# Antimicrobial Peptides can be an Alternative to Antibiotics

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**Abstract: For the rapid growth of the pathogenic bacteria to the conventional antibiotics leads to determine the urgent need for a search of fundamentally new anti-infective drugs. Antimicrobial peptides (AMPs) of the innate immune system are promising conditions for a role of such novel antibiotics. However, some cytotoxicity of AMPs towards host cells limits their active implementation in medicine and forces attempts to design numerous structural analogues of the peptides with optimized properties 1. Antimicrobial peptides are widely distributed throughout the animal and plant kingdoms. These peptides are involved in the direct destruction of various microorganisms like bacteria, fungi, parasites, viruses etc. and also can destruct tumor cells. Antimicrobial activities of AMPs, primarily disrupts membranes, so they have a lower likelihood of inducing drug resistance.**

**Extensive studies show that net charge, hydrophobicity and amphipathicity are the most important physicochemical and structural determinants endowing AMPs with antimicrobial potency and cell selectivity. Designing AMPs for therapy will need to focus on such factors like their susceptibility to proteolytic degradation and reduction of toxicity to mammalian cells. Strict guidelines pertaining to their use should also be established to prevent or hinder future bacterial resistance development to such peptides 2. This review summarizes the recent advances in the development of AMPs with respect to characteristics, structure-activity relationship, functions, their usage against microbes, expression, regulation and their applications.**

**Keywords:** ***Antimicrobial peptide, antimicrobial resistance, therapeutic agents, antibiotics, antibacterial activity, antifungal activity, antiviral peptides, antiparasitic peptides, antitumor activity.***

## I. INTRODUCTION

Bacterial resistance to various antimicrobial agents has developed as a result of the response to their direct exposure. This can be happened, if target protein is altered by mutation or enzymatic activity, or by passing of target protein, or the extrusion of the antimicrobial from the cell.

These adaptations can arise in susceptible bacteria as a result of mutations or through horizontal gene transfer, either within or between general , primarily employing mobile genetic elements such as plasmids, transposons or integrons 3.Alarmingly, antibiotic-resistant bacteria have been increasingly isolated from patients and animals treated with antibiotics,

and this resistance to the most conventional antibiotics has become one of the most pressing global public health concerns worldwide . Therefore, we need to find an alternative antimicrobial strategy 4. Antimicrobial peptides have been described as evolutionary ancient weapons 5. Found in both animal and plant kingdoms, they play a fundamental role in the innate non-specific defense system which confers resistance against infections without prior exposure to foreign pathogens 6. Antimicrobial peptides are the elective members for plan of another antimicrobial agents for their particularity, they have normal antimicrobial properties and a low inclination for the advancement of bacterial opposition. In addition to rapid and broad-spectrum activities against Gram negative and Gram-positive bacteria, fungi, parasites, viruses and tumor cells, AMPs also mediate chemotaxis, apoptosis, immunomodulatory effects and wound healing 7. Antibiotics target specific molecular receptors whereas AMPs change the membrane permeability.

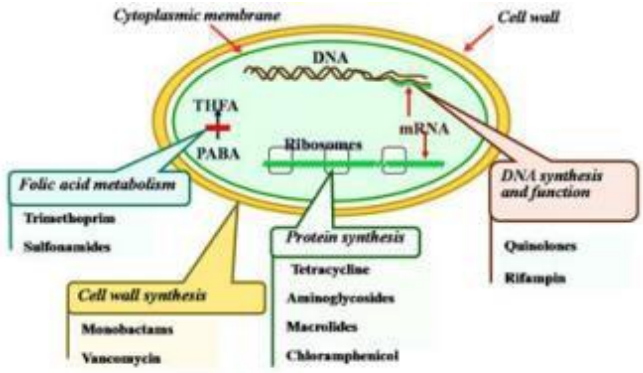



**FIGURE 1** Targets of antibiotics [Color figure can be viewed at wileyonlinelibrary.com]

These peptides are stored in granules of phagocytic cells and exert their effects in phage lysosomes or being secreted extracellularly; they are also widely expressed and released at epithelial surfaces and in a site of inflammation 8. They have different amino acid sequences and structures, but most of them are cationic and they can adopt an amphipathic conformation, for this reason they are able to easily interact with the negatively charged components on the surface of the bacterial cells and integrate into the lipid bilayers. The main mechanism of antibacterial action of AMPs is related with their ability to alter membrane permeability and damage its structure 9. Some AMPs are non-membranolytic and penetrate bacterial membranes without disturbing their integrity. They have intracellular targets and interfere with the metabolic processes, including synthesis of the vitally important cell components 10. For this wild-scale multitargeted action it is believed to be one of the reasons for the effectiveness of AMPs towards multidrug -resistance bacterial strains. For this wide beneficial feature of AMPs such as broad- spectrum activity, swift and effective bacterial hilling that also complicates the resistance development, would healing promotion, it is thought to be used as a replacement of antibiotics and also in food, animals etc.

