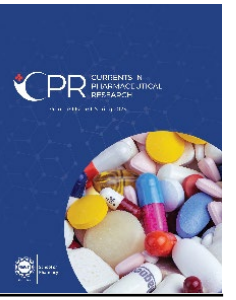
Currents in Pharmaceutical Research (CPR)
Volume 4 Issue 2, Fall 2026
ISSN$_{(P)}$: 3007-3235, ISSN$_{(E)}$: 3007-3243
Homepage: https://journals.umt.edu.pk/index.php/cpr



Title:	**Antimicrobial Peptides as Novel Therapeutics: An In-depth Exploration into Mechanisms, Resistance Challenges, and Clinical Prospects**
Author (s):	Faiza, Muhammad Asad Saeed, and Muhammad Zaman
Affiliation (s):	University of Central Punjab, Lahore, Pakistan
DOI:	https://doi.org/10.32350/cpr.42.01
History:	Received: February 20, 2026, Revised: March 26, 2026, Accepted: April 15, 2026, Published: May 15, 2026
Citation:	Faiza, Saeed MA, Zaman M. Antimicrobial peptides as novel therapeutics: An in-depth exploration into mechanisms, resistance challenges, and clinical prospects. *Curr Pharm Res*. 2026;4(2):1–22. https://doi.org/10.32350/cpr.42.01
Copyright:	© The Authors
Licensing:	This article is open access and is distributed under the terms of Creative Commons Attribution 4.0 International License
Conflict of Interest:	Author(s) declared no conflict of interest

A publication of
The School of Pharmacy
University of Management and Technology, Lahore, Pakistan

Antimicrobial Peptides as Novel Therapeutics: An In-depth Exploration into Mechanisms, Resistance Challenges, and Clinical Prospects

Faiza, Muhammad Asad Saeed*, and Muhammad Zaman

Faculty of Pharmaceutical Sciences, University of Central Punjab, Lahore, Pakistan

ABSTRACT

Antimicrobial peptides (AMPs) play a crucial part in innate immunity. They are naturally occurring, short-chain peptides. Furthermore, they show a broad-spectrum of activity against a variety of bacteria and viruses, along with immunomodulatory effects. This dual therapeutic potential has raised researchers' interest as an alternative to antibiotics. The majority of antimicrobials available in the market encounter resistance considerably. Whereas resistance of AMPs is subordinate due to their unique mechanism of action. In spite of such benefits, clinical translation of AMPs is still a challenge owing to their high manufacturing cost, toxicity, proteolytic instability, and microbial resistance. Current advancements in chemical modifications, peptide engineering, and nano delivery have emerged to address such challenges. The current study aimed to provide a comprehensive insight into resistance pathways, therapeutic applications, cellular mechanisms, critical analysis of in-progress clinical trials, structural features, and future perspectives. AMPs depicted significant interactions that modulate cytokine production, chemotaxis, and immune responses. This validates the role of AMPs as immune sentinels, regulating both adaptive and innate immunity, unlike usual antimicrobials. The key objective of this study was to explicate the organ level defensive role of AMPs in a comprehensive manner. Moreover, the study also explored multiple bacterial resistance tactics. Recent approaches, such as nano-carrier drug delivery systems, peptide engineering, and backbone modifications, enhanced evasion, tissue targeting and bioavailability of AMPs have also been traversed. By accentuating both opportunities and challenges, this study focused on the possible translational potential of AMPs in tackling the antimicrobial resistance (AMR) dilemma worldwide.

Keywords: antimicrobial peptides, antimicrobial resistance, drug delivery, host-defense, nano medicine, peptide engineering

*Corresponding Author: asad.saeed@ucp.edu.pk

1.INTRODUCTION

Antimicrobial resistance (AMR) is one of the imminent threats to global public health due to an alarming increase in multidrug-resistant strains of bacteria, which renders the majority of antibiotics ineffective. Additionally, AMR is ranked as one of the top ten global public health threats declared by the World Health Organization (WHO) [1, 2]. If not tackled well, the number of deaths due to drug-resistant infections would rise to 10 million by 2050 [3]. This has stimulated a need for alternative therapeutics of antibiotics, among which AMPs have emerged as an optimistic approach [4–6].

Antimicrobial peptides (AMPs) are found naturally in all organisms, ranging from bacteria to human beings, as a part of their innate immunity, serving as natural antibiotics. They are usually composed of 12-50 amino acids; these peptides are amphipathic and cationic in nature, which enables their interaction with microbial membranes. More than 3000 AMPs have been discovered so far, and are presented in the Antimicrobial Peptide Database (ADP) [7–9].

Classical antibiotics usually target specific biosynthetic pathways or enzymes. However, AMPs work by membrane disruption, inhibition of protein and nucleic acid synthesis, and rapid permeabilization. These mechanisms contribute to their broad-spectrum activity against gram-positive and gram-negative bacteria, viruses, fungi, and other pathogens. AMPs also have less probability of resistance development due to their broad mechanism of action. AMPs also show an immunomodulatory role, including cytokine regulation, wound healing, and regulation of chemotactic activity, along with antibiotic properties [10–12].

A significant amount of research has been conducted on AMPs. This resulted in the availability of multiple natural and synthetic AMPs, advancing successfully to preclinical and clinical trials, treating conditions ranging from minor skin infections to sepsis. The limitations of AMPs, including high production costs, potential for resistance, host cell toxicity, and proteolytic degradation, cannot be denied [13, 14].

2.STRUCTURAL CHARACTERISTICS OF AMPS

AMPs are short, cationic amphipathic molecules with a range of 10 to 50 amino acids and a net positive charge of +2 to +9 that allows their interaction with negatively-charged microbial membranes [7, 15, 16]. Their

amphipathic nature arises from the spatial arrangement of hydrophilic and hydrophobic residues and is pivotal for their insertion in lipid membranes [16].

2.1.Major Structural Classes

AMPs have four primary structural classes mentioned as follows [17]:

α-helical Peptides: **α**-helical peptides form amphipathic helices when they come in contact with cell membranes. Examples include *LL-37* and *magainins*.

β-sheet Peptides: These peptides include *defensins.* Furthermore, they are stabilized by disulfide bonds and show anti-fungal, along with anti-bacterial properties.

