

Review

Potential Application of Bacteriocin Produced from Lactic Acid Bacteria

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Lactic acid bacteria prevent the contamination of food products by inhibiting proliferation of pathogenic bacteria. This is done mainly by the production of lactic acid and antimicrobial peptides (AMPs) known as bacteriocins. The interest in these molecules resides in both their antimicrobial spectrum and safety for human health. The application of bacteriocins or producer strains has been considered to avoid the development of pathogenic bacteria, as most bacteriocins have significant inhibitory activity against food pathogens, such as *Listeria monocytogenes*. This article describes the classification, structure, mode of action, biosynthesis, and main applications of bacteriocins in different fields: agri-food, aquaculture, and medicine.

Keywords: Lactic acid bacteria, bacteriocins, food applications

Introduction

In general, fermented foods including milk and olives are considered less likely to cause foodborne infection or intoxication [1]. This reliability is due to the occurrence, during their fermentation, of different antimicrobial substances such as hydrogen peroxide, diacyls and bacteriocins produced by lactic acid bacteria, which prevent the proliferation of bacteria and pathogens in food [2, 3].

During olive fermentation, lactic acid bacteria and yeasts are in competition for the same substrate [4, 5]. Lactic cocci of the genera *Pediococcus* and *Leuconostoc* are the first to appear, followed by homofermentative strains such as *Lactobacillus pentosus* and *Lactobacillus*

plantarum. Various yeast species (which the most important are *Pichia anomala*, *Pichia membranifaciens*, *Saccharomyces cerevisiae*, *Debaryomyces hansenii* and *Candida boidinii*) can coexist with lactic acid bacteria throughout this process [6].

Lactic acid bacteria are considered among the most important microorganisms used in the food industry, be it in the fermentation of food or in the improvement of the taste and texture of fermented food products [7]. Bacteriocins are defined as protein-like molecules produced by antimicrobial bacteria (lactic acid bacteria), which act on other pathogenic bacteria by killing or inhibiting their growth [8]. Studies have described their production by lactic acid bacteria isolated from fermented olives [9–11].

Bacteriocins have traditionally been used as food preservatives, added or produced by bacterial cultures during fermentation. Several applications for this group of sub-

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stances have been studied such as food preservation, cancer, contraception, oral care, systemic infections and skin care [12].

Lactic acid bacteria

The term lactic acid bacteria (LAB) was gradually accepted in the early 20th century [13]. Other terms such as “milk acidifying bacteria” and “producing lactic acid” had already been used for the same bacteria, causing slight confusion. This ended with the publication of a monograph on lactic acid bacteria written by [14].

LAB are asporulated, generally non-motile and Gram positive aerotolerant rods and cocci. They are often unable to synthesize cytochromes and porphyrins, components of respiratory chains [15, 16]. Because they don't use oxygen during energy production, lactic acid bacteria readily grow under anaerobic conditions, but they can also grow in the presence of oxygen.

Because they have complex nutritional requirements for amino acids, vitamins, peptides, salts, fatty acids and carbohydrates, lactic acid bacteria are present everywhere in nature and they are generally associated with nutrient-rich habitats such as different food products (milk, beverages, meat products, plant products...). They also exist in the digestive system of humans, they belong to the normal flora of the gut, the mouth and the vagina [17].

Lactic acid bacteria are also characterized by the GC content of their DNA, this content varies between 33 and 54%, which classifies them among bacteria with a low percentage of GC [18].

Classification

Lactic acid bacteria are a relatively close group of bacteria that share similar morphological, metabolic and physiological characteristics.

According to Orla-Jensen [14], their classification into different genera was based initially on the morphology: Bacilli (*Lactobacillus* and *Carnobacterium*), Cocci (the other genera). After, other characteristics were used for their classification such as glucose fermentation mode (homofermentative pathway where the majority of sugar is converted to lactic acid; or heterofermentative pathway in which bacteria produce in addition to lactic acid, ethanol and acetic acid), growth at different temperatures and at high saline concentrations, acid tolerance or

alkaline and the configuration of lactic acid. For some newly described genera, additional characteristics such as fatty acid composition and motility are used in the classification [19].

Currently, lactic acid bacteria include various bacterial genera including *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus*, *Streptococcus*, *Aerococcus*, *Carnobacterium*, *Enterococcus*, *Oenococcus*, *Tetragenococcus*, *Vagococcus* and *Weissella* [20–22], with *Lactobacillus* being the largest genus, with more than 241 abundant species (<http://www.bacterio.net/lactobacillus.html>). *Bifidobacterium* bacteria are widely used and widespread in the dairy industry, but they can't be considered typical as lactic acid bacteria [23].

General metabolism of lactic acid bacteria

Lactic acid bacteria generate ATP by fermentation of hydrocarbons coupled with phosphorylation at the substrate level. The two major pathways of hexose metabolism are the glycolytic pathway (Embden-Meyerhof-Parnas pathway), of which lactic acid is generally the main end product, homofermental metabolism, (for *L. latis* more than 90% of sugar substrate is converted into lactic acid); and the phosphoketolase pathway in which other end products such as acetic acid, propionic acid, ethanol and CO₂ are formed in addition to lactic acid (heterofermental metabolism) [24].

