



REVIEW OF TEN ANTIMICROBIALS FROM BACTERIAL SOURCES

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ABSTRACT

Antimicrobial peptides (AMPs) are small natural molecules that play a crucial role in the immune response of several organisms. Many bacteria produce AMPs as part of their natural defence mechanisms against competing organisms or environmental stress. AMPs from bacterial sources have garnered significant interest due to their potent activity against a wide range of pathogens, including antibiotic-resistant strains such as *Staphylococcus aureus*. These peptides are a rich source of novel antimicrobial compounds with potential therapeutic applications. This review aims to provide an update on ten AMPs produced by Gram-positive bacteria (GPB), including novel bacterial resistance mechanisms against these AMPs, particularly those produced against *S. aureus*. Resistance of *S. aureus* to AMPs is an evolving and complex phenomenon that involves diverse mechanisms. The mechanisms include active specific genes via two-component system, alterations of the bacterial cell membrane and efflux pump activation. Understanding these resistance mechanisms is crucial for developing strategies to enhance the efficacy of AMPs, design AMP derivatives, and implement combination therapies that can avoid or overcome *S. aureus* resistance.

KEYWORDS: Antimicrobial peptides (AMPs), Resistance mechanisms, Epifadin, and Lugdunin.

INTRODUCTION

A brief history of antimicrobials from microbial sources

Antimicrobial peptides (AMPs) are important parts of multicellular organisms' immune systems. The possibility of these AMPs as possible antibiotics has drawn a lot of attention in recent years. Many bacteria generate AMPs, which are also referred to as bacteriocins.^[1] These bacteriocins are very diverse range of compounds that employed to disrupt competition. They can either stop competitors' growth or eliminate them.^[2] Bacteriocins are promising candidates for more research as antimicrobial agents for use in healthcare settings because of their capacity to suppress or kill certain antibiotic-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).^[3,4] Understanding AMPs and how they work could help us develop novel methods to fight significant infections.^[2] However, more study is required to clarify the antibacterial processes of AMPs to reduce the development of resistance and loss of efficacy.^[5] While most antimicrobials are still being studied, there are some cases where specific antimicrobial peptides are still unknown. Crucially, several microorganisms are capable of developing resistance to AMP; however, little is known about these resistance mechanisms.

Epifadin

Epifadin is a novel antimicrobial peptide produced by nasal *Staphylococcus epidermidis* IVK83. Non-ribosomal peptide synthetases (NRPSs) and polyketide synthases (PKSs) are responsible for the synthesis of this antimicrobial.^[6] Although epifadin has not been specifically classified to any type bacteriocins, like other antimicrobial peptides, it is likely to disrupt the bacterial cell membrane and cause cell damage.^[7] Epifadin has been shown to prevent nasal *S. aureus* carriage, however, recent studies in *S. aureus* have reported resistance to this antimicrobial. Although AMPs can act via more than one mechanism, epifadin resistance was linked to the two-component system (TCS) and the *desK* gene.^[6] DesKR, also known as TCS-7, is an uncharacterised TCS in *S. aureus*. Through a controlled desaturase activity that is lacking in *S. aureus*, DesKR TCS alters membrane lipid and plays a crucial part in *B. subtilis* reaction to temperature sensing. DesKR plays a role in temperature sensing, according to recent findings in *S. aureus*, and it probably works similarly to *B. subtilis*. However, it is unclear how it relates to adaptation to lower temperatures.^[8,9] The main mechanism of TCS is widely employed to control several genes (regulons) involved in pathogenicity and cell proliferation.^[10] As a type of signalling, TCS helps bacteria adapt their genetic response to environmental changes. Response regulators (RR) interact with

phosphorylated histidine kinase (HK), which is a signal sensor that phosphorylates in response to environmental changes.^[11] TCS helps *S. aureus* survive in challenging bacterial ecosystems.^[12,13]