Extended Peptides: They have rich amounts of certain residues (histidine, tryptophan and proline). Additionally, they work by nucleic acid binding. Example includes *Indolicidin*.

Loop Peptides: They form intramolecular bonds and stay stable under diverse conditions. Example includes *bactenecin*.

These classes are not rigid; sometimes, AMPs adopt flexible conformations when they come in contact with cell membranes [18].

2.2.Amino Acid Framework

The antimicrobial activity of AMPs is highly influenced by amino acid composition [19].

Cationic Residues (Lys, His, Arg): They are responsible for electrostatic interaction with microbial membranes [7].

Aromatic Residues (Ile, Leu, Val): These play a role regarding the insertion of AMPs in the membrane.

Proline and Glycine: They provide conformational flexibility, essential for membrane disruption.

A balance of amphipathicity, hydrophobicity (30-50%), and cationicity is a key factor in determining microbial selectivity over host cells.

2.3.Natural Sources of AMPs

Mammals: Cathelicidins, defensins.

Amphibians: Magainins, dermaseptins [20].

Insects: Defensins, cecropins [21].

Plants: Cyclotides, thionins.

Marine Species: Pisidians, aureins [22].

2.4.Structure-activity Relationship

The structure of AMP is highly versatile which gives it multiple modes of action ranging from immune modulation to pore formation [23]. Thus, SAR studies have been conducted to optimize AMP scaffolds for clinical applications [24]. Key AMPs are elaborated in Table 1.

3. MECHANISM OF ACTION OF AMPS

AMPs have synergistic and multifaceted mechanisms that include pore formation, immunomodulation, membrane perturbation, and translocation to intracellular targets [4, 29]. These strategies are attributed to their broad-spectrum activity with reduced resistance.

3.1. Membrane Targeting and Pore Formation

Most cationic AMPs first engage with the microbial envelope through electrostatic interaction to anionic lipids (Cardiolipin in bacteria; Lipid-A in gram-negative and lipoteichoic acid (LTA) in gram-positive, phosphatidyl glycerol), followed by interfacial partitioning that results in destabilization of bilayer [4, 30]. This disruptive step is explained by three main models and is illustrated well in Figure 1 along with the generalized mechanism of action of AMPs [31].

Barrel-Stave Model: According to this model, amphipathic helices insert perpendicularly to lipid bilayer and form a proteinaceous pore in such a way that the hydrophobic side faces the lipids, and the hydrophilic side is aligned towards the lining of the lumen [31].

Toroidal Pore Model: In this approach, peptides instigate a positive curvature, forming a pore with lipid headgroups in such a way that the lumen is lined with both lipids and peptides.

Carpet Model: According to this model, no pore formation takes place; simply, peptides lie parallel to the surface and micellize the surface without pore formation [31].

Table 1. Clinically-investigated AMPs

AMP/ Code (Trade)	Source/Class	Structure	Mechanism of Action	Indications	Clinical Trial Phase	Reference
Pexiganan (Locilex, MSI-78)	Synthetic magainin analogue	22-aa α-helical cationic	Membrane disruption	Infected diabetic foot ulcers	Phase III (completed)	[13]
Omiganan (MBI-226)	Indolicidin analogue	Short cationic peptide	Membrane permeabilization, anti-biofilm	Acne, rosacea, catheter infections	Phase II/ III	[13]
Brilacidin (PMX-30063)	Defensin-mimetic (non-peptidic AMP mimic)	Synthetic defensin-like	Membrane disruption, anti-inflammatory	COVID-19, oral mucositis, skin infections	Phase II	[25]
Iseganan (IB-367)	Protegrin derivative	Short β-sheet peptide	Rapid bactericidal action	Radiotherapy, oral mucositis	Phase III (negative results)	[13]
LL-37 (cathelicidin)	Endogenous human AMP	37-aa α-helical	Immune modulation, membrane disruption	DFU, venous ulcers, chronic wounds	Phase II	[13]
C16G2 (STAMPS peptide)	Synthetic targeted AMP	Targeting sequence + killing domain	Selective inhibition of *S. mutans*	Dental caries prevention	Phase II	[13]
DPK-060 (kininogen-derived)	Human protein fragment analogue	Synthetic short peptide	Membrane disruption	Ear infections, atopic dermatitis	Phase IIa	[26]
P113 (histatin-derived)	Salivary peptide	Short histatin fragment	Antifungal and antibacterial	Topical antifungal, oral candidiasis	Phase I/ II	[26]
Nisin	Bacteriocin (from *Lactococcus lactis*)	Cyclic AMP	Pore formation, lipid II binding	Periodontal disease, oral candidiasis	Phase II (oral gels/ topical)	[27]
Defensin mimetics (Brilacidin class)	Synthetic	Small molecule peptidomimetics	Membrane disruption	Broad systemic infections	Phase II	[28]
Other investigational AMPs (SNAPPs, ceragenins)	Synthetic mimetics	Diverse	Anti-biofilm, membrane disruption	Device coatings, MDR pathogens	Pre-clinical Phase I	[13]

Solid-state NMR and single-molecule studies reveal that the majority of AMPs can switch between these regimes according to lipid: peptide ratio, ionic strength, and lipid composition [32]. The interfacial-activity model also justifies the aptitude to reduce the free energy of the lipid-water interface, unifying diverse AMPs actions [33].