**1. Discovery of AMPs:** Most of the natural antimicrobial peptides are isolated chromatographically from bacteria, plants, fungi and animals. During the first wave, prior to 1980s, several non-gene encoded antimicrobial peptides were discovered. From 1980s, the second wave started, during this time researchers started their studies over the innate immunity and mechanisms of action of gene-encoded AMPs as potential antimicrobials. Since around 2000, immune modulation properties of AMPs have been reported. In 1922, Sir Alexander Fleming discovered lysozyme, is now recognized as the first AMP. The discovery of lysozyme did not stir up much interest at that time. Lysozyme inhibits bacteria by cleaving saccharides on the cell wall 11. The small protein may be used topically as its size makes it unstable for systemic use 12. Rogeres(1928)1st noticed the ability of nisin to inhibit bacteria, it was the 1st antibiotics. It contains multiple thioether rings. It is the only bacteriocin, which is approved by the US Food and Drug Administration (FDA) as a food preservative. It is used as preservatives of meat and dairy products (<12.5mg/kg food) in over 50 countries. Nisin attacks the cell wall of Gram-positive bacteria like Listeria monocytogens. Nisin also inhibits Gram-negative pathogens such as E.coli and Salmonella spp. When used in combination with chelators or heat treatment 13. Dubos discovered gramicidin from a soil bacterium Bacillus brevis. Gramicidin A consists of alternating L and D amino acids. The N-terminus of this peptide is formylated 14. It consists of hydrophobic amino acids. Such sequence is viral for the formation of a head-to-head dimer as a membrane channel. It is the 1$^{st}$ peptide-antibiotic which was used clinically as a topical treatment. Gramicidin S isolated from bacteria, used to treat infectious wounds. This small peptide is cyclic, forms peptide bond between the termini. It works both against Gram positive and Gram-negative bacteria. Gramicidin S is still used in topical oinments and eye drops 15. Polymyxin E (Colistin) is also a bacteriocin is still used clinically to treat infection caused by Gram negative pathogens . It has a cyclic peptide structure followed by a lipid tail 16. Daptomycin has a similar structure, with a negative charge. It requires the presence of Ca2+ to show its full activity. In 2003 Daptomycin was approved by FDA to treat Gram positive bacterial infections. Alamethicin isolated from the fungus Trichoderma viride is also an AMP. It consists of seven alpha-aminoisobutyric acids forming a helical structure. It prevents Gram positive bacteria and fungi. This is perhaps the only AMP with evidence to support to barrel-stone pore in membranes 17. Boman et al. discovered ceeropins(1980s) from the moth Hyalophora Ceeropia. Lehrer and his colleagues identified the first alpha defensins from human neutrophils 18. Subsequently the first beta defensin was discovered from cattle 19. Cyclic theta defensin was discovered by Tang et al.(1999). All of these defensins contain three pairs of disulfide bonds 20. Due to their small size and stability, there is substantial interest in developing therapeutic uses for theta defensin miniproteins 21.Lucifesin is a defensin, discovered in 2010 from insects. This is probably a key antimicrobial element for maggot therapy.

In summary, all of these peptides mentioned above, is used as antimicrobial agents, also some are under development. In addution, the induction of AMP expression, at a needed sitre and tine, provides a new avenue for antimicrobial development 22.

## II NOMENCLATURE OF ANTIMICROBIAL PEPTIDES:

Although various methods are employed for naming the newly identified peptides, there are three mostcommon methods present

i)Source base methods

ii)Peptide base method

iii)Source and peptide combined methods

**i) SOURCE BASED METHOD:** It is the most common method. In this method either species or genus name is taken. Example: Sesquin is derived from *vigna sesquipedalis* ,here the name comes from the species name. Palicourein is derived from *Palicourea condensala* , here the name derived from the genus name. Sometimes peptide name is derived from the common name of the organism e.g., termicin from termites. Also, abbreviations of animal names are utilized such that bBD-1(bovine beta defensing - 1). Other animal abbreviations include PMAP-36 where P indicates pigs. e-CATH-1, e indicates equine. Sometimes, names of organs or tissues are also utilized. eg, Human neutrophil peptide-1(HNP-1) Liver expressed antimicrobial peptide-2 (LEAP-2).

**ii) PEPTIDE BASED METHOD:** Same AMPs are named according to their peptides' properties. The name of defensin is derived from the word 'defence', implying the functional role of this family of peptides. On the other hand many AMPs are named after their amino acid sequences.Example : Human histatins are named like this as they are rich in histidine residues. PR-39 consists of 39 residues which is rich in proline and arginine residues.

**iii) SOURCE AND PEPTIDE COMBINED METHOD :** In some cases, source of organisms and peptide features are combined to assign a unique name of AMPs.For instance,Ib-AMP is abbreviated from Impatiens balsamina antimicrobial peptide. When there are multiple similar peptides, they are named by giving numbers such as Ib-AMP1,Ib-AMP2,Ib-AMP3, Ib-AMP4 etc.

## III MAJOR PARAMETERS THAT DETERMINE THE ACTIVITY OF ANTIMICROBIAL PEPTIDES

i) **LENGTH :** Length of the antimicrobial peptides play a major role to determine their activity as at least 7-8 amino acids are required to form amphipathic structures with hydrophilic and hydrophobic faces on opposite sides of a peptide molecule. In the barrel- stave model at least 22 amino acids should be present for alpha-helical AMPs and at least 8 amino acids are needed for beta-sheet AMPs. Besides the effect of length on the mode of action, it also affects its cytotoxicity. For example: an abbreviated melttin and a more limited subsidiary of HP(2-20) displayed no less than multiple times less poisonousness to rodent erythrocytes, individually, contrasted with their unique length. Consequently, the length of AMP ought to be thought about while planning other manufactured peptides with low harmfulness.

ii) **CHARGE:** The net charge of the AMPs is the amount of all charges of ionizable groups of the peptide. Charge of AMPs varies from positive to negative, and it is one of the most important factors for its antimicrobial activity. Most of them are positively charged; ranging from +2 to +9, the interaction between AMPs and cell membrane mainly relies an electrostatic attraction. It is for the most part expected that cationic AMPs at first interact with negatively charged lipid head groups on the external surface of the cytoplasmic membrane. The peptide than penetrates the outer leaflet of the cytoplasmic membrane lipid bilayer in an approximately parallel orientation to the bilayer, which leads to the displacement of lipids23. But an excessive charge can affect its antimicrobial activity. Continuously increasing the number of positive charges may not increases its activity. Same anionic AMPs are also present, they are rich in Glu and Asp, they participate in the eukaryotic innate immune response. These peptides have not charges ranging from-1 to -2, and they generally require cations for. $zn^{2+}$, as compactors for biological activity. By evolving the net charge of an AMP, its antimicrobial and hemolytic activities can be modified to accomplish specific killing of microorganisms with no or limited impacts on have cells. For e.g.: increasing positive net charge of V13 K from +8 to +9 resulted in higher hemolytic activity, while decreasing the net charge to lower than +4 abolished its activity against *P. aeroginase* 24.

