systems also limits the functional efficacy of AMPs; many AMPs require specific glycosylation or other modifications that cannot be adequately produced in bacterial systems. Consequently, non-prokaryotic systems like *Pichia pastoris* are often utilized as they can perform some of these necessary modifications.[379,380]

Selecting an appropriate host for recombinant expression is crucial but also presents its own set of challenges; *E. coli* is often the primary choice due to its well-characterized genetics and rapid growth, however, it can limit the complexity of peptide processing.[45,381] On the other hand, while *Pichia pastoris* offer advantages, such as enhanced glycosylation, it may result in lower expression levels compared to *E. coli*.[379]

A comparison of chemical synthesis and recombinant expression methods for AMP production can be found in Table 2.

Table 2 A Comparison of Chemical Synthesis and Recombinant Expression Methods for AMP Production.[382]

Aspect	**Chemical synthesis (e.g., SPPS / LPPS**	**Recombinant expression (microbial/yeast/plant/ mammalian)**
Process	Solid-phase or liquid-phase stepwise peptide assembly using protected amino acids (automated SPPS common). [383]	EGene cloning and heterologous expression of peptides as free peptides or fusion proteins in E. coli, yeast, plants or mammalian cells, followed by cleavage/ purification.[384]
Production Scale	Best suited for small to medium scale and short to moderate length peptides.[385]	More suitable for large-scale production and longer polypeptides — once an expression process is optimized, fermentation/bioreactors allow cost-effective scale up.[386]
Purity	High crude purity possible, but side-reactions, deletion sequences and aggregation can occur — requires HPLC and other purification steps.[387]	Requires removal of host-cell proteins, endotoxins and nucleic acids; fusion partners and affinity tags often used to simplify purification, but additional cleavage and polishing steps are needed.[388]
Cost	Relatively high per-gram cost for long/complex peptides; costs have fallen for short peptides and research-scale batches.[389]	Cost-effective at large scale (cheaper media vs reagents), but higher development/upstream optimization costs (strain engineering, fermentation).[390]

(*Continued*)

Table 2 (Continued).

Aspect	Chemical synthesis (e.g., SPPS / LPPS	Recombinant expression (microbial/yeast/plant/mammalian)
Efficiency / Time to product	Fast development for short sequences (rapid, automated cycles), but synthesis yields drop and cycles multiply for long peptides.[391]	Slower to develop (cloning, expression, optimization), but once established can produce large amounts continuously.[391]
Modification Feasibility	Straightforward chemical modifications during or after synthesis (D-amino acids, N-terminal modifications, PEGylation, non-canonical residues).[392]	Natural PTMs (glycosylation, disulfides) can be achieved depending on host, but installing non-natural amino acids or specific modifications often requires extra engineering or chemoenzymatic steps.[393]
Bioactivity / PTMs	High activity for many AMPs, but lacks host-derived post-translational modifications unless added chemically; folding/disulfide formation must be managed.[394]	Can incorporate natural PTMs (in suitable hosts) which may improve stability/activity; some expression systems give better folding/solubility for complex peptides.
Environmental Impact	Uses large volumes of organic solvents and reagents (waste/disposal and energy concerns); greener SPPS methods and solvent recycling are active research areas.[395]	Bioprocesses use water-based media and generate biological waste; overall chemical waste is typically lower but fermentation has its own environmental footprint (energy, biomass disposal).
Applications	Research, medicinal chemistry, clinical trial material, synthetic analogs and peptides with non-natural residues or modifications.[391]	Industrial, large-scale production, recombinant therapeutics, agro/plant applications, and cases where natural PTMs or large-scale economics are required.[391]

AMP Databases

Recent advances in systems pharmacology, chemical biology, and computational biology have led to a significant increase in the number of naturally occurring and synthetic AMPs in databases. In the following, we outline the top curated databases and accompanying computational tools for AMP discovery and engineering.