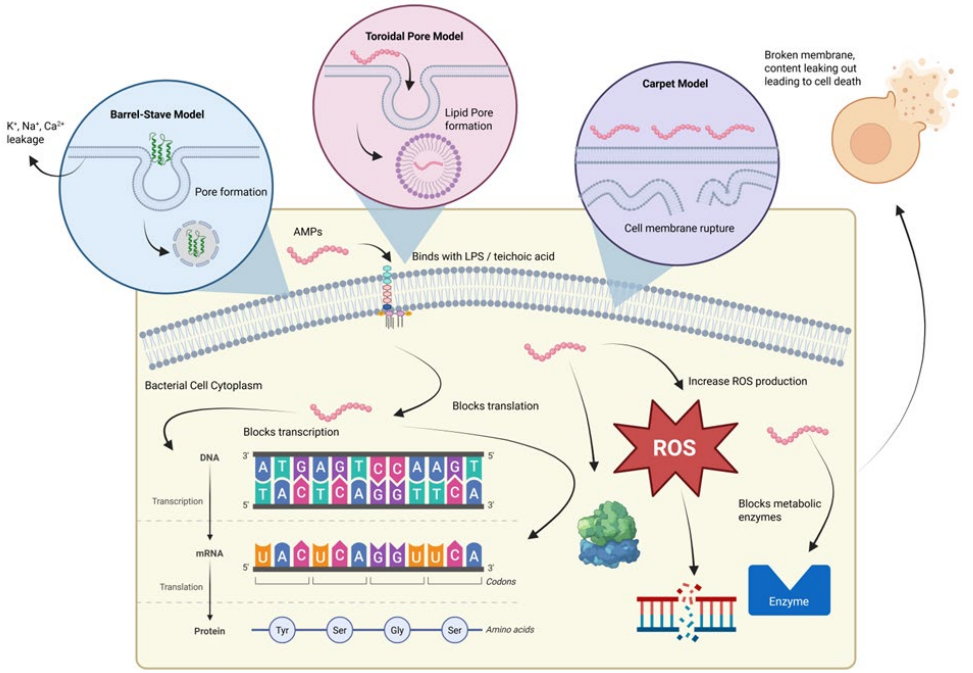


Figure 1. Illustrative Overview of the Mechanism of Action of AMPs. Membrane-disruptive Actions are Depicted through Toroidal Pore, Carpet, and Barrel-stave Models, Resulting in Membrane Destabilization, Pore Formation, Ion Leakage, and Cell Lysis. AMPs Significantly Bind to Cell Wall Modules, Such as Teichoic Acid and Lipopolysaccharide (LPS). AMPs also Block Transcription and Translation and Promote the Generation of Reactive Oxygen Species (ROS), Consequently Resulting in Cell Death.

3.2. Selectivity for Microbes over Host-cells

There are certain compositional differences between mammalian and microbial membranes. Microbes lack cholesterol and have more anionic lipids, whereas mammalian membranes are cholesterol-rich and are zwitterionic, resisting peptide insertion. Fine-tuning net charge (+2 to +7), helicity, and hydrophobic moment can make their selectivity more precise;

excessive hydrophobicity causes hemolysis, whereas inadequate hydrophobicity compromises potency [34].

3.3. Rapid Membrane Permeabilization Kinetics

According to kinetic studies, many AMPs demonstrate a loss of barrier function and sub-minute permeabilization (cecropin–melittin hybrids, magainin). This causes dissipation of membrane potential and crumple proton-motive force. This phenomenon is responsible for the scarce resistance of AMPs as compared to classical antibiotics [35].

3.4.Translocation and Intracellular Targets

Many AMPs translocate membranes without causing lysis and thus disrupts intracellular functioning.

Protein-rich AMPs: They leverage inner-membrane transporters, bind to ribosomes, and stall translation. They may also inhibit DnaK chaperone activity. Examples include: oncocin, Bac7, and apidaecins.

Arginine and Tryptophan-rich Peptides: They block DNA/RNA synthesis by binding with nucleic acids, or they restrain topoisomerases and enzyme hubs.

Some peptides block cell division, metabolism, or cell wall synthesis, fortifying a polypharmacology profile.

These actions are pivotal for persisted cells and biofilm contexts, where membrane disruption would not be enough [35].

3.5. Anti-biofilm and Anti-virulence Activity

Extracellular polymeric matrix, in the form of biofilm, protects bacteria and is responsible for the development of tolerance. Enormous AMPs (LL-37 derivatives, IDR-1018) interfere with quorum sensing, matrix assembly, and (p)ppGpp signaling, and disrupt or prevent biofilm formation at concentrations below MIC [31].

3.6. Immunomodulatory Mechanisms

Many AMPs function as host-defense peptides as indicated in Figure 2:

- Activation and chemoattraction of monocytes, dendritic cells, and neutrophils, modulation of cytokine profiles (e.g., IL-8, TNF-α), as well as TLR signaling.

- Endotoxin or LPS neutralization, by cationic amphipathic scaffolds, reduces inflammation related to sepsis.
- Pro-healing functions, for instance re-epithelialization, angiogenesis, and modulation of ROS restore barrier integrity and expedite wound healing [36].

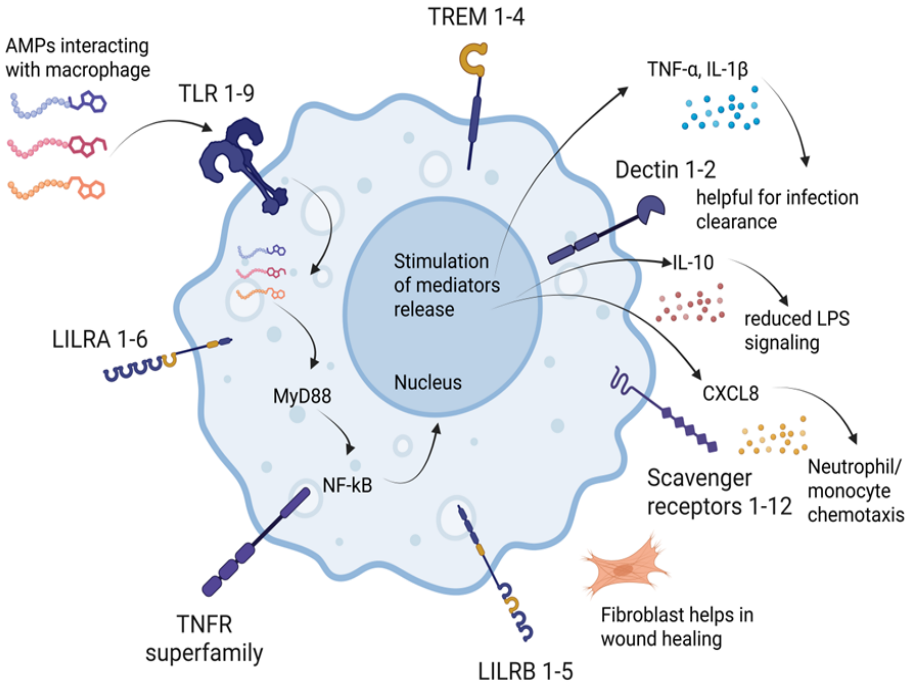


Figure 2. Host immune modulation by AMPs. AMPS interact with diverse cellular receptors including Dectin 1-2, scavenger receptors, LILRA members, TREM-1, TNFR superfamily receptors, and TLRs. This synergy activates signaling cascades, such as NF-kB and MyD88, resulting in the release of anti-inflammatory markers, for instance TNF-α, CXCL8, IL-10, and IL-1β.

