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Bio Preservation Using Bacteriocin-Producing Lactic Acid Bacteria Strains: Mechanisms and Food Application

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Abstract

This study explores the role of bacteriocin-producing lactic acid bacteria (LAB) in biopreservation, emphasizing their mechanisms of action and applications in enhancing food safety and shelf life. It discusses the imperative for natural preservatives amid growing demand for clean-label products, classifying LAB bacteriocins into Classes I (lantibiotics), II (nonlantibiotics), and III (large bacteriocins), and highlighting key producers such as *Lactococcus, Pediococcus*, and *Leuconostoc*. The antimicrobial mechanisms against Gram-positive and Gram-negative pathogens are detailed, including pore formation, cell wall inhibition, and synergistic hurdle technologies to overcome spectrum limitations. Biopreservation strategies, including in situ production and purified applications, are examined across dairy, meat, seafood, and active packaging, supported by quantitative efficacy data. Challenges such as matrix interactions, resistance development, and production economics are addressed, alongside next-generation optimizations like bioengineering, encapsulation, and synergistic combinations. The review underscores the GRAS/QPS status of LAB bacteriocins, positioning them as safe, sustainable alternatives to chemical preservatives for reducing foodborne illnesses and meeting regulatory standards.

Keywords Biopreservation, Bacteriocins, Lactic Acid Bacteria (LAB), Antimicrobial Peptides, Food Safety, Nisin, Pediocin, Hurdle Technology, Active Packaging, GRAS Status

1. Introduction

Global consumer demand is rapidly driving the food industry toward "clean label" products, necessitating the identification of safe and effective natural alternatives to conventional chemical preservatives, such as nitrates and sorbates (Yu et al., 2023). Biopreservation, which involves the use of selected microorganisms or their antimicrobial compounds, is emerging as a critical intervention strategy to enhance food safety and prolong shelf life (Singh et al., 2021). Among these natural compounds, bacteriocins derived from Lactic Acid Bacteria (LAB) represent a non-harmful and highly promising class of biopreservatives (Cleveland et al., 2001).

The successful implementation of biopreservation techniques holds immense significance for public health. Foodborne pathogens, such as *Listeria monocytogenes*, pose a severe risk,

contributing to an estimated 2,493 illnesses and 499 deaths annually in the United States alone (Jadhav et al., 2024). Furthermore, staphylococcal food intoxication is estimated to cause approximately 185,000 cases of foodborne illness each year (Selvakumar et al., 2025). Utilizing bacteriocins as biopreservatives offers a tangible pathway to reduce the incidence of these foodborne illnesses, even a small percentage of which would constitute a major public health benefit (Tian et al., 2023).

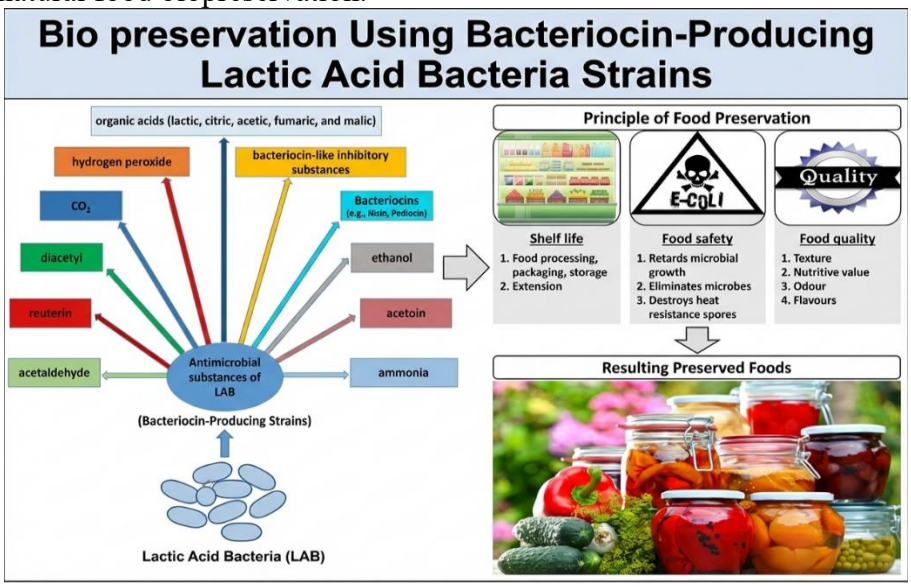
Bacteriocins possess several characteristics that make them superior candidates for industrial preservation. Unlike many conventional chemical agents, LAB bacteriocins are known for their high thermal stability, enabling them to withstand pasteurization and sterilization processes common in food manufacturing (Ojha et al., 2024). They also demonstrate tolerance to a wide range of pH conditions, exhibit high efficiency, are nontoxic, leave no residue, and importantly, do not induce widespread drug resistance in the host environment (Soltani et al., 2021).

