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Beyond Conventional Antibiotics: Molecular Design, Mechanistic Dynamics, and Clinical Translation of Antimicrobial Peptides Against Carbapenem-Resistant *Acinetobacter baumannii*

[1]Samuel Ebiloma, [1]Okoronkwo Christopher Uche, [1]Happy Uchendu Ndom, [1]Nkechi Chuks Nwachukwu, [1]Hope Chukwuemeka Okereke, [1]Happiness Adaku Ezechukwu, [1]Stanley Akudo

[1]Department of Microbiology, Faculty of Biological Sciences, Abia State University, Uturu, Abia State, Nigeria.

Corresponding author: Ebiloma Samuel, Department of Microbiology, Faculty of Biological Sciences, Abia State University, Uturu, Abia State, Nigeria.Samuel.ebiloma@abiastateuniversity.edu.ng: +2348025948991

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ABSTRACT

Background: The growing threat of antimicrobial resistance among multidrug-resistant bacteria, particularly the ESKAPE pathogens, has created an urgent need for alternative therapeutic strategies. *Acinetobacter baumannii*, a major member of this group, is commonly associated with chronic wound infections and hospital-acquired pneumonia and exhibits remarkable resistance to conventional antibiotics. Antimicrobial peptides (AMPs), both naturally occurring and synthetically engineered, have emerged as promising alternatives due to their broad-spectrum antimicrobial activity and multiple mechanisms of action. This review analyzes recent literature on the potential of antimicrobial peptides in combating infections caused by ESKAPE pathogens, with particular emphasis on *Acinetobacter baumannii*.

Methods: Relevant literature was identified through searches of PubMed, Scopus, Web of Science, and Google Scholar using keywords such as "antimicrobial peptides," "ESKAPE pathogens," "Acinetobacter baumannii," "biofilms," and "antimicrobial resistance." Articles published between 2020 and 2026 were prioritized, and non-English studies were excluded.

Findings: The reviewed evidence demonstrates that AMPs possess strong antimicrobial and antibiofilm activities against multidrug-resistant ESKAPE pathogens. These peptides disrupt bacterial membranes, inhibit biofilm formation, and enhance host immune responses. Furthermore, combining AMPs with enzymes and nanoparticle-based systems has shown improved antimicrobial efficacy against resistant pathogens, including *A. baumannii*. Antimicrobial peptides represent a promising class of next-generation therapeutics for managing infections caused by ESKAPE pathogens.

Conclusion: Continued research focusing on peptide optimization, effective delivery systems, and immune enhancement will be essential to support their clinical translation and help mitigate antimicrobial resistance.

Keywords: Antimicrobial peptides, *Acinetobacter baumannii*, Biofilms, ESKAPE pathogens.

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INTRODUCTION

Antimicrobial resistance has been a global public health challenge with a consistent increase in disease. The inappropriate and unnecessary use of existing antibiotics has contributed to a significant rise in multidrug-resistant (MDR) and antimicrobial-resistant (AMR) bacteria. As a result, there's been a noticeable rise in infections caused by drug-resistant microbes, including some that resist all available treatments. The failure of conventional drugs to provide therapeutic solutions to myriads of pathogens necessitated the need for alternative antimicrobials [1]. Antimicrobial peptides (AMPs) are considered better therapeutic options due to their ability to target multiple microbes, their cell walls and their intracellular constituents.[1]

ESKAPE pathogens have contributed to the existence and persistence of microbial infections.[2] The six ESKAPE pathogens, which include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species, continue to pose a threat to healthcare systems across the globe. They are a group of bacteria with high drug resistance and pathogenicity. Among these pathogens, *Acinetobacter baumannii* has been identified to persist in the healthcare environment.[3] The increase in the death rate and healthcare costs has been traced to the ESKAPE pathogen. The World Health Organisation (WHO) has developed an interest in combating and exploring these bacteria. The increasing resistance of these bacteria has raised critical questions about their resistance mechanisms, which will give birth to new antibiotics that will have more therapeutic effects.[4] This alarming trend makes it clear that we urgently need to improve how we treat and prevent the spread of diseases caused by the ESKAPE pathogen.[5]

Acinetobacter baumannii, one of the ESKAPE pathogens, is a key contributor to chronic wound infections, especially in individuals with weakened immune systems or diabetes. These wounds create a favourable setting for the bacteria to persist and hinder the healing process. This often leads to prolonged inflammation and less favourable treatment outcomes.[6] Due to the stubborn nature of *A. baumannii* biofilms in such wounds, patients frequently require intensive interventions like surgical cleaning and combined antibiotic treatments, further increasing the strain on healthcare resources.

