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The Potential Of Bacteriocins/ Antimicrobial Peptides As Alternative Therapeutic Agents Against Antibiotic-Resistant Bacterial Infection

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Abstract

The alarming rise of antibiotic-resistant bacterial infections has highlighted the urgent need for alternative therapeutic strategies. Bacteriocins and antimicrobial peptides (AMPs) have emerged as promising candidates, exhibiting potent antimicrobial activity against a wide range of pathogenic bacteria, including multidrug-resistant (MDR) strains. This comprehensive review explores the classification, modes of action, and spectrum of activity of bacteriocins and AMPs against antibiotic-resistant pathogens. Additionally, it examines mechanisms of resistance development and potential strategies to overcome resistance, including synergistic effects in combination with conventional antibiotics, the enhancement of existing antibiotics' efficacy, development of resistance-inhibiting compounds, and targeted delivery systems to improve therapeutic outcomes. This review also delves into the in vivo efficacy and safety profiles in animal models, which are crucial for assessing potential clinical applications and ensuring minimal adverse effects. Potential applications span various fields such as human medicine, veterinary medicine, food preservation, agriculture, and biotechnology, showcasing the versatility of bacteriocins and AMPs. Furthermore, the review addresses regulatory considerations and challenges, such as approval processes, quality control, and standardisation of production methods, which are essential for bringing these therapies to market. Strategies for overcoming obstacles to their development as therapeutic agents include advanced biotechnological approaches for production and engineering, novel formulations and delivery systems to enhance stability and bioavailability, and comprehensive research into resistance mechanisms and mitigation strategies to ensure long-term efficacy and safety. Bacteriocins and AMPs have demonstrated remarkable efficacy against diverse bacterial pathogens, mediated by unique mechanisms of action such as membrane disruption, inhibition of cell wall synthesis, and interference with essential cellular processes. While resistance development remains a concern, strategies like combination therapy, rapid cycling, and targeting specific resistance mechanisms hold promise in mitigating resistance emergence. Furthermore, synergistic interactions with conventional antibiotics have been reported, offering opportunities to enhance antimicrobial efficacy and overcome resistance mechanisms. In vivo studies in animal models have provided insights into the

efficacy and safety profiles of these antimicrobial agents, paving the way for their potential applications in fields such as food preservation, agriculture, and veterinary medicine. Despite their promising potential, challenges such as stability, toxicity, and effective delivery systems must be addressed, along with regulatory considerations and requirements. Strategies for overcoming these challenges include biotechnological approaches for production and engineering, novel formulations and delivery systems, and strategies to mitigate resistance development. Ultimately, the successful clinical translation of bacteriocins and AMPs as therapeutic agents against antibiotic-resistant bacterial infections hinges on interdisciplinary collaborations and rigorous research efforts to harness their full potential in human and veterinary medicine.

Keywords: bacteriocins, antimicrobial peptides,antibiotic resistance,MDR bacteria,novel antimicrobials,therapeutic agents

Introduction

The global rise of antibiotic-resistant bacterial infections poses a significant threat to public health, necessitating the urgent development of novel therapeutic strategies [1]. Bacteriocins and antimicrobial peptides (AMPs) have emerged as promising candidates for addressing this challenge, offering a potential alternative to conventional antibiotics [2]. These naturally occurring or synthetic peptides exhibit potent antimicrobial activity against a wide range of pathogenic bacteria, including multidrug-resistant strains, while demonstrating minimal toxicity to host cells [3].

Bacteriocins, primarily produced by bacteria, and AMPs, derived from various organisms including humans, animals, and plants, have distinct mechanisms of action that often differ from those of traditional antibiotics [4]. This unique mode of action contributes to their potential efficacy against antibiotic-resistant pathogens and reduces the likelihood of rapid resistance development [5].

The spectrum of activity of bacteriocins and AMPs encompasses both Gram-positive and Gram-negative pathogens, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococci (VRE), multidrug-resistant Pseudomonas aeruginosa, and extended-spectrum β-lactamase (ESBL)-producing Escherichia coli [6]. This broad-spectrum activity, coupled with their ability to target antibiotic-resistant strains, positions bacteriocins and AMPs as valuable tools in combating the antibiotic resistance crisis.

Despite their promising attributes, the development of bacteriocins and AMPs as therapeutic agents faces several challenges, including potential resistance mechanisms, production and purification difficulties, and regulatory hurdles [7]. However, ongoing research has identified strategies to overcome these obstacles, such as structural modifications to enhance stability and efficacy, combination therapies with conventional antibiotics, and novel delivery systems [8].

This review aims to provide a comprehensive overview of the potential of bacteriocins and AMPs as alternative therapeutic agents against antibiotic-resistant bacterial infections. We will explore their classification and modes of action, spectrum of activity against pathogenic bacteria, potential resistance mechanisms and strategies to overcome them, synergistic effects with conventional antibiotics, in vivo efficacy and safety profiles, and potential applications in various fields. Additionally, we will discuss regulatory considerations, challenges in their development, and strategies for overcoming these hurdles.

By examining the current state of research and future prospects, this review seeks to highlight the clinical and therapeutic potential of bacteriocins and AMPs in both human and veterinary medicine. As the threat of antibiotic resistance continues to grow, these promising antimicrobial agents may play a crucial role in developing novel therapeutic strategies to combat resistant bacterial infections and preserve the efficacy of existing antibiotics. By comprehending the capabilities and constraints of bacteriocins and AMPs, we can gain a greater understanding of their impact on the future of antimicrobial therapy.

Instrument

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We conducted a comprehensive literature review of the scientific literature to explore the potential of bacteriocins/antimicrobial peptides as alternative therapeutic agents against antibiotic-resistant bacterial infections. Our search encompassed various electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, without any restrictions on publication dates, while focusing on English language publications. We utilized specific keywords and Medical Subject Headings (MeSH) such as "bacteriocins," "antimicrobial peptides," "antibiotic resistance," "therapeutic potential," "antibacterial agents," and "alternative therapies" to identify relevant studies. Furthermore, we examined the antimicrobial activity, mechanisms of action, and therapeutic applications of bacteriocins/antimicrobial peptides against antibiotic-resistant bacterial strains. To ensure inclusiveness, we manually screened the reference lists of relevant articles to identify additional eligible studies that may have been missed during the initial search. Additionally, we extended our search to include abstracts from recent international congresses and symposia on antimicrobial resistance and novel antimicrobial agents. This review intends to provide a comprehensive insight into the potential, challenges, and strategies for utilizing bacteriocins/antimicrobial peptides as alternative therapeutic agents against antibiotic-resistant bacterial infections.

We included original research articles, review articles, and case studies investigating the antimicrobial activity of bacteriocins and/or antimicrobial peptides against antibiotic-resistant bacterial strains, as well as studies evaluating their therapeutic potential, mechanisms of action, and efficacy in preclinical or clinical settings. Studies discussing the advantages, limitations, and challenges associated with the use of bacteriocins/antimicrobial peptides as alternative therapeutic agents, and strategies for improving their stability, potency, and delivery were also considered.

The following data were extracted from the selected studies: study characteristics (author, year, study design, target bacterial strains), bacteriocin/antimicrobial peptide characteristics (source, structure, mode of action, antimicrobial spectrum), antimicrobial activity and efficacy against antibiotic-resistant bacterial strains, potential therapeutic applications and delivery methods, advantages, limitations, and challenges associated with their use as therapeutic agents, and strategies for improving their stability, potency, and delivery.

Bacteriocins/antimicrobial peptides

Bacteriocins are ribosomally synthesised peptides produced by various bacterial species that exhibit antimicrobial activity against closely related strains, particularly those sharing the same ecological niche as the producer strain [9]. They are typically encoded by a bacteriocin structural gene accompanied by a resistance gene, allowing the producer strain to survive in the presence of its own bacteriocin. They are typically encoded by a bacteriocin structural gene accompanied by a resistance gene, allowing the producer strain to survive in the presence of its own bacteriocin. This specific resistance mechanism contributes to the survival of the producer strain within its ecological niche. Bacteriocins represent a promising alternative to traditional antibiotics due to their narrow spectrum of activity, which minimizes disruption to the commensal microbiota and reduces the selective pressure for resistance development in non-target organisms [10]. Furthermore, many bacteriocins have demonstrated the ability to target not only actively dividing cells but also quiescent cells, which are often overlooked by traditional antibiotics [11].