Homofermentative pathway

Homolactic bacteria transform almost all the sugar substrate (especially glucose) into lactic acid. This fermentation route comprises a first phase of glycolysis leading to the formation of pyruvate. The latter is reduced to lactic acid and serves as the terminal electron acceptor (Fig. 1) [21].

The glycolysis occurring in *Streptococcus*, *Pediococcus* and some lactobacilli is characterized by the dissociation of fructose 1,6-bisphosphate, using aldolase, into two fragments of triose phosphate which are subsequently converted to lactate [25].

Heterofermentative pathway

Heterofermentative bacteria use the phosphoketolase pathway in carbohydrate metabolism. The energy efficiency of the pathway is a single ATP per metabolized glucose. In general, most lactic acid bacteria are charac-

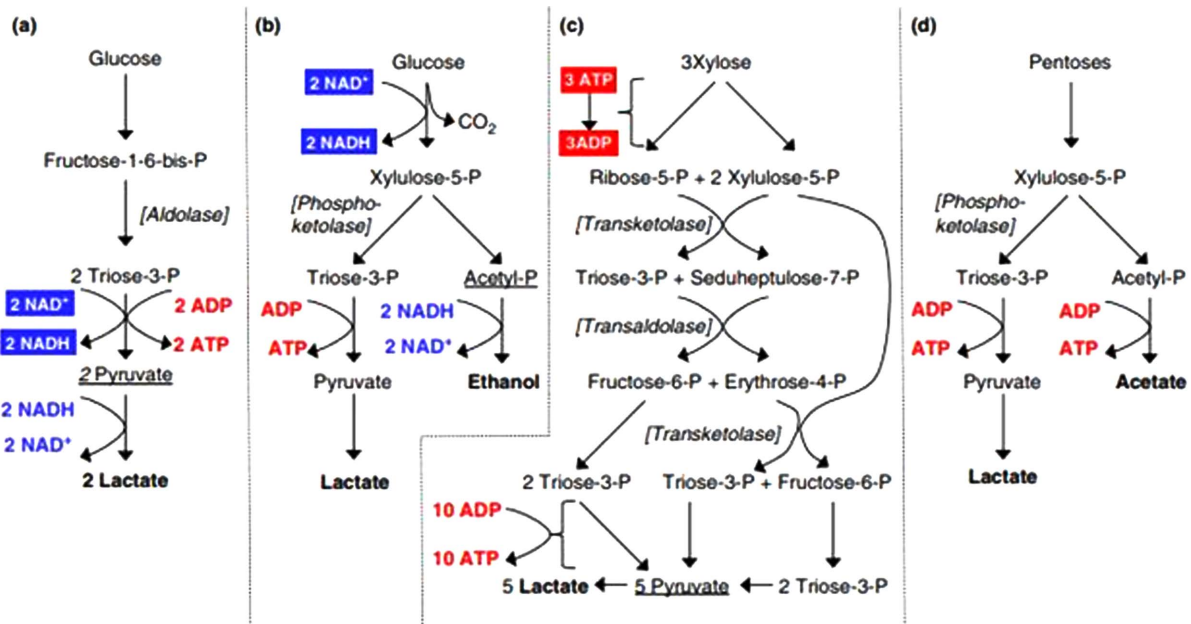


Fig. 1. Fermentation of carbohydrates by lactic acid bacteria, (a) Homofermentative metabolism of hexoses via the Emden-Meyerhof-Parnas pathway; (b) Hetero-fermentative metabolism of hexoses via the phosphoketolase pathway; (c) Homofermentative metabolism of pentoses via the pentose phosphate pathway; and (d) Heterofermentative metabolism of pentoses by the phosphoketolase pathway [24].

terized by a slow growth rate in the case where glucose is the only source of carbon [26].

Hetero-fermentative bacteria generally convert pyruvate from hexoses and pentoses to lactate. However, alternative end products of pyruvate are observed in the metabolism of citrate and pyruvate in *Leuconostoc* spp. and *Oenococcus oeni*.

Probiotic effects of lactic acid bacteria

The term “probiotic” is made up of two Greek words: “pro” and “bios”, and refers to “all living microbial preparations used as food additives and which have a beneficial effect on the host by improving digestion and intestinal hygiene.”

Another definition of probiotics is that they are living microorganisms when administered in adequate amounts, confer beneficial effects on the host [27]. They produce a wide variety of antibacterial molecules, of which nisin is the most used as a food preservative. They are among the most promising alternatives of antibiotics. Their application is widely accepted today both in the agri-food sector and in aquaculture [28, 29].

The effects of probiotics are specific to the strain. They

can improve health performance by maintaining intestinal microbial balance, inhibiting pathogens [30], strengthening the intestinal barrier and modulating the immune system [31]. Many strains have been described as probiotics (Table 1), they are often lactic acid bacteria or yeasts introduced into the diet in the form of fermented milk

Table 1. The main species of probiotics [32].

