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Popular Article

Applications of Antimicrobial peptides in non ruminants

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Introduction

The escalating issue of antimicrobial resistance poses a global challenge that not only impacts healthcare systems but also carries significant implications for political and economic realms. With the discovery of new antimicrobial agents trailing behind, one potential solution lies in innovative therapeutic approaches that can bolster our arsenal against this threat. Among the substances under investigation are antimicrobial peptides (AMPs), which serve as the body's initial defense against pathogens and play a role in innate immunity. AMPs exhibit a wide spectrum of antimicrobial activity against various microorganisms, including Gram-negative and Gram-positive bacteria, fungi, and viruses, each employing distinct mechanisms of action. Due to their very low resistance developing ability, AMPs are increasingly recognized as promising candidates for broader application in infectious disease treatment.

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are naturally occurring amino acid sequences produced by multicellular organisms, often referred to as "host defense peptides" in eukaryotes, playing a crucial role in the innate immune system across various organisms. They display a broad spectrum of activity, adaptable to different applications. A significant advantage of AMPs is their ability to prevent bacteria from developing cross-resistance. These peptides are gene-encoded and synthesized by ribosomes, typically comprising 12-50 amino acids. They carry a net positive charge (cationic) and exhibit heat stability, remaining functional even at temperatures up to 100ºC for 15 minutes. Furthermore, AMPs are amphipathic molecules, featuring both hydrophobic and hydrophilic regions. Initially inactive within the parent molecule, antimicrobial peptides become activated under specific conditions.

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AMPs can seamlessly integrate into cell membranes or penetrate into the cytosol. Ribosomally synthesized AMPs, composed solely of natural amino acids, fall into several categories: linear, α-helical peptides (like cecropins and magainins), peptides enriched with one or two specific amino acids (such as PR 39, rich in proline-arginine), and peptides containing disulfide bonds (e.g., defensins, protegrin). Moreover, extraribosomally synthesized peptides with potent antimicrobial activity undergo significant posttranslational modifications, such as lipopeptides (polymyxin, dermaseptin) and lantibiotics incorporating non-native amino acids.

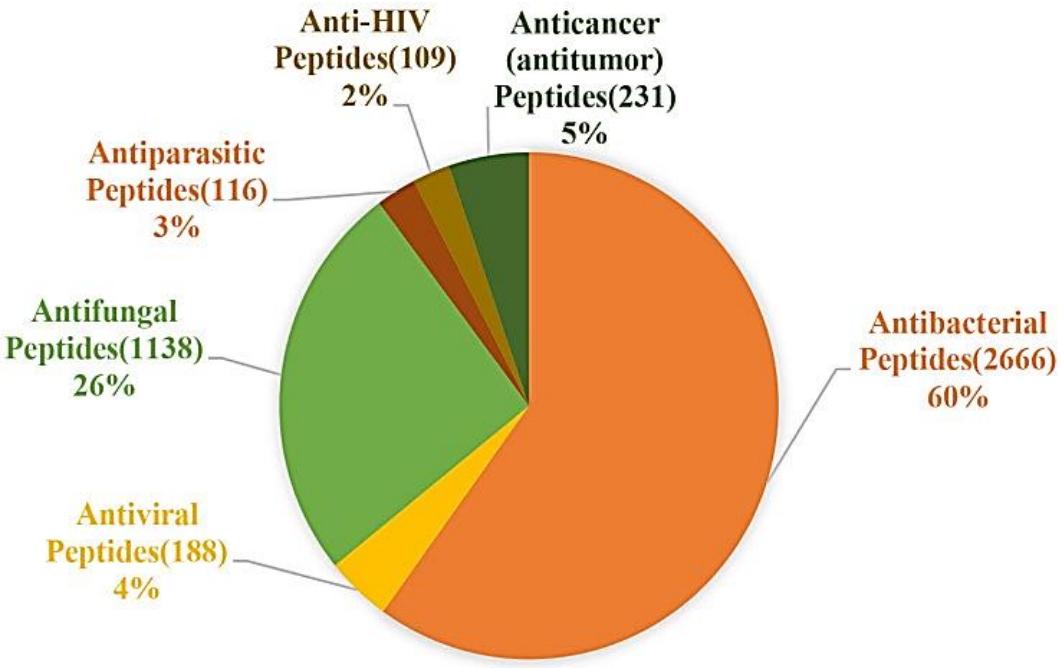

Figure 1. Classification of AMPs on basis of activity

Importance of Antimicrobial peptides

There is lower disease prevention in animals having poor farm husbandry and biosecurity measures. For treating infectious diseases, antibiotics are being used frequently nowdays and due to misuse of antibiotics, anti-microbial resistance develops in animal. Therefore, to prevent the situation of antimicrobial resistance, antimicrobial peptides are used as they have following advantages:

- Excellent selectivity
- Unique bactericidal mechanism
- Without bacterial resistance

Mechanism of action

Antimicrobial peptides (AMPs) have a fundamentally different mechanism of action against microorganisms compared to current antibiotics. Their effectiveness relies on various physicochemical properties such as charge, structure, sequence length, peptide concentration, hydrophobicity, and membrane

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composition. AMPs primarily act in two major ways:

1. Direct killing microbes: The peptides interact with biological membranes, their structure influenced by the lipids within the cell membrane itself. The interaction often leads to compromised membrane integrity, inhibiting protein, DNA, and RNA synthesis, or targeting specific intracellular components. Gram-positive and Gram-negative bacterial cytoplasmic membranes, rich in phospholipids such as phosphatidylglycerol and cardiolipin, feature negatively charged groups that attract positively charged AMPs. As a result, strong electrostatic interactions occur between the positively charged AMPs and the negatively charged bacterial cell membranes, leading to membrane rupture and inhibition of intracellular functions, ultimately causing bacterial lysis.

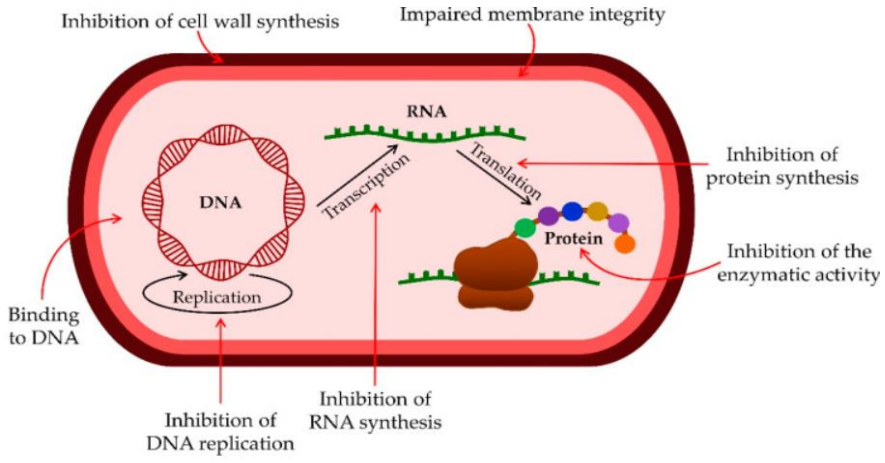

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Figure 2. Antibacterial activity mechanisms of AMPs

2. By modulating host immunity: By activation and differentiation of leucocytic cells, neutrophil, monocyte, dendritic cells etc. and also neautralize bacterial products to supress inflammation. AMPs activates the immunocytes thereby modulating host immunity.

Applications of AMPs in non-ruminants

Given their mechanism of action, AMPs offer a viable solution to numerous challenges associated with traditional antimicrobials. These challenges include the escalating threat of multidrug resistance, which poses a significant public health concern, along with potential systemic toxicity and limitations in overall efficacy. The broad spectrum of activity and rapid antimicrobial action, coupled with a reduced likelihood of resistance development, positions AMPs as promising candidates for broader adoption in

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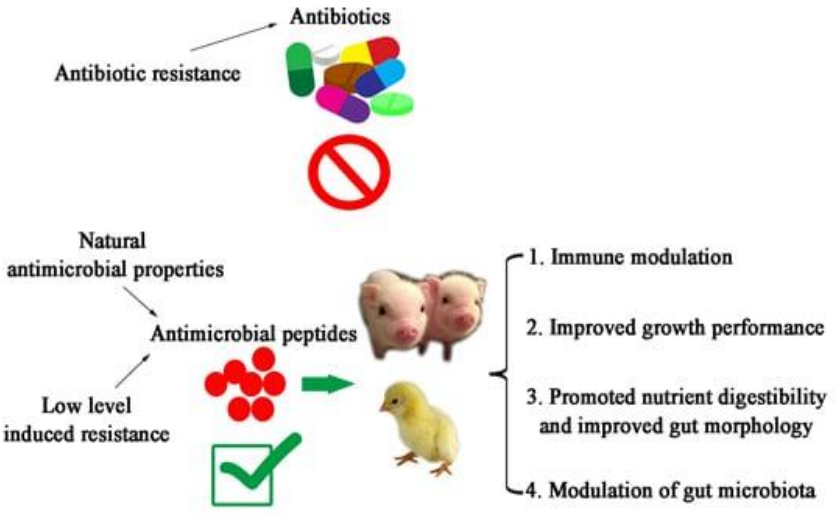
infectious disease treatment.