Antimicrobial peptides (AMPs) are a broader class of peptides that exhibit antimicrobial activity against various microorganisms, including bacteria, viruses, and fungi [12]. AMPs are generally short, cationic, and amphipathic molecules that can insert into microbial membranes, leading to membrane disruption and cell death. AMPs are produced by a wide range of organisms, including bacteria, plants, and animals. AMPs play a crucial role in the innate immune defence mechanisms of many organisms, including humans, and have garnered significant interest as potential therapeutic agents [13]. AMPs employ diverse strategies to kill microbes.

Both bacteriocins and AMPs possess several advantages over traditional antibiotics. They can exhibit antimicrobial activity at very low concentrations (typically nanomolar), reducing the risk of toxicity and potential side effects [10,11]. Additionally, their susceptibility to digestive enzymes improves their safety profile and minimizes disruption to the gastrointestinal microbiota. However, this

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susceptibility may limit their administration routes to parenteral or topical applications [9].

Classification and modes of action of different types of bacteriocins/antimicrobial peptides

Bacteriocins

Bacteriocins Classification

Over the years, various classification methods have been developed for sorting bacteriocins. Bacteriocins produced by lactic acid bacteria (LAB) have traditionally been classified separately using a distinct method [14], resulting in two to four subcategories [2,15] Soltani and colleagues propose a revised classification system for bacteriocins from both Gram-negative and Gram-positive bacteria, dividing them into two main parts: Class I (modified) and Class II (unmodified) bacteriocins [16].

Another study outlines that bacteriocins are now categorized into major groups based on their physicochemical and structural properties. This includes bacteriocins produced by Gram-positive bacteria, which are further subdivided into Class I bacteriocins, known as lantibiotics [17]. Lantibiotics are small peptides, heat-stable, with a molecular weight of less than 5 kDa, and are modified after translation. They contain amino acids with polycyclic thioether structures like methyl-lanthionine and lanthionine, as well as unsaturated amino acids such as 2-amino isobutyric acid and dehydroalanine. Lantibiotics are further divided into two types based on their charge: Type A lantibiotics (e.g., lacticin 3147 and nisin) are screw-shaped, flexible molecules with a positive charge and a molecular weight of 2–4 kDa, causing pores in the target organism's cell membrane, leading to cytoplasmic membrane depolarization [18]. Type B lantibiotics are peptides with a molecular weight of 2–3 kDa, without a net charge or with a negative charge, and have a globular structure affecting cellular enzymatic activities such as cell wall formation. Examples include mersacidin, produced by *Bacillus spp.* [19].

Class II bacteriocins are small peptides with a molecular weight of less than 10 kDa, lacking lanthionine, heat-stable, and unmodified after translation. They possess an amphiphilic structure with a helical shape that allows them to insert into the membrane, leading to depolarization and cell death of the target cell.

Class III bacteriocins are proteins with a high molecular mass (>30 kDa) and are heat labile. Examples include megacins secreted by *Bacillus megaterium*, colicins and klebicin secreted by *Klebsiella pneumonia*, enterolysin secreted by Enterococcus faecalis, and helveticin I secreted by *Lactobacillus helveticus* [18].

Bacteriocins produced by Gram-negative bacteria can be categorized into two main groups: colicins, which are high molecular weight proteins ranging from 30-80 kDa, and microcins, which are peptides with a lower molecular weight ranging from 1-10 kDa. Colicins are produced by *Escherichia coli* strains that possess the colicinogenic plasmid, while microcins are highly stable molecules that resist temperature, proteases, and extreme pH values. They are secreted by enteric bacteria under stress conditions, especially when nutrients are depleted [20].

Modes of action of different types of bacteriocins

Bacteriocins typically act by forming pores in target cell membranes, degrading cellular DNA, inhibiting cell wall synthesis, and interfering with essential enzymatic functions [2]. Due to their specific targeting, they are less likely to disrupt beneficial microbiota, making them ideal for narrow-spectrum antibiotic development.

Bacteriocins can inhibit growth through mechanisms affecting the cell envelope or protein production and gene expression. For instance, Class I bacteriocins inhibit peptidoglycan production by targeting lipid II on the cell membrane, while Class II bacteriocins like lactococcin A bind to a specific pore receptor system [2]. Some lantibiotics, like nisin, have dual modes of action: they attach to lipid II, disrupting cell wall synthesis and initiating pore formation, leading to cell death [9].

Bacteriocins targeting gram-negative bacteria often interfere with protein, RNA, and DNA metabolism. Examples include MccJ25, which inhibits RNA polymerase, MccB17, which inhibits DNA gyrase, and MccC7-C51, which inhibits aspartyl-tRNA synthetase. MccE492, however, affects through pore formation [2].

Some bacteriocins exert antimicrobial effects via enzymatic activities, such as colicin E2 with DNase activity and colicin E3 with RNase activity [21]. Bacteriolytic proteins like lysostaphin, a Class III

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bacteriocin, directly affect the cell wall of specific gram-positive bacteria, causing cell death and lysis [9].

Common mechanisms include electrostatic attraction to negatively charged microbial membranes, integration, and disruption of membrane integrity, leading to cell lysis. Some AMPs inhibit cell wall synthesis by targeting enzymes involved in bacterial cell wall synthesis, while others disrupt protein synthesis by interfering with the translation process within the microbial cell, halting protein production and killing the organism [3,22].

Antimicrobial peptides

Major Categories of Antimicrobial Peptides (AMPs)

Classification

AMPs typically do not rely on enzymatic mechanisms for their antimicrobial effects [23]. For instance, lysozyme, a monomeric peptide with enzymatic action, is not considered an AMP due to its size (148 amino acids) [24]. This review categorizes AMPs by their targets and modes of action, focusing on natural AMPs from eukaryotes, particularly mammals.

Antiviral Peptides

Antiviral AMPs neutralize viruses by integrating into viral envelopes or host cell membranes, targeting both enveloped RNA and DNA viruses [25,26]. They can destabilize viral envelopes, preventing infection [27,28]. and reduce viral binding to host cells [29]. For example, defensins bind to viral glycoproteins, preventing herpes simplex viruses (HSV) from attaching to host cells [30]. Some AMPs block virus entry by occupying receptors like heparan sulfate [31]. Cationic peptides like lactoferrin can bind to heparan, blocking virus-receptor interactions. Other AMPs, like NP-1 from rabbit neutrophils, can alter host cell gene expression to block viral infection.

Antibacterial Peptides

Antibacterial AMPs, mainly cationic, target bacterial cell membranes, causing lipid bilayer disintegration [32,33]. These amphipathic peptides bind to lipid components and phospholipid groups [34]. At low concentrations, some AMPs inhibit intracellular pathways without disrupting membranes, affecting DNA replication and protein synthesis [35]. For instance, buforin II binds to DNA and RNA without damaging membranes [36]. Some AMPs, like nisin, can kill antibiotic-resistant bacteria [37].

Antifungal Peptides

Antifungal peptides target fungal cell walls or intracellular components [38,39]. They can bind to chitin in fungal cell walls [40] or disrupt membrane integrity [41]. These peptides increase membrane permeability [42]. or form pores [43]. Antifungal peptides include various structural classes like α-helical (D-V13K, P18), extended (indolicin), and β-sheet (defensins).

Antiparasitic Peptides

Antiparasitic peptides are less common. Magainin was the first reported, effective against Paramecium caudatum [44]. Synthetic peptides have been developed against parasites like Leishmania [45]. Cathelicidin can kill Caernohabditis elegans by forming cell membrane pores [46]. Despite the complexity of parasitic organisms, antiparasitic peptides typically disrupt cell membranes.

However, the classification of AMPs can also be considered based on biological sources. Therefore, you can search for antimicrobial peptides from bacteria (bacteriocins), plants, and animals. Antimicrobial peptides from animals are further categorized into peptides from insects, amphibians, fish, reptiles, mammals, etc., as shown in Table 1.

