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# REPURPOSING THE EVOLUTION AND APPLICATION OF ANTIMICROBIAL PROTEINS AND PEPTIDES ISOLATED FROM DIFFERENT SOURCES

Arpita Dey [1], Bijayata Patra [1], Tamalika Chakraborty [*1], Sumana Chatterjee [2] and Jeenatara Begum [2]

Department of Biotechnology [1], Department of Pharmacy [2], Guru Nanak Institute of Pharmaceutical Science and Technology, Kolkata - 700114, West Bengal, India.

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**Correspondence to Author:**
**Ms. Tamalika Chakraborty**

Assistant Professor,
Department of Biotechnology,
Guru Nanak Institute of Pharmaceutical Science and Technology, Kolkata - 700114, West Bengal, India.

**E-mail:** tamalika.chakraborty@gnipst.ac.in

**ABSTRACT:** Antimicrobial proteins and peptides are also known as Host defense system. Recently, research in the food industry and therapeutic fields has seen a considerable expansion in the use of antimicrobial proteins. It has a wide spectrum of antibacterial and immunomodulatory properties against infectious bacteria, viruses, fungus, *etc*., obtained from microbes, plants, animals, and even humans. Antimicrobial peptides can potentially improve the specificity and efficacy of antibiotics by being a promising alternative because microorganisms can't metabolize them. Regulation, post-transduction modification, ribosome synthesis, *etc*. are the essential components of the AMP (Antimicrobial protein and peptide) biosynthesis process. Today, AMPs can be developed synthetically based on their activity, source, structure, and species of amino acids. They have the unique ability to rupture the cell wall, which results in cell death. As a novel approach, scientists have determined a few strategies to administer AMPs by formulating with chitosan nanoparticles, gold and silver nanoparticles, and peptide-assembly by producing microgels, mesoporous materials, and other substances that can be applied in the fields of skin disease, cancer therapy, food preservation, and processing. This overview covers the biosynthesis mechanism, its structure, classification, and mode of action, particularly emphasizing how AMP is used in the food industry, medicine, ophthalmology, and other fields.

**INTRODUCTION:** Antimicrobial proteins and peptides (AMPs) are ancient immune system building blocks that operate as broad-spectrum anti-infective against a variety of mycobacteria, Gram-positive and Gram-negative bacteria, fungi, and enveloped viruses. These proteinaceous compounds produced by bacteria, known as Bacteriocins [1], are effective antibiotics that show potency as novel therapeutic agents. These traits make these compounds an appealing substitute for traditional antibiotic medications.

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Antimicrobial proteins derived from invertebrate and mammalian origins that are synthesized by chemical, enzymatic, and recombinant methods. It has been discovered that these peptides can replace chemical protectors [2, 3]. Bacteriocins were discovered in 1925, when *E. coli* V was found to produce an active antimicrobial compound against *E. coli* [1].

These antimicrobial peptides (AMPs) or proteins are synthesized in bacteria as a part of their natural defense mechanisms and are capable of killing both related and unrelated microbes. The first discovered AMP was in Silkworm chrysalis [4]. Different types of AMPs have been extracted from microorganisms, plants, animals, including humans. Most AMPs were discovered in bacteria, such as microcin J25, tricyclic peptide RP 71955,

citrocin, and gramicidin S.; few AMPs were discovered in fungi (e.g., plectasin); some of them are derived from plants that serve as the first line of defense for the host against pathogens and herbivores (e.g., kalata B10, knottin-like peptides, PvD1, SM-985 *etc*.); AMPs derived from animals are the most abundant, accounting for 75% of all known examples, and are found in a diverse variety of organisms including flies, frogs, honeybees, snails, crabs, scorpions, crawfish, shrimp, fish, dolphins, snakes, chickens, birds, mice, rabbits, sheep, pigs, cows, monkeys, and humans (HCAP-18 /LL-37, secreted by epithelial cells and various immune cells). Defensin from rabbit leukocytes, Lectoferrin from cow milk, Lysosomes of human leukocytes, and low molecular weight antimicrobial peptide from the human female reproductive tract are further AMPs that have been identified. *Shigella*, *Salmonella*, *E. coli*, and *Staphylococcus aureus* have all demonstrated potential inhibitory efficacy against a number of *Bacillus* strains that produce antimicrobial peptide [5]. These AMPs are modified by modification of gene sequence to improve their antimicrobial activity, productivity, while lowering host toxicity and cost [4]. Numerous studies have demonstrated that the bacte riocins are protein molecules with minimum amount of carbohydrates (< 1%) and phosphorous (< 0.1%). A diverse array of particles with various morphological and metabolic components makes up bacteriocins. The different composition of amino acid sequences make differ one bacteriocin from another [3, 6]. Different AMPs have some similarities; antimicrobial peptides typically have between 10 and 60 amino acids; these peptides have a significant amount (often >50%) of hydrophobic residues and two or even more positively charged residues given by arginine, lysine, or histidine. These molecules' secondary structures fall into four categories: (a) α-helical structure due to the presence of two or more disulfide bonds, (b) β-stranded, due to the presence of two or more disulfide bonds, (c) β-hairpin or loop structure due to the presence of a single disulfide bond and/or cyclization of the peptide chain, and (d) extended structure. Most of the AMPS are cationic [7]. When these peptides are segregated into biological membranes, many of them fold into their terminal configuration after being unstructured in free solution, which is made up of a helical molecule with hydrophilic amino acid residues aligned along one side and hydrophobic amino acid residues aligned along with other, this feature enables their membrane splitting personality. Many peptides only interact with certain cell membranes to acquire their active structure. Likely, Indolicin exhibits a globular and amphipathic conformation in aqueous solutions while taking wedge-shaped in lipid bilayer stimulating condition [8, 9].

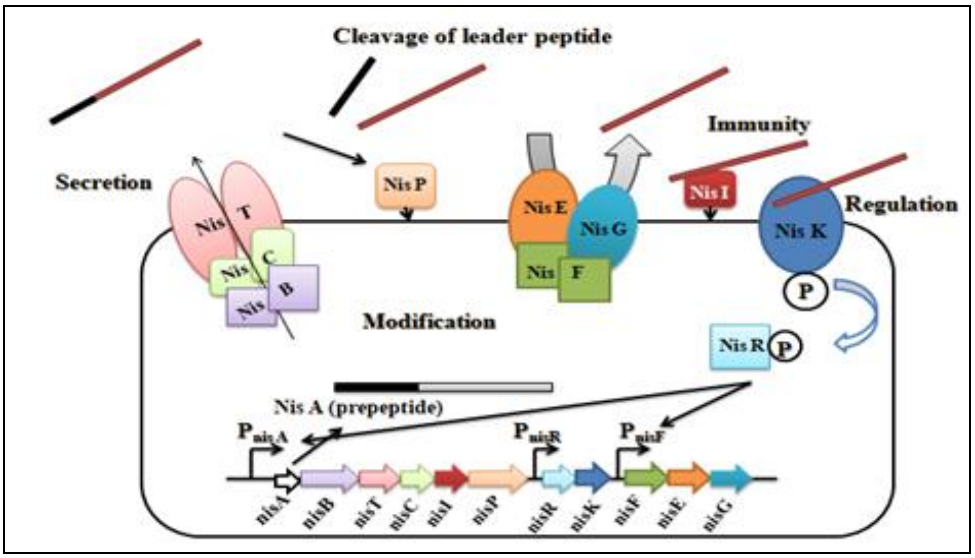


**FIG. 1: BIOSYNTHESIS OF NISIN A BY RIBOSOME SYNTHESIS.** NisinA produced as a prepeptide NisA by ribosome synthesis. NisB and NisC, modifying enzymes dehydrate and cyclize the propeptide, transported into the extracellular space by ABC transporter and NisT subsequently. The activated mature NisA generated after the NisP and protease cleave the leader peptide. The self-immunity response for NisA is made up of the lipoprotein NisI. A histidine kinase, NisK and NisR (response regulator) comprising the Two part regulatory mechanism, controls the up-regulation of the nisin gene, where NisA acts as a signal peptide.

The bacteriocins are generally synthesized by microbial expression system like prokaryotic or eukaryotic system. Expression is regulated often by two-component regulatory system and in some cases by three-component regulatory system. They are synthesized as precursors that are processed and post-translationally modified. Bacteriocins are then transmitted *via* ABC transporters and sec-dependent exporters [10] and cleaved to produce the mature form.

The operon clusters that include the active bacteriocin-producing genes are typically found in the genome, plasmids, or other mobile genetic components, that can be activated; however doing so needs the presence of auto-inducer peptides. Such operons have been found on conjugative transposable elements, the host chromosome carnobacteriocin BM1, plasmids, lactococcins ABM, and lacticin 3147. Recent research investigations have shown that *L. planterum* RUB1 boosts antibacterial action for operon activation [11]. In case of lactic acid bacteria, bacterial metabolic pathways like Response regulation, Post translational modification are responsible for stimulation and activation of bacteriocin precursor [1, 2].

