



Bacteriocins Produced by LAB Isolated from Cheeses within the Period 2009–2021: a Review

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Abstract

A survey is presented concerning original research articles published in well-reputed scientific journals on the isolation of lactic acid bacteria (LAB) from cheeses worldwide, where researchers evaluated the bacteriocin production by such isolates in searching for novel functional peptides that can exhibit potential for biotechnological applications. Seventy-one articles were published in the period of study, with contributions being American (45%), Asiatic (28%), and European (21%), being Brazil-USA-Mexico, Turkey-China, and France-Italy the countries that contributed the most for each said continent, respectively. Most of the isolated LAB belong to the genera *Enterococcus* (35%), *Lactobacillus* (30%), *Lactococcus* (14%), and *Pediococcus* (10%), coming from soft (64%), hard (27%), and semi-hard (9%) cheeses, predominantly. Also, scholars focused mainly on the food biopreservation (81%) and pharmaceutical field (18%) potential applications.

Keywords Antimicrobial peptides · Novel bacteriocins · Functional additives · Artisanal cheese · Fermentation · Purification

Introduction

Lactic acid bacteria (LAB) are a key heterogeneous group of microorganisms that have provided diverse benefits to the human being, since ancient times, in fact determining traditions, culture, and health of civilizations. LAB are Gram-positive, catalase-negative, non-spore-forming, and anaerobic, producing lactic acid as the primary end product of fermentation. Important members belong to the genera *Lactobacillus*, *Paralactobacillus*, *Holzschufelia*, *Amylolactobacillus*, *Bombilactobacillus*, *Companilactobacillus*, *Lapidilactobacillus*, *Agrilactobacillus*, *Schleiferilactobacillus*, *Loigolactobacillus*, *Lacticaseibacillus*, *Latilactobacillus*, *Dellaglioia*, *Liquorilactobacillus*, *Ligilactobacillus*, *Lactiplantibacillus*, *Furfurilactobacillus*, *Paucilactobacillus*, *Limosilactobacillus*, *Fructilactobacillus*, *Acetilactobacillus*, *Apilactobacillus*, *Levilactobacillus*, *Secundilactobacillus*, *Lentilactobacillus*, *Pediococcus*, *Lactococcus*,

Streptococcus, *Leuconostoc*, *Weissella*, *Enterococcus*, and *Oenococcus*, among others [1, 86]. LAB can produce diverse substances with antimicrobial activity, one type of them of proteinaceous nature, called bacteriocins, ribosomally synthesized by bacteria [2, 3]. The classification of bacteriocins is a matter continuously updated, and excellent references are discussing this based on the physicochemical properties, molecular weight, the inclusion of particular amino acids in the structure, heat stability, containing other compounds like lipids or carbohydrates, cyclic molecules, involved genetics, among other characteristics [4, 5]. There are three types of bacteriocins produced by Gram-positive bacteria: Class I or lantibiotics (< 5 kDa, heat-stable with characteristic amino acids, like lanthionine; i.e., nisin, mersacidin); Class II (< 10 kDa, heat-stable, without lanthionine; i.e., pediocin, plantaricin); Class III (> 30 kDa, thermolabile; i.e., helveticin) [6].

Essential sources of LAB are the traditional fermented foods, both animal and vegetable origin (i.e., (product/primary raw material): Kimchi/cabbage; Kefir/cow's milk; Pozol/maize; Amazake/rice; Cheddar cheese/milk; Plaasom/fish; Sausages/meat) [7, 8] among other possible sources as feces [9, 10]), skin [11], mouth [12], vagina [13], and herbs [14].