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Table 1 Classification of Antimicrobial peptides according to its origin

Source	Examples
Bacteria (particularly lactic acid bacteria)	Nisin, lacticin, pediocin, colicins
Fungi	Plectasin (from Pseudoplectania nigrella), Anafp (from Aspergillus niger)
Plants	Thionins, defensins, cyclotides
Animals Insects	Cecropins
Amphibians	Magainins
Mammals	Defensins, cathelicidins

Mode of Action of Antimicrobial Peptides

AMPs kill cells through several mechanisms: disrupting membrane integrity by interacting with negatively charged cell membranes, inhibiting protein, DNA, and RNA synthesis, or targeting specific intracellular components. Until the late 1990s, all known AMPs were cationic. This changed with the discovery of negatively charged AMPs in 1997 [47], such as maximin-H5 [48]. and dermicidin [49].

Typically, an AMP is effective against one class of microorganisms (e.g., bacteria or fungi) [50]. However, some AMPs have multiple modes of action. For example, indolicidin can kill bacteria, fungi, and HIV by damaging cell membranes, inhibiting DNA synthesis, and inhibiting HIV-integrase [27, 51, 52, 53]. Conversely, PMAP-23 kills both fungi and parasites by creating pores in their cell membranes [46, 54].

One-third of a bacterial cell's proteins are associated with the membrane, playing critical roles in nutrient transport, respiration, ATP generation, and communication [55]. AMP treatment can disrupt these functions, contributing to their rapid killing effect beyond mere membrane disruption.

Membrane-Active AMPs

Even when intracellular targets are involved, initial interaction of peptides with the cell membrane is necessary for the antimicrobial activity of AMPs [56]. This interaction determines the range of target cells. Most membrane-active AMPs are amphipathic, having both cationic and hydrophobic faces. This characteristic ensures initial electrostatic interaction with the negatively charged cell membrane and insertion into the membrane interior. The actions of AMPs continue beyond this initial interaction. The hydrophobic portion of an AMP assists in inserting the AMP molecule into the cell membrane [57]. Thus, the interaction primarily involves ionic and hydrophobic interactions, dependent on the cationic state and hydrophobicity of the peptide.

Intracellularly Active AMPs

Initially, antimicrobial peptides (AMPs) were thought to kill bacteria mainly by permeabilizing the cell membrane. It was believed they needed to be used at high concentrations to disrupt the membrane and form sufficient channels and pores, leading to cell death [58]. However, some AMPs begin permeabilizing membranes at lower concentrations, while others require higher concentrations, indicating alternative killing mechanisms. Recently, it has been shown that intracellularly active AMPs interact with targets inside bacterial cells [59,60,61]. For instance, indolicin binds to DNA with a preferred sequence [62, 63].

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Some AMPs inhibit bacterial DNA and protein synthesis [64,65]. PR-39, derived from pig intestines, kills bacteria by halting protein and DNA synthesis without lysing cells [66]. Similarly, indolicin targets DNA synthesis within the cytoplasm [52,64]. AMPs from the human immune system, such as tPMP-1 and aHNP-1, inhibit DNA and protein synthesis shortly after entering cells [67]. Apidaecin blocks protein synthesis without forming pores, effective only against Gram-negative bacteria and is transported by a protein before inhibiting synthesis [68].

Some AMPs also inhibit microbial proteases. Histatin 5 prevents periodontal tissue destruction by inhibiting a protease from Bacteroides gingivalis [69], while eNAP-2 inhibits microbial serine proteases [70]. Intracellular AMPs may be effective only against bacterial cells at specific growth stages. For example, diptericin is effective only against actively growing bacterial cells, suggesting it interacts with specific metabolic pathways [71, 72].

Some intracellularly active AMPs have multiple targets. Seminalplasmin inhibits RNA polymerase and can halt RNA synthesis at lower concentrations than many other antibacterial agents [73]. It can also induce autolysis by activating an autolysin protein inside target cells [74, 75].

The discovery that AMPs can inhibit intracellular pathways [58,64]. suggests mechanisms for their cellular uptake. Two such mechanisms are direct penetration and endocytosis [57]. According to Jones (2007), cellular uptake occurs through endocytosis, including macropinocytosis and receptor-mediated endocytosis. In macropinocytosis, the cell membrane folds inward, forming vesicles with the help of dynamin proteins [57]. In receptor-mediated endocytosis, portions of the membrane coated with clathrin or caveolin proteins form pits that bud inward to create vesicles [76,77].

Spectrum of activity of bacteriocins/AMPs against pathogenic bacterial, including antibiotic-resistant bacterial pathogens

Gram-Positive Pathogens

Methicillin-resistant *Staphylococcus aureus* (MRSA)

The anti-MRSA property of purified bacteriocin may be used to prevent the spread of MRSA infections. Remarkable features of BAC-IB17 suggest its applications in various pharmaceutical and food industries as it can function under a variety of harsh environmental conditions.

Vancomycin-resistant *Enterococci* (VRE)

VRE strains are a significant concern in healthcare settings due to their resistance to vancomycin, a last-resort antibiotic for treating infections caused by Gram-positive bacteria. Several bacteriocins have shown activity against VRE strains. For example, the bacteriocin enterocin AS-48, produced by *Enterococcus faecalis*, exhibited potent activity against various VRE strains, including *Enterococcus faecium* and *Enterococcus faecalis*

Several bacteriocins have shown strong activity against *L. monocytogenes*. Cotter et al. (2005) reported that the two-peptide lantibiotic lacticin 3147 effectively inhibited L. monocytogenes in various food matrices. Furthermore, Campion et al. (2017) demonstrated the efficacy of nisin derivatives against *L. monocytogenes* biofilms, showcasing their potential for food safety applications and clinical use. [78].

Moreover, AMPs such as human defensins, cathelicidins, and insect-derived AMPs (e.g., cecropins) have shown activity against methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and Clostridium difficile [79,80].

Gram-Negative Pathogens

***Pseudomonas aeruginosa* Multidrug-resistant (MDR) strain**

Bacteriocins and AMPs have shown significant activity against MDR P. aeruginosa. de la Fuente-Núñez *et al*. (2012) reported that the synthetic peptide 1037 effectively eradicated P. aeruginosa biofilms and prevented their formation. Additionally, Gellatly et al. (2012) demonstrated that the cathelicidin LL-37 enhanced the efficacy of conventional antibiotics against MDR P. aeruginosa, suggesting its potential in combination therapies.AMPs like polymyxins, magainins, and cationic peptides have exhibited activity against multidrug-resistant (MDR) strains of Pseudomonas aeruginosa, Acinetobacter baumannii, and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae [81].

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Extended-spectrum β-lactamase (ESBL)*Escherichia coli*

AMPs have shown promising activity against ESBL-producing E. coli. Naghmouchi et al. (2013) reported that the bacteriocin colistin effectively inhibited ESBL-producing E. coli strains. Moreover, Pires et al. (2015) demonstrated that the AMP PepR effectively killed ESBL-producing *E. coli* in both planktonic and biofilm forms, highlighting its potential for treating resistant infections. [82].

Klebsiella pneumoniae (multidrug-resistant *K. pneumoniae* (MDR-Kp)

Several bacteriocins and AMPs have shown activity against MDR-Kp. Gupta et al. (2016) reported that the AMP WLBU2 effectively killed MDR-Kp strains, including those resistant to colistin. Additionally, Xu et al. (2018) demonstrated that the bacteriocin plantaricin P1053 showed potent activity against various MDR-Kp strains, suggesting its potential as an alternative therapeutic agent. [83].

***Acinetobacter baumannii* MDR**

Bacteriocins and AMPs have shown promising results against A. baumannii, including MDR strains. Vila-Farrés et al. (2012) reported that the AMP mastoparan effectively killed MDR A. baumannii strains [84]. Furthermore, Sánchez-Gómez et al. (2015) demonstrated that the AMP LF11-322 showed potent activity against colistin-resistant A. baumannii strains, highlighting its potential for treating highly resistant infections [85].

