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Biotechnological potential of lactic acid bacteria derived bacteriocins in sustainable food preservation

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Abstract

This review paper discusses the biotechnological potential of lactic acid bacteria (LAB) in the food industry, specifically their ability to produce antimicrobial substances known as bacteriocins. As interest in natural alternatives to synthetic food preservatives grows, bacteriocins have gained significant attention due to their ability to enhance the shelf life and safety of food products. The paper explores the classification, biosynthesis, mode of action, production, and purification of bacteriocins. By examining how these antimicrobial peptides inhibit pathogenic bacteria, the equilibrium of microbial populations can be maintained, leading to improved food preservation. The diverse range of bacteriocins produced by LAB and their effectiveness as natural preservatives in food manufacturing are highlighted. The overall goal of the review is to provide insights into the potential of LAB and bacteriocins for biological food preservation. Understanding the various aspects of bacteriocin production and their mode of action can contribute to the development of sustainable and safe food preservation strategies, promoting the use of natural alternatives in the food industry.

Keywords: Lactic acid bacteria; Bacteriocin; Bio-preservatives; Food preservatives; Natural preservatives

1. Introduction

Bacteriocins, a diverse group of ribosomally produced peptides, exhibit potent antibacterial activity against closely related strains [1,2]. Moreover, an expanding repertoire of bacteriocins has been unveiled, showcasing broad-spectrum antimicrobial efficacy [3]. These remarkable biomolecules display their antibacterial prowess not only against diverse bacteria but also fungi, parasites, viruses, and resilient structures like bacterial biofilms [4,5,6,7]. Intriguingly, the bacterial cells responsible for bacteriocin production possess a built-in resistance mechanism mediated by specific immunity proteins synthesized by host cells [8]. The genetic control of bacteriocin synthesis and immunity typically involves their arrangement within operon clusters, with these genes residing on mobilizable elements such as chromosomes in association with transposons or on plasmids [9].

The captivating potential of bacteriocins as both natural food preservatives and therapeutic antibiotics has sparked a surge of interest in bacteriocin research, especially within the realm of lactic acid bacteria (LAB) [2,10,11]. LAB, a diverse group of catalase-negative, non-sporulating, and Gram-positive bacteria known as probiotic lactic acid bacteria, play a crucial role in producing lactic acid as the primary product from glucose. These bacteria exhibit an array of growth inhibitors, including bacteriocins, bacteriocin-like inhibitory substances (BLISs), hydrogen peroxide, diacetyls, and carbon dioxide. Their growth requires a complex array of dietary ingredients, such as amino acids, peptides, nucleotide bases, vitamins, fatty acids, and carbohydrates [12]. Due to their antagonistic properties and a long history of safe usage

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in traditional fermented food products, LAB have emerged as highly desirable biopreservatives [13,14]. LAB actively contribute to the preservation of various foods and fermented goods and have earned the distinction of being generally recognized as safe (GRAS) microorganisms. Cintas highlights their potential for exploitation in controlled environments as specific starter cultures or natural competitors within microbiota. Notably, several LAB strains produce bacteriocins, which are potent antimicrobial compounds that exert their effects even at low concentrations [16,17].

