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Design, synthesis, and structural activity relationship of antimicrobial peptides against multi-drug resistant organisms

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***Abstract*---**Antimicrobial peptides (AMPs) are a family of tiny peptides found throughout nature that play a vital role in various organisms' innate immune systems. Antimicrobial peptides and proteins (AMPs) are a varied family of naturally occurring chemicals produced by all multicellular organisms as a first line of defense. The rising prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR)

diseases is the most evident cause for concern. Traditional antimicrobial drugs work by targeting certain metabolic pathways or microbiological structures to kill or hinder bacterial growth. The development of new lead structures to combat multidrug-resistant bacteria is critical, and cationic antimicrobial peptides (AMPs) have the ability to do so. Based on the SPOT synthesis, we present an outline of a strategy for screening peptides for antimicrobial activity. Multidrug-resistant bacteria have grown fast in recent decades, leading to a rise in nosocomial infections and in-hospital mortality, as well as posing a threat to world health. We can say that he discovery of antibiotics signaled the start of a golden period in human medicine. However, bacterial infections remain worldwide healthcare danger decades later, and a return to the pre-antibiotic period is likely unless drastic efforts are taken to halt the rapid growth and spread of multidrug resistance, as well as the indiscriminate use of antibiotics. Antimicrobial peptides are found all throughout the world and serve as the host's first line of defense against infectious pathogens. The rise of multidrug-resistant diseases highlights the need for novel antimicrobial drugs to combat these organisms' resistance mechanisms. Cationic antimicrobial peptides (CAPs) could be a source of novel antimicrobial medicines in the future.

***Keywords*---**antimicrobial, peptide, multi-drug, resistant, synthesis.

Introduction

Antimicrobial peptides (AMPs) are a family of tiny peptides found throughout nature that play a vital role in various organisms' innate immune systems. AMPs have a wide spectrum of antibacterial, antifungal, antiparasitic, and antiviral properties. Antimicrobial peptides and proteins (AMPs) are a varied family of naturally occurring chemicals produced by all multicellular organisms as a first line of defense. These proteins have a wide range of activity, including the ability to kill bacteria, yeasts, fungus, viruses, and even cancer cells directly. Insects and plants use AMPs as antibiotics to protect themselves from potentially dangerous microorganisms, while microbes also manufacture AMPs to maintain their niche in the environment. AMPs are also known as 'host defence peptides' in higher eukaryotic organisms, stressing their immunomodulatory properties. These activities vary depending on the type of AMP, but they all involve cytokine and growth factor-like effects that are important for immunological homeostasis. In some cases, abnormal AMP expression can lead to autoimmune disorders, emphasizing the significance of better understanding these molecules and their complicated functions. This primer will give us a refresher on what we know about AMPs right now.

AMP properties and diversity

Cationic AMPs have an overall positive charge and typically contain between 10 and 50 amino acid residues. These peptides frequently feature a three-dimensional alignment of basic amino acids and hydrophobic residues on

opposing sides, resulting in unusual structures that are water soluble, positively charged, and hydrophobic. The secondary structure of folded AMPs can be divided into three categories: helical, sheet, and extended AMPs. The frog magainin and the human cathelicidin peptide LL37 are examples of amphipathic -helical AMPs. In aqueous solution, these peptides have little secondary structure, but when they enter a non-polar environment, such as the bacterial membrane, they assume the amphipathic-helical architecture. Other AMPs, such as bactenecins and defensins, have two or more -sheets with disulfide bonds to stabilise them. Finally, extended AMPs are peptides that are identified by a high quantity of certain residues such as histidine, arginine, glycine, or tryptophan rather than by a specific structural motif. Histatins from humans, for example, are high in histidine, while indolicidin from bovine leukocytes has many tryptophan and arginine residues.