Probiotic species		
<i>Lactobacillus</i> species	<i>Bifidobacterium</i> species	Other species
<i>L. acidophilus</i> ,	<i>B. adolescentis</i> ,	<i>Enterococcus faecium</i> ,
<i>L. brevis</i> ,	<i>B. animalis</i> ,	<i>E. faecalis</i> ,
<i>L. casei</i> ,	<i>B. bifidum</i> ,	<i>Streptococcus lactis</i> ,
<i>L. crispatus</i> ,	<i>B. breve</i> ,	<i>S. thermophilus</i> ,
<i>L. fermentum</i> ,	<i>B. infantis</i> ,	<i>Lactococcus lactis</i> ,
<i>L. gasseri</i> ,	<i>B. lactis</i> ,	<i>Bacillus cereus</i> ,
<i>L. helveticus</i> ,	<i>B. longum</i> .	<i>B. subtilis</i> ,
<i>L. johnsonii</i> ,		<i>Escherichia coli</i> Nissle 1917,
<i>L. lactis</i> ,		<i>Saccharomyces boulardii</i> ,
<i>L. paracasei</i> ,		<i>S. cerevisiae</i> .
<i>L. plantarum</i> ,		
<i>L. reuteri</i> ,		
<i>L. rhamnosus</i> ,		
<i>L. salivarius</i> .		

products or dietary supplements [32]. Lactic probiotic strains belong mainly to the genera *Lactobacillus* spp. [33], *Bifidobacterium* spp. and *Enterococcus* spp. [34, 35].

Bacteriocins

Bacteriocins are defined as antimicrobial peptides of about 30 to 60 amino acids, synthesized ribosomally and forming stable amphiphilic helices at 100°C for 10 min. They have traditionally been used as food preservatives, added or produced by starter cultures during fermentation.

They were first identified as a thermolabile product called colicin, present in *Escherichia coli* V cultures and toxic to *E. coli* S. [36]. Since then, bacteriocins have been found in all major bacterial lineages, the vast majority of which are produced by Gram-positive bacteria [37].

The bacteriocins produced by lactic acid bacteria have attracted increasing attention because they are active in a nanomolar range and have no toxicity. They are defined as protein-like molecules produced by the antibacterial bacteria called lactic acid bacteria, which cause antibacterial activity, killing or inhibiting the growth of other bacteria including pathogenic bacteria such as *Listeria monocytogenes* [38], without alteration of producing bacteria.

Several characteristics are common for bacteriocins such as heat and acid stability, resistance to proteases, a bactericidal or bacteriostatic effect and prolonged activity [39].

Its self-protection is mainly due to the synthesis of specific immunity proteins encoded by the bacteriocin operon [40].

In addition to the synthetic route and the concentration required for inhibitory activity, bacteriocins differ from antibiotics in that they have a relatively narrow spectrum of action and that the antibacterial activity is directed against taxonomically related strains of the producing strain [41]. These molecules have been found in all major bacterial lineages, and according to [42], 99% of bacteria can make at least one bacteriocin.

Classification of bacteriocins produced by lactic acid bacteria

Bacteriocins were classified according to primary structures, molecular weight, post-translational properties and

genetic characteristics. According to Klaenhammer (1993), four classes of bacteriocins have been distinguished. Subsequently, different classification schemes for bacteriocins have been proposed, taking into account new subclasses, based on the mechanism of biosynthesis and the antibacterial activity of the molecules [43, 44].

Lantibiotics

Class I bacteriocins or lantibiotics are peptidic inhibitors with molecular mass of less than 5 kDa, produced by Gram-positive bacteria [45], with nisin and lactocin as the most widely recognized. They are characterized by post-translational modifications, resulting in the formation of a mixture of atypical amino acids such as lanthionine, methyllanthionine, dehydroalanine and dehydrobutyrine [45, 46].

The lantibiotics are divided into two subgroups, A and B, differing according to their structural characteristics and their mode of inhibition [47]. The type A lantibiotics, or lantipeptides, comprise elongated hydrophobic cationic peptides containing up to 34 amino acids, they act on the target cell by depolarization of the cytoplasmic membrane [48]. Type B lantibiotics include globular peptides that are negatively charged or without net charge, are smaller than type A, and contain up to 19 amino acids [49].

Class II bacteriocins

Class II bacteriocins or non-lantibiotics are relatively small molecules (<10 kDa) ranging in size from 30 to 60 amino acids. They are thermostable and do not undergo post-translational modification.

This class comprises the largest subgroup of bacteriocins: class IIa (pediocin-like), characterized by a close activity against *Listeria monocytogenes* [50], class IIb, two-peptide bacteriocins, whose activity depends on the synergy between two different peptides. They generally have an action spectrum that inhibits a wide range of Gram-positive bacteria, they form pores in the membrane of the target cells [51]; class IIc which groups circular bacteriocins and class IId which includes all other bacteriocins [52].

Class III Bacteriocins

This class includes bacteriocins which have a high molecular weight (> 30 kDa). They are thermolabile pro-

teins that act in a different way from other classes of bacteriocins. Colicin is the most characteristic of this class [53]. It generally contains three domains, including receptor binding, translocation and the lethal domain [54].

Another proposed additional class (class VI) is defined as complex bacteriocins containing lipid or carbohydrate moieties. Little is known about the structure and function of this class, which includes leuconocin S [55] and lactocin 27 as an example [56].

Bacteriocins production

The production of bacteriocins by lactic acid bacteria is influenced mainly by the temperature, the pH, the composition of the medium [57, 58], and by the producing strain, which can produce proteases that act by degradation of bacteriocins [59]. It is usually done during the exponential phase and reaches a maximum threshold during the stationary phase of growth [60–63]. The produced bacteriocins can then be degraded by the proteases produced by the lactic acid bacterium [59] or adsorbed on its surface, which leads to a decrease in the concentration of bacteriocins in the culture [64].