Bacteriocins, with their intriguing antibacterial capabilities, hold the promise of serving as valuable alternatives to antibiotics, which are currently prohibited for use in foods and feeds [18]. These multifaceted biomolecules represent a captivating avenue for the development of novel antimicrobial strategies. The growing interest in lactic acid bacteria (LAB) has fueled the discovery of numerous new peptides, leading to the isolation and characterization of LAB producers [19]. Within the realm of lactic acid bacteria, several significant genera have been identified, including *Lactobacillus*, *Lactococcus*, *Carnobacterium*, *Enterococcus*, *Lactosphaera*, *Leuconostoc*, *Melissococcus*, *Oenococcus*, *Pediococcus*, *Streptococcus*, *Tetragenococcus*, *Vagococcus*, and *Weissella*. Additionally, other genera such as *Bifidobacterium*, *Microbacterium*, *Propionibacterium*, and *Aerococcus* contribute to the diversity of LAB species [20]. Notable LAB species encompass *Lactobacillus acidophilus*, *Lactococcus lactis lactis*, *Lactococcus lactis cremoris*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus casei rhamnosus*, *Lactobacillus delbrueckii bulgaricus*, *Lactofermentum*, *Lactobacillus reuteri*, *Bifidobacterium bifidum*, B. *infantis*, B. *adolescentis*, B. *longum*, B. *breve*, *Enterococcus faecalis*, and *Enterococcus faecium*, with some strains recognized as probiotics [21,13].

A notable success story in the field of bacteriocin research is the development of nisin, which serves as a model for inspiring new contributions. Starting from its initial biological observation, nisin has traversed the regulatory approval process and found commercial usage [22].

2. Bacteriocin

Bacteriocins, with their low molecular weight (rarely surpassing 10 kDa), posttranslational modifications, and susceptibility to degradation by proteolytic enzymes, particularly those found in the mammalian gastrointestinal system, are generally deemed safe for consumption [23,24]. These remarkable compounds often exhibit cationic and amphipathic properties, owing to their abundance of lysyl and arginyl residues [23,24]. In aqueous solutions, bacteriocins typically possess minimal structure. However, when exposed to solvents like triofluroethanol that promote structural organization, or when interacting with anionic phospholipid membranes, they adopt a helical conformation [25].

The quest for germ eradication led Belgian scientist Gratia to pioneer the field of bacteriocins. His seminal work gave birth to the first bacteriocin, colicin, an intriguing heat-sensitive substance that exhibited inhibitory effects against *Escherichia coli* S when produced by *Escherichia coli* V [26]. Gratia observed the suppression of one bacterial strain by another, although the understanding of bacteriocin's structure and generation was limited at that time. The dominance of chemically synthesized broad-spectrum antibiotics overshadowed the potential of bacteriocins. The elucidation of colicin's proteinaceous composition came through the work of Fredericq, who discovered that the presence of specific surface receptors on susceptible cells was responsible for bacteriocin's inhibitory action [27]. Subsequently, it became evident that numerous bacterial strains produced a class of chemical compounds known as bacteriocins, capable of preventing the growth of other strains or species [28].

"Most of the definitive investigations in the field of bacteriocins had centred on those of Gram-negative bacteria, but an increase in research emphasis on bacteriocins of Gram-positive lactic acid bacteria is needed," Tagg [29] wrote in their review of bacteriocins of Gram-positive bacteria. Lactic acid bacteria, being recognized as harmless organisms, have emerged as the most desirable microorganisms for exploring new bacteriocins. The growing interest in bacteriocins is closely linked to their wide-ranging applications in food preservation, industrial processes, and medical interventions against pathogenic bacteria that cause diseases [30].

Despite the significant potential of bacteriocins in various domains, nisin remains the only commercially available bacteriocin used in food applications. Interestingly, bacteriocins have immense potential beyond their current utilization. While bacteriocins have primarily been employed in clinical settings for the well-being of animals [31], the approval of nisin by the Joint Food and Agriculture Organization/World Health Organisation Expert Committee on Food Additives and its endorsement by the US Food and Drug Administration for use in pasteurized, processed cheese spreads serve as regulatory benchmarks for the use of other bacteriocins as food preservatives. To further accelerate the widespread utilization of bacteriocins in clinical applications, researchers are actively developing bioengineered bacteriocins with enhanced properties, specifically targeting clinical infections [32].