IV) **HYDROPHOBICITY:** It is another important factor which influence the activity and selectivity of APMs. Almost 50% of amino acids in primary sequence of natural AMPs are hydrophobic residues 25. In most of the cases increase in hydrophobicity on the positively charged side below a threshold value can increase its antimicrobial activity. On the other hand, decreasing the hydrophobicity can reduce antimicrobial activity. Each and every AMP has an optimal hydrophobicity, beyond which its activity decreases rapidly. Therefore, while designing new synthetic peptides, the hydrophobicity should be selected at around optimal value. Some studies shown that hydrophobicity is also a critical component for selecting the range of target cells of an AMP. By changing the hydrophobicity of an AMP its target range can be changed. For e.g., magainin is an AMP that is only effective against Gram-positive bacteria. However, some synthetic analogs with higher hydrophobicity can also kill some Gram-positive bacteria and eukaryotic cells 26. Highly hydrophobic AMPs can harm the structure of the membrane, which brings about cell lysis or the development of transient pores and the peptides are getting transported inside the cell, as a result they can interact with cellular targets.

**Amphipathicity:** It is another important property of AMPs which ensure the activity andinteraction with microbial membranes.

Fermandes -Vidal et al. showed that amphipathicity is more important than hydrophobicity for binding to microbial membranes.

Since the amphipathicity of AMPs is required for a strong partition into the membrane interface, preference should be given to the amphipathic structure while planning synthetic AMPs for peculiar target cells. It is the most important physicochemical and structural parameters for AMPs antimicrobial activity. It results from the segregation of hydrophobic and polar residues on the opposite face of the molecular framework. Some studies suggest that perfect amphipathicity often results in a simultaneous increase in both bactericidal and cytotoxic activity. Wang et al found that imperfectly amphiphilic peptides should better antimicrobial activity than the corresponding perfectly amphipathic peptides.

V) **Covalent Bonds:** Covalent bonds have profound effect on AMPs. The modification the covalent bonds should have positive or negative effect on AMPs work means it can increase or reduce it's antimicrobial activity. For eg.,Protegrin missing a disulphide bond becomes inactive against HSV; while adding disulphide bond in Sakacin P resulted in higher antimicrobial activities 28. Another studies shows that addition of a disulphide bond and a trp-trp crosslink to indolicin, increase its stability against protease with no change in antimicrobial activity.

However, increase in stability does not always lead to better AMPs. For e.g., Houston et al. introduced a covalent bond to form a lactam bridge between Gln and Lys residues in two alpha-helical AMPs, e.g., Cecropin and mellitin. This alteration assisted AMPs with framing steadier alpha-helix structures yet diminished the antimicrobial action of both.

## IV STRUCTURE OF AMPS

**Primary structure:**

**Sequence Length:** AMPs have variable sequence length ranging from 10-60 amino acid residues shorter AMPs are preferred for their low producing cost, many of them show similar antimicrobial activities to those of longer AMPs, eg., the hexapeptide MP196 (RWRWRW-$NH_2$ ) shows robust activity against E.coli and S. aureus with an minimum inhibitory concentration(MIC) value of 5microgram/liter
29. In addition, long chain straight peptides are many times more hemolytic and cytotoxic yet their N or C-terminal-truncated sequences typically have a lower cytotoxicity yet hold strong action 30. However, peptide with very short lengths shows a decreased tendency to form amphipathic secondary structures, which leads to low antimicrobial potency. So, it can be said that AMPs have a certain threshold length for binding with membranes with a high efficiency and form helical structures.

**Amino acid composition:** AMPs have mainly two types of amino acid residues, cationic and hydrophobic residues. Naturally occurring AMPs contain Arg; Lys and His amino acid residues and hydrophobic residues are mainly alipathic and aromatic amino acids. The positively charged amino acid residues of AMPs directly interact with the negatively charged component of bacterial cells. Then, at that point, the hydrophobic residues get integrated into lipid bilayers to intervene membrane permeabilization and disturbance, which lead to fast cell death.

**Characteristics of secondary structures:Alpha-helix:**

According to updated database, the proportion of the natural alpha-helical peptides is the highest among AMPs (fig 2), and they are mainly derived from different species, including insects, fish, amphibians, mammalians and plants. Many studies have found that most of these peptides, interacting with membranes are converted to alpha-helical structures. This transformation induces the segregation of hydrophilic/ charged amino acid in space from the hydrophilic residues, which results in an amphipathic structure that is recognized as a prerequisite for AMPs to act on membranes 31.

Sequence analysis of PMAP-36 showed that it has the highest proportion of cataionic amino acids (36%), most frequently at the N- terminus. Structural analysis of PMAP-36 further

demonstrate that this highly cationic sequence adopts a typical amphipathic alpha-helical conformation and random hydrophobic tail. Recent studies have indicated that N-terminal region ( alpha-helical domain) of PMAP-36 is the active region 32. Researchers have found that the disruption of amphipathicity increased antimicrobial activity with very little hemolysis.

According to the helical wheel projection, Ma et al designed a small combinatorial library of Val/ Arg - rich peptides, and the peptide G6 was found to have optimal cell selectivity. G6 has been further demonstrated to reduce peritoneal bacterial counts and increase survival after *Salmonella typhimurium* infection 33.

It was found that the net increase in charge increase antimicrobial activity and decrease hemolysis and the substituition of Gly with Pro significantly reduce toxicity. Sources of some AMPs along with their chemical and biochemical properties are summarized in Table 1.

**Beta-sheets:** Besides alpha-helixes, beta-sheets are another principal secondary structures of AMPs. In aqueous solution most of the peptides change their conformation from unstructured forms to beta- sheet structures in a membrane mimetic environment.

Generally beta-sheet peptides consist of two to ten cys residues, they form disulfide bridges for stabilizing their bioactive conformation. Additionally, peptides that contain disulfide bonds often adopt a cyclic beta-hairpin conformation, such as tachyplesin and protegrin 1 (PG 1) 34.The turn region of PG-1 contains three positively charged Arg residues, and this is considered to be active center of PG-1.
Natural beta- sheet AMPs play important role in innate immune system by killing invading pathogens or regulating immune responses. Defensins have six to eight Cys residues in defined positions, conserved across most multicellular organisms.