To better understand bacteriocin biosynthesis, Nisin A is produced by ribosome synthesis as an inactive prepeptide called NisA, which consists of a propeptide moiety coupled to an N-terminal leader sequence. The propeptide is transformed by the enzymes NisB and NisC, where Nis B converts serine and threonine into dehydroalanine and dehydrobutyrine; while NisC catalyzes the addition of thiol group in cysteine to an N-terminally located dehydroamino acid, resulting in the characteristic lanthionine rings. The modified prepeptide is then transported into the extracellular space by the ABC transporter NisT. Nisin A's active form is released after the protease, NisP, removes the leader peptide. The self-immunity system for nisin A is made up of the lipoprotein NisI, which can bind to nisin A, and the multi-protein ABC transporter complex NisFEG, which expels nisin A from the cell. The nisin is then bound to the NisK, a histidine kinase that starts autophosphorylation. Then the phosphate is transferred to NisR (transcriptional activator) and activated the promoter PnisA. Other two promoters PnisR and PnisF progress accordingly, which causes the nisin gene clusters to be up-regulated **Fig. 1** [2, 12, 13].

**Classification of AMPs:**

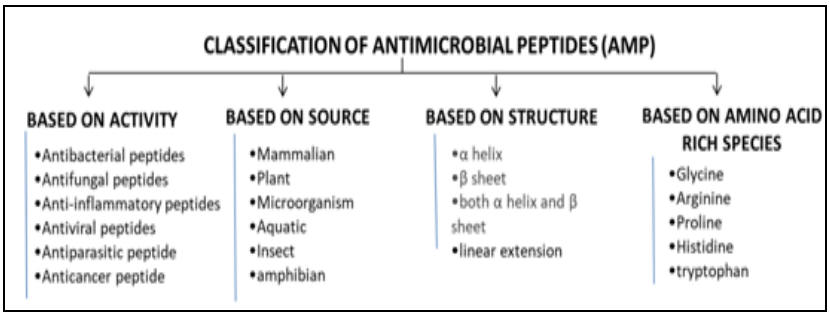


**FIG. 2: CLASSIFICATION OF ANTIMICROBIAL PEPTIDE**

**Source-Based AMP:** Using sources, the different types of AMPs **Fig. 2** include those from plants, microorganisms, aquatic life, insects, amphibians, and mammals, with a significant amount originating from human host defense peptides.

**Antimicrobial Peptides of Mammalian Origin:** Humans **Table 2**, sheep, cattle, and other vertebrates produce mammalian AMP. Alexander Fleming found human lysozyme in saliva in 1922 **Table 1**, and it is regarded as the first antibacterial protein [14].

The two primary AMP families are Cathelicidins and Defensins. Depending on the disulfide bond's position, Defensins are divided into α-, β-, and θ [15]. Human host defense peptides range in size from 10 to 150 amino acids, have a net charge between 3 and +20, and less than 60% of them are hydrophobic. Human AMPs can adopt a variety of 3D configurations and combat infections using a variety of ways because to the sequence diversity. While Human Neutrophil Peptide-1 (HNP-1) and -defensin hβD-3 can both inhibit cell wall

biosynthesis by interacting with lipid II, -defensin HD-6 can self-assemble onto the surface of bacteria to form nanonets that can entangle bacteria [16]. Human host defense peptides (HDP) defend against microbial infections, resulting in different expressions in different growth stages of humans. For instance, human β -Defensin 2(hβD-2) is frequently expressed in the old instead of younger whereas Cathelicidin LL-37, an important AMP produced from the human body, is generally observed in the skin of newborns [17]. Furthermore, AMPs in human breast milk are crucial for breastfeeding because they can lower the morbidity and mortality of nursing newborns [18]. The discovery of Casein 201, a peptide generated from -Casein 201-220 a.a, in colostrum is intriguing because it demonstrates variable levels in term and preterm human colostrums [19]. Dairy products, which are produced by milk enzymatic hydrolysis, are a significant source of AMPs. The most well-known peptide produced from the fractions of casein, lactoferrin, lactoglobulin and -lactalbumin is lactoferricin B (LfcinB) [20]. HDP can be identified in many body parts including the intestine, eyes, ears, mouth, respiratory tract, *etc* [16].

**TABLE 1: ORIGIN AND ACTIVITY OF AMP**

| Human Antimicrobial Peptide (Discovery Year) | Origin | Activity against Microbes | Reference |
|---|---|---|---|
| Lysozyme (1922) | saliva, tears, intestine | Bacteria, fungi | 14 |
| α-DefensinHNP-1 (1985) | Neutrophils, bone marrow | Bacteria, fungi , viruses, parasites, cancer cells | 21 |
| Histatin 1 (1988) | saliva | fungi | 22 |
| α-Defensin HNP-4 (1989) | neutrophils | Bacteria, fungi , viruses | 23 |
| CathelicidinLL-37 (1995) | neutrophils; skin | Bacteria, fungi , viruses, parasites, cancer cells | 24 |

**Antimicrobial Peptides Produced from Microorganisms:** Microorganisms like bacteria and fungi can induce peptides production. Prokaryotic peptides include, among others, colicin, holbiotics, microcin and lantibiotic [25]. Nisin **Table 2** and gramicidin from Bacillus subtilis, Lactococcus lactis, Bacillus brevis 26 and pediocin PA-1/AcH are two examples of antimicrobial peptides extracted from microorganisms.

In general, eukaryotic AMPs and bacteriocins are a highly heterogeneous class of molecules, but they have some characteristics in common: they are small molecules (20–50 aa), cationic, and amphiphilic or hydrophobic, which facilitates initial interactions with the negatively charged bacterial membrane on which they form pores that eventually lead to cell death. Butin contrast, eukaryotic AMPs require micro molar quantities to be active; bacteriocins are frequently quite strong, working at Pico to nanomolar concentrations [27].

Precisely, yeast species like Saccharomyces cerevisiae, Pichiapastoris, bacteria like Escherichia coli, *Bacillus subtilis*, and plants have all been used as expression systems [28], but it should be noted that AMPs are difficult to produce in *E. coli*, which is necessary to take advantage of fusion tags, due to the proteolytic degradation, toxicity, and purification [29].

**Antimicrobial Peptides Produced from Plants:** Several AMPs have been identified and taken from plant stems, seeds, and leaves. They are divided into a number of categories, including defensins, thionins, and snakins [30]. Plant AMPs **Table 2** have molecular weights between 2 and 9 kDa and are cysteine-rich. High cysteine and/or glycine content and disulfide bridges, crucial for improving structural stability under stress conditions, are essential attributes of AMPs. Plant AMPs include around 17% charged amino acids, which appear to be crucial for action toward pathogenic bacteria [31, 32]. They can be separated from a variety of plant components, including flowers, pods, leaves, and tubers. These peptides can be employed in food preservation since they have broad antibacterial action against *S. typhimurium*, *L. monocytogens*, and *E. coli* O157: H7. Plant antimicrobial peptides include Lipid Transfer Protein 2, Snakin1, Kalata B1, Thionin, and Potato Defensins [33].

**Antimicrobial Peptides Produced from Insects:** According to their amino acid sequence and structures, insect AMPs can be classified into three groups: 1. Cecropins, which are linear peptides with a -helix but no cysteine residues; 2. Defensins

have 6–8 conserved cysteine residues and three domains with a flexible amino-terminal loop; and 3. Peptides with an excess of Proline and/or Glycine residues [34]. Cecropin is such a well family of AMPs from insects, and it is present in Drosophila **Table 2**, bees, and guppy silkworm. Cecropin A exhibits efficacy against several malignancies and inflammatory disorders [35, 36]. Insects' fat bodies and blood cells primarily produce AMPs, that's one of the primary contributors to their exceptional adaptation to survival [37]. Insect peptides with antimicrobial properties the majority of antimicrobial peptides found in insects have been shown to have antimicrobial action against *Aerococcus viridans*, *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus megaterium*, and *Bacillus thuringiensis*. An important point to note isthat different species have different numbers of AMPs. For instance, Jelleines are a class of peptides includes 8–9 amino acids that were found in royal jelly isolated from the *Apis mellifera* plant [38] has promising results against a variety of bacteria and fungi, and its conjugated form with lauric acid can stop the parasite Leishmania major [39]. Pea aphids (*Acyrthosiphon pisum*) lack AMPs, butblack army flies (*Hermetiai llucens*) and invasive harlequin ladybirds (*Harmonia axyridis*) have up to 50 AMPs each [40].