A. baumannii thrives and survives in human hosts by biofilm formation. Biofilm is a complex community of microorganisms, and it is one of the strategies employed by the pathogen. It enables the pathogen to withstand antimicrobial medications and the host's immune response, which results from its ability to fix into the extracellular matrix it produces[3] Ventilator-associated pneumonia (VAP) often involves *Acinetobacter baumannii*, a bacterium commonly found on endotracheal tubes. Its ability to form biofilms allows it to persist and withstand antibiotic treatment. Infections caused by this organism are typically severe, leading to extended hospital stays, greater patient suffering, and rising treatment expenses.[3] This paper identified the mechanisms of AMP attacks on ESKAPE pathogens, specifically focusing on the effects of AMPs on *Acinetobacter baumannii.* This paper also proposed new methods for improving the efficacy of AMPs in attacking pathogens and reducing antimicrobial resistance.

METHODS

Relevant literature was identified through systematic searches of major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy used combinations of keywords such as "antimicrobial peptides," "ESKAPE pathogens," "Acinetobacter baumannii," "biofilms," and "antimicrobial resistance." Articles published between 2020 and 2026 were prioritized to ensure the inclusion of recent developments in the field. Studies that were not written in English were excluded from the review.

RESULTS

Antimicrobial peptides: Antimicrobial peptides (AMPs) are naturally occurring or synthetically produced bioactive compounds that play a crucial role in innate immunity and exhibit broad-spectrum antimicrobial, antifungal, and anti-inflammatory activities, including efficacy against ESKAPE pathogens [7]. AMPs are derived from diverse sources such as humans, mammals, amphibians, and marine organisms (Table 1) and are commonly classified by origin into natural (e.g., human- and marine-derived) and synthetic peptides, a categorization that informs their stability, efficacy, and resistance profiles.[8]

Despite their potency, AMP activity can be limited by environmental factors and enzymatic degradation, particularly following gastrointestinal administration or at infection sites[9] to enhance stability and bioavailability, strategies such as incorporating D-amino acids, synthetic residues, and peptide backbone modifications have been

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developed to protect AMPs from proteolytic degradation[9]

Advances in synthetic peptide design and peptide-mimetic engineering aim to improve antimicrobial efficacy while reducing host toxicity, thereby expanding the therapeutic potential of AMPs.[10] These developments, coupled with their broad activity against multidrug-resistant ESKAPE pathogens and biofilm-associated infections, have positioned AMPs as promising alternatives to conventional antibiotics.[11] Representative human- and marine-derived AMPs, their sources, target organisms, and sequences are summarized in Table 1.

Groups of antimicrobial peptides: Antimicrobial peptides (AMPs) possess evolutionarily conserved structural features that enable activity under diverse conditions. Lipopeptides such as peptaibols, which contain the non-standard amino acid α-aminoisobutyric acid, carry N-terminal lipid tails that promote stable α-helical conformations, facilitating membrane penetration and microbial cell disruption.[12] Their amphipathic architecture allows effective movement through biofilm matrices and destabilization of embedded cells[13]. Many AMPs are derived from aquatic invertebrates, fish, and amphibians, and these marine-derived peptides exhibit strong antimicrobial and antibiofilm activity against resistant ESKAPE pathogens.

Marine AMPs such as mytilins and tachyplesins are enriched in positively charged residues, enhancing their interaction with negatively charged bacterial membranes and biofilm extracellular polymeric substances, thereby disrupting biofilm stability across multiple pathogens [13]. Bacteriocins, another AMP class produced by bacteria, contribute to microbial competition and survival. Gram-positive bacteriocins, including lantibiotics and class II peptides, primarily target lipid II involved in cell wall synthesis, whereas Gram-negative bacteriocins such as colicins and microcins enter target cells via specific receptors and disrupt essential processes including DNA or RNA function.[14]

To overcome the limitations of natural AMPs, including proteolytic instability, toxicity, and poor bioavailability, synthetic and peptidomimetic AMPs have been developed [15]. Mimetic peptides replicate the structure or function of natural AMPs and are classified into three types: Type 1, which closely resemble native peptides (e.g., β-peptides and peptoids); Type 2, which lack natural backbones but retain partial biological activity; and Type 3, which are fully synthetic designs optimized for stability and bioavailability [16, 17]. Notable examples include the β-hairpin peptidomimetic murepavadin, which targets the outer membrane protein LptD in *Pseudomonas aeruginosa* [17] and brilacidin, an arylamide foldamer that mimics host-defense peptides and demonstrates membrane-disruptive activity with reduced toxicity in early clinical studies [18]. Additional strategies such as backbone and side-chain modification further enhance AMP stability and function (Figure 1).