Overview of Lactic Acid Bacteria (LAB) as Protective Cultures

Lactic Acid Bacteria have been utilized in food production for thousands of years, primarily for their ability to impart desirable changes in flavor and texture through fermentation (Admassie, 2018). Their natural protective function stems from competitive exclusion and the production of several antimicrobial components, including organic acids, hydrogen peroxide, and, crucially, bacteriocins (Anumudu et al., 2024).

The safety profile of LAB is robust, with most strains being recognized as Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (FDA) (Olubukola et al., 2024). This pre-established regulatory status provides a crucial advantage for their commercial application compared to novel synthetic compounds. The strategy of using bacteriocin-producing LAB as protective cultures or starter adjuncts is highly beneficial, as it promotes *in situ* bacteriocin production (Sionek et al., 2023). This production strategy is often more effective than adding purified peptides, especially in the complex, protease-rich environment of the gastrointestinal tract or various food matrices (Muhammed et al., 2025). Bacteriocins are defined as ribosomally synthesized peptides produced by bacteria that inhibit or kill the growth of other bacteria, typically those closely related to the producer (Cleveland et al., 2001). While traditionally focused on food safety, recent research has unveiled a broader functional spectrum for these antimicrobial peptides (Zimina et al., 2020).

Figure 1. Schematic overview of bacteriocin production by Lactic Acid Bacteria (LAB) and their potential for natural food biopreservation.



The scope of bacteriocin application now extends into veterinary and human medicine (Sugrue et al., 2024). They are valued for their antimicrobial and immunomodulatory effects, demonstrated by studies showing that the administration of bacteriocin-producing strains, such as *Pediococcus acidilactici*, can significantly modify serum immune components and intestinal flora in normal subjects (Simons et al., 2020). This growing recognition reinforces their significance beyond their conventional role in enhancing food safety and shelf life, positioning them as viable agents for human health interventions (Heilbronner et al., 2021).

2. Classification and Structural Diversity of LAB Bacteriocins

Bacteriocins produced by Gram-positive bacteria, particularly LAB, are classified based on a set of criteria including molecular weight, thermal stability, susceptibility to proteolytic enzymes, the presence or absence of post-translational modifications, and their primary antimicrobial action (Aljohani et al., 2023). This system categorizes them into three primary classes, with an initially described fourth class (comprising large complexes with carbohydrate and lipid residues) now generally referred to as bacteriolysins (Manoharan et al., 2022).

2.1. Standard Structural and Genetic Classification Systems

Class I: Lantibiotics

Class I bacteriocins are characterized by their small size, typically less than 5 kDa, and their composition of 19 to 50 amino acids (Musiejuk et al., 2023). Their defining feature is the extensive post-translational modification which results in the formation of atypical amino acids, specifically lanthionine and methyllanthionine (Li et al., 2018). These modifications confer remarkable heat stability upon the lantibiotics, with Nisin being the most widely studied and commercially successful example (Khan et al., 2023).

Class II: Nonlantibiotics

Class II bacteriocins are small peptides, generally less than 10 kDa that are linear, flexible, and often possess an amphiphilic helical structure (Antoshina et al., 2022). They are also heat-stable but lack the complex post-translational modifications found in lantibiotics. This class is further subdivided based on functional and structural characteristics:

- **Subclass IIa (Pediocin-like Peptides):** These are the most extensively researched Class II bacteriocins. They are distinguished by the conserved N-terminal domain motif YGNGVxCxK/NxxC (where X is any amino acid). They are highly valued for their potent antilisterial activity (Sani & Lisen, 2020).
- **Subclass IIb (Two-Peptide Bacteriocins):** These peptides require the synergistic action of two distinct peptides to achieve optimal antimicrobial activity (Zimina et al., 2020).
- **Subclass IIc (Circular Bacteriocins):** Characterized by a circular structure formed through a head-to-end peptide bond (Bahrami et al, 2024).
- **Subclass IId:** This group encompasses bacteriocins that do not share significant sequence similarity with the other Class II subclasses (Negash et al., 2020).