Lugdunin

Staphylococcus. lugdunensis IVK28 secretes lugdunin, an antimicrobial that has been suggested as a new chemical to prevent staphylococcal infections, including MRSA.^[14] Lugdunin is synthesised non-ribosomal and has not been yet specifically classified into any type of bacteriocins.^[7] The cyclic peptide lugdunin has a molecular weight of ~ 2.8 kilodaltons (kDa) and is made up of 13 amino acids grouped in a cyclic structure. A mouse skin infection model demonstrates that there is no chance of resistance to this antimicrobial.^[14] Although the precise mode of action of this antimicrobial peptide is still mostly unknown, lugdunin functions by rupturing bacterial cell membranes.^[15] Furthermore, it has been found that *S. lugdunensis* secretes lugdunin and possesses self-resistance through the usage of four ABC transporter proteins, including LugEFGH. The MIC to exogenous lugdunin was significantly reduced upon deletion of the whole gene set (lugEFGH), suggesting that the genes have a role in producer self-resistance to lugdunin.^[16]

Epidermin and Gallidermin

Gallidermin and epidermin are generated by *S. epidermidis* Tü3298 and *S. gallinarum*, respectively. These antimicrobials act against a variety of Gram-positive bacteria (GPB) and biofilm formation of MRSA.^[17,18,19] Epidermin is a ribosomal synthesised.^[18] Whereas both antimicrobials are classified under I-A lantibiotics, which are peptides with a size of less than 5 kDa.^[7] The primary mechanism of action for gallidermin and epidermin is to break bacterial membranes, allowing small chemicals to enter and eventually harm the cell.^[2] However, gallidermin resistance reported mutation in the three-component system VraH. Particularly in *S. aureus*, the three-component VraH system is essential for controlling the way bacteria react to cell wall stress and antibiotic resistance. Although research is lacking, the VraH protein is thought to help regulate the system's response to environmental stressors, improving bacteria survive antibiotics.^[20]

Hominicin

Hominicin is among the antimicrobials produced by *Staphylococcus. hominis* MBBL 2-9 against *S. aureus* ATCC 25923 and CCARM 3501.^[21] Hominicin demonstrated action in both acidic and basic settings (pH 2.0 to 10.0) and heat stability up to 121 °C for 15 minutes.^[21] However, there are currently little detailed studies on hominin resistance mechanisms.

Capidermicin

Capidermicin is a novel antimicrobial peptide secreted by *Staphylococcus. capitis* CIT060 with inhibitory activity against a variety of GPB, including *Lactococcus*, *Bacillus*, *Listeria. monocytogenes*, *Micrococcus*,

Streptococcus, and *Staphylococcus*.^[22] With a molecular weight of 5,464 Da, capidermicin was suggested to prevent biofilm formation and belongs to class II bacteriocins.^[23,22] These bacteriocins, which are heat-stable, work by creating holes in the cell membrane.^[24] Although the mechanisms causing capidermicin resistance have not been thoroughly investigated, target changes, efflux pumps, and the acquisition of immunity proteins are probably among the possible resistance pathways.

Nukacin ISK-1

Nukacin ISK-1 antimicrobial is produced by *S. warneri* that inhibits *Staphylococcus. aureus*.^[25] Nukacin ISK-1 is believed to belong to the Lacticin 481 group and comprises 27 amino acids involving a 3-methylanthionine, a dehydrobutyrine, and two lanthionine residues.^[26] Lacticin 481 is classified under lantibiotic group I-B which are negatively charged, globular, and inflexible peptides that block key enzymes in the targeted bacteria.^[27,24,28] Although nukacin ISK-1 could inhibit *S. aureus*, the BraRS system in *S. aureus* is associated with resistance to nukacin ISK-1 antimicrobials.^[25] BraS, sometimes also termed BceRS, is a member of the intramembrane sensing histidine kinases (IM-HKs), and skin-colonising staphylococci have of the BraRS TCS homologues.^[29] The BraRS resistance pathway in the case of bacitracin involves the ABC transporters of BraDE and VraDE. BraDE is essential for the detection of antibiotics, while VraDE acts as an efflux pump to provide resistance.^[30] Although single nucleotide polymorphisms (SNPs) associated with braRS can indicate Nukacin ISK-1 resistance, other antimicrobials can also activate BraR expression such as nisin.^[25,31]

