

Antimicrobial resistance menace: Bacteriocins as promising alternative to conventional antibiotics

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ABSTRACT: Antimicrobial resistance (AMR) has emerged as a critical global public health challenge, driven by the widespread misuse of antibiotics in human medicine, agriculture, and animal production. The increasing prevalence of multidrug-resistant pathogens, particularly members of the ESKAPE group, has significantly reduced the effectiveness of conventional antimicrobial therapies and necessitated the development of alternative treatment strategies. This review critically evaluates bacteriocins as promising bioactive alternatives to conventional antibiotics. Relevant literature on bacteriocin classification, mechanisms of action, antimicrobial activities, therapeutic applications, and associated challenges was systematically examined. Bacteriocins are ribosomally synthesised antimicrobial peptides produced by diverse bacterial species, particularly lactic acid bacteria (LAB), and exhibit potent antibacterial, antiviral, antifungal, antibiofilm, and anticancer activities. Their antimicrobial effects are mediated through mechanisms including membrane pore formation, inhibition of cell wall biosynthesis, induction of cell lysis, and interference with essential cellular processes. Evidence has demonstrated significant inhibitory activity against both Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Listeria monocytogenes*, and Gram-negative bacteria such as *Salmonella* spp., *Escherichia coli*, and *Pseudomonas aeruginosa*. Furthermore, synergistic interactions between bacteriocins and conventional antibiotics enhance antimicrobial efficacy against resistant pathogens and biofilm-associated infections. Despite their promising therapeutic potential, challenges such as narrow antimicrobial spectra, proteolytic degradation, limited in vivo stability, high production costs, and regulatory constraints continue to limit clinical application. Advances in peptide engineering, genomics, nanotechnology, and targeted delivery systems offer opportunities to overcome these limitations. Overall, bacteriocins represent a viable and sustainable strategy for combating AMR and may contribute substantially to future antimicrobial stewardship and global public health interventions.

Keywords: Alternative therapeutics, antibiofilm activity, antimicrobial resistance, bacteriocins, ESKAPE pathogens, lactic acid bacteria, multidrug-resistant bacteria.

INTRODUCTION

Antimicrobial resistance (AMR) has become a major global health concern due to the increasing inability of antibiotics to effectively treat infectious diseases. Antimicrobial resistance occurs when microorganisms evolve mechanisms that enable them to survive exposure to

antimicrobial agents previously effective against them. The emergence of multidrug-resistant organisms has become a major challenge to global healthcare systems. Some factors, excessive use of antibiotics in clinical settings, self-medication, poor prescription practices, agricultural

application of antibiotics, poor infection prevention and control measures and horizontal gene transfer among bacteria are major contributing factors to antimicrobial resistance (AMR) (Imran, 2019).

The misuse and overuse of antibiotics in medicine, agriculture, and animal husbandry have accelerated the emergence of resistant microorganisms, thereby reducing the efficacy of conventional antimicrobial therapies (Imran, 2019). Some of the most dangerous microbial threats in terms of resistance are united under the acronym "ESKAPE" (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), recently becoming ESCAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Clostridium difficile*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*) (Gradisteanu *et al.*, 2021). These clinically important pathogens often harbour mobile genetic elements, facilitating the spread of resistant organisms as well as the ability to develop biofilms on viable host tissues or inert substrates (Giedraitienė *et al.*, 2011). They are responsible for severe hospital-acquired infections and increased mortality rates. Antimicrobial resistance (AMR) is one of the top global public health and development threats. It is estimated that bacterial AMR was directly responsible for 1.27 million global deaths in 2019 and contributed to 4.95 million deaths (Murray *et al.*, 2022).

In addition to death and disability, AMR has high economic costs. The World Bank estimates that AMR could result in US\$ 1 trillion in additional healthcare costs by 2050, and US\$ 1 trillion to US\$ 3.4 trillion in gross domestic product (GDP) losses per year by 2030 (WHO, 2023). Consequently, there is an urgent need for alternative antimicrobial agents capable of overcoming antibiotic resistance. The urgency to develop new antibiotics was classified into medium, high and critical priority. The priority list comprised extended-spectrum β -lactamase (ESBL) or carbapenem-resistant *K. pneumoniae* and *Enterobacter* spp., while carbapenem-resistant *A. baumannii* and *P. aeruginosa* are labelled as critical priority pathogens. On the other hand, vancomycin-resistant *E. faecium* (VRE) and methicillin- and vancomycin-resistant *S. aureus* (MRSA and VRSA) are considered high-priority pathogens (Tacconelli *et al.*, 2018).

Bacteriocins are ribosomally synthesised antimicrobial peptides produced by bacteria to inhibit competing microorganisms within the same ecological niche (Imran, 2019). These peptides are produced by both Gram-positive and Gram-negative bacteria. The first bacteriocin, colicin, was discovered by Gratia in 1925. Gratia discovered bacteriocins by observing that certain strains of *Escherichia coli* naturally produced a diffusible, antibacterial substance that inhibited the growth of neighbouring, closely related bacterial strains. Because it killed *E. coli*, he named this first discovery "colicin" leading

to the subsequent identification of numerous bacteriocins from different bacterial species (Imran, 2019). Recent studies have demonstrated that bacteriocins possess antibacterial, antiviral, antifungal, antibiofilm, and anticancer activities, highlighting their therapeutic potential beyond food preservation. Bacteriocins derived from lactic acid bacteria (LAB) have attracted greater scientific interest because of their biosafety and extensive industrial applications. LAB are generally regarded as safe (GRAS) and are widely used in food fermentation processes (Rashid *et al.*, 2013).

This review critically evaluates the role of bacteriocins as promising alternatives to antibiotics in addressing antimicrobial resistance, with emphasis on their classification, mechanisms of action, antimicrobial spectrum, applications, challenges, and future prospects.