APD3

The Antimicrobial Peptide Database (APD3; available at https://aps.unmc.edu/ [accessed on 25 March 2025]) is among the largest databases of AMPs.[396] As of Jan 2024, 3940 AMPs have been cataloged, comprising 383 bacterial, 250 plant, and 2463 animal AMPs. Searchable annotations such source organism, peptide sequence, and PTM are included in the APD3. The most prevalent is PTM amidation, which is followed by Rana Box (single S-S bond) and backbone cyclization. With the Protein Data Bank database's 3D annotations, APD3 provides a thorough structural classification of AMPs. AMPs can be found by users using covalently coupled structures or 3D structures. There are 21 peptide analysis, modification, and prediction tools in the APD3 database. A prediction interface is offered by the tools to assess an amino acid sequence's capacity to generate an AMP. In addition to structural information based on amino acid composition, the submitted query yields the following: chemical formula, molecular weight, total net charge, hydrophobicity content, amino acid percentage and composition, Boman index (which estimates protein-binding potential), and GRAVY (which represents peptide hydrophobicity). Peptide potency is increased by the peptide enhancement tool.

$CAMP_{R3}$

The Collection of Anti-Microbial Peptides database ($CAMP_{R3}$; available at http://www.camp3.bicnirrh.res.in [accessed on 25 March 2025]). This database differs from other AMP databases in that it includes information of family-specific signatures for a wide range of eukaryotic and prokaryotic AMPs.[397] Four sections make up the database: patents (2083 patented AMPs), structures (757 AMP structures), sequences (8164 AMP sequences), and signatures (36 patterns and 78 Hidden Markov Models). The $CAMP_{R3}$ database classifies AMPs into 45 families based on Hidden Markov Models

signatures and patterns. One of the nine tools in the database is AMP Prediction, which may be used to predict amino acid sequences, identify antimicrobial regions in peptides, and create or enhance AMPs. (2) CAMPSign examines 45 families in the database for peptide patterns; (3) VAST uses 3D geometrical criteria to find distant homologs; (4) PRATT finds conserved patterns in protein sequence sets; (5) ScanProsite compares input sequences to Prositemotif; (6) Pattern Hit Initiated (PHI) BLAST looks for protein sequence patterns; and (7) JackHmmer finds distant homology.

DBAASP

The Database of Antimicrobial Activity and Structure of Peptides (DBAASP; available at https://dbaasp.org [accessed on 25 March 2025]) is a database that is manually curated, and as of Jan 2024, it contains 22307 peptides.[398] What makes the DBAASP database unique are the molecular dynamics (MD) simulation models that include trajectory files and self-consistency data for a significant number of peptides. The database's MD models offer a deeper comprehension of structure–activity relationships, which can be utilized to logically design peptides. Six hydrophobicity scales based on published research can be found by evaluating an AMP's physicochemical features using the property calculator tool.

AMPs as Viable Alternatives to Traditional Antibiotics

AMPs have a broad range of antimicrobial activity, making them a potential treatment for complicated soft tissue and skin infections, such as polymicrobial infections including both Gram-positive and Gram-negative organisms.[399]

AMPs have several advantages over traditional antibiotics: (i) they bypass resistance mechanisms, (ii) they are easier to synthesize due to short amino acid sequences, (iii) they kill bacteria rapidly (iv) they act on bacteria regardless of resistance phenotype, and (v) they do not harm microbiota, which are often disturbed by traditional antibiotics.[400–402] Methicillin resistance, for instance, is caused by mutations in PBP of *Staphylococcus aureus*. AMPs, on the other hand, do not exhibit cross-resistance or overlap in their mechanisms of action since they act on the cell membrane, therefore, they can be utilized to treat the rising number of antibiotic-resistant infections.[29] Additionally, the capacity of a single AMP to act through various mechanisms and pathways enhances its potency and reduces resistance; a drug that functions through several pathways minimizes the possibility of bacteria acquiring multiple mutations at the same time. Moreover, because many AMPs target evolutionarily conserved cell membrane components, bacteria must entirely remodel their membranes, necessitating numerous mutations over an extended period.[31] Cancer chemotherapy sometimes involves combining various medications with different mechanisms to limit tumor resistance. Multiple drug use during chemotherapy may result in more toxicity and adverse consequences. Multiple complimentary pathways in a single AMP medication may minimize adverse effects while producing the same antibacterial activity.[403]

Because of these advantageous characteristics of AMPs, coadministration of antibiotics is one more possible use for AMPs. Antibiotic resistance may be weakened or prevented by combinational AMP and antibiotic therapy. For instance, combination therapy was used to eradicate vancomycin and azithromycin resistance in *Escherichia coli, Pseudomonas aeruginosa*, and *Staphylococcus aureus* employing the AMP DP7.[33] Additionally, several AMPs and antibiotics have been shown to work synergistically in vitro.[34] This demonstrates a special clinical relevance where combining drugs at lower dosages may lower their toxicity or negative side effects. AMPs may also interact synergistically with immune system components in addition to exhibiting synergistic effect with antibiotics.[40,50]