3. Classification of bacteriocins

Bacteriocin production is observed in both Gram-positive and Gram-negative bacteria, and their names are often associated with the genus or species responsible for their synthesis [30]. Various factors are taken into consideration when categorizing bacteriocins, including their mode of production (ribosomal and non-ribosomal) [1], genetic characteristics, plasmid size, sugar and protein composition, molecular weight, and the specific chemical reactions they engage in [33]. Additionally, bacteriocins are classified based on their mode of action, such as nuclease activity, inhibition of murein production, or pore formation [30].

The physicochemical properties of bacteriocins lead to their division into three main classes [34,35,36]. Savadogo [36] introduced the concept of three distinct classes of bacteriocins produced by lactic acid bacteria (LAB): lantibiotics (class I), non-lantibiotics (class II), and heat-sensitive (class III) bacteriocins. However, when classifying bacteriocins, Class IV, which consists of complex bacteriocins with glycol- and/or lipid moieties, is no longer considered according to Caplice and Fitzgerald [14].

3.1. Class I: The lantibiotics

Lantibiotics, also known as Class I bacteriocins, represent a subclass of peptide compounds with unique characteristics. These compounds contain unsaturated amino acids such as dehydroalanine and 2-aminoisobutyric acid, along with the distinctive polycyclic thioether amino acids lanthionine or methyllanthionine [2,22]. Based on their structural similarities, lantibiotics are further categorized into two types.

Type A lantibiotics are positively charged, flexible, amphipathic molecules with a moderately elongated, screw-shaped structure. Notable members of this category include Nisin and Lactacin 3147, with molecular masses ranging from 2 to 4 kDa. These lantibiotics primarily function by creating pores in the cytoplasmic membrane of susceptible target species, leading to membrane depolarization [2,22].

On the other hand, Type B lantibiotics exhibit a globular shape and disrupt cellular enzymatic processes. They have a molecular weight of 2 to 3 kDa and can either carry no net charge or have a net negative charge [2,22].

The unique thioether amino acids lanthionine (Lan) and beta methyllanthionine (MeLan) are synthesized during the translation of small, heat-stable peptides known as Class I LAB bacteriocins (5 kDa) [10,23,24]. This process involves a two-step procedure. First, serine and threonine residues encoded by specific genes undergo enzymatic dehydration, leading to the formation of dehydroalanine (Dha) and dehydrobutyrine (Dhb). Subsequently, nearby cysteine residues attack the double bonds of Dha and Dhb, resulting in the formation of Lan and MeLan, respectively. These condensation reactions between adjacent residues lead to the formation of covalently closed rings, which confer both structure and functionality to the initially linear peptide. It's worth noting that all members of this group contain D-alanine residues, which are derived from dehydroalanine produced through serine dehydration [10,23,24].

3.2. Class II: the non-lantibiotics

Class II bacteriocins are a group of small peptides (10 kDa) that exhibit relatively high heat stability and possess membrane-active properties. Unlike Class I bacteriocins, they do not contain lanthionine. Class II bacteriocins can be further divided into two distinct subclasses, each with its own unique characteristics and mechanisms of action [37,38].

Subclass IIa, also known as pediocin-like or listeria active bacteriocins, feature a conserved N-terminal consensus sequence: Tyr-Gly-Asn-Gly-Val-Xaa-Cys. When the amino acid sequences of these bacteriocins are aligned, a significant degree of similarity (40-60%) can be observed. These bacteriocins are initially synthesized as precursor molecules with a leader peptide, which is subsequently removed during proteolytic processing. Typically, the removal occurs after a double glycine residue, as seen in the cases of pediocin PA-1 and sakacin A [37].

On the other hand, subclass IIb bacteriocins, referred to as two-component bacteriocins, require two distinct peptides to collaborate in order to exhibit antibacterial activity. Unlike the single-component bacteriocins, these two-component bacteriocins rely on the synergistic interaction between two peptides. Notable members of subclass IIb include lactococcin G and lactocacin F [38]. Overall, Class II bacteriocins demonstrate their unique characteristics and mechanisms, offering potential applications in various fields, as outlined in the available references [37,38].