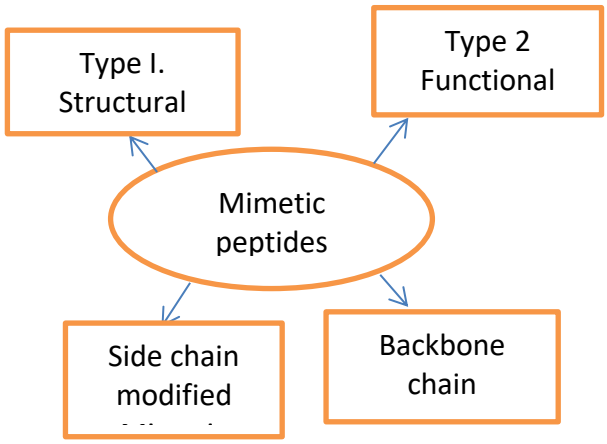

Figure 1: Understanding the different types of mimetic peptides: how structure and function shape their roles

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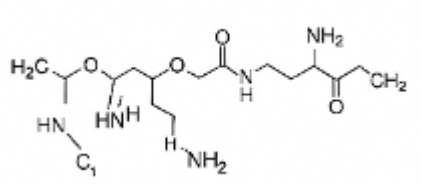
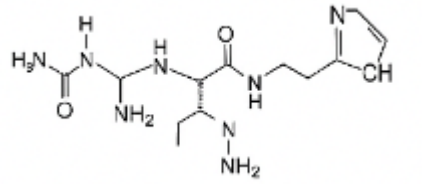
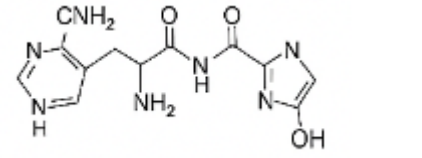
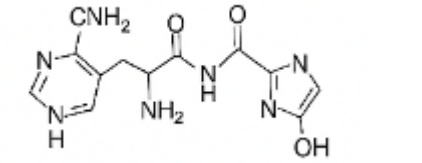
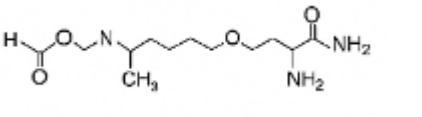
Table 1: Representative Antimicrobial Peptides, Structures, Sources, and Target Pathogens.

Peptide Name	Simplified Structure	Source	Target Organisms	Reference
LL-37		It is encoded in humans by an antimicrobial peptide known as Cathelicidin.	It targets bacteria, irrespective of their Gram reaction.	[19]
Magainin 2		They are naturally produced in the skin of the African clawed frog, and found in the skin's mucous glands.	They target a wide range of bacteria (Gram-negative and Gram-positive)	[20]
TachyplesinI		The production takes place within the hemocytes of the Horseshoe crab,	It targets specific bacteria and fungi such as *Candida albicans, Escherichia coli*, and *Acinetobacter baumannii.*	[21]
Arenicin-1		The antimicrobial peptide is produced in the coelomocytes of the *Arenicola marina.*	They aim at multi-drug-resistant microbes, particularly Gram-negative bacteria.	[22]
PGLα		It is produced and stored in the granular glands of *Xenopus laevis*	The targeted bacteria are *P. aeruginosa*, *K. pneumonia*	[8]

Antimicrobial peptides and Acinetobacter *baumannii*

Antimicrobial peptides (AMPs) inhibit biofilm formation through multiple mechanisms, including membrane disruption, matrix penetration, and quorum-sensing (QS) interference, enabling them to overcome the resilience of biofilm-forming pathogens such as *Acinetobacter baumannii* and other ESKAPE organisms[23]

[3] demonstrated that a modified cecropin-4 peptide (Cec4) effectively reduced biofilm formation in carbapenem-resistant *A. baumannii*, with a minimum inhibitory concentration of 4 μg/ml. Genetic analyses revealed that the porin-encoding gene OmpH influenced susceptibility to Cec4, as its deletion increased biofilm formation but enhanced peptide sensitivity, indicating that Cec4 compromises bacterial defense by targeting OmpH.[3]

Similarly,[23] reported that random peptide mixtures (RPMs) displayed rapid bactericidal activity against clinical *A. baumannii* isolates, significantly inhibiting and disrupting biofilms in vitro while reducing bacterial burden and improving survival in murine infection models. The compositional diversity of RPMs may also limit resistance development. In addition,[24] developed a de novo α-helical AMP, S24, which exhibited potent activity against multidrug-resistant *A. baumannii* by increasing membrane permeability and binding genomic DNA. In vivo wound infection models showed enhanced healing, while S24 maintained high stability, low hemolytic activity, and strong salt tolerance, highlighting its therapeutic potential.[24]