In general, the production of bacteriocins by lactic acid

bacteria begins with the formation of a very little or non-biologically active pre-peptide, which later undergoes post-translational modifications to lead to the active peptide [64]. This pre-peptide matured during or immediately after its secretion in the extracellular medium (Fig. 2) [65]. The mechanism of production of bacteriocins is often regulated by a system called Quorum Sensing, a mechanism that allows certain genes to be expressed according to the density of the bacterial population [66].

Two essential constituents are involved in the secretion of bacteriocin: the signal peptide or leader and the transporter, the first allows the secretion of bacteriocin in the external medium, in addition it protects the bacterium against the action of its own bacteriocin [67]. The second, a carrier formed by the products of two genes: ABC transporter gene, associated with a gene encoding an accessory protein [68].

Mode of action

The bacteriocins often act on the target cells in two steps: adsorption of the bacteriocin at the cell surface, followed by the formation of pores on the plasma membrane of the target cell [69], causing a permeability of

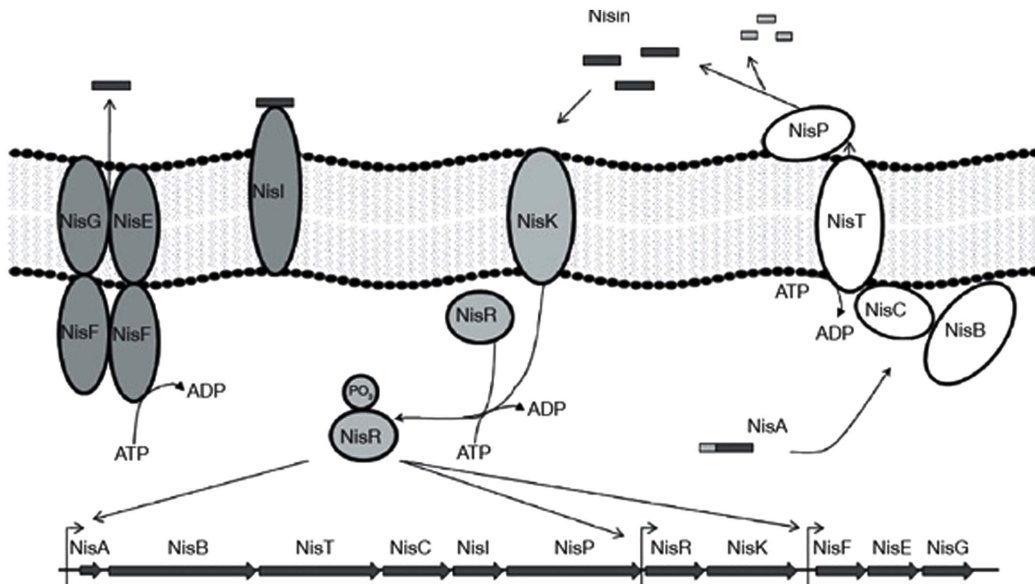


Fig. 2. Regulation of biosynthesis, post-translational modification and auto-immunity of nisin. After the prepeptide (NisA) undergoes modifications based on dehydration using (NisB), cyclization by (NisC), translocation via the ABC transporter (NisT), cleavage by protease (NisK); the response regulator (NisR) is phosphorylated, inducing the activation of transcription of nisin synthesis genes. The cell's autoimmunity to the bacteriocin produced is conferred by the lipoprotein immunity (NisI) and the ABC transporter (NisG, NisE, NisF) [74].

this one and thus cell death [70].

Their mechanisms of action on the target cell are varied, and can be divided into three types: bacteriostatic action that leads to slowing down or stopping growth, without cell death, bactericidal action during which bacteria die while keeping their physical integrity (no cell lysis) and bacteriolytic action that leads to dissolution of the bacterial cell [71].

Several lantibiotics and certain class II bacteriocins have a dual mode of action: either they bind to lipid II, an intermediate in the biosynthetic mechanism of the peptidoglycan of the bacterial cell, and therefore prevent the correct synthesis of the wall, this leads to cell death [72]; or they use lipid II as an anchoring molecule to facilitate pore formation [73], leading to the dissipation of the proton motive force and the leakage of intracellular compounds to the outside of susceptible bacteria, and ultimately cell death [70, 74].

In addition, class III which comprises bacteriocins with a high molecular weight, the mechanism of action differs totally from other bacteriocins, some act by hydrolysis of peptide bonds peptidoglycan sensitive cells [75, 66].

Applications

In recent decades, bacteriocins, given their safety, have been used as alternatives to antibiotics and recognized several applications in the food industry to extend the shelf life of food, and in medicine in the prevention and/or treatment of infections, due to bacteria that have become resistant to conventional treatments [76] and in the treatment of malignant cancers.

So far, two bacteriocins, nisin and pediocin PA-1 have been marketed as food additives. In addition, enterocin AS-48 [77] and lacticin 3147 [78], for example, have also been identified as bacteriocins produced from lactic acid bacteria containing biocidal properties of food preservation.

Bacteriocins can be used in various forms: purified; semi-purified as a food preservative, such as nisin [52]; or as a preparation bacterial strain whose bacteriocinogenic strains can be directly inoculated into foods as starter, auxiliary or protective crops [79]. Recently, bacteriocins have been incorporated into packaging films to control foodborne pathogenic bacteria.