**Antimicrobial Peptides Produced from Amphibian:** Some AMPs also have anticancer characteristics or effects [41]. For instance, Aurein has little toxicity and is extremely efficient against almost 50 different cancer cell lines. In order to defend frogs against the infections that are causing the global loss in amphibian population; amphibians' antimicrobial peptides are crucial42. The most well-known AMP produced by frogs is magainin; the skin secretions of frogs belonging to the genera Xenopus **Table 2,** Silurana, Pseudhymenochirus, and Hymenochirusin the Pipidae family are abundant in AMPs 43. The sea frog Ranacancrivora's can crin, which includes the amino acid sequence GSAQPYKQLHKVVNWDPYG, has been identified as the first AMP [44]. This indicates that amphibians are an expanded source of AMPs.

**TABLE 2: ANTIMICROBIAL PEPTIDES (AMP) FROM DIFFERENT SOURCES**

| Source | Species | Antimicrobial Peptides | Reference |
|---|---|---|---|
| Mammal | *Homo sapiens sapiens* | Cathelicidin LL-37 | 17 |
| | *Homo sapiens sapiens* | human beta-defensin 2 | |
| Microorganism | *Lactococcus and Streptococcus species* | Nisin | 45 |
| | *Bacillus brevis* | Gramicidin | 46 |
| Insect | *Drosophila melanogaster* | Drosomycin, Drosocin, Diptericin, Metchnikowin | 15 |
| | *Stomoxyscalcitrans* | Smd 1, Smd 2 | |
| Plant | *Oldenlandiaaffinis* | Cyclotides: Kalata B1 and B2 (Leave and flowers) | 30 |
| | *Zea mays* | Lipid transfer proteins (LTPs): LTP1s and LTP2s(Seeds) | |
| Amphibian | *Hylomantis lemur* | Dermaseptin-L1 | 42 |
| | *Xenopuslaevis* | Caerulein precursor fragment (CPF) | |

**Activity Based AMP:** According to the statistics of the Adenosine Diphosphate 3 (ADP3) database, there seem to be 18 categories in which AMP activity can be classified. Antibacterial, antiviral, antifungal, anti-inflammatory peptides, anti-human immunodeficiency virus (HIV), antiparasitic, anti-human immunodeficiency virus (HIV), and anti-tumor peptides can be used to describe these categories.

**Antibacterial Peptides:** Antibacterial peptides serve as the effector molecules for innate immunity. Since the production of intestinal defensins in fetal tissue begins 13. 5–17 weeks after conception, a group of peptides with antibacterial activity are the primary components of innate immunity, which is something we are all "born with" [47]. A significant portion of antibacterial peptides have a broad inhibitory effect on common pathogenic bacteria, including *S. aureus*, *Listeria monocytogenes*, *E. coli* in food, Salmonella, and Vibrio parahaemolyticus in aquatic products and Vancomycin-resistant Enterococci (VRE) Acinetobacter baumannii, and Methicillin – resistant *Staphylococcus aureus* (MRSA) in clinical

medicine. Additionally, a recent study shows that Vernixcaseosa and amniotic fluid both include the cathelicidin LL-37 and the defensin families. It turns out that LL-37 and the two classes of defensins are the elements most crucial for defending our adult lives against bacterial illnesses. They typically have a net positive charge and between 15 and 45 amino acid residues [47]. Insects were the first to discover the Cecropin type of linear peptides without cysteine, while rabbit granulocytes discovered the defensin type with three disulphide bridges. Recent studies have shown that the interferon-I-based AMPs P5 (YIRKIRRFFKKLKKILKK-NH2) and P9 (SYERKINRHFKKTLKKNLKKK-NH2), which are meant to inhibit MRSA, have little cytotoxicity [48].

**Antifungal Peptides (AFPs):** A subgroup of AMPs known as antifungal peptides treats fungal infections with increased treatment resistance. Numerous AFPs have demonstrated excellent anti-fungal activity against common pathogenic fungi, including yeast, filamentous fungus (such *Aspergillus flavus*), mould, and *Candida albicans* and Aspergillus in clinical practice. The four main classes of antifungal substances are: azoles, which prevent the synthesis of ergosterol; polyenes, which physically interact with sterols found in fungal membranes; echinocandins, which prevent the synthesis of glucan; and fluorinated pyrimidines, which prevent the metabolism of pyrimidines, preventing the synthesis of DNA and RNA [49].

In addition to brevinin, cecropins, and ranatuerin, numerous synthetic peptides exhibit potent antifungal properties. For example, the 40% lethal *C. albicans* infection can be effectively treated with AurH1, which is derived from Aurein 1.2 [50]. A. flavus produces a carcinogen called aflatoxin that is harmful to human health. *A. flavus* can be slowed down by a variety of AFPs. For instance, A. flavusMD3 can be prevented from growing by an AFP with the sequence FPSHTGMSVPPP. Fresh maize seeds can produce fewer *A. flavus* spores when treated with a mixture of antifungal peptides isolated from Lactobacillus plantarum TE10 [51].

**Antiviral Peptide (AVP):** Short (8–40 amino acids) polycationic antivirals with significant broad range antiviral activity are known as AVPs [52]. Viruses seriously endanger human life and have a significant financial impact on animal husbandry. The most recent outbreak, COVID-19, has resulted in significant loss of life and property. Therefore, finding solutions to these issues is vital, and antiviral peptides provide fresh ideas. Antiviral peptides exhibit a potent antiviral impact, mostly by (1) preventing virus attachment and fusion of the virus cell membrane, (2) destroying the virus envelope, or (3) preventing virus reproduction [53]. Mucroporin-M1 was postulated to play the part of a molecular blocker, which must locate its target before viral attachment to the host cells, based on the facts that it directly interacted with measles virus particles and had stronger anti-SARS-CoV-2 activity with pre-treatment. AIV, HIV, and the virus that causes foot-and-mouth disease are further long-term dangers to human survival. According to a recent study, AMP Epi-1 regulates the destruction of viral particles and exhibits strong inhibitory effect against the virus that causes foot-and-mouth disease.

**Anticancer Peptides:** Anticancer peptides (ACPs) are a group of brief peptides made up of 10 to 60 amino acids that can prevent the growth or migration of tumor cells and the development of tumor blood vessels. They are also less likely to result in treatment resistance. The ACPs exhibit anticancer mechanisms by (1) enlisting immune cells (like dendritic cells) to destroy tumor cells, (2) inducing the necrosis or apoptosis of cancer cells, (3) inhibiting angiogenesis to cut off the source of nutrition for the tumor and prevent metastasis, and (4) activating specific regulatory functional proteins to obstruct the transcription and translation of tumor cells' genes [54].

It should be emphasized that hydrophobicity and net charge can both constrain and influence one another and are crucial in optimizing the anticancer action of ACPs. Therefore, for greater anticancer action, maintaining a balance between net charge and hydrophobicity is crucial. Degarelix, a drug that binds to gonadotropin releasing hormone (GnRH) receptors and prevents interaction with GnRH, is in the fourth phase of development. Leukemia peptide vaccine PR1 is in the third phase [55].

**Antiparasitic Peptide:** Water, soil, food, animal-to-human or person-to-person contact, parasitic protozoa, and other vectors are only a few of the ways parasitic protozoa can infect humans and other animals and spread disease [56]. The demand for novel treatments has also grown as parasite medication resistance has developed. When applied to parasites that cause diseases like leishmaniasis and malaria, antiparasitic peptides have a lethal effect [57]. But it should be mentioned that because their antiparasitic activity depends on certain protein targets, cyanobacterial peptides have different mechanisms from higher-eukaryote AMPs. Because of this, even if they are members of the same family or genus, these target parasites can be distinguished precisely [58]. Recent studies have shown that the marine synthesized AMP Epi-1 can significantly reduce Tricho monasvaginalis by damaging its membrane [59].

**Amino Acid-rich Species-based AMPs:** Proline, tryptophan, glycine, cysteine, and histidine are only a few of the specific amino acids that are abundant in AMPs. The various modes of action of AMPs are due to these changes in amino acid length, composition, and net charge.

**Glycine-rich Antimicrobial Peptides:** Glycine-rich AMPs, like acanthoscurrins, are cationic and distinguished by having high glycine content. These two isoforms of peptides, which have a positive charge and function against Escherichia coli and the yeast Candida albicans, were recovered from the hemocytes of the spider *Acanthoscurria gomesiana*. Attacins and diptericins are just two examples of the many glycine-rich AMPs found in nature60. These peptides significantly impact the tertiary structure of the peptide chain because they include between 14 and 22 percent glycine residues. Furthermore, the glycine-rich central–symmetrical GG3 is an ideal commercial drug candidate against clinical Gram-negative bacteria [61].