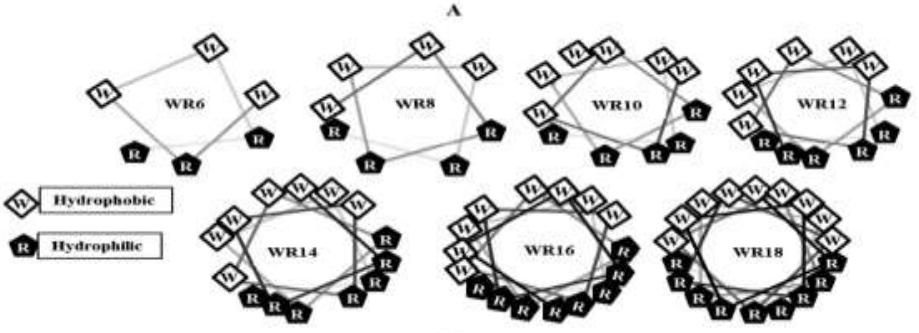
Microbes produce a variety of AMPs to inhibit the growth of other microbes, and these should be regarded a normal source of AMPs. Because they can be generated by nonribosomal peptide synthase, these microbe peptides are unique from vertebrate AMPs. Nonribosomal peptides can be glycosylated, acylated, halogenated, or hydroxylated, and can contain non-proteinogenic amino acids such as D-amino acids. They can also have modifications such as N-methyl and N-formyl groups, and can be glycosylated, acylated, halogenated, or hydroxylated. The cationic peptide polymyxin B (made by Bacillus polymyxa) and the noncationic glycopeptide vancomycin (produced by Amycolatopsis orientalis) are two examples of microbial AMPs that are FDA-approved antibiotics. Polymyxin B is effective against Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae, all of which are multidrug-resistant Gram-negative bacteria. Vancomycin is a common first-line antibiotic used to treat Gram-positive infections, such as methicillin-resistant Staphylococcus aureus infections. Toxins like cholera and diphtheria toxins, bacteriolytic enzymes like lysostaphin and hemolysins, and bacteriocins and bacteriocin-like peptides are all examples of AMPs produced by bacteria. Bacteriocins have been identified in over 250 bacteria so far, and some of them have a wide range of inhibitory properties.

Design of Arginine and Tryptophan Cationic Antimicrobial Peptides and Their Activity Against Multidrug-Resistant Pathogens

Despite the comparatively impressive advances made in the field of antimicrobial therapies over the previous century, infectious illnesses remain a global health issue. The rising prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) diseases is the most evident cause for concern. Traditional antimicrobial drugs work by targeting certain metabolic pathways or microbiological structures to kill or hinder bacterial growth. The selection of resistance-conferring mutations and/or acquisition of other resistance determinants during antimicrobial therapy are an unintended consequence of these medications. This is a significant barrier to treatment efficacy in a variety of diseases, including those related to cystic fibrosis, medical implants, critical care, and other nosocomial infections. As a result, novel antimicrobial medicines from nontraditional sources are desperately needed. In the last three decades, antimicrobial peptides (AMPs) have been extensively studied as a potential source of supplementary antimicrobial agents with a lesser proclivity for drug resistance

phenotypes than present antimicrobials. Most AMPs are cationic peptides that adopt an amphipathic structure in the presence of bacterial membranes (amphipathic β-helical peptides, e.g., cathelicidins and magainins) or constitutively (amphipathic peptides, e.g., cathelicidins and magainins) (cyclic and -sheet AMPs, e.g., the defensins, stabilised by disulfide bridges). It has been demonstrated that host-derived AMPs are an important component of most multicellular organisms' defensive systems, and that they can even be detected in prokaryotes.

More crucially, evolution has designed AMPs as anti-infective peptides that disrupt the membranes of specific pathogens in specific conditions without requiring microbial metabolic activity. It is obvious that AMPs are a reliable preventive mechanism utilised by the host defence system to prevent infections from establishing. Many infections, on the other hand, are able to bypass the host's AMPs and other immune system components. Diseases involving impaired immune systems, as well as the selection of MDR phenotypes by conventional antimicrobial drugs during failed attempts to eliminate these infections, are of major concern. Infections associated with cystic fibrosis are one such occurrence. The mucociliary apparatus is severely harmed in CF due to sodium chloride level dysregulation caused by a faulty CF transmembrane conductance regulator (CFTR). Furthermore, excessively high salt concentrations in the airway suppress the activity of AMPs associated with the respiratory epithelium (e.g., LL37 and defensins), contributing to uncontrolled colonisation by Staphylococcus aureus and other opportunistic bacteria (e.g., Pseudomonas aeruginosa). This significant finding implies that while developing AMPs for clinical applications, the working environment must also be taken into account. The design of varied engineered cationic antimicrobial peptides (eCAPs) with a spectrum of in vitro antimicrobial properties has been influenced by lessons learnt from structure-function investigations of host defense -helical peptides. Using the structure-function correlations of host-derived synthetic AMPs, our group has pioneered the design of eCAPs with robust antimicrobial activity over the last decade.