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Even many groups worldwide are conducting research on bacteriocins; nowadays, there are just a few bacteriocins that are authorized for their use in different countries and found at the commercial level. Examples of these are (a) nisin, a lantibiotic bacteriocin produced by a cheese-making starter, *Lactococcus lactis* subsp. *lactis* [15], considered a food additive with the GRAS status (i.e., generally recognized as safe) [16] and authorized in Europe as the food additive E234 [17], and (b) colicins, also recognized as GRAS additives [18] produced by *Escherichia coli*, to reduce the levels of *E. coli* on meat food products. Furthermore, the bacteriocin business is important with high growth expectations. Just concerning nisin, it is expected to encompass a market of 553 USD million by 2025, just considering food applications (i.e., meat, poultry, and seafood; dairy; beverages; bakery and confectionery; canned and frozen products (<https://www.marketsandmarkets.com>)). Moreover, in recent times, researchers have envisaged having more comprehensive applications of bacteriocins, including the combat of antibiotic-resistant pathogenic bacteria [19], the control of certain types of cancer by inducing the apoptosis process [20, 21], and even as a possible alternative as antiviral therapy against COVID-19 [22, 23], among other applications. Exciting times are waiting for us in this field.

Furthermore, cheeses have been valuable sources for the isolation of LAB with the purpose, among others, of discovering novel bacteriocins that can be useful to solve problems concerning food preservation and pharmaceutical/medical matters. Moreover, this is possible, at least partially, due

to cheese technology being about 9000 years old, giving humans the possibility to interact with microbial populations which have evolved in a vast catalogue of LAB available today, considering the lots of cheese types that are present all over the world [24, 25]. That is the reason for conducting this review concerning original research articles on the isolation of LAB from cheeses, where researchers have focused on producing bacteriocin strains with potential biotechnological value during the period 2009–2021.

Original Research Articles Database Construction

A database of 71 articles published on LAB producing bacteriocins isolated from cheese was built from 2009 to 2021. The article database was based on a search in the Dialnet, Redalyc, Scielo, Science Direct, Scopus, Springer Link, and Wiley databases. The articles were thoroughly checked to avoid duplication. All references were organized in a Microsoft Excel™ spreadsheet. The data were initially classified according to the year of publication and the country of origin of the corresponding author. The isolation of LAB from cheese for the production of bacteriocins showed that the most productive years were 2017, 2019, and 2020 (Fig. 1A), where 27 original research articles were published, and the years 2012 and 2015 showed important contributions with a total of seven publications per year.