4. THERAPEUTIC APPLICATIONS OF AMPS

AMPs not only provide innate immune defense, however, they also offer versatile therapeutic opportunities in wound healing, infectious diseases, and oncology. Furthermore, they are also utilized as novel drug delivery agents [37]. Their broad-spectrum activity and lower potential for resistance

make them highly captivating candidates for clinical translation [38]. The role of AMPs on lungs, skin, and gut is shown in Figure 3, 4, and 5.

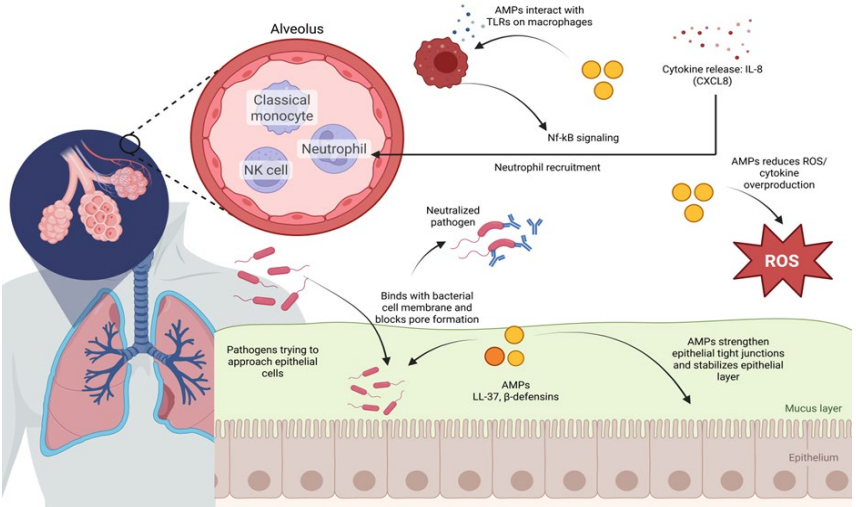


Figure 3. Schematic Depiction of AMPs' Protective Role on Lungs. AMPs, such as β-defensins and LL-37, Bind with Bacterial Membranes in Alveoli and Disrupt Pore Formation, Which Results in Neutralization of the Pathogen. AMPs also Interact with TLRs on Macrophages. This Activates a Series of Signaling Pathways, Resulting in the Release of Cytokines, Such as IL-8, which Promotes the Recruitment of Neutrophils.

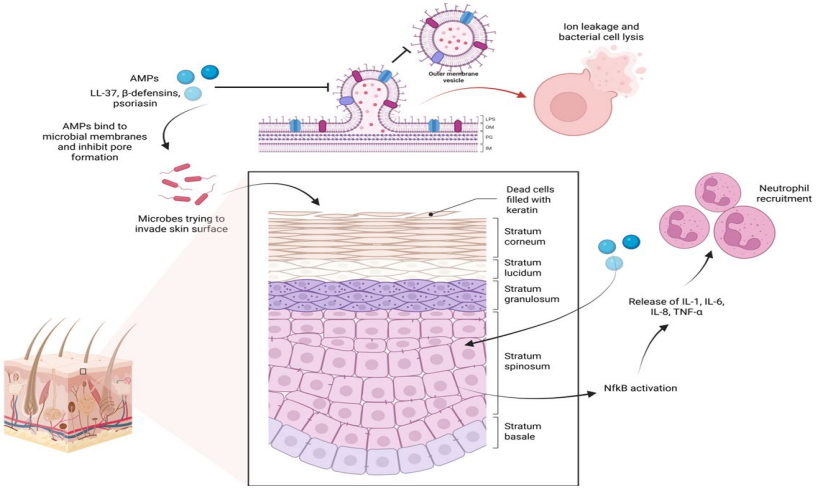


Figure 4. AMPs' Protective Role on Skin. AMPs, such as Psoriasin and LL-

37 are Produced by Keratinocytes Inside the Epidermis and are Abundantly Present across the stratified Layers (Stratum Corneum, Stratum Basale, Stratum Granulosum, Stratum Lucidum, and Stratum Spinosum). AMPs Bind to the Negatively-charged Membrane of Invading Microbes and Induce Pore Formation, Resulting in Cell Lysis. Keratin-filled Dead Cells Work in Synergism with AMPs and Activate Signaling Pathways, Leading to the Release of Pro-inflammatory Cytokines, such as IL-6, IL-1, and IL-8.

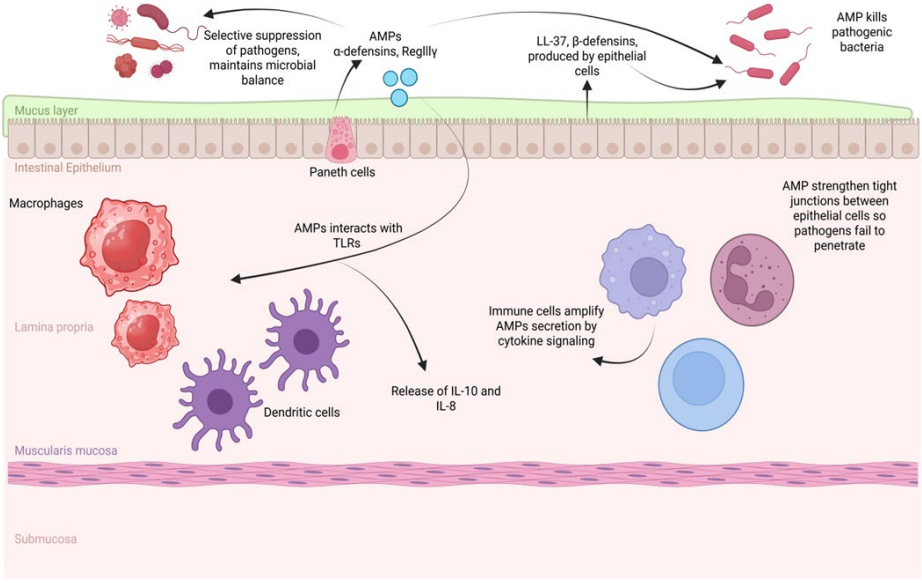


Figure 5. AMPs' Protective Role on the Gut. Paneth Cells Secrete Cathelicidins and Defensins, which Suppress Pathogens and Maintain Microbial Balance. AMPs Bind Directly to Pathogen Membranes and Cause Membrane Destabilization, Leading to Cell Death. AMPs also Brace Epithelial Tight Junctions and Minimize the Translocation of Pathogens across the Epithelial Barrier. Moreover, AMPs Interact with TLRs, Activate Innate Immunity, and Promote Cytokine Release