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***Antimicrobial peptides and other ESKAPE Pathogens*:** Antimicrobial peptides (AMPs) exhibit broad-spectrum activity against clinically significant pathogens, including multidrug-resistant organisms prevalent in healthcare settings. [25]. reported that the FWK peptide showed potent activity against *Klebsiella pneumoniae*, causing rapid membrane disruption and bacterial death. The antimicrobial efficacy of FWK was influenced by lipopolysaccharide (LPS) concentration, with higher LPS levels increasing the minimum inhibitory concentration, indicating interactions between the peptide and bacterial outer membrane components.[25]

Similarly,[5] demonstrated that the hybrid peptide GA-C16G2 effectively inhibited *Streptococcus mutans* growth and biofilm formation, outperforming its parent peptide C16G2. GA-C16G2 significantly reduced bacterial viability and suppressed biofilm development at bactericidal concentrations, highlighting its potential for controlling biofilm-associated infections.[5]

Several synthetic AMPs have also advanced toward clinical relevance. Pexiganan, a magainin analogue, exhibits strong activity against *Staphylococcus aureus* and *Enterococcus faecalis*, including resistant strains, while Brilacidin, a defensin mimetic, demonstrates broad efficacy against *S. aureus*, *K. pneumoniae*, and *Acinetobacter baumannii*, alongside anti-inflammatory properties.[26] Omiganan, an indolicidin analogue, effectively disrupts bacterial membranes with minimal cytotoxicity, making it a promising candidate for treating biofilm-related infections caused by ESKAPE pathogens.[26] In addition, several AMPs act synergistically with conventional antibiotics, restoring susceptibility in resistant strains and enhancing therapeutic outcomes.[27]

Beyond direct bactericidal effects, AMPs interfere with key resistance mechanisms, including biofilm formation, quorum sensing, and efflux pump activity. Brilacidin, for example, inhibits biofilm development in *Staphylococcus aureus* and *Pseudomonas aeruginosa*, an important advantage in managing chronic infections.[26] Collectively, the broad antimicrobial and antibiofilm activities of AMPs underscore their clinical potential, with future research focusing on improving stability, reducing host toxicity, and optimizing delivery strategies to enhance therapeutic efficacy.

A comparative summary of clinically relevant AMPs including Omiganan, Pexiganan, Brilacidin, LL-37, and Arenicin-3 is provided in Table 2.

Table 2: The mechanism of actions of selected AMPs against ESKAPE Pathogens

AMP	Structural Class	Mechanism of Action	ESKAPE Pathogens Targeted	Notable Activity / Comments	Reference
Omiganan	Tryptophan-rich, linear cationic peptide (12 aa)	Membrane disruption via intercalation and depolarization	*Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae*	High membrane selectivity; shown to reduce bacterial load in catheter infections and rosacea models.	[28]
Pexiganan	Amphipathic α-helical peptide (22 aa; magainin analogue)	Pore formation in lipid bilayers; membrane destabilization	*S. aureus, Enterococcus faecium, Klebsiella pneumoniae, P. aeruginosa*	Active against MDR strains; reformulated for topical diabetic ulcer treatment.	[29]
Brilacidin	β-sheet mimetic, non-peptidic foldamer (defensin-like)	Membrane depolarisation and ROS induction	*S. aureus, Acinetobacter baumannii, Klebsiella pneumoniae, P. aeruginosa*	Potent Gram-positive coverage; biofilm inhibition; additional anti-inflammatory properties.	[5]
LL-37	Human cathelicidin; α-helical	Membrane lysis, immune modulation, and LPS neutralization	*S. aureus, K. pneumoniae, P. aeruginosa*	Dual role: antimicrobial and immunoregulatory; enhances phagocytosis and wound healing.	[13]
Arenicin-3	β-hairpin cyclic AMP (isolated from marine polychaete)	Ion channel formation, rapid bacterial membrane permeabilization	*S. aureus, E. faecium, K. pneumoniae, P. aeruginosa*	Synthetic analogs under development; high salt tolerance and protease stability.	[13]

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Different processes of AMP attack on ESKAPE pathogens