GENERAL CHARACTERISTICS OF BACTERIOCINS

Bacteriocins are low molecular weight antimicrobial peptides synthesised ribosomally by bacteria to inhibit closely related or pathogenic bacteria species (Imran, 2019). They are typically proteinaceous compounds that exhibit bactericidal or bacteriostatic activities, are heat-stable at 100 °C for 10 min, and are extracellularly excreted to inhibit or kill other bacterial strains (Aljohani *et al.*, 2023). Qiao *et al.* (2022) found that BMP32r, a type of bacteriocin that disrupts mature biofilms by killing bacteria in the biofilm and its effectiveness in killing *Listeria monocytogenes* persists make it a promising potential anti-biofilm agent against *Listeria monocytogenes*. Normally, bacteriocins are not termed antibiotics to avoid confusion with therapeutic antibiotics (Sen and Ray, 2019); they are rapidly digested by proteases in the human digestive tract, which is the difference between them and most therapeutic antibiotics (Tkhruni *et al.*, 2020).

Bacteriocins have a different spectrum of activity, mode of action, molecular weight (MW), genetic origin, and biochemical properties (Darbandi *et al.*, 2022). Some bacteriocins target closely related bacterial strains with high precision, while others demonstrate a broader spectrum, effectively inhibiting pathogens across multiple genera (Chen *et al.*, 2025).

Lactic acid bacteria (LAB) derived bacteriocins are particularly important due to their safety profile and effectiveness against foodborne and clinically significant pathogens (Rashid *et al.*, 2013). LAB are Gram-positive, catalase-negative, non-spore-forming, acid-tolerant microorganisms commonly isolated from fermented foods and dairy products. LAB produce a large number of bacteriocins from strains like *Lactobacillus*, *Pediococcus*, *Lactococcus*, and *Enterococcus* (Trejo-González *et al.*, 2021). Their ability to remain active at various pH values, resist high temperatures, and be active against a wide range of foodborne pathogenic and spoilage bacteria makes them suitable as an alternative to antibiotics.

Studies by Rashid *et al.* (2013) demonstrated that bacteriocin produced by *Lactococcus lactis* exhibited significant antimicrobial activity against *Salmonella typhi*, with inhibition zones reaching 17.0 ± 0.7 mm under optimised conditions.

Proteinaceous nature: Bacteriocins are composed of amino acids and are ribosomally synthesised. Unlike conventional antibiotics, bacteriocins are ribosomally synthesised. This allows bacteria to easily encode, regulate, and modify them. Post-translational modifications, such as folding and cross-linking (common in lantibiotics), grant them unique structural stability (Hiemstra and Zaat, 2013).

Specific antimicrobial spectrum: They typically possess a narrow spectrum of activity, inhibiting strains closely related to the producer while leaving beneficial microbiota largely unharmed. Effective at nanomolar or picomolar concentrations, especially against microorganisms closely related to the producing bacteria (Meade *et al.*, 2020). Some engineered or broad-spectrum bacteriocins can also target a wider array of pathogens.

Bactericidal mode of action: They generally cause cell death (bactericidal) rather than just pausing growth (bacteriostatic). They often do this by disrupting the target cell's cytoplasmic membrane (causing pore formation) or inhibiting cell wall biosynthesis.

High thermal stability: Many bacteriocins (especially those from Lactic Acid Bacteria) are heat-stable, allowing them to withstand various food processing techniques like pasteurisation or sterilisation without losing antimicrobial efficacy (Bédard and Biron 2018).

Low cytotoxicity and toxicity: Ideal bacteriocins are non-toxic to eukaryotic cells, making them safe for human consumption and potential therapeutic or pharmaceutical applications.

Biodegradability: They are usually sensitive to proteolytic enzymes (digestive proteases), meaning they are safely broken down in the human gastrointestinal tract without disrupting the natural gut flora.

Sources of bacteriocin-producing bacteria

Traditional fermented foods represent important reservoirs of LAB with bacteriocin-producing potential. Hayati *et al.* (2021) isolated LAB from fermented buffalo milk ("dadih") and identified *Lactobacillus pentosus* as a potent bacteriocin producer exhibiting antimicrobial activity against *Salmonella sp.*, *E. coli*, and *Staphylococcus aureus*. Similarly, bacteriocin-producing strains have been isolated from Camel milk, Cheese, Yogurt, Fermented meat products and human intestinal microbiota.

Classification of bacteriocins

Bacteriocins are classified based on molecular weight, structure, heat stability, and post-translational modifications (Table 1 and Figure 1).

Mechanisms of action of bacteriocins

Unlike antibiotics, most bacteriocins exhibit a narrower spectrum of activity but are valued for their excellent stability, structural diversity, and low toxicity. Additionally, their specific antimicrobial mechanisms and biosynthesis processes reduce the likelihood of developing resistance (Chen *et al.*, 2025). Due to the great variation in their chemical structures, bacteriocins affect different essential functions of the cells, such as biosynthesis and molecular processes; however, the most common lytic action is by forming pores or membrane channels that destroy the energy potential of the sensitive cells (Figure 2). Most bacteriocins exert a bactericidal effect on sensitive cells (Imran, 2019). The first contact of a bacteriocin with a sensitive cell takes place due to electrostatic interactions between a positively charged, hydrophobic bacteriocin molecule and negatively charged phospholipids in the cytoplasmic membrane of a sensitive cell (Karpiński and Szkaradkiewicz, 2013).

Another mechanism of bacteriocin activity involves their ability to induce lysis of bacterial cells (Figure 3). The process is linked to the interaction of bacteriocins (please check the right spelling of bacteriocin so you can maintain a uniform spelling) with teichoic, lipoteichoic, and teichuronic acids found in Gram-positive bacteria, representing components of their cell wall. This results in the release and activation of autolytic enzymes linked to the cell, which results in cell autolysis (Karpiński and Szkaradkiewicz, 2013). Bacteriocins belonging to lantibiotics class may additionally interrupt processes of cell wall biosynthesis. They inhibit synthesis of peptidoglycan at the transglycosylation stage, which is not accompanied by a disturbed biosynthesis of DNA, RNA or protein (Moll *et al.*, 1999).

Mechanisms of cell-targeted activity manifested by bacteriocins produced by Gram-negative bacteria include depolarisation of cell membranes (e.g., colicin E1), damage to DNA (e.g., colicin E2, acting as a non-specific endonuclease) or inhibition of protein synthesis by inactivation of ribosomal RNA (colicin E3 and cloacin DF13) (Karpiński and Szkaradkiewicz, 2013).