Bacteriocins application in food processing

The bio-preservation of foods by bacteriocins has been the most studied for a long time. It consists of an increase in the life span and an improvement of food safety through the use of lactic acid bacteria and/or their metabolites, which act by reducing the food contamination by pathogens such as *Listeria monocytogenes* [80-82]. Several bacteriocins produced by lactic acid bacteria, such as *Lactobacillus plantarum*, *Pediococcus acidilactici* and *Enterococcus faecalis*, have been investigated for their antimicrobial effect against pathogenic bacteria.

Thus, many studies have indicated the application of bacteriocins in dairy products, by the addition of lactic acid bacteria as protective cultures that develop and produce bacteriocins during the manufacture and storage of dairy products [83]. Other studies have also focused on the selection and development of bacteriocinogenic cultures as agents inducing cell lysis to improve cheese maturation [84] and to prevent late infections of the food [85].

Nisin produced by *Lactococcus lactis* was the first antibacterial peptide used in the agri-food industry [86]. It is a commercial bacteriocin used as a food preservative marketed under the name of Nisaplin™. A study conducted by [87] suggested that food nisin has a mode of action similar to that of salinomycin and could be considered a dietary supplement for broilers.

In another study of [88] were able to purify a bacteriocin enterocin RM6 from *Enterococcus faecalis*, active against Gram-positive bacteria, including *Listeria monocytogenes*, *Bacillus cereus* and methicillin-resistant *Staphylococcus aureus* (MRSA). This bacteriocin caused a reduction of 4 logarithms of the *L. monocytogenes* population inoculated at a concentration of 80 AU/ml, in a cheese for at least 30 minutes of treatment. A new study conducted by [82] reported a reduction in the concentration of *L. monocytogenes* by adding three strains of *Lactococcus lactis* producing nisin A to fresh cheese.

Recently several studies have been able to present the positive effect of the use of bacteriocins in food packaging films [89, 90]. In fact, this type of antimicrobial packaging increases the shelf life, safety and quality of many food products by reducing microbial growth in non-sterile foods and minimizing the risk of post-contamination of processed products [91].

Several methods have been followed in incorporating bacteriocins into packaging films, one of which incorporates bacteriocin directly into the polymers, such as the incorporation of nisin into the biodegradable protein films [92].

Another method is to adsorb bacteriocins on the surfaces of the polymer: methylcellulose nisin coatings for polyethylene films for use on poultry meat [93].

Bacteriocins in aquacultures

The use of bacteriocins, or their producing strains as probiotics [94, 95], and animals [87] has been well documented. Recently, supplementation with probiotics in aquaculture has been reported to improve growth performance, immune responses and disease resistance.

Various kinds of lactic acid bacteria have been studied with regard to their immunomodulatory effects on many different species of fish: *Lactobacillus* [96], *Lactococcus* [97], *Enterococcus* [98]; although the majority of studies have used a specific strain of live lactic acid bacteria. Some studies have been conducted with their inactivated form of LAB.

Numerous modes of lactic acid bacteria administration have been studied: treatment of fish by intraperitoneal injection [99], immersion of fish in a bath containing lactic acid bacteria [98, 100], administration of lactic acid bacteria in the regular diets of fish ... Some studies have shown that the administration of dietary probiotics has better immunostimulatory effects.

The effect of two probiotic strains of *Lactobacillus plantarum* T8 and T13 on the growth and survival of the white-legged shrimp, *L. vannamei*, was tested by [97]). It has been shown that both T8 and T13 are significantly reduced in the incidence of 10^5 or 10^6 CFU/ml after 48 h or 24 h of infection, respectively.

Use of bacteriocins in medicine

Increasing the number of multi-resistant pathogens has become a serious problem and it is increasingly important to find or develop a new generation of antimicrobial agents. Studies are currently oriented towards finding new substances and antibacterials as natural therapy agents that are alternative to antibiotics [101].

Lactic acid bacteria or their bacteriocins being protein inhibitors of a non-toxic nature, with a high specificity of action and a potential inhibitory effect on multidrug-

resistant pathogens [102], have increased the interest of many scientists to carry out work on their applications in the medical field.

They have beneficial effects on the host by imparting a balance of intestinal microflora, and also playing an important role in the maturation of the immune system [97]. Various studies have demonstrated the preventive as well as curative role of these bacteria on several types of diarrhea [103–105] demonstrated the effect of fermented milk by different lactic strains of *Lactobacillus murinus* CRL1695, *Lactobacillus mucosae* CRL1696, *Lactobacillus johnsonii* CRL1693 and *Lactobacillus salivarius* CRL1702 on the incidence of diarrhea, animal performance, nutritional, microbiological, and hematologic parameters in calves. The study indicated a decrease in the prevalence of diarrhea and mortality in animals with significant weight gain. Other research has cited the role of lactic acid bacteria in regulating the immune system [106].

The safety of bacteriocins, and their mode of action which differs from those of conventional antibiotics, have allowed their use as an alternative to antibiotics in the prevention and/or treatment of various infections: cutaneous [107], respiratory [108], systemic [109] and/or urogenital [110] as well as contraceptive agents.