4.1.AMPs in Infectious Diseases

AMPs were developed as an alternative to classical antibiotics to bypass resistance. Many AMPs, such as daptomycin, pexiganan, and omiganan, have advanced into clinical trials for catheter-related infections, diabetic foot, and skin infections. Unlike classical antibiotics, AMPs work by intracellular targeting and membrane disruption, thus minimizing resistance

chances. Moreover, they can be used in synergism with antibiotics to have a pronounced therapeutic effect against multidrug-resistant strains.

AMPs have also showed potential in treating viral infections. For instance, cathelicidins and defensins inhibit the Herpes simplex virus, HIV, and influenza by either modulating host immunity or prohibiting viral entry into cells. Likewise, lactoferrin-derived peptides block coronavirus replication, indicating their potential in surging viral diseases.

Sometimes, fungal infections are quite difficult to handle with traditional antifungals. AMPs also serve their role in this regard since they exhibit antifungal characteristics. For instance, defensins and histatins show remarkable antifungal activity against *Aspergillus fumigatus* and *Candida albicans* [39–41].

4.2. AMPs in Cancer

AMPs show selective cytotoxicity for cancer cells, which make them promising candidates as anti-cancer peptides (ACPs) [42]. Tumor cells have phosphatidyl serine, altered glycosylation pattern, and heparan sulfate proteoglycans in their cell membrane, which imparts a negative charge to them. This facilitates AMPs binding to cancer cells, owing to their cationic nature [42]. For instance, cecropins, melittin, and temporins [43].

AMPs-based anti-cancer strategies include; mitochondrial depolarization, interference with oncogenic signaling pathways, reactive oxygen species generation, membrane disruption, and mitochondrial depolarization. *In vivo* studies indicate AMPs' potential in minimizing metastasis and tumor growth with merest toxicity to normal tissues.

4.3. AMPs in Tissue Generation and Wound Healing

AMPs, such as defensins and LL-37 modulate cytokine release, angiogenesis, and keratinocyte migration [37]. Stimulate re-epithelialization. LL-37 stimulates fibroblast proliferation and recruits immune cells to aid in tissue repair.

Topical AMPs have also been formulated for surgical wounds, burns, and chronic ulcers, where they improve healing by reducing infection risk. Moreover, they neutralize lipopolysaccharides (LPS) to prevent sepsis and overcome inflammation [38].

4.4. AMPs in Drug Delivery and Nanomedicine

AMPs are also used as delivery vectors. Their membrane-penetrating property permits conjugation to nanoparticles, small molecules, and nucleic acids for targeted drug delivery. For instance, AMP-conjugated nanoparticles improve antimicrobial activity while minimizing cytotoxicity [44]. The non-lytic translocation of protein-rich AMPs has been explored for intracellular delivery of anti-cancer agents and antibiotics [13].

In nanomedicine, AMP-functionalized biomaterials have been developed for coating catheters, implants, and medical devices to avert biofilm formation. These coatings provide long-term protection against hospital-acquired infections and reduce systemic toxicity.

5. CHALLENGES

Despite having multiple benefits, AMPs also have some limitations to tackle. Several innovative strategies are thus required for advancing AMPs from bench to beside [13, 45].

5.1.Stability and Degradation Issues

AMPs are susceptible to proteolytic degradation either by microbial enzymes or by the host itself. They are also prone to degradation by peptides, and have a very short plasma half-life. This raises a need for a higher dose which potentiates the risk of toxicity. Chemical modifications, such as incorporation of non-natural residues, D-amino acid substitution, and cyclization have been adapted to improve stability. Furthermore, nanoparticles also increase circulation time by providing a protective environment [45].

5.2.Toxicity and Selectivity Concerns

Some AMPs disrupt the cell membranes of host cells and cause cytotoxicity or hemolysis. In order to broaden the therapeutic window, peptides should be designed in a way to have optimized amphipathicity, charge, and hydrophobicity. Computational and SAR studies are ongoing on this matter.

5.3.Cost and Manufacturing Concerns

Peptide synthesis is highly expensive. Large-scale production needs advancement in recombinant expression systems, cell-free synthesis, and inexpensive purification methods. Large-scale production of AMPs is a

challenge, especially if solid-phase peptide synthesis (SPPS) is employed. This is a good combinatorial technique ensuring high purity of product. However, this technique comes with many hurdles, such as a continuous need for downstream purification, excessive solvent utilization, and low yield due to coupling discrepancies in each step. In contrast to this, recombinant DNA technology is a more scalable and cost-effective option employing eukaryotic or microbial expression system. However, it also comes with certain limitations including peptide toxicity to host cells, development of insoluble inclusion bodies, and high potential for proteolytic degradation [46].

5.4. Resistance Development

Resistance by surface charge modification, efflux pumps, and protease secretion as indicated in Figure 6 with elaborated details in Table 2, though subordinate to traditional antimicrobials, cannot be denied. Combinatorial approaches, such as continuous monitoring and co-administration of AMPs with traditional antibiotics, are key factors to delay resistance [47, 48].

5.5.Regulatory Challenges

AMPs serve as an intermediate between biologics and small molecules, rendering their regulatory classification highly complex. The Food and Drug Administration (FDA) has efficiently classified AMPs on the basis of their particle size. According to which, peptides with amino acids fewer than 40, are categorized as conventional drugs, whereas peptides exceeding 40 amino acids are included in the biologics class. The clinical trial data of AMPs is quite confined, and detailed pharmacology is not well-explored. This raises a need for standardized guidelines for long-term impact, safety, and efficacy [10, 49].