Class III: Large Bacteriocins

Class III bacteriocins are high molecular weight peptides, typically exceeding 30 kDa. In contrast to Classes I and II, they are unmodified and thermolabile, meaning they are sensitive to high temperatures (Antoshina et al., 2022). The subclass of bacteriolysins, which fall into this category, are large polypeptides (27 to 35 kDa) defined by their ability to lyse the cell walls of target bacteria (Negash et al., 2020). The inherent thermolability of Class III compounds significantly limits their applicability in food preservation streams that require thermal processing, such as pasteurization,

thus explaining the dominance of the heat-stable Class I and II bacteriocins in industrial use (Vasilchenko et al., 2018).

2.2. Key Bacteriocin Producers among LAB Genera

The primary producers of commercially relevant bacteriocins belong to key LAB genera. *Pediococcus* species, particularly *Pediococcus acidilactici* and *P. pentosaceus*, are major sources of Class II bacteriocins, notably pediocin and other Class IIa peptides (Mokoena, 2017). These species are crucial in food fermentation, acting as indigenous microflora or starter cultures in products ranging from vegetables to sausages, and also imparting desirable attributes to cheese (Juturu et al., 2018). The genus *Leuconostoc* (*L. gelidum*, *L. lactis*, *L. mesenteroides*) is also a significant producer of Class II bacteriocins, often dominated by the Class IId subgroup (Trejo-González et al., 2022).

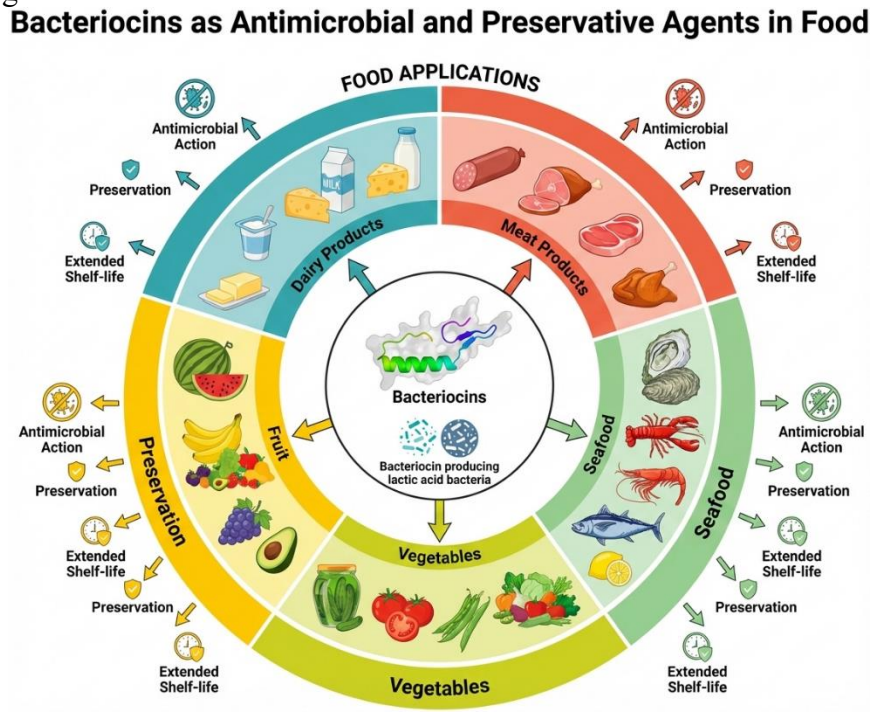
Table 1. Classification, Structural Characteristics, and Mechanism Highlights of Key LAB Bacteriocins

Classification Class	Example Bacteriocin	Structural Features	Molecular Weight	Thermal Stability	Primary Mechanism of Action	Key Producers
Class I (Lantibiotics)	Nisin	Post-translational modifications (Lanthionine, Methyllanthionine)	<5 kDa	Heat-stable (Soltani et al., 2021)	Binds Lipid II; Pore formation & Cell Wall Inhibition (Sani & Lisen, 2020)	*Lactococcus lactis*
Class IIa (Pediocin-like)	Pediocin PA-1	YGNGV motif, linear, flexible	<10 kDa	Heat-stable (Soltani et al., 2021)	Pore formation via interaction with anionic phospholipids (Sani & Lisen, 2020)	*Pediococcus acidilactici*, *P. pentosaceus* (Sani & Lisen, 2020)
Class IIb (Two-Peptide)	Enterocin L50	Requires two different peptides for optimal activity	<10 kDa	Heat-stable	Pore formation	*Enterococcus faecium*
Class III (Lytic Proteins)	Bacteriolysins	Unmodified peptide, large complex	27–35 kDa	Thermolabile (Soltani et al., 2021)	Lysis of target bacterial cell walls (Soltani et al., 2021)	Various LAB, Gram-positive