3.3. Class III: Bacteriocins

These particular bacteriocins are characterized by their large molecular weight (>30 kDa) and heat sensitivity, yet they have received relatively less research attention compared to other classes. Notable examples within this group include Helveticin I, produced by Lactobacillus helveticus, and enterolysin, generated by Enterococcus faecium, which serve as representatives for this category [39,40,41,42,43]. In addition to the proteinaceous nature of bacteriocins, Klaenhammer [43] proposed the existence of a fourth class that encompasses bacteriocins requiring the presence of glucidic and/or lipid moieties for their biological activity. This class includes lipoproteins like mesenterocin 52 [44], glycolipoproteins such as fermenticin [45], and glycoproteins like leucocin S [46] and lactocin 27 [47].

However, it should be noted that the classification of this class remains somewhat speculative until these bacteriocins are thoroughly characterized and purified, as their biological activity has thus far been determined using crude bacteriocin preparations.

4. Bacteriocin biosynthesis

During the formation of bacteriocins, they initially exist as pre-propeptides, which undergo processing and externalization facilitated by specific transport machinery [48]. The production of bacteriocin in LAB is growth-dependent, typically continuing throughout the growth phase and ceasing at the end of the exponential phase, although occasionally it may conclude before the completion of growth [49,50]. The composition and availability of carbon, nitrogen, and phosphate sources, as well as the presence of cations, surfactants, and inhibitors, all influence the synthesis of bacteriocin. Various types of media containing different carbohydrate sources can be utilized for bacteriocin production.

Until recently, class II bacteriocins were primarily associated with the presence of a double glycine leader sequence [51,52,43,53]. All bacteriocins are initially synthesized with an N-terminal leader sequence. However, it has been discovered that the translation of several small, heat-stable, and unmodified bacteriocins involves the involvement of sec-dependent leaders [54,55]. The structural gene of the bacteriocin encodes a preform of the bacteriocin with a double glycine leader sequence at its N-terminus. The function of this sequence appears to be twofold: to prevent the bacteriocin from exerting biological activity while still inside the producer and to serve as a recognition signal for the transporter system.

Lantibiotic synthesis entails the participation of multiple genes, often found in close proximity to one another. These genes include the structural gene Lan A, as well as immunity genes (such as Lan I and occasionally Lan E, Lan F, and Lan G), which encode proteins that shield the producer from the lantibiotic it produces. Additionally, there is a gene known as Lan T that encodes a membrane-associated ABC transporter, likely responsible for the translocation of the producer lantibiotic across the membrane. The biosynthetic pathway of lantibiotics involves several genes, including lan P, which encodes a serine proteinase that cleaves the leader sequence of the lantibiotic prepeptide. Additionally, there are two genes, lan B and lan C, or sometimes just one gene, lan M, which are believed to encode enzymes responsible for the production of lanthionine and methyl lanthionine. Furthermore, the pathway involves two-component systems, including LAN K and LAN R, which encode regulatory proteins that facilitate extracellular signaling and promote lantibiotic development [36].

A visual representation of the lantibiotic biosynthetic pathway is depicted in Figure 1.

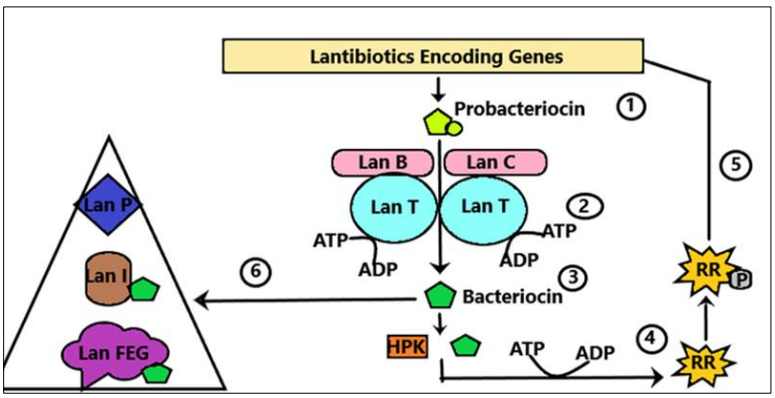

Figure 1 Biosynthesis of lantibiotics [56]