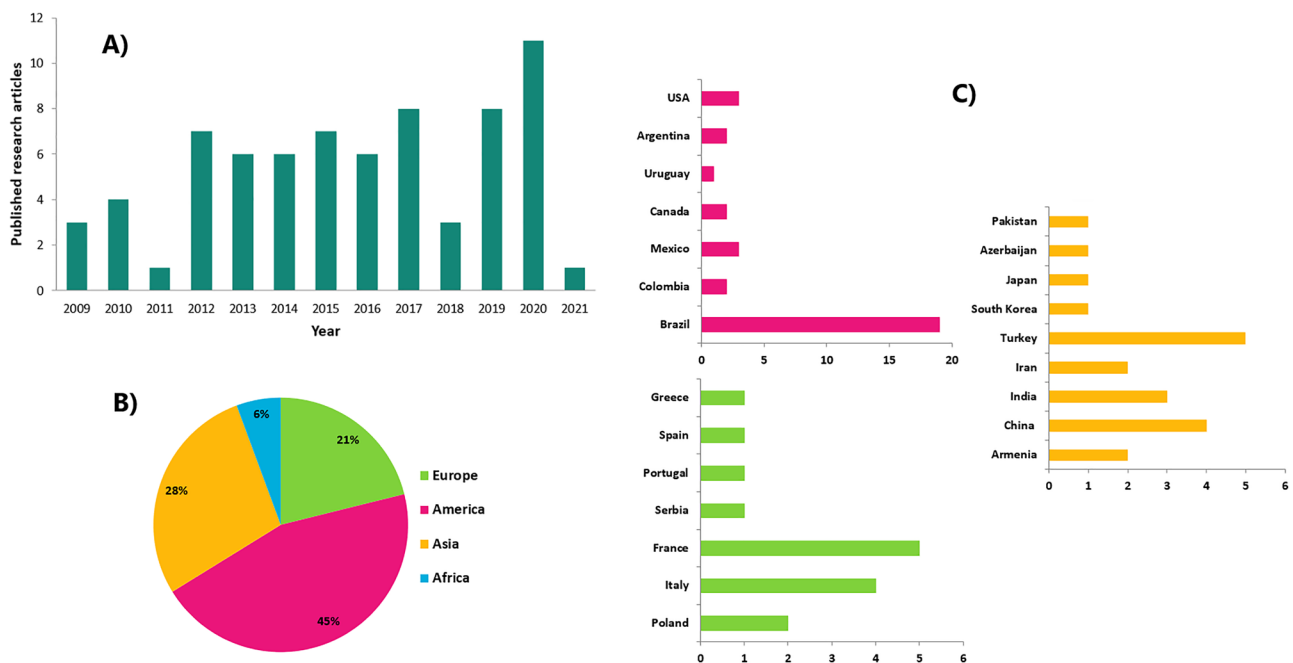


Fig. 1 Original research articles on bacteriocin-producing lactic acid bacteria isolated from cheeses from the period 2009–2021, according to Dialnet, Redalyc, Scielo, Science Direct, Scopus, Springer Link,

and Wiley databases. **A** Published articles by year. **B** Contributions percentage by continent. **C** Contributions by country, in America (pink), Asia (yellow), and Europe (green)

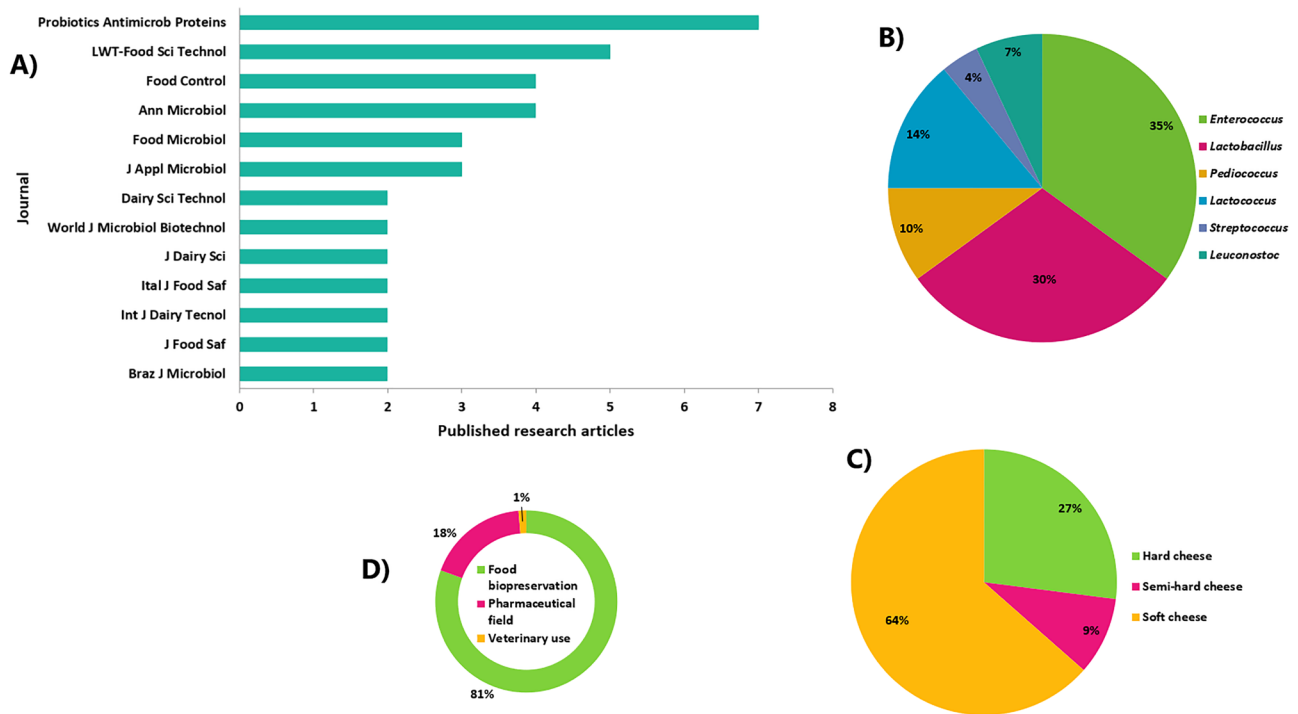


Fig. 2 Original research articles concerning bacteriocinogenic lactic acid bacteria (LAB) isolated from cheeses from the period 2009–2021. **A** Main reputed journals where articles were published. **B**