**Proline-rich Antimicrobial Peptides:** Proline-Rich Antimicrobial Peptides (PrAMPs) behave differently from other AMPs in that they kill bacteria by rupturing membranes rather than entering the bacterial cytoplasm *via* the inner membrane transporter SbmA [62]. To prevent aminoacyl-tRNA from binding to the peptidyl transferase centre or to trap decoding release factors on the ribosome following the termination of translation, PrAMPs target ribosomes once they have entered the cytoplasm. This prevents protein synthesis. The most efficient of these peptides, pyrrhocoricin, is nontoxic to healthy mice and eukaryotic cells and can defend mice against bacterial challenge when administered in minimal doses [63]. While Gram-positive bacteria are often killed by PrAMPs, pPR-AMP1, a proline-rich AMP isolated from crab (Scylla paramamosain), has antibacterial action against both Gram-positive and Gram-negative bacteria [61, 64].

**Tryptophan Rich Antimicrobial Peptides:** Tryptophan (Trp), a non-polar amino acid, has an exceptional impact on the lipid bilayer's interface region. These effects are crucial for interacting with the bacterial membrane's significant anionic component [65]. High antimicrobial activity in tryptophan-rich AMPs requires a minimum of six amino acids, and the location of these residues also influences their antimicrobial action. Additionally, they can target the heat shock protein in the target pathogens, which will result in protein misfolding [66]. Gram-negative *E. coli*, *Pseudomonas aeruginosa*, and Gram-positive *S. aureus* are all inhibited by the usual Trp rich AMP known as octa 2.

**Arginine-rich Antimicrobial Peptides:** Arginine (Arg), a basic amino acid, confers peptide charge and hydrogen bond interactions, which are crucial qualities to pair with the bacterial membrane's rich anionic component. Additionally, Trp residues appear to function as natural aromatic activators of Arg-rich AMPs through ion-pair interactions, favoring improved peptide-membrane associations [65]. Cationic AMPs (CAMPs) have high net charge values and include significant amounts of positively charged amino acids, such as arginine. CAMPs have potent antibacterial activity against bacterial infections, are quick to act, and delay the emergence of resistance [67]. Although Signal Recognition Particles-2 (SRP-2), an arginine-rich and highly -helical peptide, demonstrated broad-spectrum bactericidal activity against both Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* and multidrug-resistant *Acinetobacter baumannii*, it had

negligible hemolytic and cytotoxic effects on mammalian cells [68].

**Structure-Based AMPS:** One significant group of AMPs that interact with membranes has an amphipathic, -helical shape that enables the insertion of a clearly defined hydrophobic sector into the lipid bilayer. The sequence, size, degree of structure formation, cationicity, hydrophobicity, and amphipathicity are only a few of the factors that affect how active they are.

**α Helix:** Typically, α helix peptides are unstructured in aqueous solution, but when they come into contact with a biological membrane, they take on an amphipathic helical form. Antimicrobial peptides with amphipathic, α helix domain are a particularly common and pervasive type. These peptides have undergone extensive research and have produced a huge portion of structure-activity relationship data due to their compact size and ease of synthesis [69]. The α-helical amphiphilic peptide molecules interact with bacterial cell membranes to exhibit their amphiphilicity. They have hydrophobic and hydrophilic halves. When these peptides are adsorbed to bilayer lipid membranes, they fold into amphipathic α-helical with both hydrophilic and hydrophobic sides [71]. The α-helical cathelicidins **Table 3** have broad-spectrum antibacterial action against bacteria, fungi, and viruses, as well as notable activity against pathogenic bacteria resistant to antibiotics.

**TABLE 3 DIFFERENT TYPES OF CATHELICIDIN WITH % OF SECONDARY STRUCTURE**

| Cathelicidin | Organism | % of Secondary Structure | Reference |
|---|---|---|---|
| BMAP-27 | cattle | 70% helical | 70, 69 |
| Protegrin-3 | Wild boar | 61% helical | 70 |
| Fowlicidin-1 | chicken | 50% helical | 70, 9 |
| LL-37 (hCLD) | human | 16% helical | 70 |

**β Sheet:** Disulphide bonds act as stabilizers and allow the β-strands that are frequently arranged in polar and non-polar domains, giving the β-sheet peptides an amphipathic characteristic. Due to their rigid structure, β-sheet peptides are more ordered in aqueous solution and do not significantly alters conformation upon membrane contact as helical peptides do [71]. The cyclic α, β and θ-defensins and β-hairpin peptides make up the β-sheet AMPs. Antiparallel sheets create a hairpin structure in β-Hairpin AMPs. Plant defensins, alpha- and beta-defensins **Table 4** from mammals, defensinsfrom insects, protegrin, and tachyplins are among the majority of the beta-sheet peptides [70]. The Animalia is filled with small, beta-sheet peptide antibiotics that are cysteine-rich. Defensins have three to six disulphide bridges, and the class of the defensin depends on where the intramolecular disulphide connections are located. Positions C1-C5, C2-C4, and C3-C6 for -defensins include the disulphide-bridge connections that stabilized the triple-stranded β-sheet structure [72]. The defensins are a broad collection of AMPs that are synthesized as inactive precursors in neutrophils, macrophages, and epithelial cells. They are the best-studied -sheet peptides.

**TABLE 4: DIFFERENT TYPES OF DEFENSINS WITH % OF SECONDARY STRUCTURE**

| Defensins | Organism | % of Secondary Structure | Reference |
|---|---|---|---|
| α-defensin 6 | human | 65% beta sheet | 70, 71 |
| α-defensin 5 | human | 59% beta sheet | 70 |
| α-defensin 4 | human | 57% beta sheet | 70, 72 |
| α-defensin 1 | human | 53% beta sheet | 70 |

**Mode of Action:** The mechanism of action of antimicrobial peptides mainly depends on peptide's interaction with the cell membrane and its composition via electrostatic interaction[73]. Bacteriocin production in food is regulated by Quorum-sensing mechanisms that entail cells in the environment producing an extracellular auto-inducer molecule in response to population density [74]. Various models have been proposed to understand the mechanism of action of antimicrobial peptides, which occur when peptides attach to the cell membrane of bacteria. They mainly follow the following models.

**Carpet Model:** The carpet model or Detergent model **Fig. 3** was proposed by Gazil *et al.*[73]. This is

the most well know model of a carpet-like mechanism for membrane disruption in which peptides assemble and accumulate in parallel around microorganism membranes. Peptides disrupt the membrane in this model by covering the lipid membrane with a thick peptide layer. Peptides electrostatically bind to the surface of the lipid membrane, so that the peptides' hydrophobic groups face the membrane and their hydrophilic groups face water molecules [75]. Cationic AMPs initially bind to the membrane surface *via* electrostatic interactions and cover it in a carpet-like fashion. When a critical concentration of AMPs is reached, they insert into the membrane and distort it, eventually leading to micellization by lipid membrane disintegrating. A transient hole is formed at this stage before the membrane in completely disintegrated [73, 75]. In this model, globular bilayer destabilization occurs when the peptide concentration reaches its maximum, these molecules penetrate the lipid membrane of bacteria, resulting in microorganism membrane disruption. Example: Cecropin [73, 76].

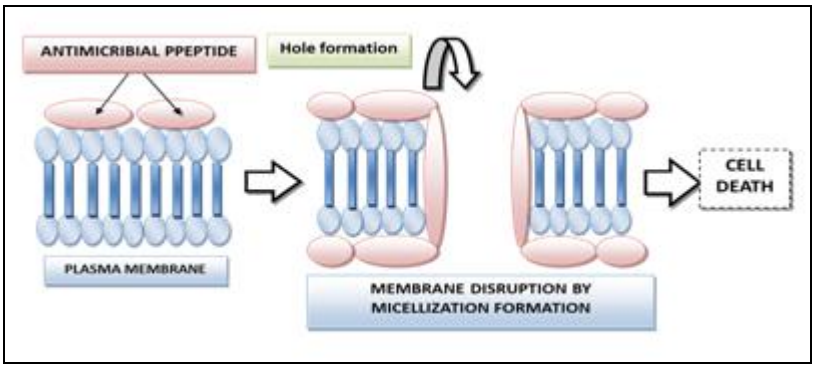


**FIG. 3: CARPET MODAL.** AMPs accumulation on the surface, followed by cell membrane destruction

**Barrel-stave Model:** This model explains the antimicrobial peptide interaction with bacterial materials **Fig. 4**. AMPs are formed into a bundle and wrapped around the bacterial membrane [74]. The peptide monomers are firstly joined together on the bilayer membrane's outer surface. The interaction of the peptide hydrophilic regions regulates this process primarily. The recruited peptides are oriented parallel to the bilayer plane; when enough peptides are recruited, the peptide complex reorients perpendicular to the plasma membrane. Finally, the complex enters the bilayer through the hydrophobic region by forming channel [77]. Peptide aggregation caused membrane disintegration, resulting in pore formation and ultimately, bacterial cell death occurs [73]. Rows of lipids form the pores interposed between the peptides, allowing interconnection of the hydrophilic regions of the pore with the polar heads of the phospholipids and in the case of cationic peptides, the polar face of the α-helix to become oriented towards the pore's interior. As a result, the bilayer's exterior and interior faces merge to form a continuous layer that defines the interior of the pore [77]. When the hydrophobic part of the AMP interacts with the membrane, transmembrane pore forms with the hydrophilic part of the AMP, that facing the inner channel. Example: Alamethicin [73, 74, 78].