Microbial membrane disruption: Antimicrobial peptides are known to disrupt the bacterial cell membranes, enhancing the absorption and efficacy of antibiotics. The peptides exhibit a positive charge, which enables them to bind tightly to electronegative bacterial membranes. After the attachment, they embed themselves in the cell's lipid membrane, either creating tiny holes or making the membrane thinner, which eventually causes the cell to break apart and die.[30] in these processes, the target is not inside the cells, making it difficult for bacteria to develop resistance as usual. Peptide 1018 renders bacterial cells' membranes more porous, allowing easy access of antibiotics to bacterial cells, which makes them more effective.[31] Several harmful bacteria form biofilms, shielding them from antibiotics. Peptide 1018 can break down the protective biofilm, exposing the bacteria to treatment by weakening them and working alongside antibiotics. Peptide 1018 helps prevent bacteria from developing resistance.[31] Human-derived peptide such as LL-37 also shows synergy with polymyxin B against gram-negative bacteria such as *E. coli* and *Pseudomonas aeruginosa*, reducing the survival and formation of biofilm. Antimicrobial peptide such as lantibiotic nisin combines with antibiotics like oxacillin work much better than using the single antibiotics, it shows efficacy against *Staphylococcus* biofilms.[9] Which is one of the ESKAPE pathogen, it might also be useful against other notorious multidrug resistant pathogenic species of *Acinetobacter*, *Pseudomonas*, *Klebsiella*.

*Matrix penetration***:** One of the significant problems in combating infection is traced to biofilm, due to the formation of a protective layer, such as extracellular polymeric substance (EPS), which makes it difficult for antibiotics and immune responses to reach. Nevertheless, antimicrobial peptides have shown possible therapeutic strategies because they are thin enough to push through this barrier and disrupt these chemical bonds that hold extracellular polymeric substances together.[2] noted that some specially designed synthetic antimicrobial peptides (AMPs), which have increased hydrophobicity and positive charge, can penetrate deeper into the core of biofilms and work against a wider variety of microbes. Similarly, peptides such as LL-37, which are humanly derived peptides and their modified forms, have been found to disrupt the biofilm's protective matrix, making it easier for treatments to spread through the biofilm and reach the bacteria hiding inside.[32]

Inhibition of quorum sensing: Beyond its bactericidal activity, antimicrobial peptides (AMPs) also interrupt the way bacteria communicate through a process known as quorum sensing (QS). This communication system is vital for bacteria to form, grow, and maintain biofilms, as well as to express their harmful traits. When AMPs disrupt these signalling pathways, they stop bacteria from coordinating the gene activity needed for building and sustaining biofilms. For example, a synthetic AMP called IDR-1018 has been shown to alter the expression of genes tied to biofilm development in bacteria like *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, ultimately weakening the biofilms and reducing their ability to cause disease.[33] Other research has spotlighted marine-derived peptides that act like QS signals, essentially "tricking" the bacteria and blocking their communication by preventing signal molecules from binding properly.[34]

***Improving the attack on ESKAPE pathogen*:** Combining antimicrobial peptides with other agent could offer a significant promise in mitigating the impact of these bacteria and overpowering the limitations of using single drug or therapeutic agent in tackling Recalcitrant ESKAPE pathogen, especially *Acinetobacter baumannii* a known notorious gram harmful bacterium [12]. The combine effect is achieved due to the strategies of antimicrobial peptides which open the bacteria protective layer that enable the penetration of antibiotics rendering the bacteria more vulnerable, enhancing the therapeutic effect of other drugs.

Antimicrobial peptide and nanoparticles: Antimicrobial peptides are small protein that are effective against biofilm forming microbes but the antimicrobial peptide faces challenges when used alone due to poor stability, low bioavailability, poor targeting, to solve this problems, tiny particle usually 1-100 nanometer (nanoparticle) is used as a delivery mechanism.[35] When AMPs are combined with nanoparticles, their stability is enhanced, preventing peptides from breaking down in the bloodstream (Table 3), enabling peptides to stay in the body for a longer period, which increases their effectiveness.[36] Silver nanoparticles synthesized through biogenic methods significantly enhanced the antibacterial activity of meropenem against carbapenem-resistant *Acinetobacter baumannii*. When used in combination, the nanoparticles and antibiotic exhibited a synergistic effect, lowering the minimum inhibitory concentration (MIC) of meropenem by four- to eightfold. Additionally, this formulation disrupted approximately 50% of pre-formed biofilms in vitro, highlighting its potential in overcoming biofilm-associated resistance.[36]

Nanoparticles can be designed to deliver AMPs to the infection site as well as protect the AMPs, enhancing their stability and bioavailability, improving deeper penetration into the biofilm's protective layers and aiding controlled drug release and effectiveness (Figure).

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Advanced nanocarriers are likely to work synergistically with positively charged antimicrobial peptides to improve the electrostatic interactions with negatively charged bacterial membrane cells and the biofilm protective layers.[29] By combining the membrane-disrupting ability of AMPs with the controlled and localized delivery offered by nanoparticles, these hybrid systems provide a dual mechanism of action**:** AMPs compromise bacterial membranes and weaken biofilm structures, while nanocarriers ensure that the AMPs (or co-delivered drugs) are released gradually and precisely at the site of infection (figure 2). It significantly enhances the target impact and termination of multidrug-resistant pathogens that are too difficult to tackle with conventional antibiotics.