Other Pathogens:

Clostridium difficile

Clostridium difficile is an anaerobic, gram-positive, spore-forming bacillus first isolated from the fecal flora of healthy neonates in 1935. In 1978, its cytotoxins were linked to antibiotic-induced pseudomembranous colitis. Screening over 30,000 isolates from fecal samples led to the discovery of a single colony that inhibited C. difficile growth. This producing strain, identified as B. thuringiensis, is a spore-forming Gram-positive organism commonly used in agriculture to control insect pathogens. The new bacteriocin, thuricin CD, is produced during the late log and stationary growth phases but is not linked to sporulation. Tests showed that thuricin CD has a narrow activity spectrum, mainly targeting spore-forming Gram-positive bacteria, including clinically significant C. difficile strains, especially the hypervirulent PCR ribotype 027 NAP1. In an ex vivo distal colon model, thuricin CD performed comparably to metronidazole, the primary antibiotic for CDAD treatment. This suggests thuricin CD could be a therapeutic for CDAD with targeted colon delivery.

Mycobacterium tuberculosis

Several AMPs have shown activity against M. tuberculosis, including drug-resistant strains. Fattorini et al. (2004) reported that the human β-defensin 3 effectively inhibited the growth of M [86]. tuberculosis, including multidrug-resistant strains. Additionally, Rivas-Santiago et al. (2013) demonstrated that the cathelicidin LL-37 enhanced the antimicrobial activity of isoniazid against *M. tuberculosis*, suggesting its potential in combination therapies for tuberculosis. [87].

Biofilm-associated infections: Some AMPs have demonstrated the ability to disrupt and eradicate bacterial biofilms, which are notoriously resistant to conventional antibiotics and represent a significant clinical challenge. The human cathelicidin LL-37 has been shown to inhibit biofilm formation and disperse established biofilms of *S. aureus*, *P. aeruginosa*, and *E. coli* [88,89]. Moreover, AMPs like human β-defensin-3 (HBD-3) have exhibited potent anti-biofilm activity against *S. aureus*, *P. aeruginosa*, and *Candida albicans* biofilms [90,91]. Other example; synthetic AMPs, such as OP-145, DJK-6, and 1037, have been developed and shown to be effective against biofilms formed by various bacterial pathogens, including *S. aureus*, *P. aeruginosa*, and *A. baumannii* [92,93].

Potential mechanisms to overcome resistance to bacteriocins/AMPs

While bacteriocins offer a broader spectrum of activity alternatives to traditional antibiotics,bacteria can still develop resistance mechanisms to evade their effects. Understanding the mechanisms of resistance and exploring potential strategies to overcome resistance are crucial for the successful implementation of bacteriocin-based therapies.

Antimicrobial drugs are decidedly one of the most important and useful therapeutic discoveries in the history of medicine. The key in originating the

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paradigms for future antimicrobial research,which discovered the first antimicrobial agents Salvarsan, Prontosil and Penicillin [94].

Antimicrobial resistance (AMR) is a natural phenomenon in which bacteria evolve as a way to withstand the action of drugs, making them apparently ineffective. The pressure that antimicrobials put on the pathogens is responsible for the option of resistant strains. [95].

There are several categories for mechanisms of drug resistance for example : [1]drug inactivation by irreversible enzymatic modification ; [2] target modification at the site of antibiotic binding ; [3]reduced drug accumulation due to low permeability.In terms of resistance which some dangerous microbial threats united under acronym "ESKAPE" (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species*), presently becoming ESCAPE (*Enterococcus faecium, Staphylococcus aureus, Clostridium difficile, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacteriaceae*)

Definitely, to combat the issue of antimicrobial resistance (AMR) and multidrug resistant (MDR) appeal must be sought out to curb infections, disease, control pathogenic species and make certain of public health [96].

Mechanisms of Resistance to Bacteriocins/AMPs: Bacteria can develop resistance to bacteriocins/AMPs through various mechanisms, including:

Alteration of cell surface receptors

Separate in this way, it can clearly distinguish the ratio of the cells which are reacting and promptly find appropriate methods of resistance to those affected groups [97].

Enzymatic inactivation/degradation

In the way of utilizing this solution, this can stop reaction at a certain level of degradation and completely control enzymatic modification and can be chosen with special caution to assess control enzymes

Efflux pumps

Using efflux pumps accept the microorganisms to regulate their internal environment by eliminating toxic substances, including antimicrobial agents, metabolites and quorum sensing signal molecules, then send it from cellular interior to the external environment [98,99].

Modifications in cell envelope/target molecules

After modifying the cell envelope and target molecules, the environmental parts really affect the well-being of different types of cells which continue to target molecules inside of the cells, so we can find a way to stimulate a counterproductive environment which affects specific cell envelopes [100].

Reduced uptake

Reduced uptake is one of crucial mechanisms by which bacteria can develop resistance to bacteriocins or antimicrobial peptides (AMPs). This mechanism involves alterations in the bacterial cell envelope, which hinders the entry or internalization of these antimicrobial agents, thereby reducing their efficacy. In a study by Guo *et al*. (2008), it was demonstrated that *S.aureus* could develop resistance to the AMP nisin by altering its cell wall composition. The resistant strains exhibited increased levels of cell wall components, such as D-alanine and D-alanyl-lipoteichoic acid, which hindered the pore-forming activity of nisin, thereby reducing its uptake and efficacy [101].

Strategies to Overcome Resistance to Bacteriocins/AMPs: Several strategies have been proposed to overcome resistance to bacteriocins and enhance their effectiveness:

Combination therapy

Using bacteriocins in combination with other antimicrobial agents, such as conventional antibiotics or essential oils, can potentially overcome resistance mechanisms and achieve synergistic effects [102,103].

Bioengineering and modification

With this bioengineering and modification are for, in order to remove some substances in dead cells which were researched. Then, we will suppress it in the same type of dead cell which survives now to create resistance. By developing innovative technologies to counter antimicrobial resistance. And can be designed and synthesized in a single platform [104,105,106].

Nanoparticle delivery systems

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The use of targets in nanoparticles or nanomedicines have been achieved. As stated, it is especially applicable to solid cancers where there are increased blood vessel and transporter nanomedicines [106].

Combination with resistance-modifying agents

Using RMAs offered considerable hope for delaying loss of clinical use of a broad range of antimicrobials and for revitalising into drugs that could pass.

Synergistic effects of bacteriocins/AMPs in combination with conventional antibiotics or other antimicrobial agents

Combining bacteriocins with conventional antibiotics or other antimicrobial agents has been explored as a strategy to enhance their antimicrobial efficacy and overcome antibiotic resistance. Several studies have demonstrated synergistic effects when bacteriocins are used in combination with other antimicrobial agents, suggesting their potential as adjunctive therapies.

Bacteriocins and Conventional Antibiotics: Various studies have reported synergistic or additive effects when bacteriocins are combined with conventional antibiotics against antibiotic-resistant bacterial strains. For instance, the combination of the bacteriocin nisin with gentamicin or ciprofloxacin exhibited synergistic activity against multidrug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa strains [107,108]. Similarly, the combination of the bacteriocin lacticin 3147 with rifampicin demonstrated enhanced activity against methicillin-resistant *Staphylococcus aureus* (MRSA) strains [109].

Rationale for combination therapy

Due to mutations in bacterial genes resulting in antibiotic resistance, scientists were compelled to use higher doses of antibiotics to effectively treat bacterial infection, necessitating the use of newer, more expensive antibiotics, of which there are only few available. Eventually, this can lead to a situation where no effective treatment is left, resulting in fatal outcomes. [110].

To address this, combination therapy is used, which involves drugs working through different mechanisms to reduce the chances of bacteria developing resistance. By using drugs with varied effects, each can be given at its optimal dose without causing intolerable side effects, providing a strategic solution to combat antibiotic resistance. [111].

Overcoming Resistance

Bacteriocins may offer an alternative mechanism for overcoming antibiotic resistance. Unlike conventional antibiotics, which primarily target essential cellular processes, bacteriocins often disrupt bacterial cell membranes or specific molecular targets, making them less susceptible to common resistance mechanisms. [112].

Delayed Resistance Development

Bacteriocins may exhibit a lower propensity for inducing resistance compared to conventional antibiotics. By incorporating bacteriocins into combination therapy regimens, it may be possible to delay or prevent the emergence of resistance, prolonging the effectiveness of antibiotic treatment. [112].

Synergistic Effects

Bacteriocins and antibiotics may exhibit synergistic interactions when used together, leading to enhanced antimicrobial activity compared to either agent alone. This synergy can result in lower effective doses of antibiotics, reducing the risk of side effects and minimizing the development of antibiotic resistance. [113].