Combination of bacteriocins with other antibacterial factors/molecules

The combination of bacteriocins with other antimicrobial agents is an approach that aims to improve the protective action. The antimicrobial agents may be of physical type such as heat treatments and high-pressure or chemical-type treatments such as some additives (organic acids, nitrite, sodium chloride, ethanol, essential oils, etc.,)

A large group of antimicrobial peptides that belong to class IIa bacteriocins can be used in medicine with antibiotics in the treatment of infectious diseases or as antiviral agents. These peptides have inhibitory activity against harmful and pathogenic Gram-positive bacteria such as *Bacillus cereus*, *Clostridium perfringens*, *Staphylococcus aureus* and *Listeria monocytogenes* [126].

Nisin has been the subject of several association studies with antimicrobial molecules to inhibit foodborne pathogens. A concentration of 6 400 IU nisin in combination with green tea extract (GTE) or in combination with

Table 2. Recent and main applications of bacteriocins in different fields.

Bacteriocin	Producer	Origin	Concentration	Product	Target	Properties	Country	Reference
Bacteriocin FAIR-E 198	<i>Enterococcus faecium</i> FAIR-E 198	Feta cheese	100 UA ml ⁻¹	Cheese		When enterocin was treated with rennet at a concentration of 0.020 mg ml ⁻¹ no activity was detected after 6 h of incubation. On the contrary, in the presence of 0.002 mg ml ⁻¹ of rennet, the enterocin activity remained intact after 6 h of incubation.	Greece	[83]
Sakacin G	<i>Lactobacillus curvatus</i> ACU-1	Artisanal dry sausages	800 UA ml ⁻¹	Meats products	<i>Listeria innocua</i> ATCC 33090 and <i>Listeria monocytogenes</i> 01/155	The addition of <i>Lb. Curvatus</i> ACU-1 CFS at the exponential phase of growth of <i>L. Innocua</i> ATCC 33090 and <i>L. Monocytogenes</i> 01/155 cell suspensions resulted in a decrease in optical density for both bacteria.	Argentina	[111]
Bacteriocin RC20975	<i>Lactobacillus rhamnosus</i>	Center of Industrial Culture Collection, China	20 mg ml ⁻¹	Apple juice	<i>Alicyclobacillus acidoterrestris</i>	Bacteriocin RC20975 as found to have a good effect on killing <i>A. Acidoterrestris</i> in apple juice. The bacteriocin influences the reduction of spore temperature of <i>A. Acidoterrestris</i> in the apple of apple.	China	[94]
Pentocin 31-1	<i>Lactobacillus pentosus</i> 31-1	Xuan-wei ham	80 UA ml ⁻¹	Pork meat	-	80 AU/ml pentocin could extend the shelf life to 15 days and the meat showed good sensory characteristics. These results suggest the potential of pentocin 31-1 as a biopreservative in tray-packaged chilled pork storage.	China	[112]
Enterocin RM6	<i>Enterococcus faecalis</i> OSY-RM6	Raw milk	80 UA ml ⁻¹	Cottage cheese	<i>L. monocytogenes</i>	Enterocin RM6 with concentration in cottage cheese, 80AU/ml, caused a 4-log reduction in population of <i>L. Monocytogenes</i> inoculated in cottage cheese within 30 min of treatment.	USA	[88]
Nisin	<i>Lactococcus lactis</i> subsp. <i>Lactis</i> IFO12007	Non mentioned	1,28.10 ⁵ UA ml ⁻¹	Fermented soybeans	<i>Bacillus subtilis</i>	<i>Lc. Lactis</i> produced high nisin activity (1.28×10 ⁵ AU/g) in cooked soybean, resulting in the complete growth inhibition of <i>B. Subtilis</i> , which had been inoculated at the beginning of the koji fermentation, throughout the process of miso production.	Japan	[113]
Plantaricin IIA-1A5	<i>Lactobacillus plantarum</i> IIA-1A5	Saucisse de boeuf	0,3%	Beef sausage	<i>Staphylococcus aureus</i> and <i>Escherichia coli</i>	The results showed that the presence of bacteriocin in the sausages inhibited the growth of pathogenic <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> bacteria until day 6, which was better than the inhibition observed in the presence of nitrite.	Indonesia	[114]
Fermentacin HV6b	<i>Lactobacillus fermentum</i> HV6b MTCC 10770	Vaginal humain ecosystem	50-200 µg ml ⁻¹	Bacterial vaginosis	Bacteroides, <i>Gardnerella vaginalis</i> , <i>Mobiluncus</i> , staphylococci, and streptococci	Fermentacin HV6b shows growth inhibition of a wide range of opportunistic pathogens of humans, for example, Bacteroides, <i>Gardnerella vaginalis</i> , <i>Mobiluncus</i> , staphylococci, and streptococci, associated with bacterial vaginosis in humans.	India	[115]
Bacteriocine CR1T5	<i>Lactobacillus plantarum</i> CR1T5	Non mentioned	3,79.10 ⁹ cfu g ⁻¹	Pangasius catfish	-	Dietary supplementation of PE and <i>L. Plantarum</i> stimulated growth, immunity and disease resistance of the <i>Pangasius bocourti</i> .	Thailand	[116]
Bacteriocin DY4-2	<i>Lactobacillus plantarum</i> DY4-2	Shrimp (<i>Trichiurus lepturus</i>)	4 mg ml ⁻¹	Turbot fillets	<i>Pseudomonas Fluorescens</i>	The addition of partially purified bacteriocin DY4-2 in turbot fillets reduced the number of <i>Pseudomonas Fluorescens</i> by 2.7 log units at 4 °C storage for 12 days.	China	[117]
Pediocin A	<i>Pediococcus pentosaceus</i> FBB61	Cucumbre	80 UA g ⁻¹	Broilers	<i>Clostridium Perfringens</i>	Diet supplementation with pediocin A improved broiler growth performance during the challenge with <i>Clostridium Perfringens</i> and tended to restore the ADG depletion during the 42-d period.	Italy	[118]

Table 2. Continued.