The synergy of AMPs and nanoparticles reduces bacteria's resistance development and weakens bacteria's defence systems, improving the penetration of AMPs and making them more effective. Moreover, delivery platforms such as lipid nanoparticles loaded with LL-37 or chitosan-based carriers functionalized with melittin have demonstrated potent antimicrobial activity against ESKAPE pathogens, notably *Pseudomonas aeruginosa* and *Staphylococcus aureus*. These systems work by enhancing the intracellular delivery of antimicrobial peptides and inducing the generation of reactive oxygen species (ROS) (Table 3), contributing to bacterial cell damage.[1] With ongoing advancements, AMP nanoparticle conjugates hold significant promise as a central strategy in developing next-generation therapies targeting chronic and biofilm-related infections.

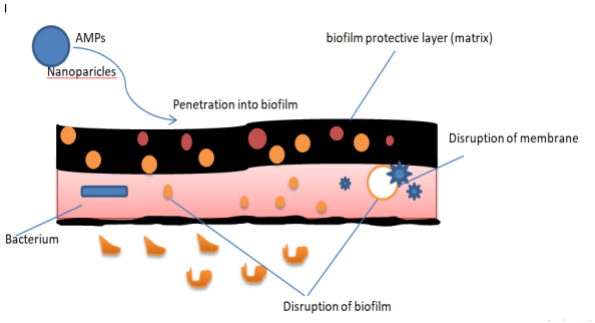

Figure 2. Mechanism of AMP and Nanoparticle Synergy against Biofilms

Combination of AMP and enzymes: Enzymes that degrade DNA, such as DNase, have shown potential in breaking down bacteria's biofilm extracellular DNA, one of the essential biofilm matrices that hold the bacterial communities together and protect them from antibiotics. Degrading this eDNA can enhance the therapeutic effect of AMPs and antibiotics.[29] Although direct evidence of synergistic interactions between antimicrobial peptides (AMPs) and DNase in *Acinetobacter baumannii* remains limited in studies from 2023 to 2025, related research has shown encouraging results. For instance, DNase-coated solid lipid nanoparticles (SLNs) have exhibited strong biofilm-disrupting activity against *Staphylococcus aureus*.[29] These findings support the hypothesis that enzymatic degradation of biofilm components, such as extracellular DNA, can substantially enhance AMP penetration and antimicrobial efficacy within biofilm-rich environments. Beyond DNase, engineered enzymes such as bacteriophage-derived endolysins have emerged as a potent class of biofilm-disrupting adjuvants. For example, the broad-spectrum endolysin LysSYL has demonstrated effective disruption of mixed-species biofilms formed by *Staphylococcus aureus* and *Acinetobacter baumannii* in vitro.[37] Notably, synergistic effects have been observed when combining the phage-derived endolysin Ply2660 with the AMP LL-37, resulting in enhanced clearance of vancomycin-resistant *Enterococcus faecalis* biofilms both in vitro and in murine infection models.[38] These outcomes highlight the therapeutic promise of combining peptidoglycan-targeting enzymes with membrane-disruptive AMPs to improve biofilm penetration and eradication.

In the case of *A. baumannii*, the endolysin Abtn 4 has been shown to inhibit biofilm formation by over 30% in vitro. At the same time, PlyF307 significantly reduced catheter-associated biofilms in mouse models, improving survival rates in treated animals.[37] Moreover, engineered constructs such as LysKP213, when conjugated with membrane-permeabilising peptides, exhibited enhanced bactericidal activity against Gram-negative pathogens in both in vitro and in vivo settings.[37] These hybrid constructs represent a promising avenue for AMP enzyme conjugate development.

Together, DNase and endolysins act on distinct yet complementary biofilm components extracellular DNA (eDNA) and peptidoglycan, respectively thereby creating access pathways for AMPs to reach embedded bacterial cells. This multi-targeted strategy has the potential to significantly improve AMP penetration and potency within resilient biofilm matrices. Future research should prioritize the development and evaluation of AMP enzyme co-formulations, particularly against persistent *A. baumannii* biofilms.[39] By combining targeted enzymatic degradation with membrane-active peptides, such integrated approaches may offer a robust and scalable solution for treating recalcitrant biofilm-associated infections.