Peptides that typically adopt alpha-helix and beta-sheet structures have been designed to improve the prospects for applying AMPs therapeutically and the relationship between structures and bio-activities has been investigated 35. The beta-sheet structure posses greater cell selectivity than that of alpha- helical peptides with equal hydrophobicity and charge. But it is difficult to form robus beta-structure for short peptides. Studies have shown that several rational designs of synthetic beta-sheet folding peptide amplify broad-spectrum and highly selective antimicrobial activities. Therefore, the protein folding theory and the common features of natural AMPs provide a basis for the design of beta-sheet AMPs, including:(1)the intrinsic beta-sheet propensities of amino acids in strands and cross-strand interactions across strands, (2) a net positive charge interceding peptide associations with adversely charged layers of microscopic organisms; (3) hydrophobic deposits giving lipophilic anchors and eventually including layer disturbance, and (4) the sensible game plan of amino corrosive buildups to frame a construction with amphipathic qualities, which isolates cationic and hydrophobic buildups to inverse appearances of the folded particle.

**Extended structures:** With a high proportion of Pro and Gly residues exhibit linear rather than secondary structures.Therefore, extended properties can be divided into Pro and Gly-rich peptides 37. Indolicidin has Pro-rich extended property and it is isolated from mammals, on the other hands apidaecins are isolated from insects. Pro-residues vary from 15-39 residues. The pro-residue is often associated in doublets and triplets with basic residues (Arg and Lys). Generally short Pro-rich peptides exhibit effective activity against Gram negative bacteria while maintain low antimicrobial activity against Gram positive bacteria. Several Gly-rich AMPs have been isolated from various insects. The size of Gly-rich peptides varies from 8kDa

(holotricin) to 30kDa (sarcotoxin II ) 38.

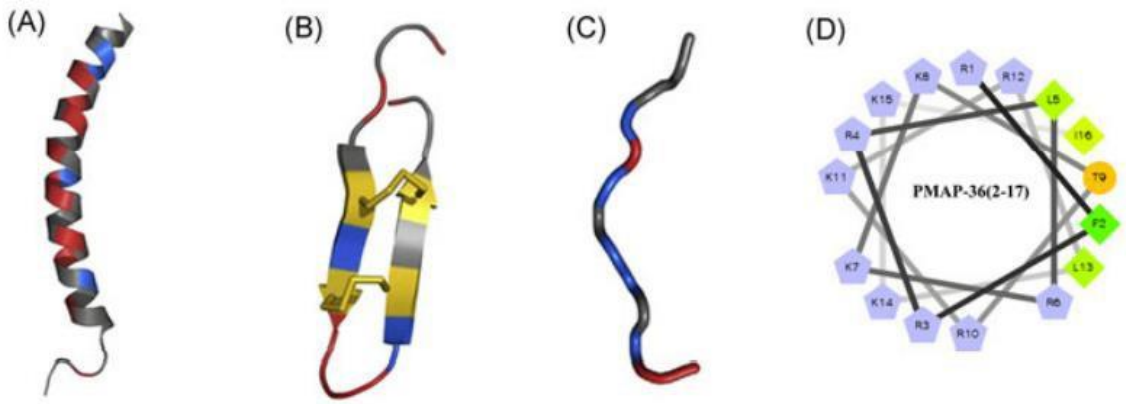



**FIGURE 2** Common structural classes of antimicrobial peptides (AMPs): A, α-helix; B, β-sheet; and C, extended structures. Reproduced with permission from Takahashi et al,[9] Copyright (2010) Elsevier Masson SAS. Helical-wheel projections of the peptides: D, PMAP-36. By default, the output presents the hydrophilic residues as circles, hydrophobic residues as diamonds, potentially negatively charged as triangles, and potentially positively charged as pentagons. Hydrophobicity is color coded as well: the most hydrophobic residue is green, and the amount of green decreases proportionally to the hydrophobicity, with zero hydrophobicity coded as yellow. Hydrophilic residues are coded red with pure red being the most hydrophilic (uncharged) residue, and the amount of red decreases proportionally to the hydrophilicity. The potentially charged residues are light blue. Reproduced with permission from Zhu et al,[30] Copyright (2014) Elsevier Ltd [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** Classification of antimicrobial peptides (AMPs)

| Classes | Representatives | Sequences | Hosts |
|---|---|---|---|
| α-Helix | Melittin | GIGAVLKVLTTGLPALISWIKRKRQQ | Honey bee |
| | Magainin-1 | GIGKFLHSAGKFGKAFVGEIMKS | Frog |
| | LL-37 | LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES | Human |
| β-Sheet | HNP-1 | AC[1]YC[2]RIPAC[3]IAGGRRYGTC[2]IYGGRKWAFC[3]C[1] | Human |
| | HBD-1 | DHYNC[1]VSSGGQC[2]LYSAC[3]PIFTKIQGTC[2]YRGKAKC[1]C[3]K | Human |
| | Protegrin 1 | RGGRLC[1]YC[2]RRRFC[2]VC[1]VGR | Pig |
| Extended | Indolicidin | ILPWKWPWWPWRR | Cow |
| | Tritrpticin | VRRFPWWWPFLRR | Pig |
| | PR-39 | RRRPRPPYLPRPRPPPFFPPRLPPRIPPGFPPRFPPRFP | Pig |

Abbreviations: HBD-1, human α-defensin 1; HNP-1, human α-defensin 1.
[1], [2], and [3] are disulfide bonds intramolecularly formed by Cys residues in one peptide.

## V MODE OF ACTION

Various AMPs have various methods of activity, some kill cells by destroying membrane integrity, some by hindering proteins, DNA, RNA synthesis or a few by cooperating with certain intracellular targets. All AMPs realized by late-90s are cationic. Notwithstanding, the idea that AMPs should be cation was changed later with the revelation of negatively charged AMPs in 1997.39. Eg.