B

Peptide	Sequence	MM(Da)	μH	μHrel
WR6	WRWWRR	1,045	5.86	0.93
WR-8	WWRRWWRR	1,387	5.85	0.93
WR-10	WRWWRRWWRR	1,730	5.93	0.94
WR-12	RWWRWWRRWWRR	2,072	6.18	0.98
WR-14	WRRWWRWWRRWWRR	2,414	6.35	1.01
WR-16	RWWRRWWRWWRRWWRR	2,757	6.4	1.02
WR-18	WRRWWRRWWRWWRRWWRR	3,099	6.3	1.0

Figure 1: Engineered cationic antimicrobial peptide (eCAP) design

Cationic peptides were constructed to produce idealized amphipathic helices with hydrophilic and hydrophobic domains made up of Arg and Trp, as shown in fig. 1(A) helical wheel diagrams. (B) Primary sequences and molecular weights in daltons of the WR peptide series employed in this work. Starting with the smallest peptide, WR6, the peptides were engineered by serially adding one Arg and one Trp residue. On a combined consensus hydrophobic scale, relative hydrophobic moments, or hydrophobic moments relative to ideal amphipathicity, were investigated using the web application HydroMCalcmolecular mass in daltons (MM(Da); mean hydrophobic moment (H); relative hydrophobic moment (Hrel).

The LBU series was created to take advantage of condensation chemistry's cost-effectiveness by serially joining LBUs to synthesis longer eCAPs as needed. The maximum activity of the LBU series was attained at 24 residues, which is similar to the length of most natural AMPs, which is between 15 and 40 amino acids. Furthermore, adding Trp to the LBU sequence increased activity against Gram-positive and Gram-negative bacteria in conditions that are known to be difficult for AMPs, such as saline, serum, and whole blood. In fact, systemic injection of the most potent of the LBU derivatives (WLBU2) provided complete protection of mice treated intravenously with a lethal dosage of P. aeruginosa while causing no evident adverse effects. We reasoned that the membrane perturbation properties of Arg and Trp, presented in the context of an optimised amphipathic helix, could be further exploited to engineer shorter and more highly potent eCAPs, thereby reducing the cost of production, based on these and other studies of Trp-rich AMPs (e.g., indolicin and tritrpticin).

Spot Synthesis of Antimicrobial Peptides with Therapeutical Potential Against Multidrug-Resistant Bacteria

The development of new lead structures to combat multidrug-resistant bacteria is critical, and cationic antimicrobial peptides (AMPs) have the ability to do so. Based on the SPOT synthesis, we present an outline of a strategy for screening peptides for antimicrobial activity. Substitution analysis of known AMPs, scrambling of known AMPs, and screening peptide libraries for novel AMP sequences are three separate methodologies for studying and optimizing antimicrobial activity of peptides that have been reported. Even if peptides have an internal target, they must still interact with the bacterial membrane; several models, such as the Barrel-Stave, Aggregate, Carpet, and Torodial Pore models, have been devised to explain the interaction of host-defense peptides with bacterial membranes. There have been approximately 1000 distinct naturally occurring peptides found and described in various databases. Natural cationic host-defense peptides are given as examples. The sequences and structures of these naturally occurring peptides are quite diverse (Fig. 2), with just a few common characteristics such as short length (12-60 amino acids), excess positive charge, and amphiphilicity.