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Challenges and limitations

Despite antimicrobial peptides' ability to kill bacteria and disrupt the formation of biofilm, many challenges have hindered their usage in clinical settings, especially against notorious multidrug-resistant ESKAPE pathogens like *A. baumannii*. The major challenges include the low stability; the emergence of resistance mechanisms, high concentration of these peptides can damage human cells, poor targeting, especially in a deeper tissue infection.[8, 30, 25, 28] One of the major challenges with antimicrobial peptides is the risk of developing resistance, although they are less likely to drive resistance compared to traditional antibiotics, mainly because that target bacterial membrane cells in non-specific and broad ways, but research has it that some bacteria will adapt over time and develop resistance, for example gram-negative bacteria such as *Acinetobacter baumannii* can alter the composition of its outer membrane especially the lipid A moiety of its lipopolysaccharides (LPS) to decrease the affinity and binding efficiency of antimicrobial peptides (AMPs).[40] Moreover, bacteria have two important defence mechanisms, such as efflux pumps and proteolytic enzymes that reduce the effectiveness of antimicrobial peptides.[24]

Instability of antimicrobial peptides: Another challenge is the limited stability of antimicrobial peptides after administration. Naturally occurring peptides are prone to rapid degradation by proteolytic enzymes present in the bloodstream and tissues. Enzymes such as trypsin and chymotrypsin can quickly break down antimicrobial peptides (AMPs), leading to a reduced half-life and limited bioavailability.[30] Consequently, unmodified AMPs often show diminished efficacy in treating systemic infections. To address this limitation, several synthetic strategies including the incorporation of D-amino acids, peptide cyclization, and the introduction of non-natural amino acid residues have been explored. However, these modifications can be costly and may alter biological activity or trigger unintended immune responses.[30]

Toxicity of AMPs: A critical limitation of AMP application is potential cytotoxicity toward human cells. Although AMPs are designed to disrupt bacterial membranes, they may also affect host cell membranes, particularly at high doses. This can result in damage to immune and epithelial cells, as well as hemolysis.[25] Achieving selective targeting of microbial pathogens while minimizing host cell toxicity remains a major challenge for therapeutic AMP use.

Ineffective AMPs cellular penetration: Biofilms are complex communities of microorganisms encased in a dense matrix of extracellular polymeric substances (EPS), including proteins, polysaccharides, and extracellular DNA, which make it difficult for AMPs to penetrate when used alone. The biofilm can act as both physical shields and chemical traps. AMPs administered systemically may be rapidly cleared before reaching the infection site, and they can be degraded by enzymes, which alter the effectiveness of AMPs against biofilm.[41] Localized delivery methods such as hydrogels, nanoparticles, and catheter coatings are being developed to concentrate antimicrobial peptides (AMPs) directly at infection sites. The goal of these strategies is to maximize the antimicrobial effect where it's needed most, while minimizing systemic side effects and degradation of AMPs in the bloodstream.[28] However, despite their delivery potential, the formulation often requires rigorous processes such as responsive release mechanisms and chemical modification. They must also undergo safety testing and efficacy testing to gain regulatory approval, which slows the transition from laboratory to healthcare centre.

Future prospects

Given the increasing threat of antimicrobial resistance among ESKAPE pathogens, particularly Acinetobacter baumannii, future treatment strategies must prioritize improving AMP stability, target specificity, and clinical applicability. Advances in peptide engineering, innovative delivery systems, and streamlined clinical evaluation frameworks offer promising avenues for managing biofilm-associated infections effectively.

Novel Peptide Designs: One of the most substantial developments in AMP formulation is the rational design of synthetic and peptidomimetic peptides. These next-generation peptides are engineered to overcome the limitations of natural AMPs, such as enzymatic degradation and cytotoxicity. Strategies include the incorporation of D-amino acids, cyclization, and backbone modifications that enhance protease resistance while preserving bioactivity.[42] For example, β-peptides, peptoids, and aryl-amide foldamers such as brilacidin have demonstrated stability in vivo and selective membrane-disruptive properties, enabling potent activity against biofilm-forming pathogens like *A. baumannii*.[18] The synthetic mimic murepavadin, a β-hairpin peptide, targets the outer membrane protein LptD in *P. aeruginosa*, highlighting the growing potential of structure-guided AMP therapies.