5.6.Future Directions

Future beholds the promising potential of AMPs if their design and applications are advanced by employing modern experimental and computational approaches. The techniques that could be employed in this regard include molecular dynamics simulations, deep learning (DL) techniques, and artificial intelligence (AI) for the design of peptides with better stability, selectivity, and subordinate toxicity [50–54]. Currently, more emphasis should be placed on improving drug delivery strategies, which could be achieved by the development of scaffolds, nanoparticles for localized delivery and controlled release, as well as formation of AMP-

loaded hydrogels [40]. Furthermore, AMP-analogs with non-peptide backbones or hybrid molecules should be explored, which may improve functional capabilities by offering better resistance to degradation [55]. Design of target-selective narrow-spectrum AMPs should be considered to minimize off-target effects [56]. The incorporation of patient-specific AMP techniques should be introduced to design drug approaches considering specific patient variability [51,52]. Furthermore, AMPs in combination with immunotherapies, vaccines, or antibiotics could also be used as a technique to delay resistance [56].

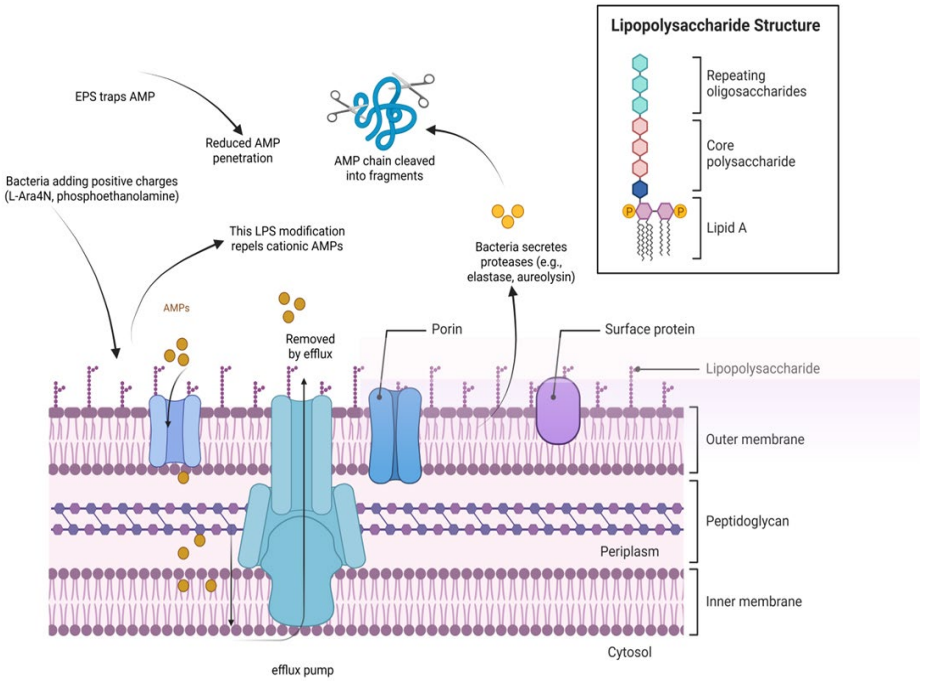


Figure 6. AMPs' Resistance Mechanisms. The resistance Mechanism Encompasses LPS Modification and the Addition of Positive Groups, which Decreases the Binding Ability of AMPs. LPS also Causes Sequestration of AMPs. Certain Enzymes Induce Proteolytic Degradation, Reduced Membrane Permeability by Porins, and Subsequent Extrusion of AMPs by Efflux Pumps

Table 2. Bacterial Resistance Mechanisms against AMPs

Resistance Mechanisms	Cellular/Molecular strategies	Bacterial Species	AMPs	Reference
Outer Membrane Charge Modification	Reducing AMP binding and negative charge, addition of phosphoethanolamine or L-Ara4N to lipid A	*Escherichia coli, Salmonella enterica*	LL-37, polymyxin B	[57]
Exopolysaccharides and Capsule Development	AMPs' penetration is inhibited by the safeguarding of the surface through anionic capsule	*Neisseria meningitidis*	defensins	[58]
Proteolytic Degradation	Proteases are secreted that cleave AMP backbone	*Pseudomonas aeruginosa*	β-defensins, LL-37	[58]
Efflux Pumps	RND-type pumps or ATP-binding cassette expels AMPs out of cytoplasm	*Escherichia coli, Pseudomonas aeruginosa*	Polymyxin, cecropins	[59]
Biofilm Formation	AMPs are sequestered by matrix polysaccharides	*Pseudomonas aeruginosa, Staphylococcus aureus*	Indolicidin, LL-37	[58]
Two-component Regulatory Systems	PhoP/PhoQ, PmrA/PmrB sense AMPs, gene responsible for resistance is triggered	*Escherichia coli, Salmonella typhimurium*	Defensins, polymyxins	[57]
Altered Membrane Fluidity	AMPs' insertion is reduced by changes in fatty acid saturation	*Lysteria monocytogenes*	Human defensins	[60]
D-alanylation of Teichoic Acid	AMP attraction is reduced by reduction of negative charge of cell wall	*Enterococcus faecalis, Staphylococcus aureus*	Defensins, LL-37	[39]

6. CONCLUSION

AMPs depicted a promising future for handling multidrug-resistant pathogens. AMPs' mechanism includes immune modulation and microbial membrane targeting. The unique mechanism of AMPs minimizes the development of resistance. The major challenges in the clinical translation of AMPs include cost, proteolytic degradation, and certain regulatory concerns. A multidisciplinary approach is needed to optimize AMPs for a better pharmacological profile.

Innovative approaches, including the use of AMPs as nanocarriers (polymeric nanoparticles, hydrogels, and liposomes) offer better stability, bioavailability, and drug delivery. Current techniques utilize hybrid molecules and immunomodulatory motifs for improved therapeutic applications.

In a nutshell, AMPs encounter subsequent challenges; advancements in nanotechnology, peptide engineering, and computational design have enhanced their therapeutic benefits. A detailed and continuous research can soon make AMPs an alternative class, overcoming microbial resistance effectively.

Author Contribution

Faiza: Muhammad: data analysis, writing-original draft, Software. **Asad Saeed:** conceptualization, supervision, writing- review & editing. **Muhammad Zaman:** writing- review & editing, supervision.

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

No new data was created or analyzed in this study.

Funding Details

No funding has been received for this research.

Generative AI Disclosure Statement

The authors did not use any type of generative artificial intelligence software for this research.