Nevertheless, AMPs have several disadvantages when compared to traditional antibiotics, which can limit their clinical applicability. Firstly, one of the primary challenges associated with AMPs is their stability; many AMPs are susceptible to proteolytic degradation, leading to a short half-life in vivo and limiting their therapeutic efficacy primarily to topical applications.[404] Traditional antibiotics, in contrast, tend to exhibit greater metabolic stability, enabling prolonged therapeutic effects. The lack of stability in AMPs could necessitate complex delivery systems, such as nano-encapsulation, to protect the peptides from degradation, which adds to the cost and complexity of their use.[405,406] Moreover, AMPs often exhibit substantial variability in minimum inhibitory concentration (MIC), making it challenging to establish standard dosages akin to traditional antibiotics.[407,408] For effective antibacterial action, peptide concentrations must be optimized, and these levels may vary significantly across different bacterial species, complicating treatment protocols. Increased variability in efficacy can result in unpredictable clinical outcomes.[407] Additionally, the toxicity of AMPs to eukaryotic cells must be considered before considering AMPs for clinical use. Due in significant part to their

Table 3 Commercially Available Antibiotics Based on AMPs

Active Compound	Source	The Targeted Organism	Mechanism of Action	Indication	Administration Route	Ref
Bacitracin	Bacteria (*Bacillus subtilis*)	Gram-positive bacteria	Inhibits the formation of cell walls	Bacterial skin infections	Topical/Intramuscular	[416]
Dalbavancin	Teicoplanin derivative	Gram-positive bacteria	Inhibits the formation of cell walls	Bacterial skin infections	Intravenous	[417]
Daptomycin	Bacteria (*Streptomyces roseosporus*)	Gram-positive bacteria	Lysis of membranes	Bacterial skin infections	Intravenous	[418]
Colistin	Bacteria (*Bacillus polymyxa*)	Gram-negative bacteria	Lysis of membranes	Gram-negative bacterial infections from multi drug-resistant strains	Intravenous	[419]
Gramicidin D	Bacteria (*Bacillus brevis*)	Gram-positive bacteria and some gram-negative bacteria	Lysis of membranes	Bacterial skin and eye infections	Topical	[420]
Oritavancin	Vancomycin derivative	Gram-positive bacteria	Lysis of membranes and inhibition of cell wall synthesis	Bacterial skin infections	Intravenous	[421]
Polymyxin B	Bacteria (*Bacillus polymyxa*)	Gram-negative bacteria	Lysis of membranes	Bacterial bloodstream and urinary tract infections	Topical/Intravenous	[422]
Teicoplanin	Bacteria (*Actinoplanes teichomyceticus*)	Gram-positive bacteria	Inhibits the formation of cell walls	Severe gram-positive bacterial infections	Intramuscular/Intravenous	[423]
Telavancin	Vancomycin derivative	Gram-positive bacteria	Lysis of membranes and inhibition of cell wall synthesis	Bacterial skin infections	Intravenous	[424]
Vancomycin	Bacteria (*Amycolatopsis orientalis*)	Gram-positive bacteria	Inhibits the formation of cell walls	Severe gram-positive bacterial infections	Oral/Intravenous	[425]

high therapeutic dosage, a number of AMPs have been shown to be extremely nephrotoxic,[39] unlike many traditional antibiotics that typically do not induce significant rates of cell toxicity.[409]

Resistance development remains another important consideration in the clinical applicability of AMPs; although AMPs tend to induce lower rates of resistance development compared to traditional antibiotics, the bacteria does have the potential to develop resistance to AMPs.[410] Specifically, mutations that confer antibiotic resistance may alter bacterial susceptibility to AMPs, potentially undermining the intended advantages of these peptides.[207,408] Also, the risk of cross-resistance associated with the synergistic use of AMPs and antibiotics may further complicate treatment options.[411]

Synthetic mimics of AMPs are a promising class of novel antibiotics. The molecular structure of these compounds is rationally designed to retain an antimicrobial pharmacophore while allowing for desired features including increased activity, reduced cytotoxicity, and proteolysis. The challenges of synthesizing complex structural motifs and non-canonical amino acids can be overcome using synthetic mimics.[412]