ANTIMICROBIAL ACTIVITY OF BACTERIOCINS

Bacteriocins demonstrate activity against a wide range of pathogens.

Activity against Gram-positive bacteria

Panina *et al.* (2020) reported that bacteriocins can inhibit

Table 1. Classification of bacteriocins based on their molecular weight, structure and heat stability.

Class	Characteristics
I (Lantibiotics)	These are small (less than 10 kDa) heat-stable peptides containing unusual amino acids such as lanthionine. Nisin is the most studied example and has broad antimicrobial activity against Gram-positive bacteria.
II	These are small, but greater than 10 kDa, heat-stable non-lanthionine, non-modified peptides; their antimicrobial activity is primarily exerted by enhancing membrane permeability. It is subdivided into: Class IIa: Pediocin-like bacteriocins characterised by a double glycine-type signal sequence. Class IIb: Two-peptide bacteriocins Class IIc: Circular bacteriocins with covalently bonded N- and C-termini, typically exceeding 30 kDa in molecular weight and exhibiting a narrow antimicrobial spectrum (Ghosh <i>et al.</i> ,2019)
III	These are large heat-labile proteins with molecular weights exceeding 30 kDa
IV	Cyclic peptides, and little is known about the structure and function of this class. Characteristics of this group have yet to be determined by purification and biochemical characterisation. These bacteriocins include leuconocin S and lactocin (Bharti <i>et al.</i> , 2015)

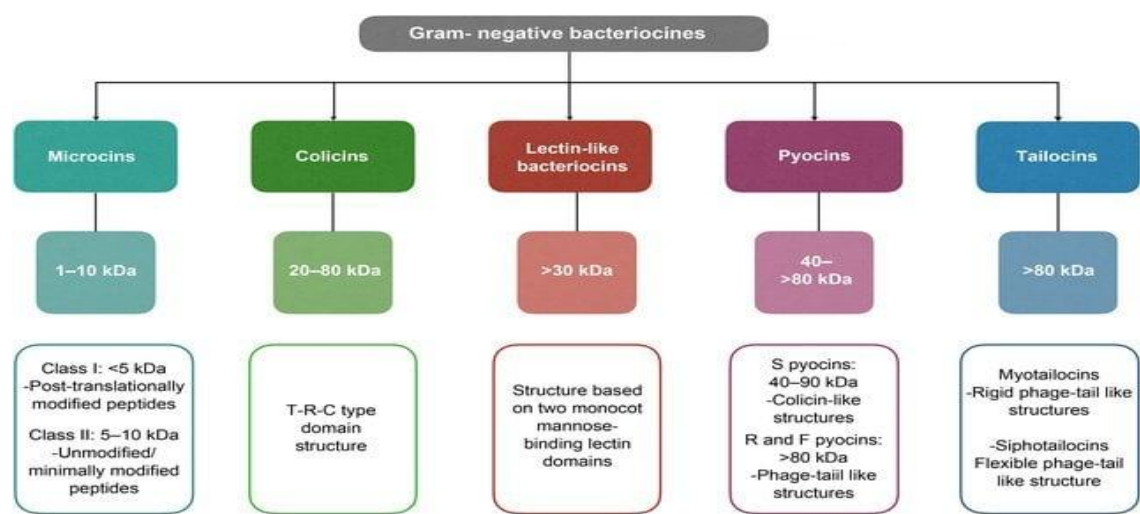


Figure 1. Structure-based classification of Gram-negative bacteriocins (Cesa-Luna *et al.*, 2021)

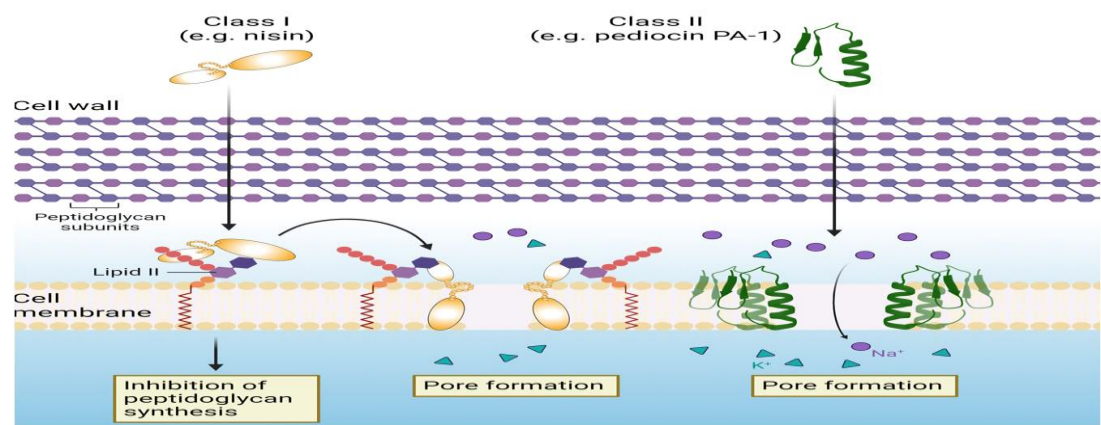


Figure 2. Illustration of the mechanism of action of bacteriocins in forming pores in the targeted cell membrane (Uniacke-Lowe *et al.*, 2024).