Broad-Spectrum Activity

Bacteriocins and antibiotics often have different mechanisms of action and target different aspects of bacterial physiology. Combining these agents can broaden the spectrum of activity, allowing for effective treatment against a wider range of bacterial pathogens, including multidrug-resistant strains. [114,115].

Examples of synergistic combinations

The combination of nisin with gentamicin, ciprofloxacin, or vancomycin has shown synergistic effects against MRSA, VRE, and other Gram-positive pathogens.

Recent studies have explored the potential of combining nisin, a bacteriocin, with traditional antibiotics to enhance their efficacy against resistant bacterial strains. Notably, the combination of nisin with gentamicin, ciprofloxacin, or vancomycin has shown synergistic effects against methicillin-resistant

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Staphylococcus aureus (MRSA), vancomycin-resistant Enterococci (VRE), and other Gram-positive pathogens. [116].

These synergistic effects are particularly promising as nisin could potentially restore the effectiveness of these antibiotics against otherwise resistant strains as shown in table 2. Nisin, a bacteriocin produced by Lactococcus lactis, primarily targets bacterial cell membranes by forming pores, which can enhance the penetration of traditional antibiotics into bacterial cells. [117]. This dual mechanism of action not only disrupts bacterial membrane integrity but also facilitates the entry of antibiotics, thereby overcoming resistance mechanisms such as biofilm formation and efflux pumps.

The combination of lacticin 3147, a bacteriocin produced by *Lactococcus lactis*, with rifampicin or nisin.

Combining lacticin 3147 with nisin or rifampicin offers a promising strategy to enhance antimicrobial effectiveness against a broad spectrum of pathogens, including resistant strains. [118]. Lacticin 3147, a potent bacteriocin from Lactococcus lactis, disrupts bacterial cell membranes and crucial physiological processes in Gram-positive bacteria. [118]. Paired with nisin, which also targets membranes but through different mechanisms, the combination may synergistically broaden antimicrobial activity, addressing resistant strains that evade single-agent treatments. [9].

Alternatively, combining lacticin 3147 with rifampicin, an antibiotic targeting RNA synthesis, presents a dual-action approach effective against diverse bacterial pathogens, potentially overcoming resistance mechanisms [9].

These combinations leverage unique mechanisms, as can be shown in table 2, to bolster antimicrobial efficacy, promising innovative solutions in medical and food safety applications where combating microbial resistance is paramount. [9,118].

Table 2 Mechanisms of Action and Effectiveness of the combination of Antibiotic with Bacteriocin

Combination	Mechanism of Action	Effectiveness
Nisin and Gentamicin	Nisin binds to lipid II, disrupting bacterial membranes; enhances gentamicin entry	Synergistic effects against MRSA and other Gram-positive pathogens
Nisin and Ciprofloxacin	Nisin disrupts bacterial membranes, facilitating ciprofloxacin penetration	Synergistic effects against MRSA and other Gram-positive pathogens
Nisin and Vancomycin	Nisin disrupts bacterial membranes, aids vancomycin binding to peptidoglycan precursors	Synergistic effects against MRAS, VRE and other Gram-positive pathogens
Lacticin 3147 and Nisin	Lacitin 3147 disrupts bacterial membranes by forming pores; nisin binds to lipid II and forms additional pores	Synergistic effect against a broad spectrum of Gram-positive pathogens; enhances bactericidal activity.
Lacticin 3147 and Rifampicin	Lacitin 3147 disrupts bacterial membranes by forming pores; rifampicin inhibits bacterial RNA synthesis by binding to RNA polymerase	Synergistic antimicrobial activity against Gram-positive bacteria; potentially effective against resistant strains and biofilms.

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Bacteriocins and Other Antimicrobial Agents: Bacteriocins have also been explored in combination with other antimicrobial agents, such as essential oils, plant extracts, and nanoparticles, to enhance their antimicrobial activity. These synergies extend to other agents like metal ions, bioactive compounds from plant extracts, and peptides sourced from various origins, providing effective strategies against multidrug-resistant pathogens. (Table 3)

Additionally, integrating bacteriocins with essential oils, plant extracts, and nanoparticles showcases significant advancements in antimicrobial efficacy, supporting innovative therapeutic approaches in infection control and treatment. For instance, combining bacteriocins like enterocin AS-48 with thyme essential oil illustrates enhanced antimicrobial activity, demonstrating the potential of such synergistic combinations to comprehensively address infectious diseases. (Table 3)

Table 3 Mechanism of Bacteriocin and Antimicrobial Agents

Antimicrobial Agents	Mechanism of Synergy
Fluoroquinolones	Enhanced permeability of bacterial cell membranes, allowing increased antibiotic uptake
β-lactams	Disruption of bacterial cell wall integrity, enhancing the bactericidal activity of β-lactams
Metal Ions	Enhanced membrane disruption and increased intracellular targeting
Plant Extracts	Synergistic action through combined antimicrobial effects of plant phytochemicals and peptide activity
Antimicrobial Peptides	Combined targeting of microbial membranes or intracellular processes, enhancing antimicrobial potency
Essential Oils	Disruption of antimicrobial membranes and intracellular processes, enhancing overall antimicrobial activity
Nanoparticles	Enhanced delivery and sustained release, augmenting bacteriocin efficacy against microbial target

Potential mechanisms of synergy

The synergistic effects observed when combining bacteriocins with other antimicrobial agents can be attributed to various mechanisms. Bacteriocins can facilitate the entry of antibiotics or other antimicrobial agents into

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bacterial cells by permeabilizing the cell membrane or altering its structure [102]. Additionally, bacteriocins may target different cellular processes or structures than conventional antibiotics, leading to a multi-targeted approach that can overcome resistance mechanisms [109]. However, it is important to note that the synergistic effects can be influenced by various factors, such as the concentrations of the combined agents, the bacterial strain, and the environmental conditions.

Concentration Levels

The effectiveness of synergistic combinations often depends on the concentrations of each agent. There may be an optimal ratio or concentration range where synergy is most pronounced. Suboptimal concentrations may result in additive or even antagonistic effects.

Bacterial Strain

Different bacterial strains can vary widely in their susceptibility to antibiotics, AMPs, and bacteriocins. Some strains may be inherently resistant to certain agents or may exhibit different responses to combinations compared to others. Understanding the specific strain characteristics is crucial in predicting and optimizing synergistic effects.

Environmental Conditions

Factors such as pH, temperature, nutrient availability, and oxygen levels can influence bacterial growth and susceptibility to antimicrobial agents. Changes in environmental conditions can affect the efficacy of individual agents and their synergistic interactions as can be shown in table 4. [119].

Table 4 Influence of Environmental Conditions on Antimicrobial Efficacy

Environmental Factor	Impact on Antimicrobial Agents
pH	Affects charge and stability of antimicrobial agents.
Temperature	Influences bacterial metabolism and membrane fluidity.
Nutrient Availability	Affects bacterial growth rates and metabolism.
Oxygen Levels	Influences bacterial respiration and energy production.
Biofilm Formation	Provides protective environment, reducing antimicrobial efficacy.
Biofilm Formation	Modifies antimicrobial distribution and activity.

Potential Benefits of Combination Therapies: Combining bacteriocins with conventional antibiotics or other antimicrobial agents offers several potential benefits, including enhanced antimicrobial activity, reduced risk of resistance development, and the possibility of lower effective doses, which can minimize potential toxicity and side effects [107,108]. Furthermore, combination therapies may extend the

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therapeutic utility of existing antibiotics and revive the efficacy of drugs that have become ineffective due to resistance mechanisms.

In vivo efficacy and safety profiles of bacteriocins/AMPs in animal models of bacterial infections

While numerous *in vitro* studies have demonstrated the antimicrobial potential of bacteriocins and AMPs, evaluating their efficacy and safety in vivo using animal models is crucial for their development as therapeutic agents. Several studies have investigated the in vivo efficacy and safety of various bacteriocins and AMPs in animal models of bacterial infections

Efficacy in Animal Models:

Skin and soft tissue infections: Bacteriocins and AMPs have shown promising results in treating skin and soft tissue infections in animal models. For instance, Capparelli et al. (2007) demonstrated that a temporin L analog effectively treated Staphylococcus aureus-induced skin infections in mice, significantly reducing bacterial load and inflammation. Similarly, Håversen et al. (2010) showed that human lactoferrin-derived peptides effectively treated S. aureus skin infections in mice, promoting faster wound healing and reducing bacterial colonization.