Using spot synthesis to test peptides for antimicrobial activity

Synthesis of Peptides

Standard Fmoc chemistry is used in SPOT synthesis. It's a technology that allows for the extremely parallel synthesis of up to 8000 addressable peptides on a cellulose membrane. Small spots (about 0.1 l amino acid per spot) are appropriate for binding experiments, such as those used to research antibody epitopes. In 96-well microtiter plates, larger spots (about 1.2 l per spot) are excellent for biological experiments. 800-1000 big peptide spots may be generated on a sheet of cellulose (18x29 cm). Large spots (diameter ca. 0.6cm) with a glycine linker have been employed in antimicrobial peptide screening; employing the glycine as a linker between cellulose (hydroxyl-groups) and the first amino acid (carboxyl-group) gives a high peptide density, up to 1.9 μmol/cm^2.

Manual SPOT synthesis is simple to integrate into a laboratory because no additional equipment is required; nonetheless, it is a labor-intensive operation. Only a tiny number of peptides are synthesised and tested manually using SPOT synthesis. Fortunately, SPOT synthesis is now automated, allowing far greater amounts of peptides or peptide combinations to be screened. Purchase semi-automatic and completely automated synthesisers (e.g., Intavis, Köln, Germany). The antimicrobial peptide synthesis presented here was carried out using a fully automated machine with a big tray (Fig. 3) and glycine linkers. The ester bond between the glycine linker and the cellulose is broken with ammonia gas after the synthesis and final side chain de-protection steps, yielding a peptide with an amidated C-terminus. After that, the peptides are punched out and transferred to a 96-well micro titer plate, which is then filled with distilled water in each well. Peptides can then be extracted from this stock solution and employed in other experiments.

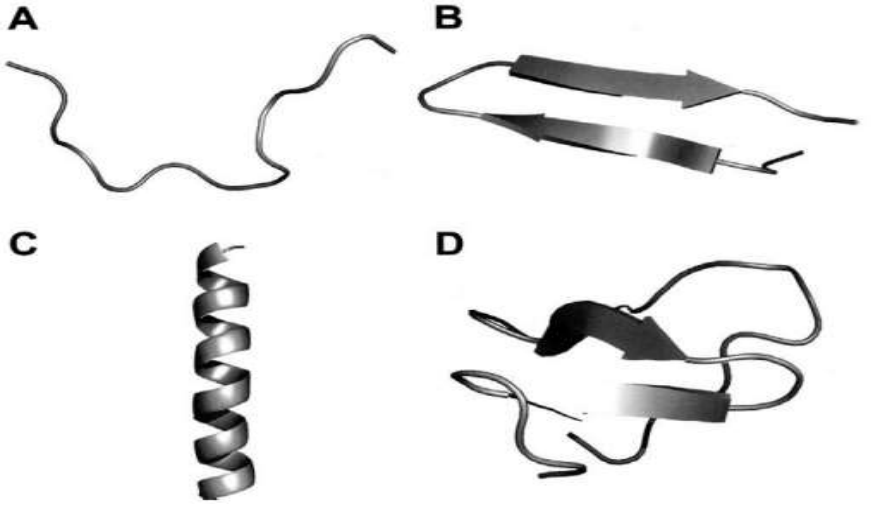


Figure 2: Cartoon structures of antimicrobial peptides A) indolicidin in dodecylphosphocholine micelles B) Tachyplesin I in dodecylphosphocholine micelles (pdb code: 1WO1) C) Piscidin 1 in sodium dodecyl sulfate micelles D) Kalata B1 bound to dodecylphosphocholine micelles

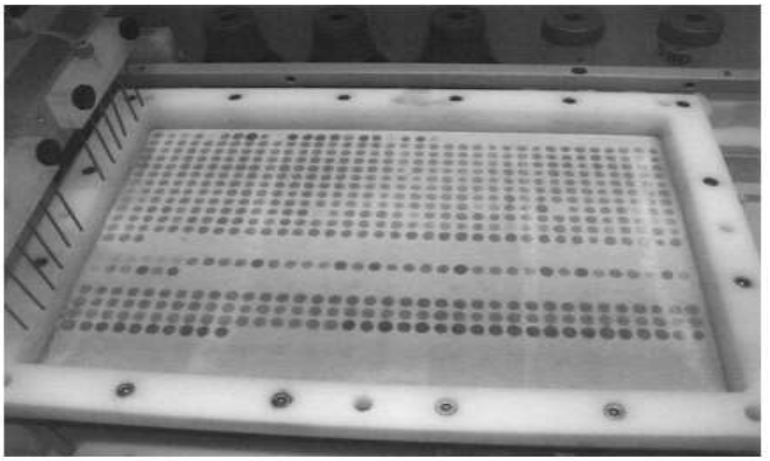


Figure 3: Large tray of a fully automated peptide synthesizerthe picture shows the large spots used for the antimicrobial assay