Main genera of LAB reported by scholars. **C** Percentage of types of cheeses where LAB are isolated. **D** Main potential fields of application

The data showed that 66% of the collected articles were made in a single nation and 34% were part of multinational research. Concerning the articles made in collaboration by several nations, 67% involved labs from two nations, 25% corresponded to articles made with the collaboration of three nations, and 8% belong to articles developed through the contribution of more than three nations. Worldwide, America, Asia, Europe, and Africa contributed with 45, 28, 21, and 6%, respectively, to the information reported on original investigations related to LAB isolated from cheese in order to produce bacteriocins in the last decade (Fig. 1B), being

Brazil, Turkey, and France the countries that contributed the most to the research in this field (Fig. 1C).

According to the data collection, thirteen reputed journals published the majority of the research articles, being *Probiotics and Antimicrobial Proteins* the one that contributed the most with seven articles, followed by *LWT-Food Science and Technology* with five articles, and *Annals of Microbiology* and *Food Control* with four articles each one (Fig. 2A). Table 1 presents the top ten most cited articles according to the Web of Science™ Core Collection (WOS, <https://publons.com/about/home/>), being the Canadian work

Table 1 Most cited original research articles published in the period 2009–2021, concerning the bacteriocin-producing lactic acid bacteria isolated from cheeses, on the basis of the Web of Science™ Core Collection

Rank	Article	Total citations	Corresponding author	Country
1	Yang et al. [26]	102	Fan, L	Canada
2	Sawa et al. [70]	84	Sonomoto, K	Japan
3	Favaro et al. [71]	65	Favaro, L	Italy
4	Alegria et al. [72]	61	Mayo, B	Spain
5	Vera Pingitore et al. [39]	60	Vera Pingitore, E	Argentina
6	Simova et al. [73]	50	Beshkova, D. B	Bulgaria
7	Rushdy and Gomaa [74]	38	Rushdy, A. A	Egypt
8	Chacon Ruiz Martinez et al. [47]	36	Chacon Ruiz Martinez, R	Brazil
9	Moraes et al. [75]	31	Nero, L. A	Brazil
10	Ahmadova et al. [54]	27	Haertlé, T	France

of Yang et al. [26] the most cited article in the decade of study, with 102 citations in total.

In this study, a metadatabase of 68 original research articles published in Bibtext format was processed with the Bibliometrix software package and R-studio for the scientific mapping analysis [27]. Figure 3 shows the conceptual structure of a framework using a keyword co-occurrence network that denotes the more common concepts that were highlighted as general research topics for the production, purification, and characterization of bacteriocins produced by LAB isolated from cheese in the period 2009–2021. The map in Fig. 3 shows the most used keywords in this field, involving four thematic clusters: food (red), cheese (blue), characterization and production (green), and genetic focus (purple). The first group includes most of the articles and references to the isolated LAB, the identification of strains, and the purification of produced bioactive

peptides as well as the description of the antimicrobial activity against indicator microorganisms such as *Listeria monocytogenes* and *Staphylococcus aureus*, among other factors related to these keywords within the analyzed articles. The second group refers to the isolation sources of LAB, which in this review has focused on cheese. It also mentions some isolated bacteria, the most representative and the most common bacteriocins within the collected articles. The third set is related to the biosynthesis of bacteriocins, as well as important responses such as antimicrobial activity against antibiotic-resistant pathogens (like pathogenic microorganisms isolated in nosocomial [28, 29]), the mechanism of action, and the conditions under which these bacterial metabolites can be produced. The fourth group includes studies on the genetics of the isolated LAB and the fermentation conditions for producing the studied bacteriocins.