3. Molecular Mechanisms of Antimicrobial Action and Self-Immunity

Understanding the molecular mechanisms by which bacteriocins exert their antimicrobial effects is fundamental to exploiting their potential in biopreservation. Most LAB bacteriocins function by targeting the integrity of the bacterial cell membrane, although the specific pathways vary based on the bacteriocin class (Choi et al., 2023).

Figure 2. Mechanisms of antimicrobial action of bacteriocins against Gram-positive and Gram-negative pathogens: Pore formation and cell wall inhibition.



3.1. Mechanistic Action against Gram-Positive Pathogens

The primary mode of action for most LAB bacteriocins is the physical disruption of the cytoplasmic membrane through pore formation. For Class IIa bacteriocins, such as the pediocins, the mechanism involves the interaction of positively charged residues, typically in the C-terminal domain, with anionic phospholipids present in the target membrane (Pérez-Ramos et al., 2021). This interaction leads to the insertion of the peptide, membrane permeabilization, depolarization, and ultimately, rapid cell death (Sharma et al., 2021).

Lantibiotics (Class I) exhibit a more sophisticated dual mechanism, exemplified by Nisin. Nisin functions not only by forming pores but also by interfering with cell wall biosynthesis (Chen et al., 2025). Crucially, lantibiotics bind to Lipid II, a critical membrane-bound precursor molecule involved in transporting peptidoglycan subunits from the cytoplasm to the cell wall (Antoshina et al., 2022). By binding to Lipid II, Nisin inhibits cell wall formation. Furthermore, the Lipid II molecule serves as a dedicated docking receptor, which accelerates and facilitates the process of pore formation, leading to swift cellular demise (Grein et al., 2019). This dependency on Lipid II, while increasing specificity and potency, also defines a vulnerability: if target bacteria evolve mechanisms to mask or structurally alter Lipid II, resistance mechanisms could emerge (Panina et al., 2020).

3.2. Efficacy and Strategies against Gram-Negative Bacteria

A significant challenge in the application of LAB bacteriocins is their generally narrow spectrum

of activity, often being ineffective against Gram-negative bacteria (Liang et al., 2025). The primary obstacle is the Gram-negative outer membrane, which is composed of lipopolysaccharide (LPS) and acts as a barrier, physically impeding the bacteriocins from reaching the cytoplasmic membrane, their ultimate target (Todorov., 2022).

To circumvent this limitation, researchers have developed synergistic strategies, often termed the Hurdle approach, combining bacteriocins with agents that transiently destabilize the outer membrane (Gradisteanu Pircalabioru et al., 2021). This rational approach leverages specific chemical or physical stresses to increase membrane permeability. Effective sensitizers include chelating agents (e.g., EDTA, citric acid, sodium citrate), which chelate divalent cations essential for stabilizing the LPS structure, and mild heating (e.g., 55°C for 10 minutes) or freezing. These treatments effectively destabilize the LPS layer, enabling bacteriocin penetration (Fernandes et al., 2022). The combination results in superior antimicrobial action by destroying the bacterial cell membrane integrity, leading to protein or nucleic acid leakage, and inhibiting intracellular metabolic pathways (Telhig et al., 2020).

3.3. Producer Strain Self-Immunity Mechanisms

To prevent autotoxicity, bacteriocin-producing LAB strains have evolved complex self-immunity mechanisms. These systems typically involve the expression of specific immunity proteins, often coupled with dedicated ABC transporter systems (Pérez-Ramos et al., 2021). The mechanisms are highly specific to the cognate bacteriocin. For example, immunity proteins against pore-forming bacteriocins are often located in the producer strain's inner membrane (Perez et al., 2022). These proteins possess a strong affinity for the corresponding bacteriocin, physically binding it and preventing the formation of channels in the producer's own membrane, thereby safeguarding the cell even at high bacteriocin concentrations (Prins et al., 2025). While the protective effect of these immune proteins is understood generally, the precise molecular mechanism by which they function against certain subclasses, such as Class IIa, remains an area of ongoing investigation (Rosenkilde, 2023).