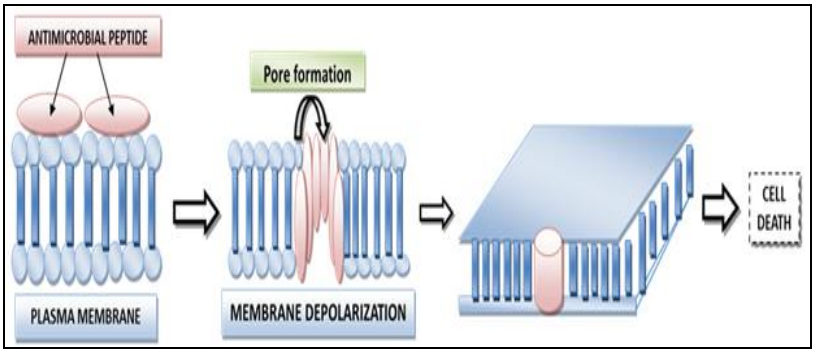


**FIG. 4: BAEEEL-STAVE MODAL.** AMPs accumulation and embedded into the bilayer of the cell membrence as multimer, assembling side-by- side to phospholiipids to form a channel

**Toroidal Pore Model:** It is also known as Wormhole Hypothesis, where peptides are assembled on a bacterial membrane by the peptide's hydrophilic region and the polar region of the phospholipids layer **Fig. 5**. When peptides interact with bacteria-charged hydrophobic cell membrane, they form a helical structure. At first, the helices remain parallel to the bacterial membrane, but when the peptide concentration reaches its maximum, all the peptides change orientation to perpendicular to the membrane. Thinning and destabilization of the membrane occur following the development of enough stress by antimicrobial peptides, causing a breakdown of membrane integrity [73]. In this model, the membrane curves the inner ward, developing a pore composed of AMPs and lipid head groups. Example: Magainin [2, 73, 74, 78].

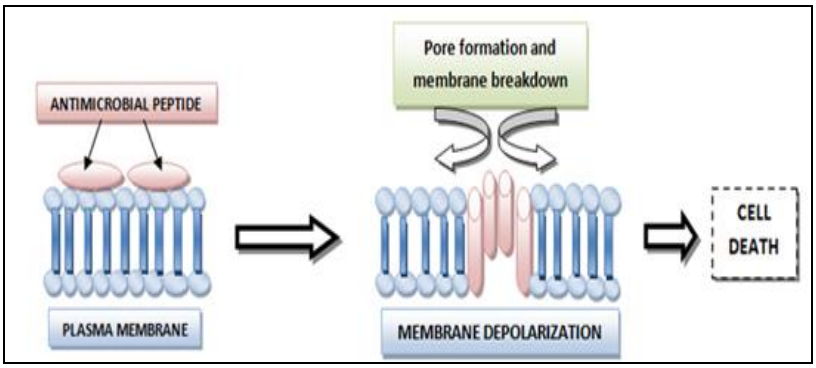


**FIG. 5: TOROIDAL PORE MODEL.** AMPs accumulate in a vertical manner within the cell membrane, and then bend to form a ring whole or circle

**Aggregate Model:** According to this hypothesis, peptide attachment happens due to electrostatic interactions between the hydrophilic part of the peptide and the phospholipid layer of the membrane [73]. The peptides reoriented and formed a haphazard micellar or aggregate-like structure that spans the membrane, implying that the dissolution of these micellar aggregates can account for translocation into the cytoplasm. Example: Indolicidin [79, 80].

**Application of Antimicrobial Peptides:**

**Application in Food Preservation:**

**Nisin:** A polycyclic, heat-stable, low-molecular-weight antimicrobial peptide known as Nisin, a member of the class of cationic peptide antibiotics known as Type A (I) lantibiotics that is produced by specific strains of *Lactococcus lactis*. The capacity of Nisin to suppress the growth of pathogens, which is beneficial for food preservation, led to its first detection in 1928 from fermented milk cultures. Nisin was first sold in England as a bio-preservative in 1953. Aplin and Barrett carried out the commercial development of the nisin preparation known as Nisaplin in 1957. Nisin has been used mainly as a food preservative for more than 30 years. It is especially sensitive to Gram-positive spore formers like Bacillus and Clostridium species but also affects vegetative cells. Nisin mainly disrupts cell growth and death by interfering with cell wall biosynthesis and blocking lipids from producing peptidoglycans, the primary component of membranes. The cytoplasmic membrane is the main site of action for vegetative cells, and nisin acts there as a voltage-dependent membrane depolarizer where nisin get the ability to counteract its inhibitory impact by combined with phospholipid components and construct nisin-phospholipid complexes that have the antibacterial properties.

To degrade the cell membrane, these complexes form pores for a brief period of time that depend on the proton motive force and liquid membrane component. The use of nisin as a food preservative in heat-processed goods is frequently sporostatic rather than sporicidal action is taken against bacterial spores, which has significant effects on its usage because it requires the maintenance of enough residual nisin throughout shelf life to continue having an impact on any spores present. There are a significant finding is the relationship between heat damage and spore nisin sensitivity; as an illustration, spores of the Clostridium anaerobe PA3679 that have endured a 3-minute heat treatment at 121.10 C are 10 times more sensitive to nisin than those that have not [81]. Scientists have demonstrated that the use of bacteriophage in

combination with nisin significantly reduced the number of planktonic and biofilm cells of *S. aureus* under various conditions [82]. Investigations have also shown that spores that open their coats through mechanical rupture are more susceptible to nisin than those that do so through lysis. Nisin is very toxic to the spores of thermophilic bacteria like Bacillus stearothermophilus and Clostridium thermosaccharolyticum. Nisin's molecular effect on spores is a result of its interaction with sulfhydryl groups found on protein residues; no phospholipids are interacted. Nisin is used in dairy products like cheese, meat, and fish and vegetable preservation. According to recent study [83], following contamination with Lactobacillus sakei ATCC 15521, nisaplin was more effective at preserving pork flesh by dipping (involved placing the meat sample into a tank filled with the Nisaplin solution) and spraying method (by spray gun).

Nisaplin was responsible for a decrease in the number of L. sakei after the storage period when applied via dipping, but when applied via spraying, it entirely repressed L. sakei growth because the spray administration enables better antimicrobial diffusion on the meat that coat the surface more widely. According to published findings, covering fish fillets with nisin+EDTA added chitosan polylactic acid (PLA) composite film significantly decreased the mesophile, coliform, and spoilage bacteria counts while extending food's shelf life [84]. In contrast to solid and heterogeneous food products, nisin functions best in liquid and homogenous food. Apple juice has a very pleasant taste and a high nutritional value, making it one of the most popular fruit juices.

However, quality declines in fresh apple juice are typically brought on by discoloration and spoiling microbial development. Pathogens must be eliminated using a specific pasteurization procedure, but that creates an unsightly brown juice with an awful flavor. Nisin is used as a game changer to solve this issue and lengthen the shelf life of fruit juice. Researchers have found that thermos sonication with nisin assistance can prolong the shelf life of fresh apple juice by inactivating naturally present germs and retaining nutritional content [85]. Nisin also extends the shelf life of pasteurized liquid egg products, crumpets (high moisture, flour-based foods popular in Australia), alcoholic beverages (like beer), and salads by preventing the growth of spoilage-causing bacteria. There are various factors that can make it resistant nisin's antimicrobial activity, proteolytic enzymes from microbial, plant, or animal origins that are present in slightly or non-heatedly processed foods can break down nisin while the product is still on the shelf. It has been demonstrated that several food additives work against nisin; for instance, titanium dioxide (a whitener) and sodium metabisulphite (an antioxidant, bleaching, and broad-spectrum antimicrobial agent) that are frequently employed in foods cause the degradation of nisin [45, 82, 83, 85, 86, 87].