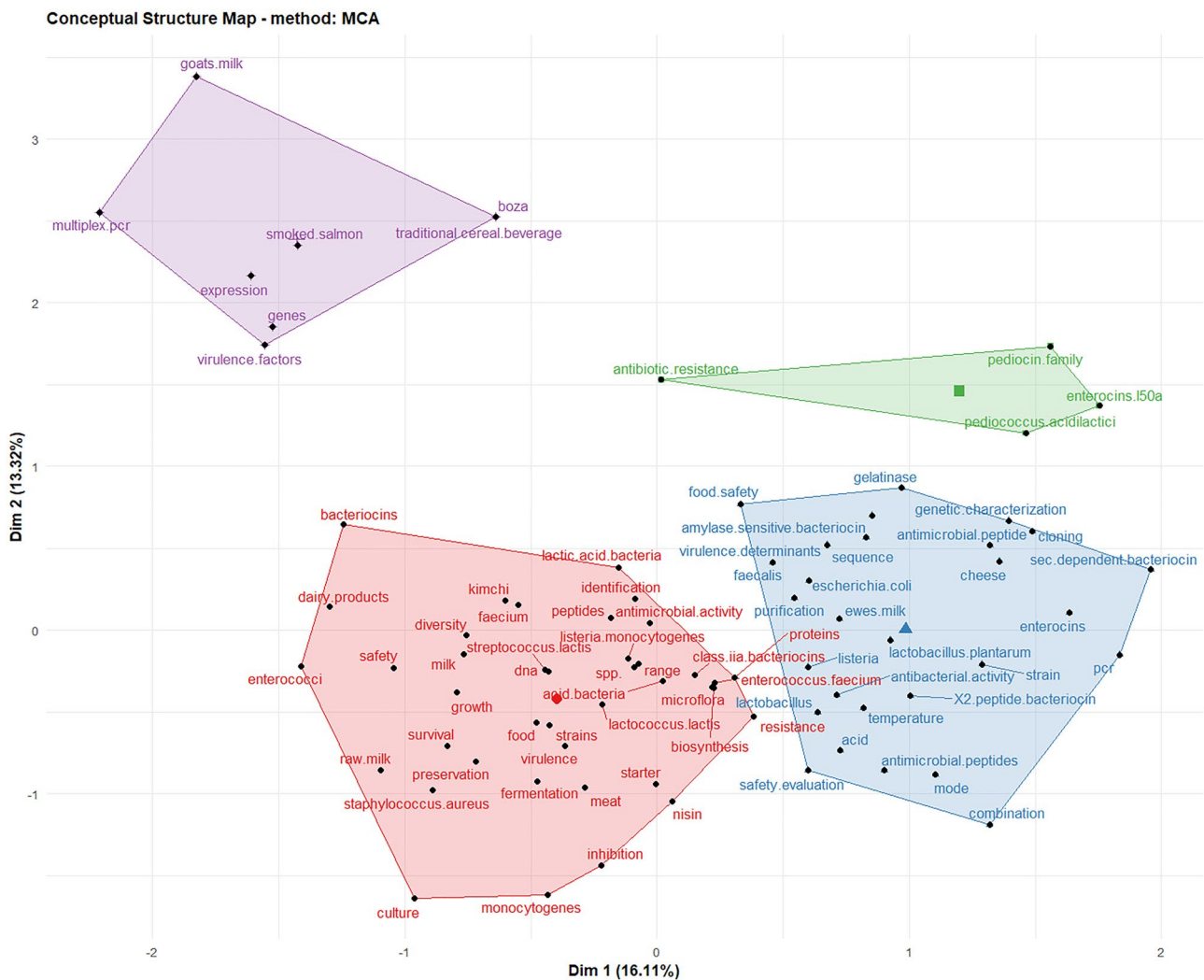


Fig. 3 Conceptual map and clusters of keywords in 68 original research articles from Web of Science™ Core Collection, concerning bacteriocin-producing lactic acid bacteria isolated from cheeses from the period 2009–2021

Cheeses as Sources of Bacteriocin-Producing LAB

LAB are a phylogenetically diverse group of Gram-positive bacteria characterized by some common traits, whether morphological, metabolic, or physiological [30]. The production of lactic acid characterizes them as the final metabolic product of carbohydrate fermentation. They are shaped like cocci or bacilli; most are aerotolerant anaerobes, catalase, and oxidase negative and synthesize ATP in the lactic fermentation of carbohydrates; they lack cytochromes and do not form spores [31].