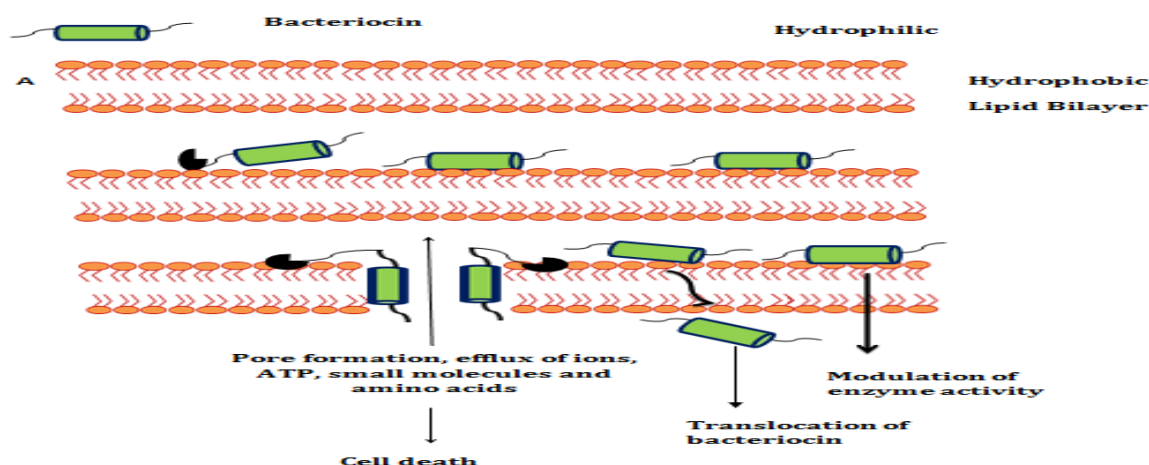


Figure 3. The general killing mechanisms of bacteriocins, including binding of bacteriocin to receptors (A, B), cytoplasmic membrane pore formation, translocation of bacteriocin and modulation of enzyme activity (C) (Ennahar *et al* 2000).

Gram-positive bacteria by forming membrane pores and blocking peptidoglycan synthesis. For example, Nisin binds to lipid II molecules, inhibiting peptidoglycan synthesis and forming pores in the cell membrane, which leads to cell lysis *in vitro*. Chen *et al* (2025) also reported that Lacticin 481, produced by *Lactococcus lactis*, was identified in 1992 as an inhibitor of various Gram-positive bacteria. In 2016, Zipperer *et al.* found that lugdunin produced by *Staphylococcus lugdunensis* had a broad spectrum of biological activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant, and glycopeptide-intermediate-resistant *Staphylococcus aureus* strains. In the same vein, Khorshidian *et al.* (2021) discovered that pediocin produced by *Pediococcus* could be effective against many Gram-positive bacteria, particularly *Listeria*, and it is commonly used in the preservation of meat and meat products. The LAB liquid isolate solution and crude bacteriocins isolated by Hayati *et al.* had inhibitory activity against Gram-positive (*S. aureus*) and Gram-negative (*E. coli* and *Salmonella sp.*) bacteria. He also reported that the inhibitory activity of crude bacteriocins against *S. aureus* was higher than the inhibitory activity against *E. coli* and *Salmonella sp.* (Hayati *et al.*, 2021). This suggests the effectiveness of bacteriocins against Gram-positive bacteria and as a possible alternative. MRSA and other *Staphylococcus aureus* strains are inhibited by *Lactobacillus* species (e.g., *Lactobacillus rhamnosus*, *Lactobacillus fermentum*, and *Lactobacillus casei*) through the production of organic acids, bacteriocins, and biosurfactants (Adeola *et al.*, 2025).

Activity against Gram-negative bacteria

Although Gram-negative bacteria are more resistant to bacteriocins due to their outer membrane, certain

bacteriocins exhibit inhibitory effects against these groups of bacteria. Rashid *et al.* (2013) observed substantial inhibition of *Salmonella typhi* by *Lactococcus lactis* bacteriocin against *Escherichia coli*, *Salmonella spp.* and *Pseudomonas aeruginosa*. Studies have shown that *Acidophilus* STRAIN 52 and *Limosilactobacillus fermentum* STRAIN 45 inhibit Cephalosporin-resistant *Escherichia coli* strains with a 100% inhibition rate (Riaz *et al.*, 2010). In research conducted by Todorovet *et al.*, 2005 they report that Acidocin exhibited a moderate antibacterial effect against drug-resistant *Pseudomonas aeruginosa*, with an inhibition zone of 15.00 mm. Lu *et al.* (2014) isolated Lactocin MXJ 32A from the *Loigolactobacillus coryniformi* sMXJ 32 strain, which strongly inhibited the growth of *Salmonella* (inhibition zone > 20 mm). The antibacterial activity against *Salmonella* strains 87T4, 1006D, 36T, 557D, and 798D was measured at 4112.4, 3812.1, 4288.4, 4422.5, and 3770.0 AU/mL (Arbitrary Units per millilitre), respectively. In addition to producing acids and bacteriocins (such as colicins from *E. coli*), probiotics (*L. rhamnosus* GR-1, *L. reuteri* RC-14, *L. crispatus*, and *Bacillus spp.*) also compete for adhesion sites in the gut and urinary tract and break up biofilms, which is one of the microbial resistance factors (Adeola *et al.*, 2025).

Synergistic effects with antibiotics

Bacteria present in a biofilm are inherently more resistant to antimicrobials than those present in a planktonic state, predominantly due to the complex polymeric matrix of which biofilms are composed, and this matrix often impedes penetration of the antimicrobial to the deepest strata of the biofilm (Mathur *et al.*, 2017). Studies on bacteriocins revealed that these are not only very effective in the food industry as probiotics but can also act as an

antibacterial and enhance the host immune response. Studies have shown synergistic interactions between bacteriocins and antibiotics, enhancing antimicrobial efficacy against resistant pathogens (Imran, 2019).

Sactibiotics (sactionine-containing antibiotics) are a subclass of bacteriocins, naturally occurring antimicrobial peptides produced by bacteria to inhibit or kill rival bacteria. The efficacy of this sactibiotic, thuricin CD, was assessed in combination with metronidazole, ramoplanin and vancomycin, with a view to targeting *C. difficile* strains. It was revealed that thuricin CD interacted in a partial synergistic manner when combined with ramoplanin against 31% of the target strains tested (Mathur *et al.*, 2013). Antimicrobial combination studies have also been conducted with the sactibiotic subtilisin A against *Gardnerella vaginalis*. It was determined that subtilisin A exhibited Bliss synergy when combined with clindamycin phosphate, metronidazole, ϵ -Poly-L-Lysine (polylysine) and lauramide arginine ethyl ester (LAE) against the pathogen (Cavera *et al.*, 2015).