Antimicrobial potential against anti-TB agent of design, synthesis, and structure-activity relationship

Though tremendous progress has been made in the last two decades in lowering tuberculosis (TB)-related mortality, the magnitude of the problem remains large. In 2014, 9.6 million people became ill with tuberculosis (TB), with 1.5 million people dying, a number equal to Estonia's whole population. As a result, TB, along with HIV, has become a significant cause of death among infectious diseases around the world. With the increasing growth of multidrug resistant and extensively drug resistant (MDR/XDR) tuberculosis, the matter is becoming even more concerning. The development of new anti-TB medications, on the other hand, has been essentially non-existent, with only one new drug being approved in the last 40 years. The gap emphasizes the significance of discovering new anti-tubercular agents to effectively address the current challenge. Antimicrobial peptides are one family of chemicals that could become anti-TB medicines (AMP). AMPs are found naturally in all forms of life as part of innate immunity or as a first line of defense by killing pathogens directly. They've recently gotten a lot of interest in the field of developing novel antimicrobial drugs to combat drug-resistant microorganisms like Mtb. Their demonstrated spectrum of activity against a wide range of diseases, selective affinity for prokaryotic negatively charged cell envelopes, fast cell killing action against the pathogen, and low immunogenicity are some of the characteristics that make them potential drug candidates. They frequently kill bacteria by reacting non-specifically with the bacterial cell wall and membrane, a method of action that is less prone to drug resistance development. Cationicity with a net charge of at least +2 at physiological pH and amphiphilicity are the most common structural properties of biologically active AMPs, whereas amino acid sequence and chain length vary widely.

In the last few decades, several AMP classes have been shown to have antimycobacterial activity against diverse mycobacterial species. Their origin, structural characteristics, antimycobacterial efficacy, potential mechanism of

action, and drug resemblance has all recently been thoroughly examined. Antimycobacterial peptides are classed as large (50–100 aa), moderate (25–50 aa), low (10–24 aa), and ultra-small (2–10 aa) based on their peptide size. The majority of the peptides studied for antimycobacterial activity are high and intermediate size peptides derived from either a mammalian host immune system or bacteria. Human neutrophil peptide, defensin, hepcidin, NK-lysin, granulysin, human host defense ribonuclases (RNase), Lysosomal ubiquitin derived peptide, lacticin 3147, and E50-52 are only a few examples. Despite their promise antimycobacterial activity, these compounds share a number of drawbacks, including difficulty isolating them from their sources, high production costs, structural impossibility, substantial enzymatic degradation, and possible immunogenicity. Small and ultra-small cyclic antimycobacterial peptides could be viable replacements to larger ones because they have similar structural properties but avoid most of the drawbacks. Several small and ultra-small cyclic peptides, such as griselmycins, depsidomycin, hytramycin, brunsvicamides, pyridomycin, hirsutellide A, and the wollamides, have been shown to have antimycobacterial activity. Wollamide B (Fig 4) is a member of a novel class of cyclic peptides that was identified from a Streptomyces nov. sp. strain found in Australian soil (MST-115088). Against M. bovis, the compound had an IC50 of 3.1 μM. In addition, it was discovered to diminish intracellular mycobacterial survival in macrophages generated from mouse bone marrow. Its activity to combat Mtb, a prevalent disease-causing pathogen, has not been reported.