**Plantaricins:** Plantaricins, isolated from L. plantarum, are also used in food preservation. The acidification of *L. plantarum* to fermented sausage samples at 30C greatly improved taste, flavor, and acceptability. Compared to commercial starters under the same circumstances, plantarum is substantially lower, leading to a notable improvement in product quality. Food-borne infections and closely related Lactobacilli species are both inhibited by the broad antibacterial range of plantaricins. For example, Plantaricin LP84 and Plantaricin ZJ008 have shownbroad-spectrum antibacterial activity against gram-positive and gram-negative bacteria as well as food-borne and spoilage germs, particularly against Staphylococcus spp. These findings imply that Plantaricin ZJ008 may be extremely helpful for managing and inhibiting Staphylococcus spp. in the food business.

Plantaricin C-19, NA, and bacteriocin AMA-K have a significant and powerful anti-listeria activity and can be employed in the future in food preservation. The utilization of plantaricins or *L. plantarum* bacteriocin-producing strains has a remarkable potential for controlling L. monocytogenes, found in a variety of habitats and foods, including raw milk, meat, fish, fruits, and vegetables. Listeria monocytogenes, Listeria ivanovii, and Listeria innocua have been discovered to have a high inhibitory capacity for Bacteriocin AMA-K, indicating that, this bacteriocin can be utilized to control food borne infections biologically.

According to current findings [88], an active antimicrobial packaging film made by polyethylene terephthalate/polyvinylidene chloride/retort casting polypropylene plastic multilayer film and added plantaricin BM-1 and chitosan to increase the antimicrobial activity, that has the ability to lower the viable counts of Listeria monocytogenes by breaking the barriers against oxygen and changing the tensile strength and extend the fresh meat's shelf life [89, 90, 91, 92].

**Enterocin:** A circular bacteriocin made up of 70 amino acid chains, enterocin is produced by the gram-positive bacteria Enterococcus spp. There are four types, of which Enterococcus faecalis and *Enterococcus faecium* can be found in the human intestines. However, due to their capacity to prevent a variety of infections that result in food spoiling, class II and III enterocins, including enterocin AS-48, have attracted attention. There are two approaches to employ enterocin as a food preservative: introducing purified or semi-purified enterocin to food to prevent food spoiling, or creating enterocin *in-situ* by adding enterocin-producing strains to food. Eating ready-to-eat vegetables may result in food contamination by microorganisms, which could spread infectious diseases to people. In order to address this issue, it was discovered that the antibiotic agent enterocin AS-48, which E. faecalis A-48-32 produces, is efficient in preventing the growth of *S. aureus*, *B. cereus*, *Bacillus macroides*, *Paenibacillus* spp., and *B. macroides* in fresh vegetable sources.

It has been demonstrated that enterocin AS-48 inhibits the growth of *B. cereus*, *B. macroides*, *Paenibacillus polymyxa*, *Paenibacillus amylolyticus*, and *S. aureus* in food. By preventing the growth of L. monocytogenes and *Bacillus coagulans*, enterocin AS-48 is also used to preserve soybean sprouts, canned fruits, and vegetable goods and also keep milk and milk products fresh. In a bid to prevent B. cereus from growing, enterocin AS-48 is also applied during the manufacture of non-fat hard cheese. In order to protect Munster cheese from the pathogen L. monocytogenes, enterocins A and B are also combined [93, 87].

**Other AMPs:**

**TABLE 5: AMPS WITH THEIR SOURCE, TARGET PATHOGENS AND APPLICATIONS ON FOOD PRODUCTS**

| Name of AMPs | Source | Targeted Pathogen | Application on Food Products | Reference |
|---|---|---|---|---|
| Pediocin PA 1 | *P. acidilactical MCH14* | *L. monocytogenes and C. perfringens* | Soymilk, fermented meats, and dried sausage | 94 |
| Leucocin A | *Ln. gelidum UAL187* | *L. monocytogenes* | Fresh meat, milk,& sausage | 95 |
| Leucocin K7 | *Ln. mensenteroides K7* | *L. monocytogenes* | Milk | 96,87 |
| Leucocin BZ | *L. lactis BZ* | *L. monocytogenes* | Skim & full fat milk | 87 |
| Sukacin | *L. sakei* | *L. monocytogenes* | Meat | 97 |

**Application in Therapeutic Field:**

**Nisin:** Due to nisin's long history of safe use in the food industry, researchers have found it a viable alternative treatment for infectious disorders, especially infections that are resistant to antibiotics. Major medical issues in hospitals around the world include vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staph. aureus* (MRSA) that cause bacterial nosocomial infections, urinary tract infections, skin infections, bacteraemias, pneumonia, and postsurgical infections as symptoms; here nisin is used as an antimicrobial therapeutic. A biofilm can be created by bacteria that stick to tissue damage or implanted medical equipment, leading to chronic illness, but it's very costly. Researchers discovered that nisin had antibiofilm properties against MRSA biofilms on medical equipment and reported that nisin A was the most successful bacteriocin in preventing biofilm development compared to lacticin Q and nukacin ISK-1. Nisin has been reported to have antimicrobial properties against mastitis, respiratory, gastrointestinal, and skin diseases. *Staphylococcus aureus* primarily affects the upper and lower respiratory tract, and nisin F safely suppressed the growth of *Staphylococcus aureus* there. Additionally, researchers have demonstrated that nisin can have synergistic effects when combined with the antibacterial proteins lysozyme and lactoferrin, which are regularly released in the human respiratory tract. Dental plaque and other oral biofilms are important contributors to the development and causative agents of oral disorders linked to oral biofilms. Johnson *et al.* (1978) was

the first to establish the potential of nisin as an oral antibacterial, showing that nisin-fed monkeys had fewer *streptococci* in their dental plaque.

Nisin A has been demonstrated to prevent the development of Gram-positive oral microorganisms like *Streptococcus sanguinis* and *Streptococcus gordonii*. Gram-negative oral colonizing pathogens such *Porphyromonas gingivalis*, *Prevotella intermedia*, *Aggregatibacter action-mycetemcomitans*, and *Treponema denticola* can all grow slowly when nisin Z is present [45]. Nisin is also used in diabetic foot infections treatment. Diabetes mellitus frequently results in diabetic foot infections (DFIs), which are also a primary factor in nontraumatic limb amputations. The most common DFI pathogen is *Staphylococcus aureus*, which is renowned for its durable biofilms and drug resistance profile. Nisin-biogel demonstrated strong antibacterial efficacy against DFI *S. aureus* biofilms.

A combined approach using nisin-biogel and chlorhexidine that demonstrated the highest efficacy in inhibiting biofilm formation could be used in hospitals, reducing the need for antibiotics, the selection pressure on DFI bacteria, and the spread of resistant strains [98]. Recent studies have revealed the cytotoxicity and anticancer effects of nisin A and nisin Z and demonstrated that it inhibits the carcinogenesis of head and neck squamous cell carcinoma (HNSCC) from forming oraspheres. In HNSCC cells as opposed to primary oral keratinocytes, nisin preferentially induced apoptosis, arrested the cell cycle, and decreased cell proliferation [99]. Nisin has the influential ability to increase immune response.

According to research, short-term dietary nisin supplementation increased CD4 and CD8 T-lymphocyte counts while lowering B-lymphocyte levels, but continued nisin treatment caused both B- and T-lymphocyte levels to revert to normal. In human peripheral blood mononuclear cells, pure nisin Z was able to regulate the innate immune response by increasing chemokine synthesis and inhibiting LPS-induced (Lipopolysaccharide) pro-inflammatory cytokines. This property of nisin demonstrated its potentiality for application in treating a range of human disorders, including periodontal disease, wound healing, which is mediated by the host immune response and pathogenic biofilms [100, 87].

**Plantaricins:** It has been discovered that several *Lactobacillus plantarum* strains express numerous bacteriocins that are Plantaricin C and W, included in class I; Plantaricin C19 and 423, included in class IIa; Plantaricin EF, JK, S, and NC8, included in class IIb; and Plantaricin 1.25B, included in class IIb. Plantaricin NC8 α and β are dietary supplements that demonstrate structural stability against heat and pH and broad-spectrum bactericidal action against microorganisms. They are short peptides of 29 and 34 amino acids, respectively. These bacteriocins are produced by *L. plantarum via* the PlnF and PlnE genes and exported and processed PlnG and PlnH proteins.