ANTIVIRAL AND ANTICANCER POTENTIAL OF BACTERIOCINS

Beyond their established antibacterial activity, bacteriocins have attracted considerable attention because of their antiviral and anticancer properties. Their diverse structures and mechanisms of action enable them to interact with viral particles and mammalian cells, suggesting potential applications beyond conventional antimicrobial therapy.

Antiviral potential

Several bacteriocins and bacteriocin-like peptides have demonstrated activity against important human viruses, particularly enveloped viruses. Subtilisin, a cyclic bacteriocin produced by *Bacillus* species, has shown significant antiviral activity against Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). Torres *et al.* (2013) reported that subtilisin inhibited HSV-1 replication and produced a direct virucidal effect at higher concentrations. Similarly, Quintana *et al.* (2014) demonstrated that subtilisin inhibited HSV-2 replication at non-cytotoxic concentrations, indicating that its antiviral effect was not simply a consequence of toxicity to host cells.

Another important example is labyrinthopeptin A1, which has demonstrated activity against both HIV and HSV. Férrir *et al.* (2013) reported that labyrinthopeptin A1 inhibited HIV-1, HIV-2 and HSV-1/HSV-2, principally by interfering with viral entry. The peptide also showed additive or synergistic effects when combined with established antiviral agents, suggesting potential application in combination therapy. Further evidence indicates that labyrinthopeptins can act against a broader range of

enveloped viruses by interacting with viral membrane lipids and disrupting viral envelopes (Prochnow *et al.*, 2019). These findings suggest that membrane disruption, inhibition of viral attachment and interference with viral entry or replication may contribute to the antiviral activity of bacteriocins.

Anticancer potential

Bacteriocins have also demonstrated promising anticancer activity, particularly against several tumour cell lines. Their anticancer effects have been associated with disruption of cancer-cell membranes, inhibition of proliferation, cell-cycle arrest and induction of apoptosis (Kaur and Kaur, 2015). The membrane-active nature of some bacteriocins is particularly important because cancer cells frequently possess negatively charged membrane surfaces, which can favour their interaction with positively charged antimicrobial peptides.

One extensively studied example is **nisin**, which has demonstrated cytotoxic and antiproliferative effects against cancer cells. Joo *et al.* (2012) reported that nisin induced apoptosis in human head and neck cancer cells, while subsequent studies have associated bacteriocin-mediated anticancer effects with mitochondrial dysfunction, changes in apoptotic proteins and activation of caspase-dependent pathways (Soltani *et al.*, 2022). In addition to apoptosis, bacteriocins may inhibit tumour-cell proliferation and interfere with processes involved in tumour progression (Kaur and Kaur, 2015).

The structural diversity of bacteriocins may explain their ability to affect different cellular processes. Their cationic charge, hydrophobicity, peptide conformation and post-translational modifications influence their interactions with biological membranes and intracellular targets. Consequently, bacteriocins may exert anticancer effects through membrane pore formation, disruption of membrane potential, mitochondrial damage, inhibition of biosynthetic processes and activation of programmed cell death (Kaur and Kaur, 2015; Soltani *et al.*, 2022).

Comprehensively, the antiviral and anticancer activities of bacteriocins expand their potential biomedical applications beyond antibacterial therapy. However, most available evidence remains based on in-vitro and preclinical investigations. Further studies are required to establish their pharmacokinetics, therapeutic doses, selectivity, toxicity and clinical efficacy before these promising activities can be translated into routine antiviral or anticancer treatments (Flynn *et al.*, 2021; Sugrue *et al.*, 2024).

CHALLENGES LIMITING CLINICAL APPLICATION

Despite the promising antimicrobial properties of bacteriocins and their potential to address the growing

problem of antimicrobial resistance, several challenges continue to limit their translation from experimental research into routine clinical practice. These challenges relate to their antimicrobial spectrum, stability, pharmacokinetic properties, production, safety and regulatory requirements.

Narrow antimicrobial spectrum

A major limitation of bacteriocins is their relatively narrow antimicrobial spectrum. Many bacteriocins exert their activity against specific bacterial species or closely related groups because their mechanisms of action depend on recognition of particular receptors or cell-envelope components on susceptible bacteria. Consequently, a bacteriocin that is highly effective against one pathogen may have little or no activity against another pathogen, even when both are responsible for similar clinical infections. This specificity differs from the broader activity of some conventional antibiotics and can make bacteriocins less suitable for empirical treatment, particularly when the causative organism has not yet been identified (Cotter *et al.*, 2013; Yang *et al.*, 2014).

The narrow spectrum may also present a challenge in polymicrobial infections, where several bacterial species occur simultaneously. In such situations, administration of a single bacteriocin may not provide adequate antimicrobial coverage, potentially requiring combinations of different bacteriocins or bacteriocin–antibiotic combinations. Nevertheless, the same specificity can be therapeutically advantageous because it may allow selective elimination of pathogenic bacteria while causing less disruption to the beneficial intestinal microbiota than broad-spectrum antibiotics (Cotter *et al.*, 2013; Sugrue *et al.*, 2024). Thus, future clinical development needs to identify bacteriocins with sufficiently broad activity or develop rational combinations capable of covering clinically important pathogens.

Susceptibility to proteolytic degradation

Susceptibility to proteolytic degradation is another important obstacle to the therapeutic use of bacteriocins. Since most bacteriocins are peptides, they can be degraded by proteolytic enzymes present in the gastrointestinal tract, blood and tissues. This is particularly problematic for orally administered bacteriocins because digestive enzymes may break down the peptide before it reaches its intended site of action, thereby reducing its bioavailability and antimicrobial effectiveness (Yang *et al.*, 2014; Soltani *et al.*, 2021).

Proteolytic degradation can also influence the effectiveness of bacteriocins administered through other routes because endogenous proteases can reduce the concentration of intact, biologically active peptide in circulation. Consequently, strong antimicrobial activity observed *in vitro* does not necessarily translate into

equivalent activity *in vivo*. Soltani *et al.* (2021) identified protection of bacteriocins from degradation and improvement of their delivery as important considerations in developing them as next-generation antimicrobial agents. Approaches such as chemical modification, peptide engineering, encapsulation, liposomal delivery and nanoparticle-based formulations may improve resistance to enzymatic degradation and prolong the availability of bacteriocins at the site of infection (Soltani *et al.*, 2021).