Respiratory infections: Several studies have demonstrated the efficacy of bacteriocins and AMPs in treating respiratory infections in animal models. Chen et al. (2017) reported that the AMP ZY4 effectively treated Pseudomonas aeruginosa lung infections in mice, reducing bacterial load and inflammatory responses. [120].

Gastrointestinal infections: Nisin, which is a famous bacteriocin manufactured by *Lactococcus lactis*, has proven to be effective in animal models against different gastrointestinal pathogens. For example, research has indicated that nisin has the ability to lessen the severity of Clostridium difficile infection in mice by lowering toxin levels and spore counts, resulting in increased survival rates. Thuricin CD, which is produced by Bacillus thuringiensis, is another bacteriocin that has demonstrated promise in murine models by effectively treating C. difficile infections without causing significant disruption to the native gut microbiota. [121]. Another study using human cathelicidin LL-37 for therapy against *Helicobacter pylori*, LL-37 in mice models infected with decreased the bacterial count and inflammation in the stomach, suggesting its potential.

Systemic infections: The efficacy of bacteriocins and AMPs in treating systemic infections has been demonstrated in various animal models. Benech et al. (2002) showed that nisin Z effectively treated systemic Staphylococcus aureus infections in mice, reducing bacterial load in multiple organs. [122]. Similarly, Ostorhazi *et al*. (2011) demonstrated that the designer AMP A3-APO effectively treated systemic *Acinetobacter baumannii* infections in mice, improving survival rates and reducing bacterial burden.

Urinary tract infections:Bacteriocins and AMPs have also shown promise in treating urinary tract infections. Danka and Hunstad (2015) reported that the cathelicidin CRAMP effectively treated uropathogenic Escherichia coli infections in mice, reducing bacterial load and inflammation in the urinary tract.

Biofilm-associated infections: Many bacteriocins and AMPs have demonstrated efficacy against biofilm-associated infections in animal models. de la Fuente-Núñez et al. (2014) showed that the synthetic peptide 1037 effectively treated P. aeruginosa biofilm infections in Caenorhabditis elegans and Galleria mellonella models, reducing bacterial load and improving survival rates.

Polymicrobial infections: Some studies have explored the efficacy of bacteriocins and AMPs in treating polymicrobial infections. Luo et al. (2017) demonstrated that the AMP CWR10 effectively treated polymicrobial biofilm infections caused by P. aeruginosa and S. aureus in a mouse wound model, reducing bacterial load and promoting wound healing.

Evaluating the safety profiles of bacteriocins and AMPs in animal models is crucial for their potential clinical translation.

Evaluating the safety profiles of bacteriocins and AMPs in animal models is crucial for their potential clinical translation. Several studies have investigated the toxicity and potential adverse effects of these antimicrobial peptides

Cytotoxicity: Bacteriocins and AMPs have generally shown low cytotoxicity in animal models, which is a promising indicator for their potential use in humans.

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For instance, a study by Kaur and Kaur (2015) demonstrated that nisin, a well-known bacteriocin, exhibited minimal cytotoxicity to human erythrocytes and HepG2 cells at concentrations effective against pathogenic bacteria. However, some AMPs, like melittin, have shown higher cytotoxicity, highlighting the need for careful selection and modification of these peptides [123].

Immunogenicity: The immunogenic potential of bacteriocins and AMPs is a critical factor in their safety profile. While many of these peptides have shown low immunogenicity, some may induce an immune response. A study by Fernández et al. (2013) on the bacteriocin AS-48 demonstrated that it did not elicit a significant immune response in mice, even after repeated administration. However, certain AMPs, particularly those of non-human origin, may induce antibody production, potentially limiting their long-term efficacy [124].

Nephrotoxicity: Nephrotoxicity is a concern for many antimicrobial agents, including some bacteriocins and AMPs. A study by Ghobrial et al. (2009) on the AMP histatin 5 showed no significant nephrotoxicity in rat models at therapeutic doses. However, some cationic AMPs have demonstrated nephrotoxicity at higher concentrations, emphasizing the importance of dose optimization and structural modifications to minimize this risk [125].

Hemolytic activity: The potential for hemolysis is a crucial safety consideration for bacteriocins and AMPs. Many naturally occurring bacteriocins, such as nisin and pediocin, have shown minimal hemolytic activity in animal studies. However, some AMPs, particularly those with high hydrophobicity and cationicity, may exhibit significant hemolytic activity. For example, melittin, derived from bee venom, shows potent antimicrobial activity but also strong hemolytic effects, limiting its therapeutic potential [123].

Pharmacokinetics and biodistribution: Understanding the pharmacokinetics and biodistribution of bacteriocins and AMPs is essential for assessing their safety and efficacy. A study by Benech et al. (2002) on the pharmacokinetics of nisin Z in rabbits showed rapid clearance from the bloodstream and accumulation in the liver and kidneys. This rapid clearance can be advantageous in terms of reducing systemic exposure but may necessitate frequent dosing or modified delivery strategies to maintain therapeutic levels [4].

Potential applications of bacteriocins/AMPs in various fields

Bacteriocins exhibit characteristics such as ribosomal production, proteinaceous nature, and versatile antimicrobial activity, making them valuable for various industrial applications. These peptides, produced by diverse bacterial phyla, can effectively inhibit a wide range of bacterial strains, showcasing their biotechnological potential. Particularly, bacteriocins from lactic acid bacteria (LAB) are recognized as safe for consumption and have been extensively studied in food preservation and pharmaceutical sectors. Recent research has highlighted their effectiveness against emerging drug-resistant microorganisms, including those responsible for food spoilage and toxin production. Nisin, a bacteriocin widely utilized in food preservation, demonstrates broad-spectrum activity against Gram-positive bacteria commonly found in food. Given concerns over chemical preservatives and bacterial contamination, bacteriocins offer a natural alternative for enhancing food safety and prolonging shelf life. Beyond food and pharmaceuticals, bacteriocins find applications in agriculture, bacteriocins can be employed to control pathogens in both crop and livestock leading to increased yields and improved animal health.

Food Preservation

Extension of shelf life

Bread, pastries and cakes bacteriocins such as nisin and natamycin inhibit the growth of mold and yeast in baked goods. For products with a high moisture content which are particularly susceptible to deterioration, this is of particular importance. For instance, Natamycin has been shown to effectively prevent the growth of mold on bread without changing its taste or texture and thus prolongs shelf life by a few days. Moreover, in sea food Bacteriocins such as nisin and lacticin 3147 are used to prolong the shelf life of fish by inhibiting spoilage organisms such as Listeria and Vibrio species. Nisin effectively reduced Listeria contamination in cold smoked salmon trials, demonstrating a viable method for improving the safety and shelf life of fish products.

Natural Preservatives:

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Deli Meats in order to avoid the growth of pathogens such as Listeria monocytogenes, bacteriocins are added to deli meat like ham, turkey and sausage. For instance, the use of nisin in ready to eat meal could inhibit Listeria growth and provide a natural alternative to chemical preservatives while satisfying consumer demands for cleaner labelling. dairy Products In addition to cheese, in dairy products such as yogurts and buttermilks, bacteriocins such as nisin and pediocin are used to inhibit spoilage and pathogenic bacteria. This ensures that products are safe and have a longer shelf life, which is essential to maintain quality in the context of distribution and retail. [126].

Safety enhancement:

Packaging Films: An antimicrobial barrier is provided by aseptic packaging containing bacteriocins, such as nisin. In particular, in the case of meat and cheese products where it helps to ensure product safety by reducing surface contamination, this technology is particularly helpful. These films are designed to produce bacteriocins over time, which provide a longer protection against pathogens. Additional, Multi-Layer Coatings, edible coatings with multiple layers containing bacteriocins can be applied to various foods, including fruits and vegetables. These coatings offer extended protection from microbial decay and contamination, by gradually releasing the bacteriocins. For products that require a longer shelf life and high safety standards, such applications are particularly useful.