Application of AMPs in swine nutrition

Antimicrobial peptide	Animal	Application effects
Antimicrobial peptide-A3 (AMP-A3); 60 or 90 mg/kg	Weanling piglets	Has beneficial impacts on growth-performance, intestinal morphology and total tract apparent digestibility of nutrients.
AMP colicin E1; 11 mg/kg	Weanling piglets	Improves the performance, reduces incidence of postweaning diarrhoea.
AMP cecropin AD; 400 mg/kg	Weaned barrows	Improve immune status and reduce intestinal pathogens.
Composite antimicrobial peptide CAP; 400 mg/kg	Weanling piglets	Attenuate the metabolic disturbances in AA, lipid, and energy metabolism induced by DON.

Effects of AMPs in broilers:

Antimicrobial peptide	Application effects
Cecropin A-D	Decreased aerobic bacteria counts in both jejunal and caecal digesta.
Antimicrobial peptide-A3	Reduced coliforms and Clostridium spp. counts in faeces.
Antimicrobial peptide-P5	Reduced excreta total anaerobic bacteria and coliforms.
Sublancin	Reduced *Clostridium perfringens* in the cecum.

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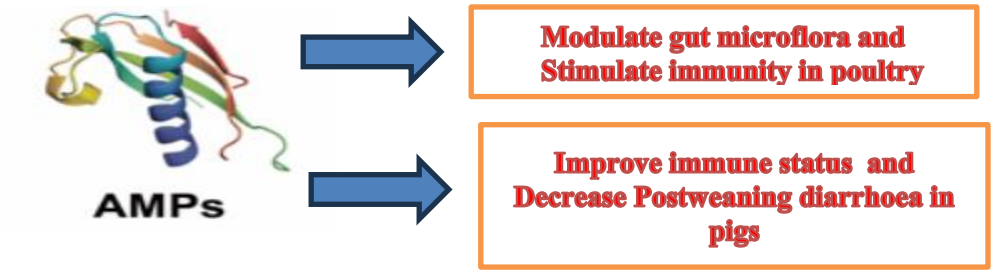
Many researchers found that antimicrobial peptides that are rich in proline amino acids, like pPR-AMP1 have immunostimulant activity. Antimicrobial peptides having high tryptophan and arginine amino acids exhibit inhibitory action against bacteria. Glycine rich antimicrobial peptides activates phagocyte mediated microbicidal mechanisms whereas, histidine rich AMPs exhibit strong anti-inflammatory actions.



Challenges

- **High production costs:** The significant expenses associated with producing antimicrobial peptides (AMPs) pose a considerable challenge to scaling up their production for market use. Moreover, the lack of comprehensive toxicology studies and clinical data complicates regulatory approval processes. Thus, there is a clear need for substantial evidence before AMPs can be widely adopted in clinical practice. One potential solution is synthesizing AMPs in the laboratory, using natural peptides as templates, to mitigate production costs.
- **Susceptibility to protease degradation:** AMPs are susceptible to degradation by proteases, which can significantly reduce their efficacy. For example, LL-37, known for its potent inhibitory effect on chlamydial infection, is inhibited by the protease CPAF secreted by Chlamydia. Efforts have focused on designing AMP carriers to protect against protease degradation, with encapsulation being a viable approach to prevent degradation.
- **Allergic reactions:** To address the risk of allergies associated with AMPs, appropriate in vitro models that simulate in vivo conditions could be utilized to assess allergenic effects and mitigate potential allergic reactions.
- **Poor bioavailability:** Oral formulations of AMPs often suffer from low bioavailability and metabolic stability, making them less favorable for administration. Consequently, topical formulations are preferred. Intravenous administration is also hindered by proteolytic cleavage in the blood and liver, leading to a short half-life of these compounds.
- **Cytotoxicity:** Some AMPs exhibit cytotoxic effects, which can limit their clinical utility. Structural modifications can be employed to mitigate cytotoxicity and enhance safety profiles.

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Conclusion

In an era dominated by escalating antimicrobial resistance, antimicrobial peptides (AMPs) emerge as a potentially effective solution for combating resistant and multi-resistant pathogenic microorganisms. Despite their promise, the integration of AMPs into routine clinical practice encounters numerous challenges, resulting in limited current usage. These challenges notwithstanding, the prospects for AMPs remain highly optimistic. This optimism is rooted in the extensive diversity of potential AMPs, their ability to target multiple sites and exert rapid effects (often synergizing with traditional antimicrobial agents), immunomodulatory properties, enhancement of growth performance, facilitation of nutrient digestibility, and reduced likelihood of promoting antimicrobial resistance. From understanding their mechanisms of action to navigating application hurdles, this field of research holds significant promise in addressing antimicrobial resistance and other pertinent animal health challenges.

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