Limited stability *in vivo*

The limited stability of some bacteriocins under physiological conditions further restricts their clinical application. Their activity may be affected by pH, temperature, ionic strength, proteases, serum proteins and other components of the biological environment. Conditions encountered in the human body can therefore differ considerably from the controlled conditions under which bacteriocins are normally evaluated in laboratory experiments (Yang *et al.*, 2014; Soltani *et al.*, 2021).

Poor physiological stability may result in rapid loss of antimicrobial activity, reduced half-life and inadequate concentrations at the site of infection. In addition, some bacteriocins may undergo structural changes or aggregation that affect their biological activity. These problems are particularly important for systemic infections, where a therapeutic agent must remain sufficiently stable in the bloodstream and reach infected tissues in an active form. Soltani *et al.* (2021) therefore emphasised the importance of formulation and delivery strategies for protecting bacteriocins and improving their stability and pharmacokinetic behaviour. Similarly, Sugrue *et al.* (2024) highlighted the need to overcome biological and delivery barriers before the full therapeutic potential of bacteriocins can be realised. Encapsulation and other targeted delivery systems may consequently be important for improving *in vivo* stability, bioavailability and therapeutic efficacy.

High production costs

The cost and complexity of bacteriocin production and purification constitute another significant barrier to clinical development. Although bacteriocins can be produced naturally by their bacterial hosts, production yields may be relatively low, and the organisms may require carefully controlled growth conditions. Following fermentation, the active peptide must generally be recovered and purified to a level appropriate for pharmaceutical use. These downstream processes can involve precipitation, filtration, chromatography and concentration steps, which increase both production time and cost (Garsa *et al.*, 2014).

The problem becomes more pronounced when laboratory-scale production is transferred to industrial-scale pharmaceutical manufacturing. Maintaining consistent peptide yield, purity, biological activity and structural

integrity during large-scale production can be technically demanding. Garsa *et al.* (2014) noted that bacteriocin recovery and purification can involve substantial losses of the active product, thereby reducing overall process efficiency. Similarly, Cotter *et al.* (2013) identified production and purification as important considerations in the development of bacteriocins as therapeutic agents.

Therefore, commercial clinical application will require high-yield fermentation systems, optimised purification processes, recombinant production platforms and cost-effective downstream processing. Advances in synthetic biology and heterologous expression may provide opportunities to increase production yields and reduce manufacturing costs, but these technologies must still demonstrate reproducibility and pharmaceutical-grade quality on an industrial scale (Sugrue *et al.*, 2024).

Potential cytotoxicity

Although many bacteriocins have demonstrated favourable safety profiles, potential cytotoxicity remains an important consideration in their development as therapeutic agents. Bacteriocins generally exert their antimicrobial effects by interacting with bacterial membranes or specific cellular targets. However, depending on their structure, concentration and mechanism of action, some antimicrobial peptides can interact with mammalian cell membranes and potentially cause undesirable effects, including membrane damage or haemolysis (Darbandi *et al.*, 2022).

This concern is particularly important because an effective therapeutic bacteriocin must selectively damage pathogenic bacteria without producing significant toxicity to host tissues. A bacteriocin may therefore demonstrate strong antimicrobial activity *in vitro* but have a limited therapeutic window if the concentration required for bacterial killing approaches the concentration associated with host-cell toxicity. Darbandi *et al.* (2022) emphasised that toxicity and safety assessment are essential components of bacteriocin development, particularly because safety requirements differ considerably between food applications and pharmaceutical applications.

Accordingly, potential therapeutic bacteriocins require extensive evaluation for haemolytic activity, cytotoxicity, immunogenicity, tissue toxicity and systemic adverse effects before clinical use. Such assessments should include appropriate cell-based studies, animal models and ultimately controlled human clinical trials. Structural modification and targeted delivery may also help improve bacterial selectivity while reducing unwanted interactions with mammalian cells (Soltani *et al.*, 2021).

Regulatory approval limitations

Finally, regulatory requirements constitute a major barrier to the clinical application of bacteriocins. Demonstrating

antimicrobial activity in laboratory studies is insufficient for approval as a therapeutic product. Bacteriocins intended for human treatment must undergo rigorous evaluation of safety, efficacy, pharmacokinetics, pharmacodynamics, manufacturing consistency, purity and stability. Darbandi *et al.* (2022) emphasised that the regulatory framework for bacteriocins differs according to their intended application, and the requirements for therapeutic use are substantially more demanding than those associated with their use as food preservatives.

The regulatory challenge is also associated with the biological nature of bacteriocins. Their activity can depend on peptide sequence, post-translational modifications, formulation and manufacturing conditions. Consequently, pharmaceutical developers must demonstrate that each production batch has consistent composition, purity, potency and safety. In addition, adequate preclinical toxicological studies and properly designed clinical trials are required before regulatory authorisation can be obtained (Darbandi *et al.*, 2022; Soltani *et al.*, 2022).

The regulatory pathway is therefore considerably more complex than simply demonstrating that a bacteriocin kills a pathogen *in vitro*. The limited number of bacteriocins that have progressed to therapeutic approval illustrates the considerable gap between experimental promise and clinical translation. Addressing this gap will require standardised production processes, well-defined quality-control criteria, robust pharmacological studies and clinical evidence demonstrating that bacteriocins provide a meaningful benefit over existing antimicrobial therapies (Sugrue *et al.*, 2024).

CONCLUSION

Bacteriocins represent promising bioactive molecules with substantial potential to combat antimicrobial resistance. Their broad-spectrum antimicrobial activity, safety profile, and multiple mechanisms of action make them attractive alternatives to conventional antibiotics. Evidence from various studies demonstrates their effectiveness against multidrug-resistant pathogens, foodborne bacteria, and certain viruses. However, further research addressing toxicity, stability, and large-scale production is necessary before widespread clinical application can be achieved. Continued exploration and development of bacteriocins may contribute significantly to global efforts aimed at controlling antimicrobial resistance and improving public health outcomes.