REFERENCES

1. Salam MA, Al-Amin MY, Salam MT, et al. Antimicrobial resistance: a growing serious threat for global public health. *Healthcare (Basel)*. 2023;11:e1946. http://doi.org/10.3390/healthcare11131946

2. Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629-655. https://doi.org/10.1016/S0140-6736(21)02724-0

3. Gargate N, Laws M, Rahman KM. Current economic and regulatory challenges in developing antibiotics for Gram-negative bacteria. *npj Antimicrob Resist.* 2025;3:e50. http://doi.org/10.1038/s44259-025-00123-1

4. Mookherjee N, Anderson MA, Haagsman HP, Davidson DJ. Antimicrobial host defence peptides: functions and clinical potential. *Nat Rev Drug Discov.* 2020;19:311-332. http://doi.org/10.1038/s41573-019-0058-8

5. Islam T, Tamanna NT, Sagor MS, Zaki RM, Rabbee MF, Lackner M. Antimicrobial peptides: a promising solution to the rising threat of antibiotic resistance. *Pharmaceutics.* 2024;16(12):e1542. http://doi.org/10.3390/pharmaceutics16121542

6. Raza A, Mushtaq N, Jabbar A, Ellakwa DE. Antimicrobial peptides: a promising solution to combat colistin and carbapenem resistance. *Gene Rep.* 2024;36:e101935. http://doi.org/10.1016/j.genrep.2024.101935

7. Li X, Zuo S, Wang B, Zhang K, Wang Y. Antimicrobial mechanisms and clinical application prospects of antimicrobial peptides. *Molecules.* 2022;27(9):e2675. http://doi.org/10.3390/molecules27092675

8. Kim SH, Min YH, Park MC. Antimicrobial peptides: current status, mechanisms of action, and strategies to overcome therapeutic limitations. *Microorganisms.* 2025;13(11):e2574. http://doi.org/10.3390/microorganisms13112574

9. Wang G, Schmidt C, Li X, Wang Z. APD6: antimicrobial peptide database expansion. *Nucleic Acids Res.* 2026;54(D1):D363-D374. http://doi.org/10.1093/nar/gkaf860

10. Júnior NGO, Souza CM, Buccini DF, Cardoso MH, Franco OL. Antimicrobial peptides: structure, functions and translational applications. *Nat Rev Microbiol.* 2025;23:687-700. http://doi.org/10.1038/s41579-025-01200-y

11. Yang R, Ma X, Peng F, et al. Advances in antimicrobial peptides. *Biotechnol Adv.* 2025;81:e108570.

http://doi.org/10.1016/j.biotechadv.2025.108570

12. Ngashangva N, Huidrom S, Devi IS. Antimicrobial peptides: natural templates for next-generation therapeutics. *Front Cell Infect Microbiol.* 2025;15:e1720027. http://doi.org/10.3389/fcimb.2025.1720027
13. Zheng S, Tu Y, Li B, et al. Antimicrobial peptide delivery systems and clinical translation challenges. *J Transl Med.* 2025;23:e292. http://doi.org/10.1186/s12967-025-06321-9
14. Yang B, Yang H, Liang J, et al. Screening methods for antimicrobial peptides. *J Pharm Anal.* 2025;15(1):e101046. http://doi.org/10.1016/j.jpha.2024.101046
15. Rewak-Soroczynska J, Dorotkiewicz-Jach A, Drulis-Kawa Z, Wiglusz RJ. Culture media effects on antimicrobial ions. *Biomolecules.* 2022;12(7):e963. http://doi.org/10.3390/biom12070963
16. Zhang L, Zheng Q, Zhang Z, et al. Metal-organic frameworks in biosystems. *Int J Mol Sci.* 2023;24(3):e2145. http://doi.org/10.3390/ijms24032145
17. Haney EF, Straus SK, Hancock RE. Reassessing host defense peptides. *Front Chem.* 2019;7:e43. http://doi.org/10.3389/fchem.2019.00043
18. Mazurkiewicz-Pisarek A, Baran J, Ciach T. Antimicrobial peptides in pharmaceutical applications. *Int J Mol Sci.* 2023;24(10):e9031. http://doi.org/10.3390/ijms24109031
19. Li P, Yin R, Cheng J, Lin J. Biofilm formation on biomaterials. *Int J Mol Sci.* 2023;24(14):e11680. http://doi.org/10.3390/ijms241411680
20. Zhu YY, Zhao LM, Jia XY, Liao GJ, Wang YP. Amphibians as sources of antioxidant peptides. *Zool Res.* 2025;46(5):1219-1243. http://doi.org/10.24272/j.issn.2095-8137.2025.127
21. Wang Y, Tang J, Chen Y, Chen S, Yu X, et al. Insect gut microbiome ecology. *Vet Sci.* 2025;12:e866. http://doi.org/10.3390/vetsci12090866
22. Gao B, Yang N, Teng D, Hao Y, Wang J, Mao R. Marine antimicrobial peptides. *Mar Drugs.* 2025;23(12):e463. http://doi.org/10.3390/md23120463
23. Talha M, Roque-Borda CA. AMP-antibiotic synergy. *FEMS Microbes.* 2026;7:extag003. http://doi.org/10.1093/femsmc/xtag003

24. Ancajas CM, Oyedele AS, Butt CM, Walker AS. Natural product SAR methods. *Nat Prod Rep.* 2024;41:1543-1578. http://doi.org/10.1039/D4NP00009A

25. Xu C, Wang A, Honnen W, Pinter A, Weston WK, et al. Brilacidin antiviral activity. *EC Microbiol.* 2022;18(4):1-12.

26. Machado M, Silva S, Costa EM. AMPs in atopic dermatitis. *Int J Mol Sci.* 2023;24(17):e13460. http://doi.org/10.3390/ijms241713460

27. Vladkova TG, Smani Y, Martinov BL, Gospodinova DN. Terrestrial antibacterial agents. *Molecules.* 2024;29(20):e4889. http://doi.org/10.3390/molecules29204889

28. Nawrot D, Ambrożkiewicz-Mosler W, Doležal M, Bouz G. Antistaphylococcal pipeline. *Eur J Med Chem.* 2024;266:e116077. http://doi.org/10.1016/j.ejmech.2023.116077