Due to their qualities of exhibiting low toxicity towards eukaryotic cells, being regarded as safe and innocuous to humans, and being active against pathogenic bacteria that have developed antibiotic resistance, that are appealing possibilities in human medicine. The Gram-negative oral pathogen *Porphyromonas gingivalis* is made permeable by PLNC8, which also blocks its cytotoxic and immunomodulatory effects on human cells. Numerous Staphylococcus species, including S. aureus and S. epidermidis, can infect people severely and have developed resistance to various types of antibiotics, including gentamycin, vancomycin, methicillin, and rifampin. *Lactobacillus plantarum's* plantaricin EF and JK are effective at permeabilizing *Staphylococcus epidermidis.*

The bacterial cell membrane is ruptured via the action of PlnEF and PlnJK. PlnEF collaborates with the anti-*S. epidermidis* effects of gentamycin, tetracycline, vancomycin, and teicoplanin. PlnEF was particularly efficient at considerably lowering the amounts of gentamycin, tetracycline, and teicoplanin at sub-MIC values. Recent studies have demonstrated that the usage of PLNC8 and increases the effectiveness of medicines against *Staphylococcus* species. According to recent research, PLNC8 β could partially permeabilize *S. epidermidis* because of its clear membrane activity in bacterial lipid bilayer model systems, however PLNC8 α did not exhibit this impact. However, substantial antibacterial activity was seen when the

two peptides were combined at a 1:1 ratio, and they were very effective against both planktonic and surface-associated bacteria [101, 102].

**Salivaricin:** *Streptococcus salivarius* produces the bacteriocin salivaricin, which is a member of the class II lantibiotics. It has been demonstrated that salivaricin can be utilized to treat or prevent skin and lung infections in addition to maintaining oral health. Salivaricin B, a 25 amino acid polycyclic peptide isolated from *S. salivarius K12*, has a lethal effect on Gram-positive bacteria and requires lantibiotics at a micro molar concentration. Salivaricin B inhibits *S. pyogenes*, the pathogen responsible for several infectious disorders that affect people, including pharyngitis, tonsillitis, cellulitis, erysipelas, and necrotizing fasciitis. Salivaricin B interfered with cell wall biosynthesis, as demonstrated by the accumulation of the final soluble cell wall precursor UDP-MurNAc-pentapeptide, which is the building block of the bacterial peptidoglycan. It did not cause pore formation or dissipate the membrane potential in susceptible cells. Additionally, it has been demonstrated that salivaricin B inhibits the growth of *Corynebacterium spp. GH17*, a pathogen that can cause pharyngitis, endocarditis, gastrointestinal tract infections, and skin infections. It has been demonstrated that the salivaricin D from *S. salivarius 5M6c* has inhibitory effects on *Clostridium bifermentans*, a Gram-positive, spore-forming, anaerobic bacteria that consistently causes infectious illnesses in people like empyema and pneumonia, and also on *S. pneumoniae D39, TIGR4 and R6* [103, 87].

**Other AMPs:**

**TABLE 6: AMPS WITH THEIR SOURCE, TARGET PATHOGENS AND APPLICATION IN MEDICINE**

| Name of AMPs | Source | Target | Application in Medicine | Reference |
|---|---|---|---|---|
| Lacticin 3147 | *L. lactis* | MRSA, C. acnes S. mutants | Skin, surgical site & prosthetic joint infection, dental carries | 104 |
| Lacticin A164 | *L. lactis A164* | *H. pylori* | Stomach ulcer | 105 |
| Mersacidin | *Bacillus spp.* | *MRSA* | Furuncle, pneumonia, blood stream infection | 87 |
| Enterocin A | *L. lactis MG1614* | *L. monocytogenes AGS Human cancer cells* | Listeriosis, Gastric cancer | 106 |
| Epidermin | *S. epidermidis* | *S. aureus* *P. acnes* | Respiratory tract infection, Skin & surgical site infection Acnes | 107 |

**Application on Livestock Health:** Domestic animals are raised as livestock in agricultural settings to supply labor and goods including milk, meat, eggs, furs, and leathers. Proteins, lipids, and vitamins are all components that people need on a daily basis and are provided by livestock as food sources. Correct nutrition and hygiene are crucial to maintain the cattle's health and increase the economy through increased production. There are restrictions on utilizing antibiotic treatments to address this issue, such as gentamycin, which could cause the growth of microorganisms that are antibiotic-resistant. Numerous studies have looked into the use of antimicrobial compounds or bacteriocin from lactic acid bacteria or other bacteria that exert inhibitory power to suppress or kill the infections in livestock as an alternative to antibiotics.

**Nisin:** Nisin is crucial for treating respiratory tract infections in pigs and cows. The most frequent respiratory diseases brought on by swine germs are pneumonia and pleurisy, which have a negative economic impact on the nation. *S. aureus*, *S. suis*, *Actinobacillus suis*, *Actinobacillus pleuropneumoniae*, and *Haemophilus parasuis* are just a few of the pathogens that can cause these illnesses in pigs and can spread through contact between swine on a farm. Nisin was discovered to stop *S. suis* from growing by rupturing its cell membrane, which results in cell lysis. Nisin helps treat meningitis, arthritis, endocarditis, pneumonia, septicemia in pigs, and respiratory tract infections. Nisin Z is used to treat subclinical mastitis in cows that are breastfeeding. It has been shown that nisin A is an antibacterial agent that can stop the growth of pathogens such *S. aureus*, *Staphylococcus intermedius*, *Streptococcus agalactiae*, *S. dysgalactiae*, *E. faecalis*, and *E. coli* that cause mastitis in lactating dairy cows [87, 108].

**Garvicin:** *L. garvieae* produces the class II bacteriocin known as garvicin. Lactic acid is the byproduct of fermentation produced by *L. garvieae*, a gram-positive, facultative, and non-spore forming lactic acid bacteria. The first bacteriocin created by *L. garvicin* L1-5. *L. garvieae*, which can be isolated from cow's milk, will be reported. Very few garvicins have the ability to have antimicrobial activity against pathogen found in livestock, which in turn causes mastitis in cows. Garvicin KS, for example, has been shown to have antimicrobial action against Acinetobacter baumannii and *S. aureus* [109].

**Other AMPs:**

**TABLE 7: AMPS WITH THEIR SOURCE, TARGET PATHOGENS AND APPLICATIONS ON LIVESTOCK**

| Name of AMPs | Source | Targeted Pathogens | Application on Livestock | Reference |
|---|---|---|---|---|
| Nisin A & Cefazolin | *L.lactis* | *S. aureus, S. agalactiae, E. coli, S. dysgalactiae* | Mastitis in lactating dairy cows | 108 |
| Lacticin 3147 | *L. lactis* | *S. aureus, S. uberis, S. dysgalactiae* | Mastitis in lactating dairy cows | 110 |
| Macedocin | *S. gallolyticus* | *S. aureus, S. epidermidis* | Mastitis in lactating dairy cows | 87 |

**Application in Ophthalmology:** AMPs are also used in ophthalmology; earlier research reported using rabbit α defensin (NP-1) to treat a number of eye infections. Hecate, a cecropin analogue, recently demonstrated inhibitory activity *in-vitro* against numerous *Acanthamoeba* species. SHIVA-11 is one of many studied cecropin analogues that is frequently used to treat various eye infections in *S. aureus*, *S. pneumoniae*, *P. aeruginosa*. Additionally, HB43, HB55, HBPM4, Protegrin-1, and Thiazomycin A have antagonistic effects against pathogenic organisms like *S. aureus* in ocular infection. Mucins, HBCM2, HBCM3, HB14, COL-1, and HBCM3 are inhibitory towards *Pseudomonas aureus*. In parallel, Lactoferrin inhibits Haemophilus influenzae's growth, while Lactoferricin B inhibits *Aspergillus fumigatus* and *Candida albicans*, respectively [111].

**Delivery Mechanisms and Formulation of Antimicrobial Peptides:** Antibiotics transformed how humans fought off bacterial infections, but due to misuse of the drugs and the bacteria's quick adaptation, drug-resistant types of bacteria have since emerged. Antimicrobial peptides (AMPs), which could replace traditional antibiotics and fight multidrug-resistant microorganisms, have garnered a lot of interest. The inherent constraints of peptides, such as their instability, cytotoxicity, and bioavailability, provide technical challenges to their therapeutic uses. The researchers find out some ways to deliver and formulate AMPs **Fig. 6.**