Use of enhanced drug delivery systems: Although antimicrobial peptides (AMPs) exhibit potent therapeutic activity, their systemic administration remains limited due to challenges such as low biochemical stability, rapid systemic clearance, and insufficient tissue-specific targeting. To overcome these barriers, advanced drug delivery systems are being

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engineered. Nanocarriers, including chitosan-based nanoparticles, liposomal vesicles, and polymeric hydrogels, are increasingly utilised to protect AMPs from proteolytic degradation, enhance their circulatory half-life, and enable controlled, site-specific release.[43, 29] For example, silver nanoparticles functionalized with the antimicrobial peptide LL-37 have demonstrated superior antimicrobial activity and enhanced penetration capabilities within *Acinetobacter baumannii* biofilms.[1] These intelligent delivery systems not only enhance the retention of antimicrobial peptides (AMPs) at the site of infection but also promote stronger interactions with bacterial membranes and biofilm extracellular matrices, thereby facilitating deeper penetration and more effective disruption of biofilm structures. Moreover, stimuli-responsive delivery platforms such as pH-sensitive and enzyme-activated systems are being investigated to enable the controlled release of antimicrobial peptides (AMPs) specifically within infected microenvironments, thereby reducing off-target cytotoxicity [24]. These advanced strategies present a promising avenue for the development of safer and more efficacious AMP-based therapies, especially in the management of complex infections such as chronic wounds and ventilator-associated pneumonia.

New AMP development with potential clinical trial prospects

Although antimicrobial peptides (AMPs) hold significant therapeutic potential, their clinical translation has been relatively limited, with only a few candidates, such as omiganan and pexiganan, progressing into clinical trials. Major obstacles impeding their development include high production costs, potential immunogenicity, and regulatory challenges. Nonetheless, a new generation of AMP candidates is advancing through preclinical development, facilitated by the emergence of more representative *in vivo* biofilm models and refined toxicity assessment methodologies [9]. Ongoing clinical trials are investigating the efficacy of AMP-based therapies both as standalone agents and in combination with conventional antibiotics or biofilm-disrupting enzymes in treating conditions such as diabetic foot ulcers, implant-associated infections, and respiratory tract biofilms [36]. Furthermore, co-formulation strategies incorporating antimicrobial peptides (AMPs) with enzymatic adjuvants such as endolysins and deoxyribonucleases (DNases) are gaining traction in clinical development. These combinations exhibit synergistic mechanisms that facilitate biofilm degradation and enhance bacterial susceptibility to therapeutic agents [24]. With sustained interdisciplinary collaboration and evolving regulatory support, AMP-based therapeutics is anticipated to achieve broader clinical implementation within the coming decade.

Clinical and Public Health Implications in Nigeria

Nigeria is experiencing an escalating healthcare challenge driven by the prevalence of hospital-acquired infections (HAIs).[44] Increasing antimicrobial resistance (AMR), constrained ICU resources, limited availability of last-line antibiotics, and ongoing deficiencies in infection prevention and control (IPC).[45] These obstacles hinder effective patient management and exacerbate clinical outcomes in both tertiary and secondary healthcare settings.[46] The prevalence of HAIs in Nigerian teaching hospitals spans 15–25%, with ventilator-associated pneumonia, catheter-associated urinary tract infections, surgical site infections, and bloodstream infections representing the most frequent cases.[44] Key contributing factors comprise patient overcrowding, suboptimal sterilization practices, and restricted access to microbiological diagnostics

Of significant concern is multidrug-resistant (MDR) *Acinetobacter baumannii*, frequently exhibiting resistance to carbapenems, cephalosporins, and fluoroquinolones, with certain centers documenting meropenem resistance exceeding 70%.[47] ICU overcrowding, frequent invasive interventions, and variable antimicrobial stewardship facilitate the propagation of MDR pathogens. Limited availability of last-resort agents such as colistin and tigecycline necessitates dependence on older or less effective treatment regimens.[48] Structural IPC shortcomings such as inconsistent water supply, insufficient isolation facilities, limited PPE availability, and suboptimal hand hygiene adherence further promote cross-transmission.[49]

Mitigating these challenges necessitates enhanced IPC infrastructure, comprehensive antimicrobial stewardship, and novel therapeutic strategies including antimicrobial peptides and biofilm-targeted approaches to control MDR infections within resource-constrained Nigerian healthcare settings.

CONCLUSION

Antimicrobial peptides (AMPs) have emerged as a formidable class of therapeutic agents capable of addressing the urgent global threat posed by multidrug-resistant ESKAPE pathogens, particularly *Acinetobacter baumannii*. Their unique mechanisms, including membrane disruption, biofilm penetration, and quorum-sensing inhibition, position them as versatile tools in the fight against chronic and biofilm-associated infections. The integration of synergistic strategies such as AMP–antibiotic combinations, nanoparticle-based delivery, and enzymatic adjuvants has demonstrated enhanced

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therapeutic efficacy, deeper biofilm disruption, and reduced potential for resistance development. Despite these promising advances, the clinical application of AMPs remains limited due to challenges such as proteolytic instability, off-target toxicity, and delivery inefficiency. However, recent innovations in synthetic peptide engineering, peptidomimetic development, and smart delivery platforms have shown significant potential in overcoming these limitations.

Declarations

Conflict of interest: The authors declare no conflict of interest

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