Maximin-H5 is an anionic peptide, isolated from frog skin.

Generally, a particular AMPs is active against only one specific class of microorganisms (e.g. Bacteria or fungi). But there are some exceptions, some AMPs have several mechanisms of action. For e.g., Indolicidin can destroy bacteria, fungi and HIV 40. It also kills E. coli by entering into the cells and repressing DNA synthesis, and it shows anti- HIV activities by hindering HIV integrase 41. Also, there are some AMPs which kill different types of cells by the same mode. For e.g., PMAP-23 can destroy parasites as well as fungi by generating pores in their cell membranes. 42.

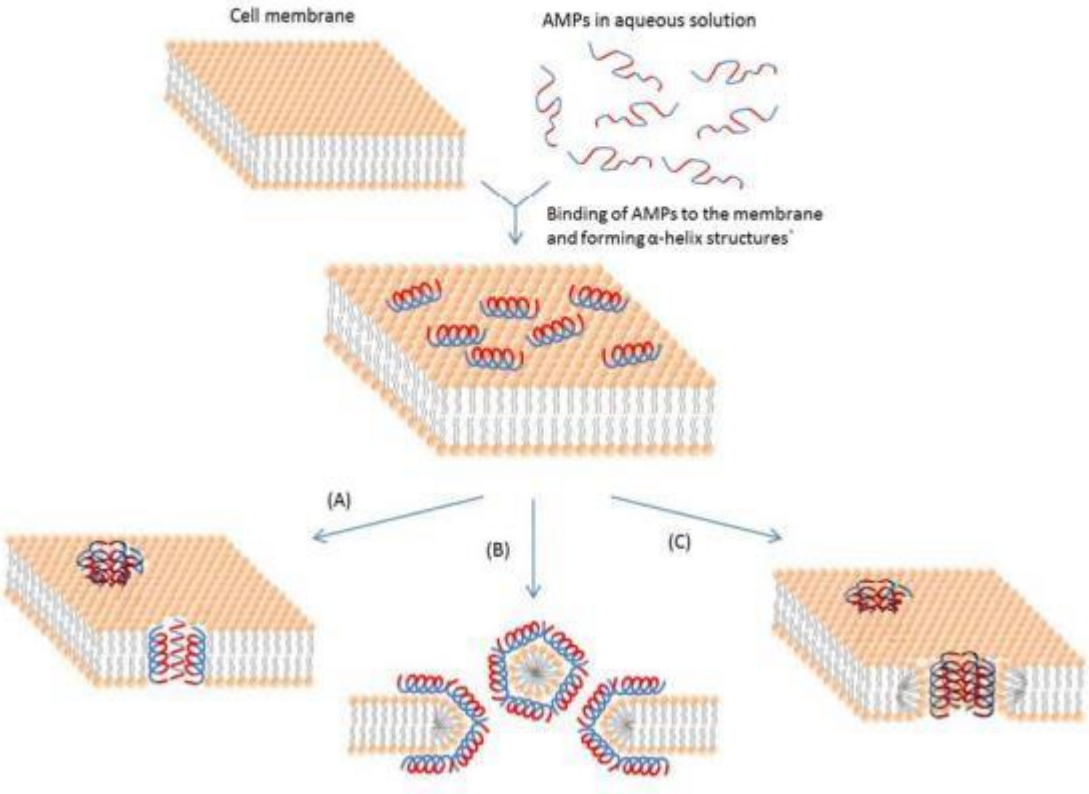
Roughly 33% of the proteins of a bacterial cell are related with the membrane and these proteins have many capabilities that are basic to the cell including ATP generation, respiration, PMF etc. 43. Without complete cell lysis, with AMP treatment, the function of these proteins can be changed. Therefore, AMPs does not only can disrupt cell membrane but can also inhibit some functional proteins.

**Membrane-active AMPs:** Most membrane-active AMPs are amphipathic, i.e., they both have hydrophobic and cationic faces. This component guarantees the initial electrostatic interaction with the cell membrane and the hydrophobic part helps the AMP atom to embed into the cell membrane. Thus, the interaction basically relies upon cationic state and hydrophobicity of the AMP particle. The significant types of membrane-active AMPs and their mode of action are summed up in Table 2 and fig. 3.

Table 2 The mode of action of membrane -active AMPs

| Interaction model | Mechanism | References |
|---|---|---|
| Carpet like (Detergent-like) | The peptide micelle touches the membrane first and coats a small area of the membrane. Then AMP molecules penetrate the lipid bilayer to let pore formation occur leaving holes behind. | [115–117] |
| Membrane thinning | AMPs insert themselves into only one side of the lipid bilayer. It can form a gap between lipid molecules at the chain region. This gap creates a force and pulls the neighboring lipid molecules to fill it. | [118–120] |
| Aggregate | AMPs stick to the membrane parallel to the surface. Then reorientation of AMPs occurs and they insert themselves into the membrane vertically to form sphere-like structures. | [115,121–123] |
| Toroidal pore | AMPs align perpendicularly into the bilayer structure with their hydrophobic regions associated with the center part of the lipid bilayer and their hydrophilic regions facing the pore. | [83,123] |
| Barrel-stave | Staves are formed first parallel to the cell membrane. Then barrels are formed and AMPs are inserted perpendicularly to the plane of the membrane bilayer. | [82,124,125] |

Figure 3 Schematic representation of some action mechanisms of membrane-active AMPs. (**A**) Barrel-Stave model. AMP molecules insert themselves into the membrane perpendicularly. (**B**) Carpet model. Small areas of the membrane are coated with AMP molecules with hydrophobic sides facing inward leaving pores behind in the membrane. (**C**) Toroidal pore model. This model resembles the Barrel-stave model, but AMPs are always in contact with phospholipid head groups of the membrane. The blue color represents the hydrophobic portions of AMPs, while the red color represents the hydrophilic parts of the AMPs.