Bacteriocin	Producer	Origin	Concentration	Product	Target	Properties	Country	Reference
Bactériocine NC0209951	<i>Enterococcus casseliflavus</i> -nc0209951	Rainbow trout gut	10 ⁷ cfu g ⁻¹ 10 ⁸ cfu g ⁻¹ 10 ⁹ cfu g ⁻¹	Rainbow	-	<i>Enterococcus casseliflavus</i> is indicated by its capability in improving growth performance and modulating the innate defenses of the host (rainbow).	Iran	[119]
Fermencin SA715	<i>Lactobacillus fermentum</i> GA715	Goat's milk	2.0714 mM	Banana	<i>Streptococcus</i> spp., <i>Enterococcus</i> spp., <i>Escherichia coli</i> , <i>Listeria monocytogenes</i> , and others	Fermencin SA715 doubled the shelf life and improved the microbiological safety of fresh banana.	Malaysia	[95]
Bacteriocin DF04Mi	<i>Lactococcus lactis</i> DF04Mi	Goat's milk	10 ⁶ cfu ml ⁻¹	Cheese	<i>Listeria monocytogenes</i>	Addition of nisin (12.5 mg/kg) caused a rapid decrease in the number of viable <i>L. monocytogenes</i> in the cheeses.	Brazil	[120]
Bacteriocine-like E204	<i>Enterococcus durans</i> E204	Camel milk	10 ⁶ cfu ml ⁻¹	Jben	<i>Listeria</i>	In jben batches prepared with <i>E. Durans</i> , <i>Listeria</i> counts decreased progressively from the beginning of storage and were undetectable at 8 and 6 days post-contamination with 10 ⁶ and 10 ⁴ CFU/ml, respectively.	Morocco	[85]
Enterocin AS-48	<i>Enterococcus faecalis</i> UGRA10	Not cited	100, 50, and 25 µg ml ⁻¹	Rainbow	<i>Lactococcus garvieae</i>	In broth cultures, enterocin at 100, 50, and 25 µg/ml reduced 10 ⁸ CFU/ml lactococci after 2, 5, and 10h, respectively. In co-cultures of UGRA10/ <i>Lactococcus garvieae</i> at a 1/10 CFU/ml ratio, lactococci were eliminated after 24 h.	Spain	[98]
Not cited	<i>Lactobacillus plantarum</i> T8 et T13	Animaux marins et chou fermenté	10 ⁸ cfu ml ⁻¹	White-leg shrimp	-	<i>Lactobacillus plantarum</i> T8 and T13, exerted antimicrobial activities against all tested <i>Vibrio</i> isolates. T8 enhanced significant growth and survival of shrimps after bath challenge with XN9.	Vietnam	[97]
Not cited	<i>Lactococcus lactis</i> spp. <i>Lactis</i> PTCC1336	Not cited	10 ⁶ CFU ml ⁻¹	Rainbow trout fillets	Psychrotrophic, psychrophilic, mesophilic bacteria, molds and yeasts	The 4% supernatant and live bacteria were more effective than that of 2% and control (p<0.05). The amounts of corrosive bacteria in 4% and live cells in storage time were less than human consumption limits (7log cfug-1), whereas in control and 2% supernatant treatments were more than that limits.	Iran	[121]
Nisin F	<i>Lactococcus lactis</i> subsp. <i>Lactis</i> F10	Not cited	1280 AU ml ⁻¹	Respiratory tract infections	<i>Staphylococcus aureus</i>	Nisin F inhibited the growth of <i>Staphylococcus aureus</i> K in the respiratory tract of immunocompromised rats. Treatment with nisin F at 8192 AU proofed safe, as the trachea, lungs, bronchi and haematology of the rats appeared normal.	South Africa	[108]
Not cited	<i>Lactobacillus salivarius</i> LS03	Not cited	LS03-soaked disks	Acne therapy	<i>Propionibacterium acnes</i>	<i>Lactobacillus Salivarius</i> Is03 exerted a significant inhibitory capacity against the target pathogen strain. This antagonistic activity was primarily ascribable to the feature of Is03 strain of secreting active bacteriocins against <i>Propionibacterium acnes</i> . Concerning the il-8 analysis, 3 different <i>Lactobacillus Salivarius</i> strains were able to inhibit the release of this chemokine by 10% to 25%	Italy	[107]
Nisin nisaplin®	Not cited	(Nisaplin® from Danisco, Copenhagen, Denmark	15 mg ml ⁻¹	Biofilm formation	<i>Staphylococcus aureus</i> Xen 31, Xen 30, Xen 36 and Xen 29	Biofilm formation decreased by 88% after 24 h of exposure to nanofibers containing nisin and DHBA (NDF), compared to a 63% decrease when exposed to nanofibers containing only DHBA (DF) and a 3 % decrease when exposed to nanofibers containing only nisin (NF).	South Africa	[122]

Table 2. Continued.

