

Antimicrobial Peptide: Redefining the Anti-Infective Therapeutics Through Natural Architecture

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Modern medicine, particularly antimicrobials, is approaching a critical turning point as conventional treatments lose their efficacy. The efficacy of small-molecule antibiotics has formed the clinical architecture of healthcare for nearly a century. However, evolutionary changes in microbes are leading to the collapse of this foundational healthcare infrastructure¹. In 2019, infections due to resistant bacteria led to about 4.95 million deaths globally, and by 2050, these numbers are expected to reach 10 million². The exhaustion of chemicals available against multidrug-resistant microbes is fast becoming a dangerous reality. The antimicrobial resistance (AMR) crisis is being amplified by antibiotic misuse, weak regulatory frameworks, and a thin discovery pipeline influenced by high development costs. Antimicrobial peptides may not be just a supplementary clinical candidate but an essential component of next-generation therapeutics³.

Limitations of Traditional Small-Molecule Antibiotics

Traditional small-molecule antibiotics act through specific interactions with single metabolic targets via a lock-and-key mechanism. For example, penicillin-binding proteins target enzymes involved in bacterial cell wall synthesis; macrolides and aminoglycosides act on the ribosomal subunit responsible for translation; and fluoroquinolones target topoisomerases that regulate DNA replication⁴. Although the target-specific activity of these antimicrobials reduces toxicity in the human body, it also provides bacteria with a specific target for evolution. A single point mutation in a ribosomal protein or a beta-lactamase gene, mediated by a single plasmid, can render an existing antibiotic useless^{5,6}. Additionally, bacterial biofilms serve as structural barriers against which traditional antibiotics are ineffective. This biofilm

slows antibiotic penetration and supports metabolically quiescent, persistent cells, which lead to recurrent and chronic infections^{7,8}.

Nature's Multi-Targeted Defense Strategy

Evolutionary biology has led to the development of a multi-targeted, diverse defense network in the form of antimicrobial peptides (AMPs), unlike the single-target approach of conventional antimicrobials⁹. AMPs are small molecules, usually cationic and amphipathic, that are found across six biological kingdoms. These molecules serve as frontline defenders in innate immunity¹⁰. The AMP database has documented thousands of natural sequences across bacteria, fungi, plants,

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animals, and archaea. The fundamental mechanism of action is biophysical membrane disruption¹¹. The outer leaflets of bacterial membranes are enriched in negatively charged phospholipids, whereas the outer leaflets of mammalian membranes contain neutral zwitterionic lipids and cholesterol. AMPs exploit this difference. The cationic region of the peptide selectively binds to the microbial surface. The hydrophobic region of the peptide inserts into the lipid bilayer and disrupts structural integrity through ‘toroidal pore’, ‘carpet’, and ‘barrel stave’ mechanisms^{12,13}.

This lysis is electrostatically driven and presents a high resistance barrier. A mutation in a single enzyme does not allow pathogens to develop resistance to AMPs, and to do so, the pathogen would need to change its biochemical composition and the net charge of its entire cellular membrane, which is almost impossible^{14,15}. AMPs have other therapeutic effects, including the ability to pass through the membrane and target intracellular structures, disrupting the cytoplasmic processes of nucleic acid synthesis, protein folding, and enzymatic pathways¹⁶.

Limitations and Possible Solutions for Using AMP As A Systemic Drug

However, these natural AMPs have historically been limited to topical use for several reasons. In systemic human circulation, natural AMPs exhibit proteolytic instability. Because AMPs are composed of L-amino acids, they are rapidly recognized and degraded by host proteases present in the blood, kidneys, and liver, thereby shortening their half-life^{17,18}. The AMP’s hydrophobic property may cause it to target human red blood cells, leading to hemolysis and nephrotoxicity¹⁹. Producing long, disulfide-bonded amino acid chains is more expensive than synthesizing conventional small-molecule antimicrobials²⁰.

The rapid degradation of natural AMPs can be countered by incorporating D-amino acids into their structure, thereby modifying the peptide backbone, or by synthesizing peptidomimetics such as peptides and β -peptides. These changes can protect AMPs from proteolytic destruction within the body^{21,22}. The metabolic stability and tissue penetration of AMPs can be enhanced using chemical ‘stapling’, in which a synthetic hydrocarbon bridge locks the peptide into its active form^{23,24}. Encapsulating AMPs can address toxicity and delivery challenges in biocompatible nanocarriers such as liposomes, solid lipid nanoparticles,

or polymeric micelles.^{25,26} Such approaches can mask the peptide’s positive charge in the systemic circulation, preventing harm to host cells and protecting it from proteolytic enzymes^{27,28}. Once at the lesion site, the local environment, such as altered pH or bacterial enzymes, can trigger the controlled release of AMP onto the microbe^{29,30}.

There has been a synthetic evolution of AMPs, including the development of innate defense regulators and conjugated AMPs. These exhibit dual therapeutic action, with immunomodulatory capabilities and the ability to kill bacteria directly. They can bind selectively to circulating lipopolysaccharides and neutralize them, thereby preventing an overactivated inflammatory cascade^{1,31}. The peptides also act as chemical signals, attracting macrophages and neutrophils to the site of infection and promoting tissue repair and angiogenesis^{32,33}. Thus, the endogenous immune response is enhanced, and the pathogen’s biofilm is degraded, making it almost impossible for the microbe to develop resistance or survive³²⁻³⁴.

AMPs are now a viable option for next-generation medicine. However, beyond scientific hurdles, the economic framework for developing AMPs needs to be addressed by the international scientific community³⁵. To make AMPs globally available, targeted public-private partnerships should be pursued, regulatory approvals obtained, and large-scale production secured, all of which require substantial investment; more research is needed to lower production costs^{36,37}. As traditional antibiotics lose efficacy and bacteria develop resistance, the use of AMPs is becoming increasingly necessary. These natural templates need to be transformed into stable, safe, and mass-producible therapeutics. If used effectively, AMPs can be a vital determinant of global public health protection in the fight against rising AMR.

Consent for publication

The author has reviewed and approved the final version and agrees to be accountable for all aspects of the work, including any issues related to accuracy or integrity.

Disclosure

The authors declare that they have no financial involvement or affiliations with any organization, association, or entity, whether directly or indirectly related to the subject matter or materials presented in this review paper.

Data availability statement

The data will be available only for research purposes.

Authorship contribution

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, or interpretation of data, or in all these areas. They also participated in drafting, revising, or critically reviewing the paper, gave their final approval of the version to be published, decided on the journal to which the article would be submitted, and made the responsible decision to be accountable for all aspects of the work.

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