Commercially Available Antibiotics Based on AMPs

There are currently ten commercially available antibiotics based on AMPs (Table 3). Seven of these active compounds, like many conventional antibiotics, were extracted from bacterial strains. The remaining three are known chemical derivatives that are semi-synthetic. These AMP-based antibiotics target bacterial cell membranes, causing membrane lysis or inhibiting cell wall formation. As evident from the antibiotics currently available in the market and based on

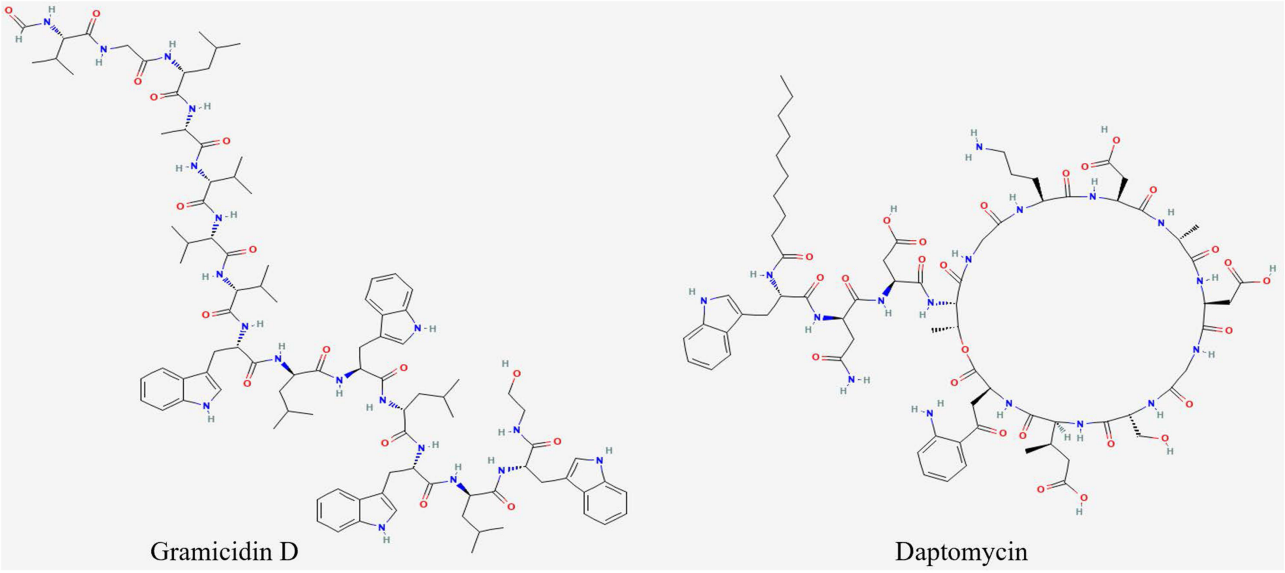

Figure 5 Chemical structures of two AMPs approved by FDA for topical treatments (PubChem; available at https://pubchem.ncbi.nlm.nih.gov/ [accessed on 25 March 2025]).

AMPs; AMPs can have diverse chemical compositions despite sharing similar mechanistic targets (bacterial cell membranes). Cyclic peptides have increased stability in vivo when compared with their linear counterparts.[413] Soil bacteria frequently produce a family of antibiotics called glycopeptides. Dalbavancin, oritavancin, and telavancin are glycopeptide derivatives that have a lipid component attached to the peptide backbone, which increases their affinity for bacterial cell membranes.[414] Despite having gram-negative action, colistin and polymyxin B are extremely toxic and should only be used as a last resort after all other options have been tried. Similarly, gramicidin is used as a topical agent only because of its cytotoxicity.[415] Vancomycin, teicoplanin, polymyxin B, gramicidin, colistin, daptomycin, and bacitracin are non-ribosomally synthesized peptides produced by bacteria and fungi. Peptide synthetases are utilized as a catalyst for the synthesis of these peptides.[265]

Table 4 Recently Completed Clinical Trials with Studies Involving AMPs (Source: https://clinicaltrials.gov/)