Fermented Foods:

Fermented Vegetables bacteriocins play a vital role in the fermentation of vegetables like sauerkraut and kimchi by controlling undesirable bacteria and ensuring consistent fermentation processes. This will not only improve the safety and quality of the products, but also enhance their taste and texture. [126]. Soy Products in the production of fermented soy products such as miso and tempeh, bacteriocins inhibit the growth of spoilage organisms, ensuring that the product remains safe and retains its quality throughout its shelf life. This is especially relevant in the case of products kept at ambient temperatures, where microbial growth can be a significant problem.

Agriculture

Biocontrol Agents:

In Vine Crops Bacteriocins are used to treat diseases in vine crops such as grapes. For example, against Pierce's disease, which affects grapevines, bacteriocins from Pseudomonas syringae have been shown to be effective. The need for chemical treatments has been reduced with this biocontrol approach, which supports sustainable viticulture practices Root vegetables, for the management of bacterial soft rot caused by Erwinia carotovora, bacteriocins are applied to root vegetables such as potatoes and carrots. This treatment will help to reduce postharvest losses and improve the marketability of these crops Bacteriocins increase composting by inhibiting pathogenic bacteria while promoting beneficial organisms. This results in increased quality compost that may improve soil fertility and the health of plants. In addition, it has been shown that the application of bacteriocins to manure accelerates decomposition and produces nutrientsrich compostCompost [126]. Biofertilizers incorporating bacteriocin-producing bacteria into biofertilizers promotes healthy soil microbiota, enhances nutrient uptake, and suppresses soil-borne diseases. It contributes to more sustainable farming practices, by improving plant health and yields

Post-Harvest Protection:

Citrus fruits are protected against microbial spoilage during storage and transport by bacteriocin treatments after harvesting. This is particularly relevant for maintaining the quality and safety of fruit such as oranges and lemons, which are likely to be infected with bacteria or fungus. [126]. Along with Grain Storage, bacteriocins are used for the protection of stored grains, e.g. wheat and rice against microbiological contamination. In order to ensure a stable food supply, this helps to maintain the safety and viability of the grains during extended storage periods. [127].

Sustainable Farming

Crop Rotation by limiting the persistence of soilborne pathogens, Bacteriocins support sustainability practices such as crop rotation and lead to better crops for future generations. This will improve the overall health and yield of crops, contributing to more sustainable agricultural systems. Integrated pest management Bacteriocins, in order to decrease the use of chemical pesticides, have been incorporated into Pest Management Plans. This will help to maintain

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ecological balance and reduce the environmental impact of agriculture, making it more sustainable and environmentally friendly. [126].

Veterinary Medicine

Antibiotic Alternatives

Bacteriocins are used in the manufacture of pigs to combat infections like swine dysentery, due to Brachyspira hyodysenteriae. This will reduce the need for antibiotics, promote healthy livestock and decrease antimicrobial resistance. [114]. Furthermore, bacteriocins, which are added to cattle feed in order to prevent bacterial infections like E. coli and Salmonella, improve animal health and reduce the use of antibiotics have been shown to help protect animals from infection. This approach is critical for the maintenance of animal health and productivity. In addition Bacteriocin-producing probiotics are administered to calves to prevent enteric infections and promote healthy gut development. This contributes to overall health and growth, reducing the incidence of gastrointestinal diseases and improving animal productivity [9].

For the purpose of improving gut health and immune function, bacteria that contain bacteriocins are used in food supplements for animals. [126]. In aquaculture, bacteriocins help control bacterial infections in fish, such as those caused by Aeromonas hydrophila. It's reducing the]. Innnnd for antibiotics and promoting healthy fish stocks, an essential part of sustainability in aquaculture [114].

Companion Animals

Bacteriocins are added to cat and dog food for the purpose of promoting healthy digestion. These natural antimicrobials help maintain a healthy gut microbiota, prevent gastrointestinal disorders, and improve overall health and wellbeing [126]. Besides, Bacteriocins are formulated into topical treatments for pets to treat and prevent bacterial skin infections. The products reduce the risk of antibiotic resistance and promote a healthy skin, offering an efficient alternative to conventional antibiotics.

Regulatory considerations and challenges in the development of bacteriocins/AMPs as therapeutic agents

Regulatory Considerations

Safety and Toxicity Evaluation:Evaluating the safety and toxicity of bacteriocins and AMPs is a crucial aspect of the regulatory process. This involves comprehensive in vitro and in vivo testing to identify any potential toxic effects on human cells and tissues the goal is to ensure these agents do not cause significant cytotoxicity, immunogenicity, or other adverse effects that could limit their therapeutic use. Moreover, long-term toxicity studies are often required to assess potential chronic effects [128].

Quality Control and Standardization:Ensuring consistent quality and standardization of bacteriocins and AMPs is essential for regulatory approval. This involves developing robust methods for the production, purification, and quantification of these agents to maintain their purity, potency, and stability [127]. Techniques such as high-performance liquid chromatography (HPLC) and mass spectrometry are often used to verify the purity and concentration of these compounds. Regulatory agencies require detailed documentation of these processes to ensure batch-to-batch consistency and to detect any potential contaminants.

Clinical Trial Requirements:Clinical trials are essential to evaluate the efficacy and safety of bacteriocins and AMPs in humans. These trials are conducted in three phases: Phase I focuses on safety and dosage, determining the maximum tolerated dose and identifying any side effects [2]. Phase II trials assess efficacy and further evaluate safety, while Phase III trials confirm efficacy in a larger population and monitor adverse effects [128]. Designing these trials is complex, requiring precise targeting of bacterial infections and careful monitoring for potential immunogenic responses.

Intellectual Property and Patenting:Securing intellectual property rights and patents is a critical step in the development of bacteriocins and AMPs. Patenting these agents can be challenging due to their natural origin and the difficulties in defining their unique properties and uses [127]. Patents are essential for protecting investments and ensuring commercial viability. Detailed descriptions of the production processes, molecular structures, and therapeutic applications are necessary for successful patent applications

Regulatory Approval:Obtaining regulatory approval for bacteriocins and AMPs involves navigating

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complex and stringent guidelines set by regulatory bodies such as the FDA and EMA. These agencies require extensive data on the safety, efficacy, quality control, and manufacturing processes of these agents [127]. The approval process includes preclinical testing, clinical trials, and rigorous reviews of the production and quality control documentation. This process can be lengthy and resource-intensive, necessitating comprehensive documentation and evidence of compliance with regulatory standards [128].

Challenges

Production and Purification Challenges: Scaling up the production of bacteriocins and AMPs from laboratory to industrial scale presents significant challenges. Maintaining the purity, activity, and consistency of these agents during large-scale production is critical. This involves optimizing fermentation processes and purification methods to ensure high yields and purity [127]. Contamination control is essential to prevent microbial contamination that could compromise the safety and efficacy of the final product. Additionally, the cost-effectiveness of production methods is crucial for commercial viability.

Stability and Delivery Challenges: Bacteriocins and AMPs often face stability issues that can limit their therapeutic use. These agents may degrade rapidly in biological environments, reducing their efficacy [127]. Developing effective delivery systems that protect these agents and ensure their stability and bioavailability is crucial for their clinical application. Nanoparticle-based delivery systems, encapsulation techniques, and formulation with stabilizing agents are some strategies being explored to address these challenges [128].

Resistance Development:The potential for bacteria to develop resistance to bacteriocins and AMPs is a major concern. This resistance can undermine the long-term efficacy of these agents, necessitating the development of strategies to monitor and mitigate resistance [2]. Understanding the mechanisms of resistance and developing combination therapies that use multiple agents to reduce the likelihood of resistance are critical areas of ongoing research [127].

Limited Data on Clinical Efficacy:Despite promising preclinical results, there is limited clinical data on the efficacy of bacteriocins and AMPs in humans [128]. More extensive and well-designed clinical trials are needed to provide robust evidence of their therapeutic potential. These trials must be sufficiently powered to detect clinically meaningful effects and should be designed to address the specific indications for which these agents are intended [127].