4. Biopreservation Strategies and Commercial Applications

The deployment of bacteriocins in the food industry follows two primary strategies application as a purified ingredient or application as an *in situ* protective culture. The choice of strategy is often dictated by cost, food matrix characteristics, and the target pathogen (Silva et al., 2018).

4.1. Application Modalities: Purified, Semi-Purified, and *In Situ*

Bacteriocins can be introduced into food products in several ways, including the inoculation of food with purified or semi-purified peptides, or through the addition of bacteriocin-producing LAB strains that generate the preservative *in situ* during the fermentation or storage process (Cleveland et al., 2001).

The use of bacteriocin-producing LAB strains as protective or adjunct cultures offers a significant advantage over adding purified peptides. Purified peptides are susceptible to degradation by proteolytic enzymes and can lose activity due to non-specific adsorption onto complex food matrix components like lipids and proteins (Bahrami et al., 2024). *In situ* production mitigates these challenges, ensuring a continuous supply of active bacteriocin localized within the product. This strategy also favors the establishment and colonization of the producing organism in the digestive tract, offering probiotic benefits when consumed (Comitini et al., 2023).

4.2. Biopreservation in Dairy Products: Case Studies

Dairy products constitute a primary application sector for bacteriocins because LAB are naturally

abundant in these matrices and have a long history of safe use (Pujato et al., 2024).
Specific applications in dairy products demonstrate reliable pathogen control and quality enhancement:

Pathogen Control: In fermented milk (lben), the use of a bacteriocinogenic starter culture (*Lactococcus lactis* ssp. *lactis*) demonstrated rapid efficacy against *L. monocytogenes*, reducing the pathogen load to below detectable levels within 24 hours of storage at 7°C. This efficacy was maintained even with high initial contamination levels (10^7 cfu/ml) for up to six days (Favaro et al., 2015). Similarly, the addition of Nisin A-producing *Lc. lactis* strains to fresh cheese resulted in a reduction of *Listeria* contamination by 2 log units within seven days of storage (Bali et al., 2016).

Quality and Maturation: Bacteriocin-producing LAB have been investigated as cell lysis-inducing agents to accelerate cheese maturation and enhance flavor profiles. Furthermore, they are proposed as a method to prevent the late blowing defect in ripened cheeses, a common spoilage issue caused by *Clostridium* spores (Parada Fabián et al., 2015).

Managing Spectrum Limitations: The broad-spectrum activity of Nisin presents a unique challenge in dairy, as it can inhibit the desirable LAB starter cultures required for fermentation (Ahansaz et al., 2023). A solution has been demonstrated where a nisin-producing *Lactococcus* sp. strain was incorporated into raw milk and then killed prior to the addition of the traditional yogurt starter cultures. This approach successfully increased the storage life of the yogurt by inhibiting spoilage bacteria without compromising the starter activity (Nebbia et al., 2020).

4.3. Biopreservation in Meat and Seafood: Quantitative Data Review

Meat and seafood are highly perishable food categories with a high risk of microbial spoilage and pathogenic contamination (Siddiqui et al., 2024).

Ready-to-Eat (RTE) Meat Efficacy: The control of *Listeria monocytogenes* in RTE meat products is a major regulatory concern. A study demonstrated that the addition of a multi-Mode of Action (MoA) bacteriocin mixture resulted in a critical approximately 2-log reduction of *L. monocytogenes* within the first 1–3 days of application (Vijayakumar & Muriana, 2017). More critically, the treatment maintained a 7-log difference from untreated controls over a 12-week challenge study (Luong et al., 2020). This quantitative performance is essential as it satisfies the requirements for the USDA-FSIS Alternative 1 product classification, confirming the bacteriocin mixture's utility as a robust risk mitigation tool in a high-liability industrial setting (Karbowiak et al., 2023).

Seafood Preservation: The perishability of seafood, characterized by a relatively high post-mortem pH (> 6.0) and high content of growth substrates like trimethylamine oxide (TMAO), necessitates potent preservation methods (Kontominas et al., 2021). The application of Bacteriocin GP1, produced by *Lactobacillus rhamnosus* GP1, in stored fish was effective in controlling spoilage microflora, including *Aeromonas* sp. and *Vibrio* sp.. Notably, the spoilage indicator TMA remained within the acceptable limit of 10–15 mg/100 g even at the 21st day in the treated fish samples (Sarika et al., 2019).

4.4. Application in Active Packaging

An advanced application modality involves incorporating purified bacteriocins or bacteriocin-

producing LAB strains directly into polymeric materials to create bioactive films and coatings. This method ensures the localized, continuous release of the antimicrobial peptide onto the food surface, providing protection directly where contamination is most likely to occur (Silva et al., 2018).