Most LAB can only get energy from sugars and other related compounds. Due to their limited biosynthetic capacity, they are very nutritionally demanding and require complex growth factors such as amino acids, vitamins, purines, and pyrimidines; therefore, they are frequently located in habitats rich in nutrients, characterized by the presence of soluble carbohydrates and degradation products from proteins and vitamins, and with low oxygen tensions such as milk and dairy products, like cheese, among other ecological environments [32, 33]. Within dairy products, cheese is understood as the soft, semi-hard, hard, and extra-hard product, matured or unripened, and that can be coated, in which the proportion between whey proteins and the casein is not higher than that of milk, obtained by total or partial coagulation of milk protein, skim/skim milk, partially skim/skim milk, cream, whey cream or buttermilk or any combination of these materials, by the action of rennet or other suitable coagulants, and by partial draining of the whey that emerges as a result of said coagulation, respecting the principle that the production of cheese results in a concentration of milk protein (especially the casein portion) and that, consequently, the protein content of the cheese should be higher than that of the mixture of dairy materials already mentioned [30, 34–36]. The different types of cheese depend on the used milk (i.e., mammal species, fat content), the particular species of bacteria and/or fungi involved in the process, and the aging time and other processing treatments [37]. LAB play different roles in the cheese-making process. Some species are more involved in fermentation, and others are primarily involved in maturation. They carry out the initial acidification of the milk, promoting coagulation, curd strength, gel syneresis, and dissolution of colloidal calcium phosphate, among others [25]. LAB can be deliberately added as starter cultures or occurred as natural native microbiota of the raw milk selected by the conditions of the fermentation process, allowing microbial diversity, and contributing to the significant differences in organoleptic characteristics found in raw milk cheeses [38]. Furthermore, the presence of LAB in fermented

foods improves the safety, innocuousness, and shelf life of foods through the production of various antimicrobial compounds, organic acids (lactic, acetic, etc.), hydrogen peroxide, diacetyl, and antimicrobial peptides (i.e., bacteriocins) [26, 39].

In this survey, based on the collected articles, the main LAB strains that have been isolated from cheese belong to the following genera: *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Pediococcus*, *Leuconostoc*, and *Streptococcus*, where the first three genera contributing 35, 30, and 14%, respectively, of the isolated LAB during the analyzed period (Fig. 2B). Furthermore, 64% of the reported bacteriocinogenic-LAB isolations came from soft cheeses (moisture > 55%), 27% from hard-cheeses (moisture 20–42%), and 9% from semi-hard cheeses (moisture 45–55%) [24] (Fig. 2C), being the food application focus (i.e., preservation additives; probiotic function) the main interest (81%), followed by the pharmaceutical applications (18%; i.e., bacteriocins as alternatives to “common” antibiotics; the antitumoral function), and the still scarce but not less critical, veterinary uses (i.e., animal health) (Fig. 2D). Moreover, most of the authors use “standard” techniques for the isolation of LAB and its characterization: Media MRS and M17 for bacterial growth; commercial kits like API 50 CHL and API 20 Strept, and catalase test for biochemical profile; Gram staining and 16S rDNA gene sequencing for taxonomy, mainly.