5. Mode of action of bacteriocins

Bacteriocins are specialized proteins that exhibit bactericidal properties by inhibiting the growth of specific bacterial species. While they are commonly classified as narrow-spectrum antibiotics, the classification itself remains a topic of debate [33,30]. The categorization of bacteriocins extends beyond their structural characteristics and includes the mechanisms through which they exert their antibacterial effects. Among these mechanisms, the creation of selective pores or channels in the target bacterial cell membrane is one of the most well-understood. The existence of membrane-bound receptors in the target cell is suggested by the narrow range of action exhibited by certain bacteriocins, although conclusive evidence is yet to be established [57]. Figure 2 Illustrates the diverse modes of action employed by class I and II bacteriocins.

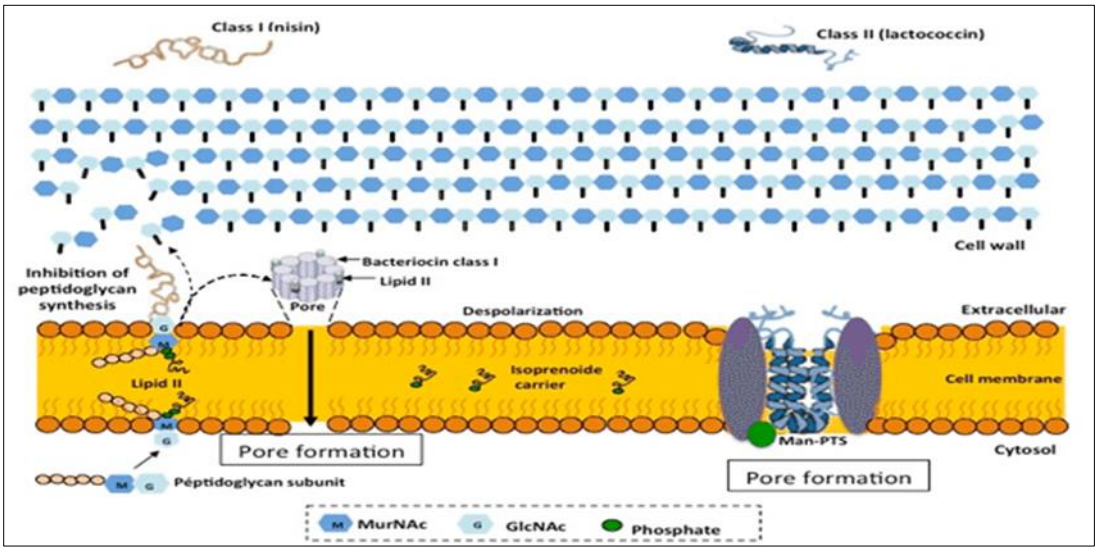

Figure 2 Mode of action of class I and class II bacteriocins GlcNac=N-acetylglucosamine; MurNac= N-acetylmuramic acid [31,58]

Lantibiotics, a subset of class I bacteriocins, such as nisin, have been found to possess a dual mode of action. On one hand, they can bind to lipid II, a universal receptor involved in peptidoglycan transport, thereby disrupting proper cell wall synthesis and leading to cell death. Additionally, they can interact with bacteriocin and exploit lipid II to initiate the formation of membrane pores, resulting in rapid cell death [57]. Furthermore, bacteriocins often exert their effects by targeting the bacterial membrane, causing alterations in its integrity and function. They selectively bind to specific sites on the cell membrane, exhibiting bacteriostatic effects on some bacterial species and bactericidal effects on others [59].