Table 2. Quantitative Efficacy of LAB Biopreservation in Major Food Matrices

Food Matrix	Bacteriocin/LAB Strain	Target Pathogen/Spoilage Microorganism	Application Method	Observed Efficacy/Result	Reference
Fermented Milk (Lben)	*L. lactis* ssp. *lactis* (Nisin Producer)	*L. monocytogenes*	*In Situ* Production	Decreased below detectable level within 24 hours of storage at 7°C	(Silva et al., 2018)
Ready-to-Eat (RTE) Meat	Multi-MoA Bacteriocin Mixture	*L. monocytogenes*	Purified/Semi-purified Additive	Approx. 2-log reduction within 1-3 days; 7-log difference from control over 12 weeks	(Vijayakumar & Muriana, 2017)
Stored Fish	Bacteriocin GP1 (*L. rhamnosus* GP1)	Spoilage Flora (*Aeromonas* sp., *Vibrio* sp.)	Additive	Controlled spoilage growth; TMA level remained acceptable (<15 mg/100 g) at 21 days	(Sarika et al., 2019)
Fresh Cheese	Nisin A-producing *Lc. lactis* strains	*L. monocytogenes*	*In Situ* Production	Reduction of 2 log units within 7 days of storage	(Silva et al., 2018)
Meat and Poultry	s-PA-1 (Synthetic Pediocin Analog)	*L. monocytogenes* specific	Surface Application (Processing Aid)	Approved for use up to 5 mg/kg as an antimicrobial agent	(Yu et al., 2023)

5. Technical and Biological Constraints in Food Systems

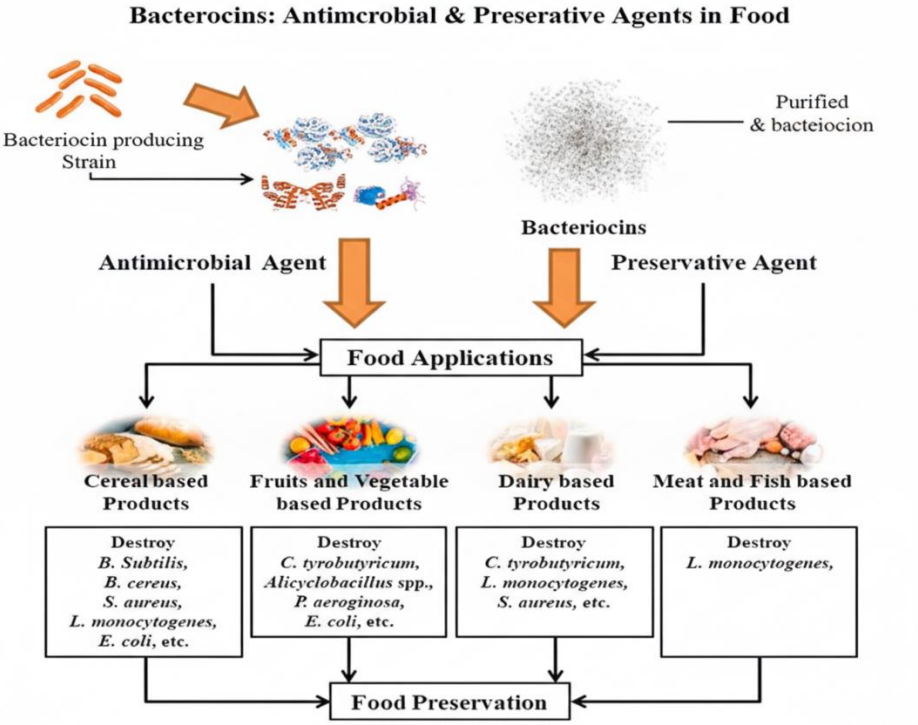
Despite their profound advantages and demonstrated efficacy, the widespread industrial adoption of bacteriocins is currently hindered by specific biological, chemical, and economic constraints (Khan et al., 2021).

5.1. Impact of Food Matrix Components on Stability

Bacteriocins are peptide structures, rendering them sensitive to proteolytic degradation by enzymes that may be indigenous to the food or produced by co-existing microbiota (Amankwah

et al., 2021). Furthermore, non-specific binding, or adsorption, to various food components particularly fats and proteins can dramatically reduce the effective concentration and biological activity of the bacteriocin within the food matrix (Coppola et al., 2025). This requires careful formulation or favors the application of *in situ* production methods to maintain efficacy throughout the product's shelf life (Ranjitha et al., 2021).