Bacteriocin	Producer	Origin	Concentration	Product	Target	Properties	Country	Reference
Nisin ZP	Not cited	Handary (s.a., brussels, belgium)	2.5-50 µg ml ⁻¹	Oral cavity	Streptococcus oralis 3, Streptococcus mutans UA159 and others	Nisin inhibited planktonic growth of oral bacteria at low concentrations (2.5–50 µg/ml), and also retarded development of multi-species biofilms at concentrations ≥1 µg/ml.	USA	[123]
Nisin	<i>Lactococcus lactis</i> subsp. <i>Lactis</i> ATCC11454	Not cited	100, 300, 900 et 2700 IU g ⁻¹	Broiler chickens	-	Dietary nisin exerts a mode of action similar to salinomycin and could be considered as a dietary supplement for broiler chickens. Nisin supplementation improved broiler growth performance in a dose-dependent manner.	Polande	[87]
Bactériocine LABW4	<i>Lactococcus lactis</i> subsp. <i>Lactis</i> LABW4	Fermented milk	10% de CFS LABW4	Meat	<i>L. monocytogenes</i>	Both cell free and heat killed supernatants of LABW4 were effective to produce zones of inhibition against <i>L. monocytogenes</i> in vitro.	India	[124]
Paracin C	<i>Lactobacillus paracasei</i> CICC 20241	China Center of Industrial Culture Collection, China	20, 50, 100, et 200 µg ml ⁻¹	Apple juice	<i>A. Acidoterrestris</i>	Paracin C produced by <i>Lactobacillus paracasei</i> CICC 20241 is a safe and efficient bacteriocin active against <i>A. Acidoterrestris</i> . It is able to inhibit and kill the cells of <i>A. Acidoterrestris</i> present in apple juice and has a broad activity spectrum.	China	[94]
Lactococcin bz enterocin kp	<i>L. Lactis</i> spp. <i>Lactis</i> bz and <i>e. Faecalis</i> kp		400 AU ml ⁻¹ 400 AU ml ⁻¹	Milk	<i>L. monocytogenes</i>	Lactococcin BZ at 400–2500 AU ml ⁻¹ level displayed strong antilisterial activity, and decreased the viable cell numbers of <i>L. monocytogenes</i> to an undetectable level in all types of milk samples during the entire storage periods at 4 °C or 20 °C.	Turkey	[125]
Nisin	<i>Lactococcus lactis</i> N5764		(1/4) 110 µg ml ⁻¹ (1/4) 125 µg ml ⁻¹	Cow milk	<i>Staphylococcus aureus</i> ATCC 25923 and <i>Listeria monocytogenes</i> ATCC 15313	The study aimed to investigate the antibacterial activities of carvacrol, thymol, eugenol, cinnamaldehyde, and lantibiotic nisin. Inhibitory activities of nisin and the tested compounds, as well as synergism in the combinations, were found against <i>Staphylococcus aureus</i> ATCC 25923 and <i>Listeria monocytogenes</i> ATCC 15313 in cow milk.	Brazil	[80]

Grape Seed Extract (GSE) resulted in effective cell damage in a target strain of *L. monocytogenes* [127]. Another study investigated the antibacterial activity of nisin combined with phenolic compounds against *Staphylococcus aureus* and *L. monocytogenes* in cow's milk (Table 2), the study showed bacteriostatic effects of nisin combined with the different phenolic compounds tested, with a significant difference in the reduction of *L. monocytogenes* compared to control tests.

The effect of nisin combined in inhibiting biofilm formation was illustrated by the research of [122], in which biofilm formation was reduced by 88% after 24 h of exposure to biofilms nanofibers containing nisin and 2,3-dihydroxybenzoic (DHBA), compared to a 63% decrease due to exposure to nanofibers containing only DHBA (Table 2).

It has been shown that a very delayed latency phase was apparent in the growth curves, when nisin V at 0.02% was combined with essential oils tested, compared

to the nisin A equivalent [128].

On the other hand, combinations of bacteriocins and antibiotics can reduce the concentration of antibiotics needed to kill a target pathogen, thereby decreasing the risk of adverse side effects associated with the antibiotic.

In a study by [129], nisin interacted synergistically with several antibiotics and these combinations were effective against staphylococci biofilms. Thus, nisin was effective when used with polymyxins against *Pseudomonas aeruginosa* biofilms [130].

A recent study of [131] showed that durancin 61A, a broad-spectrum bacteriocin combined with antibiotics, were highly synergistic inhibitors of multidrug-resistant pathogens of clinical interest (*S. aureus*, *C. difficile* and *Streptococcus* spp.). With regard to Gram-negative germs, researchers were able to show a synergy of nisin combined with polymyxin B against *Acinetobacter* spp. and *Escherichia coli*.

Bacteriocins are usually recognized as safe because

they are sensitive to digestive proteases, not toxic to eukaryotic cells and have generally bactericidal antimicrobial potency. Their antimicrobial spectrum can be wide or narrow, so they can selectively target pathogenic or damaging bacteria without inhibiting essential bacteria.

The bacteriocins of lactic acid bacteria find their use in different fields where they prevent the development of pathogenic and harmful bacteria. In the field, the foods are either supplemented with bacteria producing bacteriocin, purified or semi-purified bacteriocin.

Conflict of Interest

The authors have no financial conflicts of interest to declare.

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