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ANTIMICROBIAL PEPTIDES/HOST DEFENCE PEPTIDES-A REVIEW

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Abstract: Antimicrobial peptides (AMPs), which have evolutionary conserved characteristics shared by almost all living organisms, are essential elements of the innate immune system. Scientific attempts to investigate alternatives have been fueled in recent years by the emergence of germs that are resistant to antibiotics and the sluggish pace of new antibiotic discoveries. Research on AMPs has shown encouraging proof of both their potential as novel immunotherapeutic agents and their capacity to fight infectious illnesses. Because they are natural compounds, they have extensive biological activity, create low microbial resistance, promote improved wound healing, and exhibit little harm to the host. The risk of livestock-associated antimicrobial resistance has increased dramatically in veterinary medicine due to the extensive use of high-dose antibiotics, frequently combined with insufficient withdrawal procedures. This worldwide issue calls for immediate action to create plans that minimize the use of antibiotics in animals while maintaining their safety for coming generations. The range of AMPs unique to farm animals is highlighted in this article, which also examines their biochemical characteristics, modes of action, and possible therapeutic uses. Additionally, it offers a methodical division of these peptides into main and minor groups, describing their antipathogenic properties as well as associated host bioactivities. Future research and development directions are delineated, along with the difficulties associated with their clinical application.

Keywords: Anti-microbial peptide, Cathelicidin, Antimicrobial resistance, Immunomodulation, Ruminants.

INTRODUCTION

Antimicrobial peptides (AMPs) are naturally occurring molecules with amphipathic structures that enable them to disrupt bacterial membranes, often forming pores and causing cell death. They are produced by humans, animals, plants, and microorganisms. In higher organisms like mammals, AMPs play roles as effectors in innate immunity, being primarily responsible for the direct inhibition of pathogens, while also modulating innate and adaptive immune responses (Magana et al., 2020) (Mookerjee et al., 2007) (Lazzaro et al., 2020). Since they are innate,

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they have the lowest cytotoxicity to the host and engage in a variety of biological activities, such as promoting wound healing and lowering microbial resistance.

ANTI MICROBIAL RESISTANCE –THE SILENT GLOBAL CRISIS

Fleming's discovery of penicillin revolutionized medicine, drastically reducing mortality from bacterial infections and paving the way for modern antibiotics. (Aslam et al.,2018). However, antimicrobial resistance (AMR), a serious concern to global health as bacteria evolve and grow resistant, is a result of the overuse and misuse of antibiotics. In 2017, the WHO identified 12 priority antibiotic-resistant pathogens, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa,* which cause severe infections like pneumonia and bloodstream infections. (WHO).

DISCOVERY

Since the 1990s, the development of new antibiotics has slowed, with most recent drugs combining existing antibiotics or adding molecules like enzyme inhibitors. (Dutescu et al.,2021). To combat antibiotic resistance, global initiatives are essential, focusing on alternative therapies like phage therapy, (Lin et al.,2017) new antimicrobial molecules, vaccines, and rapid diagnostic tools. A comprehensive approach combining antibiotics, vaccines, diagnostics, and innovative treatments is crucial to address antimicrobial resistance effectively. (Bloom et al., 2018). AMPs are small bioactive of 10–50 amino acids with a molecular weight of less than 10 KDa. Most AMPs are positively charged (2–13 net positive charges), derived primarily from lysine and arginine (a few may be histidine) in the sequence forming a specific cationic domain (Lourenco et al., 2023) (Fjell et al.,2011). In 1939, a Brevibacillus soil bacterium yielded the first AMP, gramicidin, which demonstrated antibacterial action against a variety of Gram-positive bacteria both in vitro and in vivo (Guan et al.,2019). Based on origin, natural AMPs can be categorized as bacteriophage/viral AMPs, bacterial AMPs, fungal AMPs, plant-derived AMPs, and animal-derived AMPs. (Bin et al., 2021). Defensins, cecropins, proline rich peptides and attacins have been identified in insect orders such as the Diptera, Hymenoptera, Hemiptera, Coleoptera and Lepidoptera (Yi et al., 2014). The two primary families of AMPs obtained from mammals are human cathelicidins and defensins, which are mostly produced by neutrophils and epithelial cells. (Roncevic et al., 2019) (Wang et al., 2016).