Figure 3. Application of bacteriocin-producing LAB strains in various food matrices for shelf-life extension and safety enhancement.



5.2. Antimicrobial Resistance and Spectrum Limitations

The potential for target microorganisms to develop resistance mechanisms represents a serious challenge that could obstruct the broad use of bacteriocins (Mazzotta & Montville, 1999). For example, resistance to Nisin has been documented in toxigenic spores of *Clostridium botulinum*, which retain the ability to germinate and grow even at concentrations of Nisin that reduce susceptible germinating spores by 7–8 log10/ml (Shanmugam et al., 2020). The precise mechanism underlying this spore resistance remains unidentified, highlighting a significant gap in fundamental molecular understanding that must be addressed to inform the design of future resistant-proof variants (Jones et al., 2017).

Additionally, while many bacteriocins possess a narrow spectrum of activity (inhibiting only closely related species. this characteristic is viewed positively in clinical and therapeutic contexts, as highly selective bacteriocins (e.g., Thuricin CD, which targets *C. difficile*) minimize the risk of disrupting the beneficial host microbiota balance (Bhagwat, 2020). However, for broad-spectrum food preservation, this narrow focus often requires the use of bacteriocin combinations or synergistic treatments to achieve comprehensive pathogen control (Manzoor, 2025).

5.3. Production Economics

The economic viability of bacteriocins is a key determinant of commercial success. While bacteriocins offer compelling safety and efficacy benefits, the high costs associated with large-scale production and purification, or even partial purification, to achieve the required concentrations for industrial application remain a bottleneck (Todorov et al., 2022). Only a few

bacteriocins, notably Nisin (Nisaplin) and Pediocin PA1 (Microgard™), have achieved widespread commercialization (Selvan et al., 2025). This limited adoption underscores that the industrial future of biopreservation is critically dependent not just on discovering new antimicrobial peptides, but on optimizing bioprocess engineering to achieve economic feasibility and competitive production costs (Contessa et al., 2024).

6. Next-Generation Bacteriocins and Optimization Technologies

To overcome the inherent limitations of bacteriocins specifically spectrum, stability, and delivery innovative technologies are focusing on peptide modification and advanced application methods (Isaac et al., 2025)

6.1. Bioengineering and Semi-Synthetic Strategies

Modern bioengineering and semi-synthetic strategies are critical for developing novel bacteriocin variants with enhanced industrial performance. These techniques aim to optimize peptide stability, boost biological activity, and tailor pharmacokinetic profiles including characteristics such as rapid distribution, good bioavailability, and targeted elimination (Huang et al., 2025).

The development of chemically synthesized analogs represents a major advancement for industrial standardization. For instance, a chemically synthesized analog of Pediocin PA-1 (s-PA-1), which replicates the naturally occurring 44-amino acid sequence, has been produced (Yu et al., 2023). This synthetic compound has successfully achieved GRAS status from the FDA for use as an antimicrobial agent on various food products, including meat, poultry, dairy, and produce, at levels up to 5 mg/kg (Food and Drug Administration, 2024). The ability to chemically synthesize these peptides ensures a consistent, high-purity product, stabilizing production costs and simplifying regulatory pathways (Zgheib, 2020).

6.2. Advanced Delivery Systems

Protecting bacteriocins from degradation and ensuring their sustained activity in the food matrix is essential. This often requires the implementation of advanced delivery systems Nanotechnology-based encapsulation, using materials such as liposomes, chitosan, proteins, and polysaccharides, is a promising strategy (Arthur et al., 2014).

Encapsulation offers multiple benefits: it shields the bacteriocin from proteolytic attack, increases stability within the food environment, enables controlled release, and can potentially extend the antimicrobial spectrum (Mohanty et al., 2025). The focus on designing delivery systems based on the required "pharmacokinetic profiles" suggests that the food matrix is increasingly treated as a complex, dynamic biological environment where traditional peptide application is insufficient. This interdisciplinary approach, integrating material science with food microbiology, is necessary to unlock the full commercial potential of bacteriocins (Terra et al., 2021).

6.3. Synergistic Combination Treatments (Mechanistic Rationale)

Combining bacteriocins with other chemical substances, such as organic acids, plant extracts, or chelating agents, is a widely studied approach to enhance antibacterial effectiveness and overcome spectrum limitations. The synergy often relies on a shared mechanism of disrupting the bacterial cell membrane integrity (Bukvicki et al., 2023).