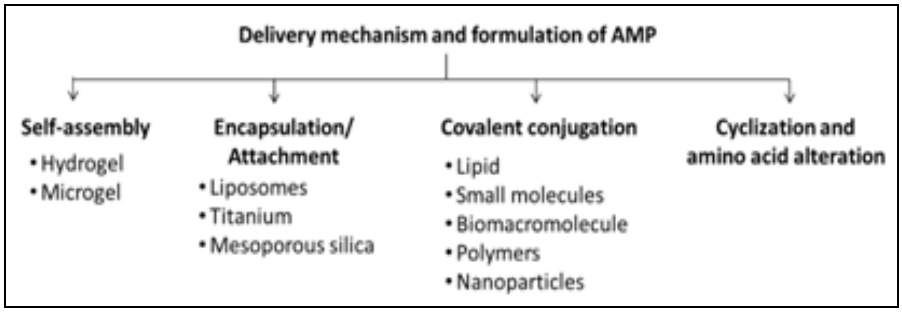


**FIG. 6: DELIVERY MECHANISM AND FORMULATION OF AMP**

Delivery by method of Encapsulation using porous materials with cavities and an organized network **Fig. 7**. The porous materials are the best carriers to encapsulate visitor molecules because of their high pore volume and vast surface area. Mesoporous silica nanoparticles (MSN) have indeed been widely utilized as a drug delivery system. In contrast, a conventional silica mesoporous matrix is filled with free AMPs that are completely inactivated after being exposed to protease to preserve AMPs from enzymatic degradation**.** Additionally, polymer-coated MSN can enclose AMPs in a host-guest relationship, where bacterial cells and the polymer capping on the surface of MSN interact electrostatically, leading to partial opening of the caps and exposing pores. When

titanium-based materials are employed in transplantation, encasing AMP, mesoporous titania nanoparticles with high surface area and large porosity are also an appropriate choice. Here, different pore diameters of titania thin films are produced and loaded with various AMPs [112, 113]

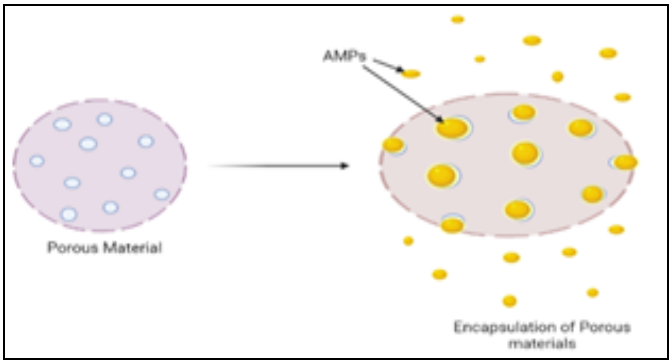


**FIG. 7: DELIVERY OF AMPS BY ENCAPSULATION USING POROUS MATERIALS.** AMPs can be formulated as an encapsulated model where the AMPs are attached within porous materials

Delivery by means of material surface attachment **Fig. 8** by which AMPs may be physically integrated into the carrier material's cavity or affixed to the carriers' surface before delivery. The hydrophilic, cationic, and hydrophobic groups on AMPs may interact with the surface of various materials via electrostatic interactions, the hydrophobic effect, *etc*.

Polymer micelle surface groups might engage with, transport, and deliver AMPs, where amphiphilic compounds are served as nanoscopic drug carriers by self-assemble into polymeric micelles. Polymer nanofibers can also be used in AMPs deliveries. Nanofibers are advantageous for tissue restoration because they have a large specific surface area and a satisfactory drug loading capacity. The peptide-loaded nanofibers reduced bacterial growth and demonstrated its efficacy as a wound dressing [112, 114]. The liposomal system has been widely used to deliver cancer therapies with many beneficial properties, such as reduced cytotoxicity to healthy cells and physical and chemical stability. According to recent studies, AMPs have also been tested as an adjunct treatment in cancer chemotherapy using polyethylene glycol-modified liposomes that contain the anticancer drug epirubicin and the AMP tilapia hepcidin 2-3, which has been shown to suppress MDR transporters and regulate apoptotic cell death in human cervical cancer HeLa cells. Alternative carriers to liposomes including solid lipid nanoparticles (SLNs) and nanostructured lipidcarriers (NLCs) are also used in AMPs delivery, where NLCs are created by a matrix composed of both solid lipid and oil droplets, while SLNs are created by a nano solid lipid matrix with biodegradable surfactants as anchors [112, 113].

Delivery by metal-based nanoparticles **Fig. 8**, in which the delivery mechanism for AMPs makes extensive use of both silver nanoparticles and gold nanoparticles, while gold nanoparticles have activity against waterborne pathogens including *E. coli*, *S. Typhimurium*, *etc*., silver nanoparticles demonstrate activity against bacteria both in vivo and *in-vitro* [112, 113].

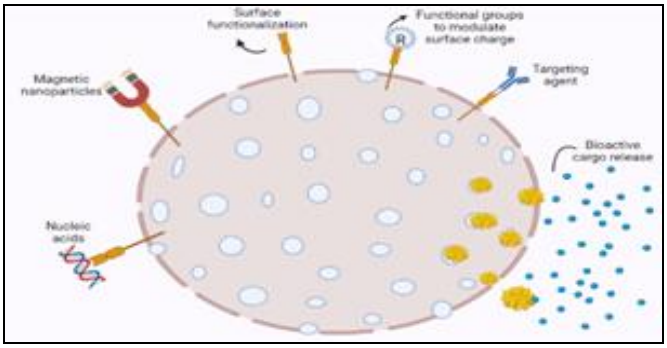


**FIG. 8: OTHER MECHANISMS OF AMPS DELIVERY.** AMPs can be formulated within a porous bead by using following methods, Bioactive cargo release, Targeting agent, Functional groups to modulate surface charge, Surface functionalization, and by using several agents like Magnetic nanoparticles and nucleic acids

Additionally, AMPs can be formulated for use in medicine using a variety of techniques, such as peptide self-assembly, co-assembly with peptide to generate microgels, among others. Due to their amphipathic nature, peptides can self-assemble into a variety of organized nanoscale structures, such as nanofibers, nanotubes, nanoparticles, and nanogels.

These structures can be tailored for mechanical properties, drug loading capacity, and drug release. Conversely, where AMP is loaded, cross-linking between avidin and biotin allows peptides to combine to create microgels with the aid of other molecules. Compared to an AMP-loaded microgel monolayer, the antibacterial capabilities of AMP-loaded microgel multilayers are more effective. The co-assembly of AMPs can also be mediated by synthetic biodegradable polymers. The U.S. Food

and Drug Administrationhave approved the use of PLA and polylactic-co-glycolic acid (PLGA) for medical purposes. Both substances are highly biodegradable and biocompatible. Along with PLA and PLGA polymers, mostly AMPs were introduced, and these materials later self-assembled into AMP-loaded particles [112, 113]. AMPs can also be formulated by conjugation with chitosan nanoparticles and antibiotics **Fig. 9**. It is common to find chitosan, a biocompatible natural polymer, in crustacean and other animals' exoskeleton. It possesses inherent antibacterial action, bioadhesive qualities, and the capacity to encourage cell growth and wound healing. Here, a disulfide link is used to combine short-chain peptides with thiolated chitosan. The carriers may influence how conjugation affects the action of AMP. Due of their ability to attach to and target membranes, covalent antibiotic-AMP conjugates combine the advantages of both components. They can adhere to the membrane and lyse it, enabling the conjugated antibiotics to be transported within cells [113].

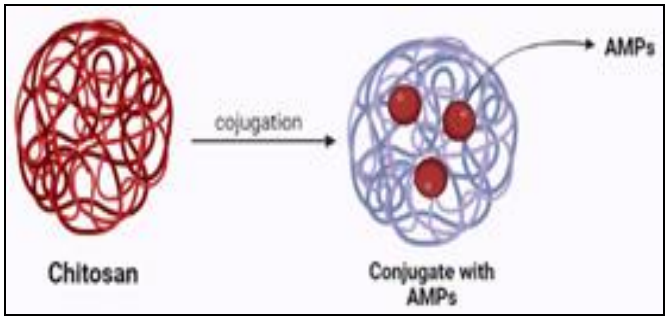


**FIG. 9: AMP FORMULATION BY CONJUGATION WITH CHITOSAN.** Conjugated form of AMP and Chitosan formulated with antibiotics improves the efficacy of antibiotic potentiality.

**CONCLUSION:** Antimicrobial Peptides (AMPs) are a varied family of small peptides found in the environment and an essential component of an organism's innate immune system. In the fight against microorganisms, identifying AMPs is unquestionably a turning point. The only way to stop the spread of microbes that cause food spoilage is through bio-preservation. Except for nisin, no other peptide is recognized internationally for safe food preservation, despite antimicrobial peptides appearing promising for food preservation. This suggests that study into the various restraints that prevent the use of AMPs needs to be improved. In contrast to conventional antibiotics, cationic AMPs interact with bacterial cell membranes by neutralizing the charge before further penetrating them to kill the bacterium, hence lowering the risk of bacterial drug resistance. They are also efficient against strains that are resistant to conventional antibiotics, have rapid germ-killing capacity, low bactericidal concentration, and even work synergistically with conventional antibiotics to neutralize endotoxin. In light of the existing low success rate of AMPs' clinical use, AMPs, as a subset of peptide medications must advance alongside the development of medical research, food, farming, and animal husbandry, can receive more attention. This study gives a thorough overview of antimicrobial proteins and peptides, including biosynthesis, mechanisms, classifications, applications in different fields, and its approaches for using AMPs in clinical settings by compiling the most recent research on their composition and distribution.

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