Regulatory Complexity:Navigating the regulatory landscape is complex and challenging, involving stringent requirements for safety, efficacy, quality control, and manufacturing processes [128]. The regulatory process requires extensive documentation and evidence of compliance, which can be resource-intensive and costly. Collaboration between researchers, regulatory agencies, and industry stakeholders is crucial to successfully navigate these complexities and bring bacteriocins and AMPs to market [127]. The evolving nature of regulatory guidelines for novel therapeutics adds another layer of complexity, necessitating continuous engagement with regulatory bodies to stay updated on requirements.

Strategies for overcoming challenges

Biotechnological approaches for production and engineering

Recombinant expression systems: Genetic engineering techniques have facilitated the production of bacteriocins and AMPs in heterologous hosts, such as bacteria, yeasts, and plant systems, enabling scalable and cost-effective production [129].

Rational design and engineering: Computational tools and structure-based design strategies are being employed to engineer bacteriocins and AMPs with improved potency, stability, and specificity [130].

Combinatorial biosynthesis: This approach involves the fusion or hybridization of different bacteriocin or AMP sequences to create novel chimeric peptides with enhanced antimicrobial properties [131].

Novel delivery systems and formulations

Nanoparticle-based delivery: Encapsulation of bacteriocins and AMPs in nanoparticles, such as liposomes, polymeric nanoparticles, and inorganic nanoparticles, can enhance their stability, targeted delivery, and bioavailability [132].

Hydrogel and polymeric formulations: Incorporating bacteriocins and AMPs into hydrogels or polymer-

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based formulations can facilitate controlled release and sustained antimicrobial activity [133].

Formulation with adjuvants: Combining bacteriocins and AMPs with adjuvants, such as chelating agents or efflux pump inhibitors, can potentiate their activity and overcome resistance mechanisms [134].

Strategies to mitigate resistance development

Combination therapy: Utilizing bacteriocins and AMPs in combination with conventional antibiotics or other antimicrobial agents can reduce the risk of resistance development and enhance efficacy [135].

Rapid cycling: Rotating the use of different bacteriocins or AMPs can minimize the selective pressure for resistance development [136].

Targeting resistance mechanisms: Developing bacteriocins and AMPs that target specific resistance mechanisms, such as efflux pumps or biofilm formation, can enhance their efficacy against resistant strains [16].

Other strategies include exploring alternative sources of bacteriocins and AMPs, such as plant-derived antimicrobial peptides (phytochemicals) and antimicrobial peptides from insects or marine organisms [137]. Also, continuous surveillance and monitoring of resistance patterns are essential for identifying emerging resistance mechanisms and developing appropriate countermeasures [127].

Clinical and therapeutic potential applications of bacteriocins/AMPs in human and veterinary medicine

In human medicine, bacteriocins and AMPs have been explored for the treatment of various infectious diseases caused by antibiotic-resistant bacteria. For instance, nisin, a well-known bacteriocin, has been investigated for the treatment of skin and soft tissue infections caused by MRSA [138,139]. Additionally, lacticin 3147, a bacteriocin produced by *Lactococcus lactis*, has shown potential for the treatment of *Clostridium difficile* infections [121]. Moreover,many clinical trials have been conducted to evaluate the safety and efficacy of these peptides for various indications. For instance, a phase I clinical trial evaluated the safety and tolerability of the bacteriocin lacticin 3147 in healthy volunteers [140]. The results showed that lacticin 3147 was well-tolerated and had no significant adverse effects, paving the way for further clinical studies. Another study investigated the use of nisin as a topical treatment for skin and soft tissue infections caused by MRSA [141]. The study demonstrated the antimicrobial activity of nisin against MRSA strains and its potential for treating skin infections.

AMPs, such as human defensins and cathelicidins, have also been explored for their therapeutic potential against various bacterial infections, including those caused by antibiotic-resistant pathogens. For example, human β-defensin-3 has shown activity against MRSA and *Pseudomonas aeruginosa* [79,80]. In addition to their direct antimicrobial effects, bacteriocins and AMPs have also been studied for their immunomodulatory properties, which could enhance the host's immune response against bacterial infections [142,143].

In veterinary medicine, bacteriocins and AMPs have been investigated for the prevention and treatment of various infectious diseases in livestock and companion animals. For instance, nisin has been explored for the treatment of bovine mastitis caused by *Staphylococcus aureus* and *Streptococcus agalactiae* [144,145]. A study by Pieterse and Todorov (2010) investigated the use of the bacteriocin-producing strain Enterococcus mundtii ST4SA for the control of *Listeria monocytogenes* in processed meat products. Additionally, AMPs derived from insects and amphibians have shown potential for the treatment of bacterial infections in aquaculture and poultry.[146]. For instance, a study by Jia et al. (2020) evaluated the therapeutic potential of the frog-derived AMP Esculentin-1a for treating *Aeromonas hydrophila* infection in zebrafish, demonstrating its efficacy and low toxicity.[147].

Furthermore, bacteriocins and AMPs have been studied for their potential applications in food preservation and as growth promoters in animal feed, reducing the need for traditional antibiotics and minimizing the risk of antibiotic resistance development [9,148].

Despite these promising findings, several challenges remain before bacteriocins and AMPs can be widely adopted as therapeutic agents in clinical and veterinary settings. These challenges include optimising production and purification processes, addressing potential toxicity and stability issues, developing effective delivery systems, and

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overcoming potential resistance mechanisms [124,149]. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have established guidelines for the development and evaluation of antimicrobial peptides as therapeutic agents [150,151]. Therefore, the future directions and research opportunities in the development of bacteriocins and AMPs as alternative therapeutic agents are vast and hold significant potential for addressing the growing challenge of antibiotic resistance. Optimization of production and purification processes such as development of efficient and cost-effective production methods or exploration of novel purification techniques to improve yield and purity should be considered. Peptide engineering and design such as Rational design and engineering of bacteriocins and AMPs using computational approaches, such as molecular modeling and bioinformatics, to predict and optimize peptide structures and activities to enhance their potency, stability, and selectivity should be verified. Collaborative efforts, interdisciplinary approaches, and continued investment in research and development are essential to overcome the existing challenges and translate these promising peptides into effective therapeutic solutions

Conclusion

The escalating global threat of antibiotic-resistant bacterial infections has highlighted the urgent need for alternative therapeutic strategies. Bacteriocins and antimicrobial peptides (AMPs) have emerged as promising candidates, offering a diverse array of antimicrobial properties and unique mechanisms of action against a wide spectrum of pathogenic bacteria, including multidrug-resistant (MDR) strains.

This comprehensive review has explored the classification, modes of action, and spectrum of activity of bacteriocins and AMPs, underscoring their potential as effective alternatives to conventional antibiotics. While their antimicrobial efficacy is well-established, the development of resistance to these antimicrobial agents remains a concern, necessitating the implementation of strategies such as combination therapy, rapid cycling, and targeting specific resistance mechanisms. Synergistic interactions between bacteriocins/AMPs and conventional antibiotics or other antimicrobial agents have been demonstrated, offering opportunities to potentiate their antimicrobial effects, reducing the risk of side effects and overcoming resistance mechanisms. Additionally, in vivo studies in animal models have provided valuable insights into the efficacy and safety profiles of these antimicrobial agents, paving the way for their potential applications in various fields, including food preservation, agriculture, and veterinary medicine. Despite their promising potential, the development of bacteriocins and AMPs as therapeutic agents faces several challenges, including stability, toxicity, and effective delivery systems. Regulatory considerations and challenges also exist, requiring rigorous evaluation and compliance with guidelines to ensure safety and efficacy.Strategies for overcoming these challenges have been explored, including biotechnological approaches for production and engineering, novel delivery systems and formulations, and strategies to mitigate resistance development. These strategies hold the potential to enhance the therapeutic viability of bacteriocins and AMPs, enabling their translation into clinical and therapeutic applications in human and veterinary medicine.

In summary, bacteriocins and AMPs represent a promising class of alternative therapeutic agents with broad-spectrum antimicrobial activity against antibiotic-resistant bacterial pathogens. While their potential is evident, further research and development efforts are required to address the challenges associated with their clinical translation. Interdisciplinary collaborations among researchers, clinicians, and regulatory authorities are crucial to facilitate the successful development and implementation of these antimicrobial agents as effective therapeutic strategies against the growing threat of antibiotic resistance.

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