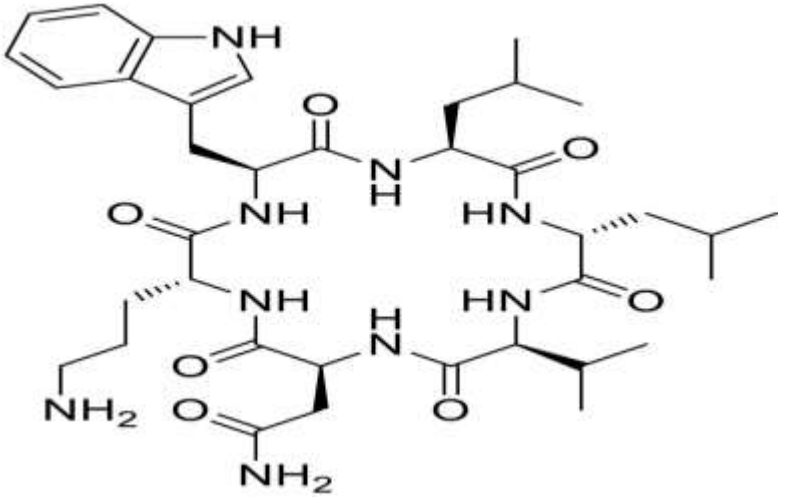


Figure 4: Structure of wollamide B.

Antimicrobial peptide development and challenges for therapeutical applications

Multidrug-resistant bacteria have grown fast in recent decades, leading to a rise in nosocomial infections and in-hospital mortality, as well as posing a threat to world health. Furthermore, since 1987, the rate of discovery of new antibiotic classes has declined. The paucity of fresh discoveries could be due to our conservative approach to searching for antibiotics, or the field could be saturated; in other words, many of the huge natural structures with antimicrobial activity

may have already been discovered. Our last lines of effective antibiotics are failing due to the rise of antibiotic resistance. Antimicrobial peptides (AMPs), which are found in all forms of life and play a role in innate immunity, have been extensively explored and show promise as small-molecule antibiotics.

Drug Approvals and Databases from the FDA (Food and Drug Administration)

More than 3000 AMPs have been identified and described, however most are unsuitable for use as medicines in humans in their natural condition. Many of them, in fact, failed before or during clinical testing. These seven peptides have now been commercialised and are generally used as topical treatments, however some have been injected into the body to treat serious bacterial infections. We looked into peptide drugs that have been approved by the US Food and Drug Administration to better comprehend this issue (FDA). We studied all of the peptide treatments approved by the FDA so far using the Therapeutic Proteins Database [THPdb, a subset of the FDA database (Drugs@FDA)]. There are 852 peptide and protein therapies in this database. 239 of them have been validated, while the others are derivatives and/or comparable medicinal components, with 27 of the 239 being short peptides (fewer than 50 amino acids). Gramicidin D, daptomycin, vancomycin, oritavancin, dalbavancin, and telavancin are six of the short peptides that constitute AMPs (Figure 5).