Upon cellular uptake, bacteriocins can induce various biochemical reactions, including suppression of peptidoglycan formation, disruption of cellular DNA, and interference with the precise cleavage of 16S ribosomal RNA. Extensive research on bacteriocins produced by lactic acid bacteria has demonstrated their inhibitory effects on both Gram-negative and Gram-positive bacteria. Studies by Muriana P.M & Klaenhammer [60] and Jamuna and Jeevaratnam [61] suggest that some bacteriocins exhibit surfactant-like activities on cell membranes, thereby disrupting cellular functions.

In contrast, other bacteriocins have a very specific bactericidal effect that is only present in certain Gram-positive bacteria, according to Tagg [29]. An excellent example of such an agent that inhibits *Staphylococci, Streptococci, Bacilli, Clostridia,* and *Mycobacteria* is nisin [2,33].

6. Production and purification of bacteriocins

Bacteriocins can be naturally produced during food fermentation, but higher quantities can be generated by lactic acid bacteria (LAB) through in vitro fermentations conducted under optimal physical and chemical conditions [62]. In vitro production offers advantages such as reduced limitations due to diffusion, protease inactivation, and adsorption to food particles, leading to increased bacteriocin yields [63]. Environmental variables such as temperature, pH, salinity, and medium components significantly influence biomass and bacteriocin production by LAB [64,65].

Even in controlled fermentor tests, notable variations in activity yields are observed, highlighting the impact of ambient process parameters on bacteriocin activity. For example, a decrease in pH reduces the capacity of bacteriocin molecules to bind to the producing cells, enhancing their bioavailability [66,70]. Temperature, pH, and nutrient availability are also known to greatly influence bacteriocin production [50,68,71], while high concentrations of sodium chloride generally result in lower production levels [72,69]. Overall, cultivation conditions directly affect bacteriocin production, including specific bacteriocin production, as well as indirectly through biomass production. This can be attributed to the fact that bacteriocin synthesis is governed by primary metabolite kinetics, a physiological characteristic dependent on growth [67,50,69].

There are three primary methods for homogeneous purification of bacteriocins produced by LAB:

- The traditional method involves a rigorous series of subsequent processes, including ammonium sulfate precipitation, ion exchange, hydrophobic interaction, gel filtration, and reversed-phase high-pressure liquid chromatography [73,74,75].
- A simplified three-step process has been developed [76], which includes ammonium sulfate precipitation, chloroform/methanol extraction/precipitation, and reversed-phase high-pressure liquid chromatography as the sole chromatographic step.
- An alternative approach involves optimizing the bio-available bacteriocin titer by adjusting the pH of the crude fermentation medium, followed by bacteriocin extraction using an innovative technique called expanded bed adsorption with a hydrophobic interaction gel [77,78].

7. Application of bacteriocins in food preservation

Modern consumers have a growing preference for minimally processed, safe, healthy, and flavorful food products. Lactic acid bacteria (LAB) are widely used in the production of fermented foods and have obtained Generally Recognized as Safe (GRAS) and Qualified Presumption of Safety (QPS) status. Consequently, bacteriocins and other metabolites produced by LAB are generally considered safe compounds with intriguing properties such as stability, antimicrobial activity, non-toxicity, and minimal flavor modification [20, 79]. Currently, only nisin and pediocin PA-1 have been commercialized as food additives. However, other LAB bacteriocins, such as lacticin 3147 [80] and enterocin AS-48 [81], hold promise as biopreservatives in food.

Various techniques are commonly employed for the bio-preservation of foods using bacteriocins:

- Direct inclusion of lactic acid bacteria capable of producing bacteriocins during food processing [34]. This approach leverages the inherent ability of LAB to grow and secrete metabolites in the food matrix [82, 2].
- Another approach involves extracting the desired bacteriocin and incorporating it into food [82]. This can be achieved by using purified bacteriocin extracts or incorporating a portion of it into a mixture of other substances [34]. Additionally, nanotechnology-based encapsulation techniques are being explored [83].
- Foods already produced using the desired LAB strain can be used as ingredients in the processing of other foods [82].