**Intracellularly Active AMPs:** Intracellularly active AMPs have been displayed to interact with targets inside the cells 44. For instance, indolicin was displayed to tie to DNA with a favored sequence 45. A few AMPs can hinder DNA and protein synthesis 46. One illustration of this is PR-39, an AMP from pig digestion tracts, which kills microbes in a non-lytic process by behaving like a proteolytic agent and halting protein and DNA synthesis. 47. Like PR-39, indolicin doesn't lyse cells straightforwardly. It enters the cytoplasm and kills bacterial cells by focusing on DNA synthesis 48.

## VI BROAD SPECTRUM ACTIVITY:

**Antifungal activity:** AMPs have strong antifungal activity and it is also useful in addressing fungal infections. AMPs generally lyse the cell and they interfere with fungal cell wall synthesis. Cathelicidin peptides kills Candida albicans and Cryptococcus neoformans cells through membrane permeabilization and harm the microorganism Vylkova et al. found that human beta-defensin 2 (Hbd-2)(Synthetic) and Hbd-3(synthetic) could kill Candida albicans in an energy - reliant and salt-touchy way without causing gross membrane disturbance or lysis 49. Research has shown that LL-37 could diminish the C.albicans connection to abiotic

surfaces, oral epidermis and murin urinary bladders by interfacing with Yeast carbohydrate and protein cell-wall parts, which is of basic significance in counteraction C.albicans colonization and disease by AMPs 50.

**Antiviral peptides:** Antiviral AMPs kill viruses by interacting in either the viral envelope or the host cell membrane. AMPs can incorporate into viral envelopes causing membrane instability, this renders the viruses unfit to contaminate host cells. For e.g., defensins tie to the viral glycoproteins making herpes simplex viruses (HSV) unfit to tie to the outer layer of the host cells 51. There are a few antiviral AMPs which can keep viral particles from entering host cells by possessing explicit receptors on mammalian cells. For eg., heparan sulfate is significant for the attachment of HSV viral particles to the host cell surface. The heparan sulfate particles are negatively charged glycosaminoglycan atoms. In this way, a few alpha-helical cationic peptides, eg., lactoferrin, can forestall HSV contaminations by restricting to heparan particles and impeding virus- receptor interactions 52. A few AMPs can cross the cell membrane and limit in the cytoplasm and changes in the gene expression profile of host cells, which can assist with facilitating host defense system against viruses or can hinder viral gene expression. For e.g., NP-1, forestalls Vero and CaSki cell lines from infection by herpes simplex virus type 2 (HSV-2). This AMPs stops the virus by forestalling the relocation of a significant viral protein, VP16, into the core. 53.

**Antibacterial activity:** Antibacterial AMPs are the most common AMPs. The majority of them are cationic AMPs. These AMPs target bacterial cell layers and cause breaking down of the lipid bilayers. Most of these AMPs are likewise amphipathic with both hydrophilic and hydrophobic domains. Such structures give AMPs the capacity to tie to lipid parts (hydrophobic regions) and phospholipid groups (hydrophilic regions) 54.

Scientists have shown the way that a few AMPs at low concentration can kill microorganisms by repressing a few significant pathways inside the cell. For eg., buforin II can diffuse into cells and tie to DNA and RNA without harming the cell membrane 55. Drosocin, pyrrhocoricin, and apidaecin are different examples of such AMPs. It is generally hypothesized that three main mechanisms could account for peptide permeation of the membrane of the target cell, including “barrel-stave model”, “carpet model” and “toroidal-pore model” 56. The linked peptides combine to create a bundle with a central lumen in the "barrel-stave model" and insert into the hydrophobic core of the membrane to generate a trans-membrane pore. The "carpet model" contends that, over a threshold concentration of membrane-bound peptide, AMPs bind to the phospholipid head covering membrane surfaces in a way like to carpeting and break the bilayer's curvature like a detergent. 57

The "torroidal-pore model" entails the accumulation of peptide helices within the membrane, which causes the lipid monolayers to constantly bend through the pore, lining the water core with both the inserted peptides and the lipid head groups.
58.

**Antiparasitic peptides:** Magainin was the first antiparasitic AMP discovered. Paramecium caudatum is susceptible to it. Later, a synthetic peptide against the parasite Leishmania was created. 59 The Caernohabditis elegans parasite is killed by the antiparasitic AMP cathelicidin, which works in a similar manner to other AMPs by creating pores in the cell membrane. They destroy cells by directly interacting with the cell membrane.

**Antitumor activity:** Cancer was the subsequent driving reason for death, after coronary illness, in the US in 2019. In this manner, improvement of antitumor medication is required. A few cationic AMPs display cytotoxic movement against tumor cells AMPs fundamentally single out cell membrane through a non-receptor-mediated pathway, for which it is more trying for cancer cells to encourage resistance diverged from standard chemotherapeutic subject matter experts.60. For instance, the antitumor system of B1 and its analogs includes three stages: cell membrane disturbance coming about because of changes in membrane porousness; entrance of the cytoplasm after membrane disruption; mitochondrial membrane disruption and release of cytochrome C 61.

AMPs with ideal antitumor movement ought to fulfill somewhere around three circumstances: (1) high net positive charge. The presence of the great net positive charge of AMPs adds to electrostatic affinity between the adversely charged parts, (for example, phosphatidylserine) of growth cells and the emphatically charged AMPs 62. (2) High structural adaptability. The pliancy of AMPs considers changes in conformity in various conditions (watery and membrane- emulate conditions), which permits them to cross the phospholipid layer of growth cells. (3) High oligomerization. AMPs ought to be effortlessly bunched on the layer surface of a tumour cell so they can create a pore on the tumour cell membrane.

## VII APPLICATION OF ANTIMICROBIAL PEPTIDES:

**In Food:** In food industries natural AMPs are required without harmfulness, to safeguard food varieties. Lately, much consideration has been centered around use of AMPs as a choice to control bothersome microbial development on foodstuffs. For e.g., Nisin, a polycyclic peptide with 34 amino acids residues derived from Lactococcus lactis, is normally utilized in handled cheddar, meats and refreshments.