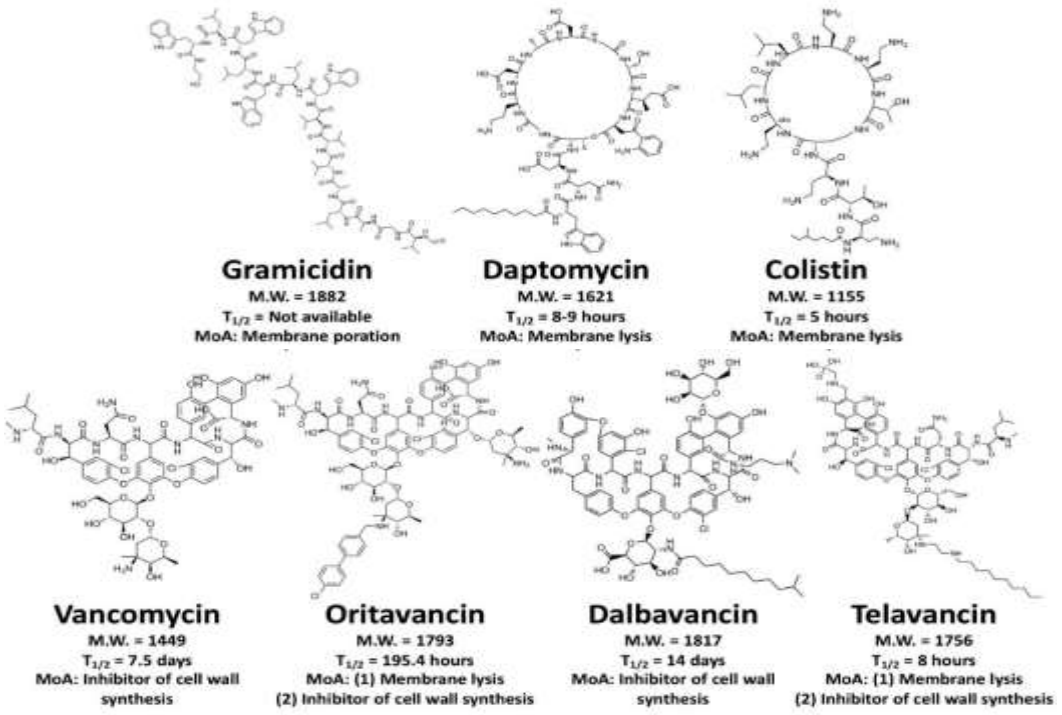


Figure 5: Chemical structures of seven FDA-approved AMPs

Figure 5 shows gramicidin (linear peptide; pore-forming peptide), daptomycin (cyclic lipopeptide; membrane-lytic peptide), colistin (cyclic lipopeptide; membrane-lytic peptide), vancomycin (lipoglycopeptide; inhibitor of cell wall

synthesis), oritavancin (lipoglycopeptide; dual-mechanism: membrane-lytic peptide and inhibitor of cell wall synthesis) (lipoglycopeptide; dual-mechanism: membrane-lytic peptide and inhibitor of cell wall synthesis). The acronym MoA stands for "mechanism of action." Gramicidin D is a heterogeneous mixture of three pore-forming peptides: gramicidins A (80%), B (5%), and C (5%). It was initially isolated and identified in 1941 from the soil bacteria Bacillus brevis (15 percent). The FDA authorised Gramicidin D as a component of Neosporin®, a triple antibiotic ointment for treating bacterial conjunctivitis, in 1955. Daptomycin is a 13-residue cyclic lipopeptide antibiotic that attaches to, aggregates, and destroys the bacterial cell membrane. The FDA approved daptomycin (also known as LY146032) and its derivative Cubicin (made by Cubist Pharmaceuticals, now Merck & Co.) to treat and prevent infectious illnesses in 2003. Cubicin and Cubicin RF, a novel formulation that may be injected directly into the body, are antibiotics used to treat difficult skin and skin structure infections (cSSSI) and Staphylococcus aureus bloodstream infections. Oritavancin, dalbavancin (previously BI-397), and telavancin are vancomycin-derived small lipoglycopeptide antibiotics (approved by the FDA as an oral solution in 1983). These lipoglycopeptides are more powerful and bactericidal than their progenitor vancomycin, and they can kill bacteria that are resistant to vancomycin.

Mechanism of action, activity, and clinical potential of antimicrobial peptides

Antimicrobial peptides (AMPs) are tiny molecular peptides that aid the host's innate immunity against a variety of pathogens, including bacteria, fungi, parasites, and viruses. To present, the AMP database has identified 3791 AMPs from six kingdoms, including 431 bacteria, 4 archaea, 7 protozoal, 6 fungal, 824 plants, and 2519 animals. AMPs have been discovered to have a number of biological functions, including immunological modulation, angiogenesis, wound healing, and anticancer activity, in addition to their antibacterial properties. Antibiotics have long been the primary treatment for harmful bacteria. However, the evolution of drug resistance as a result of antibiotics' single target, long-term and broad use, is posing a significant problem for clinical infection control. AMPs, on the other hand, have the benefit of acting on many pathogenic bacteria targets on the plasma membrane and intracellular targets, as well as having robust activity against drug-resistant bacteria.