PEPTIDE PRODUCTION

Extracting natural AMPs from animals and plants is challenging, prompting the use of genetic engineering and chemical synthesis for production. Genetic Engineering*:* Prokaryotic Systems

(e.g., E. coli): Offer fast, cost-effective production but lack post-translational modifications. (Musa et al., 2016). Eukaryotic Systems (e.g., yeast, plants): Provide non-toxic expression and extracellular secretion but involve higher costs and longer production times. (Mattanovich et al., 2012). Chemical Synthesis: Solid-phase peptide synthesis (SPPS) is an established method for producing homogeneous AMPs with fewer impurities compared to recombinant systems. Techniques like mass spectrometry and HPLC (High Performance Liquid Chromatography) are used to assess peptide purity. (Merrifield et al., 1963).

UNLOCKING THE SHAPES OF AMPS

Four structural characteristics have been observed, namely alpha-helical, beta stranded, beta-hairpin or loop, and extended conformation. They are linear in aqueous solutions, but when they contact with bacterial membranes, they form amphipathic helices (Mahlapuu et al., 2016). This structure enables them to penetrate the phospholipid bilayer and disrupt membrane integrity.

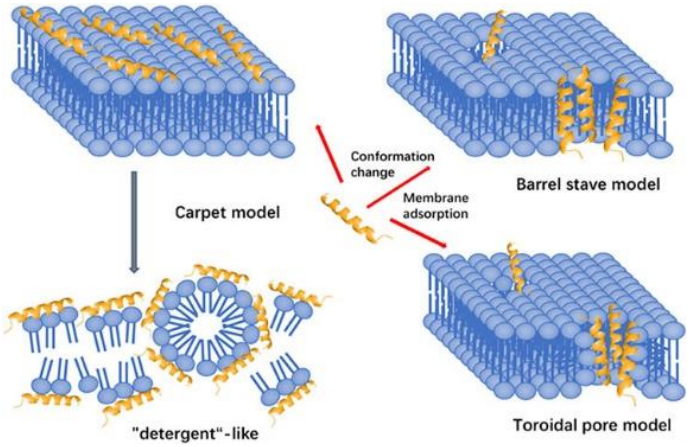
BREAKING BARRIERS: HOW AMPS DISRUPT CELL MEMBRANES

(A) The toroidal pore model: hydrophilic region of AMPs are consistently in contact with the polar head groups of the phospholipid bilayer, causing the membrane to curve inward.***(B) The barrel-stave model:*** hydrophobic region of AMPs interact with the lipid core of phospholipid bilayer, while the hydrophilic region points inward forming a channel-like structure.***(C) The carpet model:*** above critical threshold concentration, AMPs distort the lipid bilayer structure resulting in the micellization of the structure. The selectivity of AMPs for bacterial over host cells is due to differences in membrane composition: bacterial membranes contain negatively charged phospholipids, while mammalian membranes are composed of neutral phospholipids. (Graham et al., 1997). Many AMPs are more bactericidal than being bacteriostatic (Reddy et al., 2004).

AMPS IN MEDICINE: TACKLING CHALLENGES AND PIONEERING SOLUTIONS

The clinical development of antimicrobial peptides (AMPs) faces challenges like high production costs, reduced efficacy in clinical settings, and bacterial resistance. AMPs can exhibit toxicity to eukaryotic cells, including haemolytic and cytotoxic effects. Their antimicrobial activity often decreases under physiological conditions due to reduced electrostatic interactions, protein binding (e.g., albumin) (Li et al., 2017), or proteolytic

degradation. Strategies to address these issues include modifying AMPs to enhance stability, selectivity, and efficacy for clinical use.