29. Junior ED, Barbosa RD, Silva RD, et al. Rifampicin nanohybrid. *Pharmaceutics.* 2023;15(2):e512. http://doi.org/10.3390/pharmaceutics15020512

30. Ye Z, Fu L, Li S, Chen Z, Ouyang J, et al. AMP synergy mechanisms. *Nat Commun.* 2024;15:e7319. http://doi.org/10.1038/s41467-024-51730-x

31. Min KH, Kim KH, Ki MR, Pack SP. AMPs biomedical applications. *Antibiotics (Basel).* 2024;13(9):e794. http://doi.org/10.3390/antibiotics13090794

32. Doolan JA, Williams GT, Hilton KL, et al. Nanoscale antimicrobial systems. *Chem Soc Rev.* 2022;51:8696-8755. http://doi.org/10.1039/D1CS00915J

33. Ma X, Wang Q, Ren K, et al. AMP optimization strategies. *Fermentation.* 2024;10(11):e540. http://doi.org/10.3390/fermentation10110540

34. Rogers NJ, Postings ML, Dixon AM, et al. Metallohelices selectivity. *RSC Med Chem.* 2025;16(5):2249-2260. http://doi.org/10.1039/D4MD00973H

35. Liu Y, Cui P, Tan R, Ru S. Hybrid peptides antibiofilm activity. *ACS Omega.* 2024;9(24):26133-26148. http://doi.org/10.1021/acsomega.4c01577

36. Chatterjee D, Sivashanmugam K. Immunomodulatory peptides. *Front Microbiol.* 2024;15:e1505571. http://doi.org/10.3389/fmicb.2024.1505571

37. Adnan SB, Maarof M, Fauzi MB, et al. AMPs wound healing. *Int J Mol Sci.* 2025;26(13):e5920. http://doi.org/10.3390/ijms26135920

38. Zhu A, Chen B, Ma J, et al. AMPs wound dressings. *Drug Des Devel Ther.* 2025;19:8523-8539. http://doi.org/10.2147/DDDT.S543233

39. Tabarzad M, Torshabi M, Haeri A, et al. Peptide antibiotics strategies. *Bioorg Med Chem.* 2025;133:e118486. http://doi.org/10.1016/j.bmc.2025.118486

40. Zhang H, Lv J, Ma Z, et al. AMP design innovations. *Molecules.* 2025;30(7):e1529. http://doi.org/10.3390/molecules30071529

41. Lombardi L, Genio VD, Albericio F, et al. Peptidomimetics review. *Chem Rev.* 2025;125(15):7099-7166. http://doi.org/10.1021/acs.chemrev.4c00989

42. Varela-Quitián YF, Mendez-Rivera FE, Bernal-Estévez DA. AMPs anticancer potential. *Front Med.* 2025;12:e1548603. http://doi.org/10.3389/fmed.2025.1548603

43. Dong Z, Zhang X, Zhang Q, et al. AMPs anticancer nanomedicine. *Int J Nanomedicine.* 2024;19:1017-1039. http://doi.org/10.2147/IJN.S445333

44. Nedyalkova M, Vecini DP, Paluch AS, Lattuada M. AMP nanoparticles. *Phys Chem Chem Phys.* 2025;27:16284-16294. http://doi.org/10.1039/D5CP01880C

45. Su Z, Yu H, Lv T, et al. AMP classification and applications. *Front Microbiol.* 2025;16:e1582863. http://doi.org/10.3389/fmicb.2025.1582863

46. Chaudhary S, Ali Z, Mahfouz M. Molecular farming AMPs. *Plant Biotechnol J.* 2024;22(8):2282-2300. http://doi.org/10.1111/pbi.14344

47. Elshobary ME, Badawy NK, Ashraf Y, et al. Antibiotic resistance review. *Pharmaceuticals (Basel).* 2025;18(3):e402. http://doi.org/10.3390/ph18030402

48. Farrukh M, Munawar A, Nawaz Z, et al. Foodborne resistance. *Food Sci Biotechnol.* 2025;34(10):2101-2129. http://doi.org/10.1007/s10068-

024-01767-x

49. Raka V, Nandanwar H. AMPs as antibiotics. *Indian J Microbiol.* 2025. http://doi.org/10.1007/s12088-025-01510-y
50. Mesa A, Orrego A, Branch-Bedoya JW, et al. Deep learning AMP design. *Curr Microbiol.* 2025;82:e379. http://doi.org/10.1007/s00284-025-04346-3
51. Meng H. AI-driven AMP discovery. *Probiotics Antimicrob Proteins.* 2025. http://doi.org/10.1007/s12602-025-10856-0
52. Shen X, Wang Y, Zhang P, Ji J. AI antimicrobial peptides. *Sci China Technol Sci.* 2025;68:e2200205. http://doi.org/10.1007/s11431-025-3100-9
53. Bahar A, Porbaran M, Khazaei M, et al. AMPs antiviral therapy. *Discover Oncol.* 2025;16:e1991. http://doi.org/10.1007/s12672-025-03855-8
54. Szymczak P, Zarzecki W, Wang J, et al. AI-driven AMP discovery. *Acc Chem Res.* 2025;58(12):1831-1846. http://doi.org/10.1021/acs.accounts.0c00594
55. Akimbekov NS, Sakhanova SK, Digel I, et al. Vitamin D AMPs. *Engineered Sci.* 2026;39:e2047. http://doi.org/10.30919/es2047
56. Edlo AA, Akhbari K, Henry DJ. Beyond antibiotics. *Mater Adv.* 2025;6:7662-7684. http://doi.org/10.1039/D5MA00552C
57. Sasal WM, Gmiter D, Kaca W. Polymyxin resistance. *Mol Biol Rep.* 2026;53:e223. http://doi.org/10.1007/s11033-025-11368-4
58. Tajer L, Paillart JC, Dib H, et al. Resistance to AMPs. *Microorganisms.* 2024;12(7):e1259. http://doi.org/10.3390/microorganisms12071259
59. Smith BL, Fernando S, King MD. AcrAB-TolC efflux pump. *Sci Rep.* 2024;14:e2742. http://doi.org/10.1038/s41598-024-52536-z
60. Canales CS, Cazorla JI, Cazorla RM, et al. AMPs nanotechnology. *Mater Today Bio.* 2025;35:e102381. http://doi.org/10.1016/j.mtbio.2025.102381