AMPs' Activity

a. Antibacterial activity: Antibacterial activity is mediated by membrane or nonmembrane AMPs. Because of the presence of specific anionic components in the plasma membrane of bacteria and fungi, such as LPS in Gram-negative bacteria, lipoteichoic acid in Gram-positive bacteria, and mannan in fungi, cationic AMPs have a better affinity with microbial pathogens. Membrane permeability or perforation causes intracellular contents to seep out, or AMPs permeate the membrane to exert intracellular activities. Bacterial resistance to AMPs is prevented by the quick death and generic membrane and intracellular effects that do not target specific

molecules or pathways. As a result, the use of AMPs in the control of antimicrobial resistance seems appealing.

b. Immunomodulatory activity: Antimicrobial activity and immunomodulatory effects of AMPs, also known as host defence peptides, protect the host from infection. Pathogen invasion triggers a cascade of immunological responses (Fig. 6). Cathelicidins and defensins are mostly produced by neutrophils. The role of AMPs in the immune system is complicated. AMPs regulate the section of cytokines like interleukins; tumour necrosis factors (TNFs), IFNs, and chemokines, as well as the activities of immune cells like dendritic cells (DCs), monocytes, macrophages, mast cells, granulocytes, and lymphocytes, to keep the immune microenvironment in a dynamic balance.

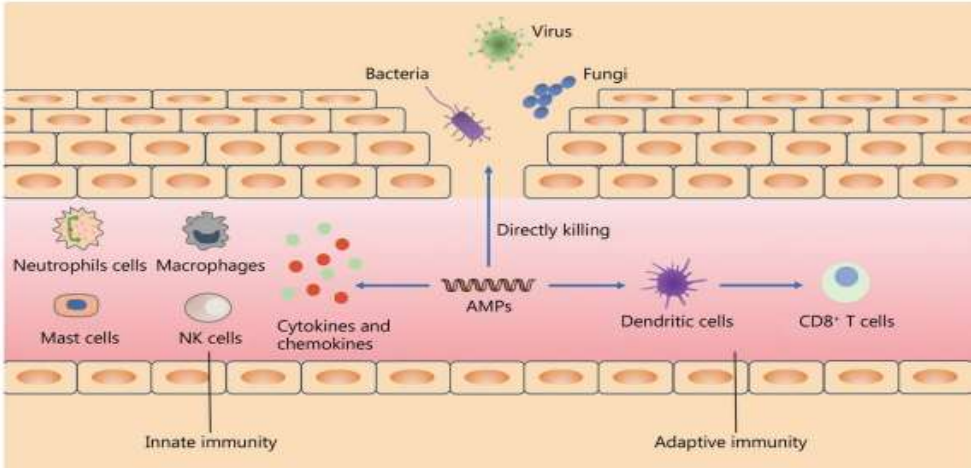


Figure 6: The immunomodulatory mechanisms of AMPs

AMPs not only destroy invading pathogenic bacteria directly, but they also kill them indirectly by stimulating the immune system. On the one hand, AMPs can activate immune cells in the innate immune system, such as neutrophils, macrophages, mast cells, and NK cells, and trigger the release of cytokines and chemokines to engulf and destroy harmful germs. AMPs, on the other hand, can trigger adaptive immune responses, deliver antigens to T cells via dendritic cells (DCs), and activate cytotoxic T cells to kill pathogenic germs AMPs antimicrobial peptides; NK natural killer.

Conclusion

We can say that he discovery of antibiotics signaled the start of a golden period in human medicine. However, bacterial infections remain worldwide healthcare danger decades later, and a return to the pre-antibiotic period is likely unless drastic efforts are taken to halt the rapid growth and spread of multidrug resistance, as well as the indiscriminate use of antibiotics. Antimicrobial peptides are found all throughout the world and serve as the host's first line of defense against infectious pathogens. The rise of multidrug-resistant diseases highlights the need for novel antimicrobial drugs to combat these organisms' resistance mechanisms. Cationic antimicrobial peptides (CAPs) could be a source of novel antimicrobial medicines in the future. Antibiotic-resistant microorganisms pose a

significant threat to human health. Cationic antimicrobial peptides are gaining popularity as a treatment for bacterial infections. Understanding the sequence requirements of short cationic AMPs will move research considerably closer to the level of drug development; several screening procedures can be used to accomplish this. Chemically synthesis massive amounts of peptides or peptide mix using the SPOT technology, a fast, totally automated technique. Because of the increasing evolution of antibiotic-resistant bacteria, treating bacterial infections has become a serious clinical concern. Antimicrobial peptides (AMPs) derived from synthetic and natural sources exhibit broad-spectrum antimicrobial activity, high specificity, and low toxicity, making them a potential candidate for combating antibiotic resistance.

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