Ple/PVA fiber, an AMP Ple (pleurocidin, an novel AMP with 25 amino acids, derived from the skin-discharged mucous of the colder time of the winter flounder) integrated into ultrafine PVA fiber mats through electrospinning technology, was exhibited to be effectively applied in apple juice, with productive hindrance activity against *E.coli.*

**In medicine:** AMPs additionally use in drug treatment in the centers. Eg, Lucifensin and Lucifensin II, two insect defensins, can be used as wound healing agent, particularly in patients who are disable to heal wounds due to disorders (eg. Diabetes). This strategy is known as debridment treatment. Pexiganan, a 22-amino- acid membrane disruptor analog of the Xenopus peptide magainin, has been clinically demonstrated to supplant ofloxacin in the treatment of diabetic foot ulcers as soon as 1996, and may and may avoid the selection of resistant bacteria. As of now the stage III clinical trials of this peptide are being led again to treat somewhat diabetic foot disease by Dipexium Drugs 63. Omiganan is an indolicidin analog. It has an broad range antibacterial activity. It has finished stage III clinical trials for catheter contaminations and

rosacea, finished stage II for the utilization of omiganan in patients with vulvar intraepithelial neoplasia atopic dermatitis and skin break out vulgaris. POL7080 as an antimicrobial peptidomimetic explicitly targets P. aeruginosa at the nanomolar level by means of non-membrane disrupting activity.

Notwithstanding antibacterial movement, a few AMPs have likewise been displayed to have immune-promoting impacts, for example, PXL01, which is derived from human lactoferricin and been surveyed for its viability, wellbeing and taking care of in patients with flexor ligament wounds in stage II trials 64.

**In animals:** It has been reported that few AMPs included the eating routine make valuable impacts, including body weight, supplement edibility and gastrointestinal morphology as well as consequences for digestive and fecal microflora. A few reports likewise showed the way that AMPs can give protection to piglets from challenge with the mycotoxin deoxynivalenol (DON)201 and fix the digestive injury prompted by Wear 65. In addition, AMPs upgrade gastrointestinal barrier function and improve microbiota organization in the digestion tracts of weaned piglets and decrease rates of loose bowels in them.

TABLE 3 Some specific antimicrobial peptides (AMPs) in clinical phase of development

| AMPs | Description | Condition or disease | Administration | Phase | Status company | Clinical trial identifier if available |
|---|---|---|---|---|---|---|
| Pexiganan (MSI-78) | Analog of magainin | Diabetic foot infection | Topical | Phase 3-C | MacroChem Corporation | NCT00563433<br>NCT00563394 |
| | | | | | Dipexium Pharmaceuticals, Inc. | NCT01594762<br>NCT01590758 |
| Omiganan | Derived from indolicidin | Catheter infections | Topical | Phase 3-C | Mallinckrodt | NCT00231153 |
| | | Atopic dermatitis | | Phase 2-C | Cutanea Life | NCT03091426 |
| | | Rosacea | | Phase 3-C | Sciences, Inc. | NCT02576847 |
| | | Vulvar intraepithelial neoplasia | | Phase 2-C | | NCT02596074 |
| | | Acne vulgaris | | Phase 2-C | | NCT02571998 |
| Lytixar (LTX-109) | Synthetic antimicrobial peptidomimetic | Gram-positive, skin infections Mild Eczema/Dermatoses Atopic Dermatitis | Topical | Phase 2-C | Lytix Biopharma AS | NCT01223222 |
| | | Nasal carriers MRSA | | Phase 1/2-C | | NCT01158235 |
| | | Non-bullous Impetigo | | Phase 2-C | | NCT01803035 |
| Surotomycin | Cyclic lipopeptide | Clostridium difficile-associated diarrhea (CDAD) | oral | Phase 1-C | Merck Sharp & Dohme Corp. | NCT02835118<br>NCT02835105 |
| Novexatin (NP-213) | Cyclic peptide | Onychomycosis | Topical | Phase 2-C | NovaBiotics | [197] |
| LL-37 | Host-defense peptide | Melanoma | Intratumorally in cutaneous or subcutaneous tumors | Phase 1/2-A | M.D. Anderson Cancer Center | NCT02225366 |
| PXL01 | Derived from lactoferricin | Surgical adhesions | Hyaluronic acid-based hydrogel | Phase 2-C | Pergamum AB | NCT01022242 |
| Iseganan (IB-367) | Derived from protegrin 1 | Oral mucositis in head and neck cancer. | Oral rinse | Phase 3-U | National Cancer Institute (NCI) | NCT00022373 |
| PAC-113 | Derived from histatin 3 | Oral candidiasis | Mouth rinse | Phase 2-C | Pacgen Biopharmaceuticals Corporation | NCT00659971 |

(Continues)