1) Resistance to AMPs: AMPs, in contrast to conventional antibiotics, have several ways of working and were previously believed to be unlikely to induce resistance. Bacteria may, however, become resistant to AMPs either naturally or through acquisition. Features like changed lipid A charges or environmental adaptations are examples of intrinsic resistance, whereas horizontal gene transfer is one example of acquired resistance. For instance, E. coli's mcr-1 gene alters lipid A, which lowers the effectiveness of AMP. Resistance is still an issue in clinical and environmental contexts, even though AMPs typically carry a lesser risk of resistance than antibiotics.

2) Chemical alterations: PEGylation is the process by which polyethylene glycol (PEG) is covalently attached to biological molecules, enhancing their stability, solubility, and resistance to proteolytic enzymes and immunological reactions. Lipidation enhances AMP antimicrobial activity by attaching fatty acid chains to the peptide, increasing hydrophobicity, membrane interaction, permeability, and proteolysis resistance.

NANOCARRIERS: A STRATEGY TO OVERCOME AMP TOXICITY

Nanocarriers, such as inorganic nanoparticles (e.g., gold NPs) and organic nanoparticles (e.g., PLGA-Poly lactic-co-glycolic acid), are used to encapsulate antimicrobial peptides (AMPs) to reduce toxicity while preserving their antimicrobial activity. This strategy enhances the stability and controlled release of AMPs.

MILK DERIVED AMPs

Milk proteins, primarily composed of 80% casein and 20% whey protein, *Casein-Derived Peptides:* 1. Caseinomacropeptide (CMP): Derived from κ-casein, inhibits bacterial/viral adhesion and binds endotoxins. 2. Kappacin: A non-glycosylated CMP derivative that inhibits

Streptococcus mutans by forming membrane pores. (Malkoski *et al.,* 2001). 3. κ-Casecidin: Trypsin-digested κ-casein fragment with antibacterial properties. 4. Isracidin: It is effective against Gram-positive and Gram-negative bacteria, particularly in preventing mastitis. 5. Caseicins A, B, and C: Produced during Lactobacillus acidophilus fermentation of bovine casein; effective against pathogens like Cronobacter sakazakii. 6. Casocidin-1: Derived from αs2-casein, inhibits Escherichia coli and Staphylococcus carnosus. *Whey Protein-Derived Peptides:* 1. α-Lactoglobulin: Digestion produces fragments active against Gram-positive bacteria. 2. β-Lactoglobulin: Trypsin digestion generates fragments active against Gram-positive bacteria, with potential to target Gram-negative bacteria through amino acid modifications. 3. Lactoferrin: A glycoprotein with activity against bacteria, viruses, and fungi, mainly due to peptides like lactoferricin and lactoferrampin (stronger against pathogens like Pseudomonas aeruginosa). These peptides demonstrate potential for developing therapeutic drugs targeting diverse pathogens.

CONCLUSION

Farm animals produce a diverse range of antimicrobial peptides (AMPs), primarily from cathelicidins and β-defensins, which are evolutionarily conserved but show species-specific variations. Key points include:1. Potential as Antibiotic Alternatives: AMPs exhibit broad antimicrobial activity and may help address antibiotic resistance.2. Mechanisms of Action: While many disrupt cell membranes, secondary mechanisms remain poorly understood and need further study.3. Roles Beyond Antimicrobial Activity: AMPs also act as immunomodulators, angiogenic factors, vasodilators, and chemoattractants.4. Clinical Applications: Although some AMPs have advanced to clinical trials, more research is needed to realize their therapeutic potential. The robust innate immunity of farm animals, aided by AMPs, highlights their potential use in human medicine as a sustainable and effective therapeutic alternative.

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