Trial Number	Phase	Results	Ref
NCT03634150	2	This study evaluated the safety and efficacy of dTCApFs; a novel hormone peptide targeting the T1/ST2 receptor, in patients with advanced/metastatic solid tumors. The study suggests dTCApFs is well-tolerated and potentially effective, particularly in T1/ST2-positive tumors.	[436]
NCT00293423	2	This study examined the effectiveness and safety of an autologous heat-shock protein peptide complex-96 (HSPPC-96) vaccination for individuals with recurrent glioblastoma multiforme (GBM). The study concluded that HSPPC-96 vaccination is safe and recommends further studies on HSPPC-96 vaccine as a treatment of recurrent GBM.	[437]
NCT05530252	4	This study evaluated the effects of AMPs on the treatment of Stage III and Grade B periodontitis. The study concluded that the application of AMPs as an adjunct to minocycline hydrochloride shows clinical and microbiological improvements in the treatment of Stage III Grade B periodontitis.	[438]
NCT05431218	4	This study evaluated the plasma levels of the AMP LL-37 and nuclear factor-kappaB (NF-κB) in patients Chronic Obstructive Lung Disease (COPD). The study concluded that plasma LL-37 and NF-κB may play a crucial role in chronic immune inflammation, recommending LL-37 as a target for treatment of COPD.	[439]

Bacillus brevis, a soil bacterium, was the initial source of gramicidins, they are frequently used topically in combination with other antibiotics to treat infected wounds or as eye drops to disinfect the eyes. They can also cause hemolysis and are toxic to human cells in high doses.[426] Gramicidin S is a 10-amino acid cyclic decapeptide and kills gram-positive and gram-negative bacteria, as well as fungus, whereas Gramicidin D is a 15-residue mixture of many linear peptide isoforms. Both contain D-amino acids. The mode of action of Gramicidin D is to permeabilize bacterial membranes, notably those of gram-positive bacteria like *Staphylococcus aureus* and *Bacillus subtilis*.[426]

Gramicidin D was licensed by the FDA in 1955 as a component in Neosporin®,[427] a topical antibiotic ointment for infected conjunctiva (Figure 5). Daptomycin is a cyclic branched lipopeptide that was first licensed by the FDA in 2003 to treat skin infections brought on by methicillin-resistant gram-positive bacteria, and reapproved in 2006 to treat systemic infections[428,429] (Figure 5).

Polymixins are cationic lipopeptide antibiotics that were first isolated from *Bacillus polymyxa* and are also utilized clinically.[430] With a molecular weight of about 1200 Da, these lipopeptides have a cationic cycle and a tail consisting of three amino acid residues to which fatty acids are connected. Due to the amphiphilic nature, polymyxins can enter cell membranes and cause them to break down. Although polymyxins are very effective against gram-negative bacteria, they can also be toxic to humans.[430] Decanoic acid is bonded to the tryptophan residue at the amino-terminal of this 13-amino acid peptide, which also contains D-alanine and D-serine.[428,429]

Currently, small cationic peptides are being studied in pre-clinical or clinical settings. Some of these are as follows: LL-37, a human cathelicidin, has antibacterial and immune-stimulating/modulating properties and can help treat venous ulcers.[96,431] Since it has antibacterial activity against *Listeria monocytogenes* and other gram-positive bacteria, nisin, a naturally occurring peptide generated by *Lactococcus lactis*, has been utilized as a food preservative for decades.[432] Similar to magainin, pexiganan is a synthetic peptide that has a broad-spectrum antibacterial activity and is produced when the cell membrane breaks down through the toroidal pore mechanism.[433] Omiganan, a synthetic peptide (ILRWPWWPWRRK-NH2) that is particularly effective against a variety of fungal infections;[434] and PXL01, a lactoferrin-derived peptide that is useful in post-operative adhesion care.[435] A summary of recently completed clinical trials involving AMPs can be found in Table 4.

Designing and optimizing peptide mimetics is a viable approach for developing novel bioactive molecules. Telavancin, for example, is a semisynthetic vancomycin derivative, the hydrophobic (decylaminoethyl) side chain on vancosamine sugar encourages bacterial cell membrane adhesion. Further hydrophilic (phosphonmethyl aminomethyl) bonding to the resorcinol moiety prolongs the half-life of the molecule.[440] A second mode of action for telavancin is thought to be related to membrane lysis. Lipid II, a peptoglycan found in the bacterial membrane, is anticipated to interact with the hydrophobic appendage. Although the precise molecular pathways are yet unknown, preliminary research on *Staphylococcus aureus* indicates that lipid II binding quickly depolarizes the cell membrane.[441,442]