Combination with Chelating Agents and Organic Acids: Combining Nisin with agents like EDTA or citric acid destabilizes the Gram-negative outer membrane, a key barrier (Khalid et al., 2025). For example, Nisin combined with citric acid in pasteurized milk caused significant cell surface damage and the leakage of vital cell contents (K+, PO4(3-), DNA, and RNA) in *S. aureus*

and *L. monocytogenes*. Similarly, chelating agents like EDTA and organic acids (citric, gluconic) enhance Nisin's activity against Gram-negative pathogens like *Salmonella enterica Typhimurium* and *Yersinia enterocolitica* by disrupting the LPS layer (Duarte, 2024).

Combination with Plant Extracts: Plant extracts, such as grape seed or garlic extract, can also contribute by changing the cell membrane permeability. This disruption allows the bacteriocin to penetrate and accumulate in the plasma membrane, causing toxic effects and interfering with metabolic pathways (Cirat et al., 2024).

These combination treatments represent a scientifically grounded method for expanding the functional range of bacteriocins and maximizing efficacy while simultaneously allowing for reduced reliance on high concentrations of synthetic chemical preservatives (Machado et al., 2023).

Table 3. Strategies for Enhancing Bacteriocin Activity against Gram-Negative Bacteria

Bacteriocin	**Target Microorganism**	**Associated Synergistic Treatment**	**Concentration/Condition**	**Mechanism of Enhancement**	**Reference**
Nisin	*S. enterica Typhimurium*	EDTA	20 mM	Chelating agent destabilizes LPS outer membrane, permitting bacteriocin access	(Yu et al., 2023)
Nisin	*P. putida*	Citric Acid, Gluconic Acid, Sodium Citrate	7 mM (Citric), 100 mM (Gluconic/Citrate)	Outer membrane destabilization, increased permeability	(Yu et al., 2023)
Nisin	*E. coli*	Heating / Low Temperature	55 °C, 10-15 min / 6.5 °C	Thermal/Chill stress breaches the outer membrane integrity	(Yu et al., 2023)
Nisin	*L. monocytogenes*, *S. aureus*, *E. coli*	Garlic Extract	N/A	Damages membrane integrity; causes protein/nucleic acid leakage	(Yu et al., 2023)
Bacteriocins (L.	*E. coli* O157:H7	Na2EDTA	N/A	Decrease in bacterial	(Yu et al., 2023)

curvatus/L. lactis)				population via outer membrane destabilization	
Nisin	*L. monocytogenes*	Citric Acid	N/A	Caused cell surface damage; release of cell contents (K+, DNA, RNA)	(Yu et al., 2023)

7. Safety, Regulatory Status, and Consumer Acceptance

The successful integration of bacteriocins into the food supply chain hinges on established safety protocols and regulatory approval worldwide (Bisht et al., 2024).

7.1. Global Regulatory Frameworks and GRAS/QPS Status

Lactic Acid Bacteria and their bacteriocins are highly favored due to their long history of safe consumption. In the United States, the FDA grants Generally Recognized as Safe (GRAS) status for food applications. Most LABs have achieved this designation (Chen et al., 2025). In Europe, the equivalent safety assessment is conducted by the European Food Safety Authority (EFSA), which grants Qualified Presumption of Safety (QPS) status (Fischer et al., 2023). Bacteriocins produced by specific LAB genera, such as *Pediococcus* (*P. acidilactici* strains are GRAS) and *Lactobacillus*, are considered superior in safety profile compared to those isolated from genera like *Enterococcus* (Plavec et al., 2020).

Emphasizing the GRAS/QPS status is fundamental to promoting the broader application of bacteriocins, ensuring consumer confidence and streamlining regulatory acceptance (Uhegwu et al., 2025).

Conclusion

In conclusion, bacteriocin-producing LAB strains offer a promising, natural approach to food preservation, effectively combating foodborne pathogens like Listeria monocytogenes and extending shelf life across diverse food matrices while aligning with consumer preferences for clean-label products. Despite challenges in stability, spectrum, and economics, advancements in bioengineering, delivery systems, and synergistic treatments enhance their efficacy and broaden applications. With established safety profiles under GRAS and QPS frameworks, LAB bacteriocins represent a sustainable strategy for the food industry, potentially reducing reliance on chemical preservatives and improving public health outcomes. Future research should focus on cost-effective production and resistance mitigation to fully realize their commercial potential.

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