The specific method of biological preservation depends on the type of product and the intrinsic and extrinsic conditions encountered during manufacturing, storage, and distribution. In situ production of bacteriocin using starter cultures holds promise for application in fermented foods [84].

Commercially, bacteriocin-producing cultures are readily available [85, 86]. For example, *Lactococcus lactis* subsp. *lactis* BS-10, which produces nisin A, is utilized under the trade name BioSafe™ for the biopreservation of cheeses. Various bacteria, including *Leuconostoc carnosum* (Bactoferm™ B-SF-43), *Lactobacillus sakei* (Bactoferm™ B-2), *Staphylococcus xylosus*, and L. *sakei* (Bactoferm™ B-FM), are used to control *Listeria monocytogenes* in vacuum-sealed meat products [87].

LAB that produces bacteriocins can be employed to preserve plant-based foods, particularly minimally processed vegetables found in prepackaged mixed salads and fermented vegetables. Inclusion of bacteriocin-producing LAB has been shown to reduce initial bacterial loads in ready-to-use mixed salads [88]. Furthermore, starter cultures that produce bacteriocins can aid in the fermentation of sauerkraut or olives, preventing the growth of spoilage organisms [82]. Another notable example is Lacticin 3147, a two-component bacteriocin derived from *Lactobacillus lactis* subsp. lactis DPC 3147. This bacteriocin demonstrates a broad spectrum of activity, effectively targeting various microbes. Its

application in cheddar cheese has been found beneficial, as it restricts the growth of non-starter LAB during the ripening stage, thereby enhancing the overall quality of the cheese [89].

In the realm of seafood and seafood products, the metabolites produced by several lactic acid bacteria have shown promising results as effective biopreservatives. Ghanbari [90] highlights their potential in preserving seafood items such as salmon and prawns [91]. Furthermore, research on bacteriocins released by *Lactobacillus plantarum* F12 reveals their inhibitory activity against a wide range of bacteria known to cause food deterioration [92]. For many other food products, the use of packaging films has been explored as a means of protection. Incorporating bacteriocins into packaging films is currently being investigated [93]. By placing an antimicrobial peptide-infused packaging sheet in close contact with the food surface, the bacteriocin permeates into the food matrix. This controlled diffusion process offers advantages over spraying or dipping the food in bacteriocin. It is worth noting that certain food-related components or decreasing bacteriocin concentration when mixed with the food matrix may affect the antibacterial effectiveness [94].

In addition to the commercially available bacteriocins, the use of multi-bacteriocin producing bacteria, combining nisin A with other bacteriocins, has been proposed for controlling foodborne infections [95]. Furthermore, ongoing research projects aim to enhance the functionality of existing bacteriocins, specifically in the context of food preservation. These studies [96, 97, 98] focus on addressing current limitations by molecular engineering of bacteriocins and their derivatives. The objectives include improving activity, broadening the antimicrobial spectrum, and enhancing delivery and release rates in food environments. One potential approach in this field involves modifying and altering the amino acid sequences of bacteriocins [99].

8. Conclusion

A large number of remarkable LAB-bacteriocins have surfaced recently, fascinating scientists with their potential to completely alter food hygiene. Some of these compounds have revealed their secrets after careful investigation, creating a enthusiasm for bacteriocin study. Although Nisin is the only bacteriocin authorized for use as a biopreservative, there is still an untapped pool of broad-spectrum bacteriocins. We must understand the molecular mechanisms driving synthesis, immunity, and mode of action if we are to successfully harness their potency. Knowing how these agents operate paves the way for a time when they precisely protect our food supply.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors have no conflicts of interest to declare.

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