AMPs are prone to serum proteases and may cause toxicity in eukaryotic cells at high therapeutic doses. Additionally, they have low oral bioavailability due to their hydrophilicity, making it challenging to cross biological membranes, including the blood-brain barrier, intestinal mucosa, and cell membranes.[443] Therefore, they are frequently used as topical antibacterial agents. Intramuscular, intravenous or subcutaneous administration are some other common applications.[443] Because of its hemolytic side effects and protease breakdown, bacitracin and gramicidin are only used as topical therapies. Topical treatments, however, pose unique challenges; to properly treat skin wounds, topical creams and gels need to penetrate the tissue sufficiently. Therefore, the efficiency of antibacterial drugs is greatly impacted by their distribution.[207,444]

Activity Against MDR Bacteria

In vivo antibacterial activity against resistant bacteria has been demonstrated by hundreds of AMPs.[445] Interestingly, AMPs can inhibit bacteria from the ESKAPE complex (*Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P. aeruginosa*, and *Enterobacter* spp).[446] These pathogens are usually MDR, and they limit treatment options and put patients' lives at risk. For example, bip-P-113, dip-P-113, and nal-P-133 are derivatives of AMP p-133 that effectively treat *E. faecium* with a low minimum inhibitory concentration (MIC) of 4 μg/mL, compared to 64 μg/mL for vancomycin.[447] *S. aureus* resistance to methicillin remains a significant issue, leading to high mortality

rates.[448] Methicillin-resistant *S. aureus* (MRSA) can be eliminated by many AMPs. One such AMP that is thought to be a promising antimicrobial candidate is poly(2-oxazoline)s, an easy-to-synthesize polymer mimetic of AMPs that exhibits strong and selective antimicrobial activity against MRSA and has low MIC of 12.5 μg/mL.[449,450] ΔM3 is a newly developed synthetic peptide with a short amino acid sequence that combines strong biological activity with minimal toxicity, particularly against strains of *S. aureus*. The low MIC of ΔM3 against MRSA (7.5 μg/mL) and *S. aureus* (ATCC25923) (5 μg/mL), make it a promising AMP candidate.[451] Furthermore, SAAP-148, a human LL37 peptide derivative, exhibits activity against many resistant ESKAPE bacteria including biofilms that arise in wound infections.[452]

Because *K. pneumoniae* may be encapsulated, which limits the antibiotic's ability to penetrate, it presents a challenge for traditional antibacterial therapy. Nonetheless, this bacterium is susceptible to pepW, an AMP with low MIC (2–4 μg/mL) that targets, aggregates, and destroys *K. pneumoniae*'s capsules. PepW is also effective against *E. coli*, with MIC as low as 1–2 μg/mL.[453] Moreover, the AMPs: AA139 and SET-M33 are promising new treatments against MDR *K. pneumoniae* strains, with MICs ranging from 4 to 16 μg/mL, and they also show activity against colistin-resistant isolates.[454] The AMPs: Aurein 1.2, CAMEL, citropin 1.1, LL-37, Cec4, and omiganan exhibit high activity against MDR *A. baumannii*, with MICs ranging from 2 to 16 μg/mL.[455] The AMP ZY4 permeabilizes and kills MDR *P. aeruginosa* with MICs ranging from 2 to 4.5 μg/mL.[456]

Consequently, AMPs exhibit low MICs against bacterial strains with few treatment choices, making them a promising target for novel therapeutics.

AMP Resistance

Several studies have demonstrated that bacteria can develop resistance to AMPs, albeit at a slower rate compared to antibiotics.[279,457] Bacterial AMP resistance can be caused by a variety of mechanisms, such as encasing AMPs in proteins, cleaving them with the aid of proteases, reducing their binding affinity by modifying cell surface charge, modifying the fluidity of the bacterial cell membrane, generating efflux pumps in the membrane, generating exopolymers and molecules that build biofilms, and stimulating the expression of specific genes.[458–461]

Genetically, bacterial adaptation to AMPs frequently involves mutations affecting surface structures, particularly those contributing to the integrity of the outer membrane in Gram-negative bacteria. For instance, modifications in the lipopolysaccharides (LPS) through the PmrA-PmrB two-component regulatory system can lead to alterations that reduce susceptibility to cationic AMPs like polymyxins.[462] This system governs modifications like the addition of 4-aminoarabinose to lipid A, which not only shields bacteria from the cationic nature of AMPs but also may assist in survival by lowering inflammatory responses.[462] Additionally, diverse mutations within genes regulating membrane permeability can create a barrier that diminishes AMP access, as shown in *Pseudomonas aeruginosa*, where PhoPQ regulation plays a significant role in conferring resistance.[463]