Table 3 continued

| AMPs | Description | Condition or disease | Administration | Phase | Status company | Clinical trial identifier if available |
|---|---|---|---|---|---|---|
| Dalbavancin | Lipoglycopeptide | Bone infection Osteomyelitis Septic arthritis Joint infection Prosthetic joint infection | Intravenously | Phase 4-R | Infectious Diseases Physicians, Inc | NCT03426761 |
| | | Infectious Peritonitis | Intravenously | Phase 4-A | University of Colorado, Denver | NCT02940730 |
| | | Methicillin-resistant *Staphylococcus Aureus* skin infections | Intravenous administration in children | Phase 3-R | Durata Therapeutics Inc | NCT02814916 |
| SGX942 | 5-amino acid peptide | Oral mucositis in head and neck cancer | Intravenously | Phase 3-R | Soligenix | NCT03237325 |
| OP-145 | Derived from LL-37 | Chronic otitis media | Eardrops | Phase 2-C | Leiden University, The Netherlands | ISRCTN84220089 |
| Brilacidin (PMX-30063) | Defensin mimetic | Bacterial skin infection | Intravenously | Phase 2-C | Cellceutix Corporation | NCT02052388 |
| | | Mucositis in head and neck Neoplasms | Oral Rinse | Phase 2-C | Innovation Pharmaceuticals, Inc | NCT02324335 |
| POL7080 | Peptidomimetic | Renal impairment | Intravenously | Phase 1-C | Polyphor Ltd | NCT02110459 |
| | | Ventilator-associated pneumonia aeruginosa | | Phase 2-C | | NCT02096328 |
| | | Healthy; Synergism with amikacin | | Phase 1-C | | NCT02897869 |
| AP-214 | Derivative from HDP | Prevention of (acute) kidney injury after cardiac surgery | Intravenously | Phase 2-C | Action Pharma A/S | NCT01256372 |
| | | Prevention of kidney injury after thoracic aortic aneurysm repair | | Phase 2-C | | NCT00903604 |
| CD-NP | Chimeric 37-mer derived from combination of two natriuretic peptides | Acute decompensated heart failure | Infusions | Phase 2-C | Nile Therapeutics | NCT00839007 |
| Ghrelin | Endogenous host-defense peptide | Chronic respiratory infection | Intravenously | Phase 2-C | University of Miyazaki, Japan; | JPRN-UMIN000002599 |
| | | Airway inflammation | | Phase 2-C | | JPRN-UMIN000001598 |

Abbreviations: A, active, not recruiting; C, completed; HDP, host-defense peptide; R, recruiting; U, unknown.

**Table 4 Report on application of antimicrobial peptides (AMPs) in animal**

| Animals | AMPs | Treatments/Doses | Effects |
|---|---|---|---|
| Weanling piglets | CAP[a] | Basal diet with 4 ppm deoxynivalenol and 4% CAP | Attenuating the metabolic disturbances in amino acid, lipid, and energy metabolism induced by DON; Improving intestinal morphology, intestinal epithelial cell proliferation and protein synthesis; Improving feed efficiency, immune function, and antioxidation capacity, alleviating organ damage |
| Weanling piglets | SyntheticAMP-A3[b]and AMP-P5[c] | Basal diet with 60 mg/kg AMP-A3 and basal diet with 60 mg/kg AMP-P5 Basal diet with 40 and 60 mg AMP-P5/kg diet Basal diet with 0, 60 and 90 mg AMP-A3/kg diet | Improving the performance, nutrient digestibility, intestinal morphology and reducing pathogenic bacteria |
| Weaned piglets | Cecropin AD[d] | Basal diet with 400 mg/kg cecropin AD and piglets were orally challenged with *E. coli* K88 | Increasing immune status and nitrogen and energy retention as well as reducing intestinal pathogens |
| Weanling piglets | Recombinant Lactoferrampin-lactoferricin | Basal diet with 0.1 g Lactoferrampin-lactoferricin and 0.1 g chlortetracycline/kg diet | Improving performance and affecting serum parameters |
| Weanling piglets | cipB-LFC-LFA | Basal diet with no addition, 100 mg cipB, 100 mg cipB-LFC-LFA/ kg diet | Improving performance, the regulation of immune function and the absorption of Fe, reducing the incidence of diarrhea |
| Weanling piglets | Colicin E1 | Basal diets with0, 11, or 16.5 mg Colicin E1/kg and piglets were orally inoculated with *E. coli* | Improving the performance and reducing the incidence of postweaning diarrhea |
| Weaned female piglets | Lactoferrin | Basal diet with 1.0 g/kg lactoferrin | Increasing ADG, efficiency of gain, intestinal villus height and relative abundance of mRNA for PR-39 and protegrin 1 |
| Indigenous male chickens | Cecropin AD-Asn (CADN) | Basal diets with a CADN liquid sample at 0, 2, 4, 6, and 8 ml/kg | Increasing nutrient utilization, enhancing intestinal villus heights, decreasing aerobic bacterial counts |

TABLE 4 (Continued)

| Animals | AMPs | Treatments/Doses | Effects | References |
|---|---|---|---|---|
| Arbor Acre male broiler chickens | Pig AMP (PMAP)[e] | Basal diet with PAMP at 150 and 200 mg/kg | Improving the performance, the intestinal mucosal immunity, and increasing the intestinal ability to absorb nutrients | Bao et al[212] |

Abbreviations: AD, atopic dermatitis; CAP, composite antimicrobial peptides; cipB-LFC-LFA, cipB-lactoferricin-lactoferrampin; DON, deoxynivalenol.

[a]CAP consists mainly of antibacterial lactoferrin peptides, along with plant defensins and active yeast.

[b]AMP-A3 (amino acid sequence: AKKVFKRLEKLFSKIWNWK-$NH_2$) is an analog of antimicrobial peptide HP 2-20 (amino acid sequence: AKKVFKRLEKLFSKIQNDK-$NH_2$).

[c]AMP-P5 (amino acid sequence: KWKKLLKKPLLKKLLKKL-$NH_2$) is an analog of the hybrid antimicrobial peptide CA-MA [Cecropin A (1–8)-Magainin 2 (1–12); KWKLFKK IGIGKFLHSAKKF-$NH_2$].

[d]Cecropin AD is expressed in *Bacillus subtilis* and the amino acid sequence of Cecropin AD is KWKLFKKIEKVGQRVR-DAVISAGPAVAT-VAQATALAK-$NH_2$.

[e]PAMP is isolated from pig small intestine.

## VIII PERSPECTIVE AND CONCLUSIONS

Because of the antifungal, antibacterial, antiviral, antiparasitic properties of AMPs, they can be used as alternatives of conventional antibiotics. But there is a limiting factor, that is it has low in vivo stability. To extent the half-life of AMPs, AMP mimics with an amphiphilic studies have made extraordinary advances recently, yet further investigations are required. However many investigations had done on AMPs, disease control by AMP is yet blocked by certain elements including low specificity, high production cost, expected harmfulness to creature cells and so on.

In this review we have discussed about various applications of AMPs, it's mechanism of action, it's various types and it's broad- spectrum activity etc.

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