Nisin

Nisin is produced by *Lactococcus lactis* subsp that can inhibit Gram-negative and GPB including *Escherichia coli*, *Helicobacter pylori*, and *Acinetobacter baumannii*, as well as *Staphylococcus*, *Pediococcus*, and *Listeria monocytogenes*.^[32] Some studies suggest that nisin can inhibit the formation of biofilms.^[33] Ribosomal synthesis produces nisin, which belongs to a 57-amino acid peptide.^[34] This antimicrobial is a small peptide less than 5 kDa in size classified under class I-A lantibiotics that involve post-translationally modified amino acids lanthionine and methylanthionine.^[25, 24] I-A lantibiotics are flexible, elongated, stable to heat peptides that have a positive charge and show inhibitory activity against many GPB.^[7]

Nisin is proposed to have a mode of action that involves interaction with the cell membrane of bacteria via a peptidoglycan precursor molecule called lipid II as binding sites. This interaction occurs through electrostatic interactions with phospholipid headgroups, resulting in membrane dissipation.^[35] Similar to nukacin ISK-1, nisin has associated bacteria resistance that activates the expression of BraR.^[36] Recently, *L.*

monocytogenes reported resistance to nisin.^[37] Mechanisms such as modifications to the bacterial membrane, efflux pumps, and decreased permeability may contribute to this resistance in *L. monocytogenes*, however, there is limited information available about the specific mechanism.

Salivaricin

Streptococcus salivarius produces salivaricins, which are active against oral streptococci and other bacterial species in the mouth area.^[38] This antimicrobial peptide has members of β -methylanthionine and/or lanthionine and primary structures with masses between 2,315 and 2,767 Dalton (Da) and 22 to 25 amino acids.^[39,40] Salivaricins work as an antimicrobial compound via binding to lipid II and are then followed by pore formation in the cytoplasmic membrane or interference with cell wall synthesis, resulting in bacterial cell damage.^[38] There are several types of salivaricins, including salivaricin A, salivaricin B, salivaricin D, salivaricin 9, and salivaricin G32 (Barbour et al., 2016). However, in general, salivaricins belong to the lantibiotic group I-B.^[24] Salivaricin A (SalA) was identified by *S. salivarius* strain 20P3 using the structural gene *salA*.^[41] Salivaricin B (SboB) peptide is with masses of 2,740 Da and has been reported to be produced by *S. salivarius* strain K12.^[42] Whereas salivaricin D shares major similarity with the nisin and is produced by *S. salivarius* 5M6c and a 34-amino-acid residue with masses of 3,467.55 Da. The *sall* gene was reported to be responsible for the production against salivaricin D.^[40] Salivaricin 9 Lantibiotic is produced by *Streptococcus salivarius* NU10.^[43] Although salivaricin G32 can be produced by *S. salivarius* NU10 and *S. salivarius* G32, a 2667 Da novel member antimicrobial peptide has been characterised from *S. salivarius* strain G32.^[44] The understanding of salivaricin resistance remains incomplete in maintaining the efficacy of this antimicrobials in clinical applications and oral health.

Lysostaphin

Lysostaphin is an antimicrobial enzyme belonging to class III bacteriocin that is secreted by strains of *S. simulans* biovar *staphylolyticus*. Lysostaphin is a single-molecule amino acid consisting of 246 molecules and containing zinc. Its optimal pH is 7.5 and molecular mass ~27 kDa.^[45] This antimicrobial act via breaking down peptidoglycan that is found in the bacterial cell wall of *S. aureus*, including biofilm and other GPB. However, *S. aureus* has shown resistance to lysostaphin, including mutations affecting the *femA* or *femB* genes.^[46] The biovar *staphylolyticus* bacterium *S. simulans* is self-resistant to the hydrolytic activity of lysostaphin, and this resistance involves the existence of *FemA* or *FemB*.^[46,45] In addition, a similar type of lysostaphin, staphylolytic has been described and characterised, which secretes secreted by *S. capitis* EPK1-acting agents *S. aureus*. Its targeting method, chemical structure, and resistance seem to be comparable to those of lysostaphin.^[47]

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