A pivotal biochemical strategy used by bacteria to resist AMPs is the formation of biofilms, which provides a protective matrix that limits peptide penetration. Biofilms can sequester AMPs and reduce their effective concentration at the cell surface, thereby facilitating persistent infections in clinical settings.[463] Moreover, extracellular DNA in biofilms has been linked to cation chelation, which can further inhibit AMP activity and promote survival in hostile environment.[463] Bacteria have also developed biochemical pathways that can actively counteract the effects of AMPs. For example, some pathogens can secrete proteases that degrade AMPs or produce molecules that neutralize their charge, further diminishing their effectiveness.[42,464]

Some studies suggest that combining AMPs with conventional antibiotics can reduce resistance due to synergistic effects,[465–467] for example, it has been shown that the reduction in net positive charge of bacterial cell surface by ampicillin correlates with enhanced bactericidal effects of daptomycin and other cationic peptides in vitro.[468]

In clinical settings, the frequency of resistance development to AMPs is more difficult to induce in comparison to conventional antibiotics[469] because AMPs primarily target bacterial membranes, which are less prone to mutation than specific protein targets of conventional antibiotics. However, some studies indicate that antibiotic-resistant bacteria often demonstrated increased susceptibility to AMPs.[408] This is largely due to mutations in canonical resistance genes that have continually evolved in response to several antibiotic pressures. These findings suggest that mutations that confer resistance to one or more antibiotics concurrently increase sensitivity to multiple AMPs.[408]

Nanoformulation of AMPs

Nanotechnology has been instrumental in addressing the inherent limitations of AMPs, which include poor stability, rapid degradation, and systemic toxicity.[470] By encapsulating AMPs within various nanocarriers, we it is possible to enhance their therapeutic efficacy, reduce adverse effects, and facilitate targeted delivery to infected sites.[471,472] A predominant method of AMP nanoformulation involves using biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA). This approach has been shown to extend the release of AMPs, thereby maintaining effective concentrations over time while enhancing stability.[472,473] The use of PLGA nanoparticles for encapsulating AMPs has demonstrated promising results in treating bacterial infections, including in vivo studies showing potential benefits against pathogens such as *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA).[473,474]

Chitosan, a biocompatible and biodegradable polymer, has also emerged as a preferred matrix for AMP delivery systems due to its ability to protect peptides from enzymatic degradation. By forming nanocarriers with chitosan, studies have reported increased encapsulation efficiency and extended release profiles of AMPs, which are critical for clinical applications.[475] Therefore, advancing nanoformulation of AMPs has significant implications for enhancing their clinical applicability, by offering enhanced stability, improved pharmacokinetics, and targeted delivery.[476]

Conclusions

Antimicrobial peptides (AMPs) represent a versatile and vital component of the innate immune system, offering potent defense mechanisms against a wide range of pathogens. With their unique structural diversity and dual mechanisms of action—membrane disruption and inhibition of intracellular processes—AMPs hold significant promise as therapeutic agents. Advances in structural analysis and synthesis techniques, including chemical synthesis and computational modeling, have enhanced our understanding of their biological roles and enabled the development of AMP-based drugs. The increasing availability of curated databases and computational tools further facilitates AMP discovery and engineering, paving the way for novel therapeutic applications.

Despite their broad-spectrum activity and proven efficacy against multidrug-resistant bacteria, challenges remain. The emergence of bacterial resistance to AMPs, although slower than traditional antibiotics, emphasizes the need for continuous research and innovation in AMP design and application. Furthermore, the inherent limitations of AMPs such as low efficacy, poor stability and toxicity towards human cells remain critical for their widespread adoption in clinical settings. In this context, nanoformulation of AMPs has emerged as a promising avenue for enhancing their clinical applicability.

This review highlights the importance of AMPs in addressing antibiotic resistance. Future research on AMPs should prioritize the integration of computational design, therapeutic combinatory approaches, and the exploration of their immunomodulatory roles, alongside techniques to enhance their pharmacokinetics and stability. With sustained efforts in research and development, AMPs are poised to play a pivotal role in the future of antimicrobial therapy and beyond.

Disclosure

The authors report no conflicts of interest in this work.

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