Future Perspectives

Advances in biotechnology, genomics, and peptide engineering are expected to improve bacteriocin production and therapeutic efficacy. Future research should focus on:

- Genetic engineering of bacteriocin-producing strains.
- Nanoformulation and targeted delivery systems.
- Clinical trials for therapeutic applications.
- Combination therapies with antibiotics.
- Exploration of novel bacteriocins from unexplored ecosystems.

The integration of bacteriocins into antimicrobial stewardship programs could significantly reduce dependence on traditional antibiotics.

CONFLICT OF INTEREST

There is no conflict of interest on the part of the authors with regard to the publishing of this article.

REFERENCES

- Adeola, M. O., Ofesi, A. O., & Amhanriamhen, I. R. (2025). Mechanisms and therapeutic potential of probiotics as biofilm disruptors. *FNAS Journal of Applied Biological Sciences*, 2(4), 27-35. <https://doi.org/10.63561/jabs.v2i4.1005>
- Aljohani, A. B., Al-Hejin, A. M., & Shori, A. B. (2023). Bacteriocins as promising antimicrobial peptides, definition, classification, and their potential applications in cheeses. *Food Science and Technology*, 43, e118021.
- Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., & Tasak, N. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, 399(10325), 629-655.
- Bédard, F., & Biron, E. (2018). Recent progress in the chemical synthesis of Class II and S-glycosylated bacteriocins. *Front Microbiol*, 9, 1048.
- Bharti, V., Mehta, A., Singh, S., Jain, N., Ahirwal, L., & Mehta, S. (2015). Bacteriocin: a novel approach for preservation of food. *Int. J. Pharm. Pharm. Sci*, 7(9), 20-29.
- Cavera, V. L., Volski, A., and Chikindas, M. L. (2015). The natural antimicrobial Subtilisin A synergises with lauramide arginine ethyl ester (LAE), ϵ -Poly-L-lysine (Polylysine), clindamycin phosphate and metronidazole against the vaginal pathogen *Gardnerella vaginalis*. *Probiotics. Antimicrob. Proteins*, 7, 164-171.
- Chen, X., Bai, H., Mo, W., Zheng, X., Chen, H., Yin, Y., Liao, Y., Chen, Z., Shi, Q., Zuo, Z., & Peng, H. (2025). Lactic acid bacteria bacteriocins: safe and effective antimicrobial agents. *International Journal of Molecular Sciences*, 26(9), 4124.
- Cotter, P. D., Ross, R. P., & Hill, C. (2013). Bacteriocins-A viable alternative to antibiotics? *Nature Reviews Microbiology*, 11(2), 95-105.
- Darbandi, A., Asadi, A., Mahdizade Ari, M., Ohadi, E., Talebi, M., Halaj Zadeh, M., Darb Emamie, A., Ghanavati, R., & Kakanj, M. (2022). Bacteriocins: Properties and potential use as antimicrobials. *Journal of Clinical Laboratory Analysis*, 36(1), e24093.
- Ennahar, S., Sashihara, T., Sonomoto, K., & Ishizaki, A. (2000). Class IIa bacteriocins: biosynthesis, structure and activity. *FEMS Microbiology Reviews*, 24(1), 85-106.
- Féris, G., Petrova, M. I., Andrei, G., Huskens, D., Hoorelbeke, B., Snoeck, R., Vanderleyden, J., Balzarini, J., Bartoschek, S., Brönstrup, M., & Schols, D. (2013). The lantibiotic peptide labyrinthopeptin A1 demonstrates broad anti-HIV and anti-HSV activity with potential for microbicidal applications. *PLoS one*, 8(5), e64010.
- Flynn, J., Ryan, A., & Hudson, S. P. (2021). Pre-formulation and delivery strategies for the development of bacteriocins as next generation antibiotics. *European Journal of Pharmaceutics and Biopharmaceutics*, 165, 149-163.
- Garsa, A. K., Kumariya, R., Sood, S. K., Kumar, A., & Kapila, S. (2014). Bacteriocin production and different strategies for their recovery and purification. *Probiotics and Antimicrobial Proteins*, 6, 47-58.
- Ghosh, B., Sukumar, G., & Ghosh, A. R. (2019). Purification and characterisation of pediocin from probiotic *Pediococcus pentosaceus* GS4, MTCC 12683. *Folia Microbiologica*, 64(6), 765-778.
- Giedraitienė, A., Vitkauskienė, A., Naginienė, R., & Pavilionis, A. (2011). Antibiotic resistance mechanisms of clinically important bacteria. *Medicina*, 47(3), 19.
- Gradisteanu, P. G., Popa, L. I., Marutescu, L., Gheorghe, I., Popa, M., Czobor Barbu, I., Cristescu, R., & Chifiriuc, M. C. (2021). Bacteriocins in the era of antibiotic resistance: rising to the challenge. *Pharmaceutics*, 13(2), 196.
- Hayati, F., Yuliana, T., & Rialita, T. (2021). Antimicrobial activity of bacteriocin like inhibitory substance (BLIS) and lactic acid bacteria (LAB) isolated from traditional fermented buffalo milk from West Sumatra, Indonesia. *IOP Conference Series: Earth and Environmental Science*, 924, 012082.
- Hiemstra, P. S., & Zaat, S. A. (eds.). (2013). *Antimicrobial peptides and innate immunity*. Springer Science & Business Media.
- Imran, S. (2019). Bacteriocin: A potential antiviral and antimicrobial agent; an alternative to antibiotics. *EC Microbiology*, 15(4), 263-266.
- Joo, N. E., Ritchie, K., Kamarajan, P., Miao, D., & Kapila, Y. L. (2012). Nisin, an apoptogenic bacteriocin and food preservative, attenuates HNSCC tumorigenesis via CHAC 1. *Cancer Medicine*, 1(3), 295-305.
- Karpiński, T. M. & Szkaradkiewicz, A. K. (2013). Characteristics of bacteriocins and their application. *Polish Journal of Microbiology*, 62(3), 223-235.
- Kaur, S., & Kaur, S. (2015). Bacteriocins as potential anticancer agents. *Frontiers in Pharmacology*, 6, 272.
- Khorshidian, N., Khanniri, E., Mohammadi, M., Mortazavian, A. M., & Yousefi, M. (2021). Antibacterial activity of pediocin and pediocin-producing bacteria against *Listeria monocytogenes* in meat products. *Frontiers in Microbiology*, 12, 709959.
- Lu, X., Yi, L., Dang, J., Dang, Y., & Liu, B. (2014). Purification of novel bacteriocin produced by *Lactobacillus coryniformis* MXJ 32 for inhibiting bacterial foodborne pathogens including antibiotic-resistant microorganisms. *Food Control*, 46, 264-271.
- Mathur, H., Field, D., Rea, M. C., Cotter, P. D., Hill, C., & Ross, R. P. (2017). Bacteriocin-antimicrobial synergy: a medical and food perspective. *Frontiers in Microbiology*, 8, 1205.
- Mathur, H., O'Connor, P. M., Hill, C., Cotter, P. D., & Ross, R. P. (2013). Analysis of anti-*Clostridium difficile* activity of thuricin CD, vancomycin, metronidazole, ramoplanin, and actagardine, both singly and in paired combinations. *Antimicrobial Agents and Chemotherapy*, 57(6), 2882-2886.
- Meade, E., Slattery, M. A., & Garvey, M. (2020). Bacteriocins, potent antimicrobial peptides and the fight against multi drug resistant species: resistance is futile? *Antibiotics*, 9, 32.