In South America, relevant work has been conducted in Brazil (Fig. 1C). *Pediococcus pentosaceus* was isolated from ripened Minas cheese, an artisanal cheese made with raw cow’s milk, detecting the presence of the pediocin PA-1 gene in the LAB isolated [40]. Cabral Carvalhaes Costa et al. [41] isolated *L. lactis* QMF11 from fresh Minas cheese. Two strains of *Lactobacillus plantarum*, LCN 17 and LCN 43, were isolated from artisanal ewe’s cheese from Rio Grande do Sul [42]. Two strains of *Enterococcus faecium*, EM485 and EM925, possessing genes encoding for enterocin A and B, were isolated from artisanal Coalho cheese [43]. *Ent. faecium* 130 was recovered from mozzarella cheese by Tulini et al. [44]. The bacteriocinogenic LAB, *Lact. plantarum* B391, was isolated from Tomme-de-Savoie cheese of French origin made with raw skimmed cow’s milk, ripened for 2–4 months [45]. The bacteriocinogenic *Lact. pentosus* B231 was isolated from the Portuguese Pico cheese, an artisanal cured food with a protected designation of origin (PDO) produced in the Azores Islands [46]. Bacteriocinogenic *Lact. plantarum* ST71KS was isolated from Bulgarian goat milk feta cheese, which produces a class IIa bacteriocin [47].

Mexican cheese is also studied as LAB sources. *Ped. acidilactici* QC38 which produces the bacteriocin Pediocin PA-1 was isolated from Cotija cheese, a ripened artisanal product of raw milk, produced in the state of Michoacán

[48]. *Ent. durans* 41D which produces Duracin GL was isolated from Mexican-style cheese samples [49].

In the case of Europe, there were also valuable contributions in the analyzed period (Fig. 1C). Eight bacteriocin-producing strains identified as *Lact. lactis* and *Ent. faecalis* were isolated from artisanal Portuguese Pico cheese produced in the Azores [50]. Two *Lact. plantarum* strains, Os4 and Kor 14, isolated from Polish regional cheeses (Oscypek and Korycinski) exhibit important activity against *Staph. aureus* and potential as probiotics [51]. *Lact. plantarum* LpU4, which produces a novel plantaricin, was isolated from Italian “Pecorino” cheese, an artisanal raw sheep’s milk food [52]. Lactococci G-producer *L. lactis* subsp. *lactis* BGBM50 strain was isolated from artisanal semi-hard cheese produced in the village of Žanjic, Montenegro [53]. *Ent. faecium* AQ71, an enterocin producer strain, was isolated from artisanal Motal cheese produced by nomadic tribes of Azerbaijan [54].

On the other hand, in Asia, Turkey has made important contributions (Fig. 1C). Five strains of *Lact. plantarum* isolated from Lighvan cheese, an artisanal raw sheep’s milk food of Iran, produced compounds of proteinaceous nature that exhibited antifungal activity [55]. From Kouzeh cheese, a traditional cheese in north-western Iran, *Lact. plantarum* strains were isolated, showing vigorous antimicrobial activity against *Staph. aureus* and *Staph. epidermidis* [56]. *Lact. rhamnosus* BTK 20–12, a potential probiotic which produces two bacteriocins (BCN1 and BCN2), was isolated from the artisanal salty cheese of Armenia [29]. Twelve strains belonging to five species of enterococci (i.e., *Ent. faecium*, *Ent. faecalis*, *Ent. durans*, *Ent. gallinarum*, and *Ent. italicus*) were isolated from traditional white semi-hard cheese of the Northern Black Sea region of Turkey. The presence of enterocin B gene was evidenced in all tested enterococci [57]. *Ent. faecium* T1, isolated from Chinese Tibet cheese, produced enterocin T1, which inhibit the growth of some Gram-positive and negative bacteria of economic importance (i.e., *Pseudomonas putida*, *Ps. aeruginosa*, *Ps. fluorescens*, *E. coli*, *Salmonella typhimurium*, *Shigella flexneri*, *Sh. sonnei*, *Staph. aureus*, and *L. monocytogenes*) [58]. *Lact. plantarum* SLG1 was isolated from traditional Qinghai yak cheese from Tibet and has the ability to produce a novel plantaricin that exhibited antimicrobial activity against diverse Gram-positive and negative bacteria, and yeasts, all of economic importance [59].