- Moll, G. N., Konings, W. N., & Driessen, A. J. (1999). Bacteriocins: mechanism of membrane insertion and pore formation. *Antonie Van Leeuwenhoek*, 76(1), 185-198.
- Panina, I., Krylov, N., Nolde, D., Efremov, R., & Chugunov, A. (2020). Environmental and dynamic effects explain how nisin captures membrane-bound lipid II. *Scientific Reports*, 10, 8821.
- Prochnow, H., Rox, K., Birudukota, N. S., Weichert, L., Hotop, S. K., Klahn, P., Mohr, K., Franz, S., Banda, D.H., Blockus, S., & Brönstrup, M. (2020). Labyrinthopeptins exert broad-spectrum antiviral activity through lipid-binding-mediated virolysis. *Journal of Virology*, 94(2), 10-1128.
- Qiao, Z., Zhang, L., Wang, X., Liu, B., Shan, Y., Yi, Y., Zhou, Y., & Lü, X. (2022). Antibiofilm effects of bacteriocin BMP32r on *Listeria monocytogenes*. *Probiotics and Antimicrobial Proteins*, 14(6), 1067-1076.
- Quintana, V. M., Torres, N. I., Wachsmann, M. B., Sinko, P. J., Castilla, V., & Chikindas, M. (2014). Antiherpes simplex virus type 2 activity of the antimicrobial peptide subtilisin. *Journal of applied microbiology*, 117(5), 1253-1259.
- Rashid, F., Sharif, N., Ali, I., Naz, S., Sharif, S., & Nisa, F. U. (2013). Antimicrobial potential of *Lactococcus lactis* bacteriocin against *Salmonella typhi*. *African Journal of Microbiology Research*, 7(6), 436-439.
- Riaz, S., Nawaz, S. K., & Hasnain, S. (2010). Bacteriocins produced by *L. fermentum* and *L. acidophilus* can inhibit cephalosporin resistant *E. coli*. *Brazilian Journal of Microbiology*, 41(3), 643-648.
- Sen, C., & Ray, P. R. (2019). Biopreservation of dairy products using bacteriocins. *Indian Food Industry*, 1(4), 51-60.
- Soltani, S., Hammami, R., Cotter, P. D., Rebuffat, S., Said, L. B., Gaudreau, H., Bédard, F., Biron, E., Drider, D., & Fliss, I. (2021). Bacteriocins as a new generation of antimicrobials: toxicity aspects and regulations. *FEMS Microbiology Reviews*, 45, Article number 1.
- Sugrue, I., Ross, R. P., & Hill, C. (2024). Bacteriocin diversity, function, discovery and application as antimicrobials. *Nature Reviews Microbiology*, 22(9), 556-571.
- Tacconelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet, D. L., Pulcini, C., Kahlmeter, G., Kluytmans, J., Carmeli, Y., & Zorzet, A. (2018). Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *The Lancet Infectious Diseases*, 18(3), 318-327.
- Tkhruni, F. N., Aghajanyan, A. E., Balabekyan, T. R., Khachatryan, T. V., & Karapetyan, K. J. (2020). Characteristic of bacteriocins of *Lactobacillus rhamnosus* BTK 20-12 potential probiotic strain. *Probiotics and Antimicrobial Proteins*, 12(2), 716-724.
- Trejo-González, L., Gutiérrez-Carrillo, A. E., Rodríguez-Hernández, A. I., del Rocío López-Cuellar, M., & Chavarría-Hernández, N. (2022). Bacteriocins produced by LAB isolated from cheeses within the period 2009–2021: a review. *Probiotics and Antimicrobial Proteins*, 14(2), 238-251.
- Uniacke-Lowe, S., Stanton, C., Hill, C., & Ross, R. P. (2024). The marine fish gut microbiome as a source of novel bacteriocins. *Microorganisms*, 12(7), 1346.
- World Health Organisation (WHO) (2023). Antimicrobial Resistance. Retrieved from <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>
- Yang, S. C., Lin, C. H., Sung, C. T., & Fang, J. Y. (2014). Antibacterial activities of bacteriocins: application in foods and pharmaceuticals. *Frontiers in Microbiology*, 5, 241.
- Zipperer, A., Konnerth, M. C., Laux, C., Berscheid, A., Janek, D., Weidenmaier, C., Burian, M., Schilling, N. A., Slavetinsky, C., Marschal, M., & Krismer, B. (2016). Human commensals producing a novel antibiotic impair pathogen colonisation. *Nature*, 535(7613), 511-516.