Further, in Africa, *L. lactis* subsp. *lactis* A15 and *Ent. faecium* A15 were isolated from traditional Egyptian cheeses (i.e., Domiatti, Ras, and Kareish cheeses), and genetic analysis exhibited the presence of nisin Z and enterocin B genes, respectively, suggesting the potential of these strains in biopreservation applications [60].

Production, Purification, and Characterization of Bacteriocins

The search for new LAB with the capacity of producing novel bacteriocins with application potential in diverse fields (i.e., food, pharmacy, and veterinary) has considered cheeses as good sources for such bacteria. Most of the time, once the isolated LAB is re-activated, the bacteriocin production is carried out in batch systems and occurred during the exponential growth phase or at the end of it, being frequently directly correlated to the produced bacterial biomass, which usually occurred during the first 24 h of fermentation (Table 2). Also, researchers commonly use complex media for these purposes, being the MRS medium [61] the most frequently used, but M17 [62] and tryptone-yeast extract-lactose (TYL) [63] media are also used for bacteriocinogenic LAB cultivation. These media are rich in carbohydrates, proteins, and peptides that can act as inducers for the bacteriocin synthesis, which is also affected by the fermentation conditions (i.e., temperature, pH, agitation, aeration) [64]. LAB produce bacteriocins by ribosomal synthesis, giving inactive molecules which become biologically active after chemical modifications [65]. Also, bacteriocins can be produced constitutively or by conditional systems (i.e., Quorum sensing) [66], which involves complex regulation systems (i.e., ComD/E, ComR/S) mediated by genes located in the LAB-chromosome in association with transposons and plasmids (i.e., genes encoding enterocins: *entA*, *entB*, *entP*, *entQ*, *L50A*). Moreover, it is common for LAB to produce more than one bacteriocin (Table 2) [67].

Once the fermentation is finished, the recovery of the produced bacteriocins is carried out based on their physico-chemical properties. This task is a challenge due to the presence of a mixture of bacteriocins with diverse chemicals (i.e., other metabolic products, residual nutrients) in the culture broth, which usually requires a carefully tuned method specific for the produced bacteriocins [68]. Researchers based the downstream processing by the precipitation of peptides with ammonium sulfate from the culture broth supernatants, after centrifugation to separate LAB cells, then involving steps like dialysis and diverse chromatographic separations (i.e., cation exchange, gel filtration, hydrophobic interaction, and reverse-phase liquid chromatography) where the used pH is an essential factor (Table 2). Pei et al. [59] explored an innovative methodology for bacteriocin separation, involving the adsorption of the produced bacteriocins into magnetic nanoparticles, later isolating them with a magnetic column.

In order to envisage possible applications of the bacteriocins produced by the LAB isolated from cheeses (i.e., food preservation, systemic infections, woman care,

Table 2 Research articles concerning the isolation of bacteriocinogenic lactic acid bacteria (LAB) from cheeses, wherein provided are some data on the size/structure and/or involved genes of the produced peptides, and relevant functionality. Analyzed period: 2009–2021

Cheese	Isolated LAB	Bacteriocins	Production and Purification methods	Characterization/size/amino acid composition/genes	Assayed antimicrobial activity/ other relevant results	Reference
Raw milk cheese	<i>Ped. pentosaceus</i> ST65ACC	Coagulin A	LAB grown in MRS (37 °C, 24 h). Supernatant → precipitation with ammonium sulfate (40% saturation), followed by RP-HPLC	Nano LC-MS/MS resulted in the partial sequence KYYNGVTCG-KHSCSVDWVGK, corresponding to a bacteriocin Class IIa, with high similarity to coagulin A	The bacteriocin exhibited low cytotoxicity against Madine and Darby bovine kidney cells (MDBK) with 50% cytotoxicity concentration of 4.2–4.6 mg/mL	[76]
Cheddar cheese	<i>Lact. plantarum</i> KIBGE-IB45	Bac-IB45	LAB grown in MRS (35 °C, 24 h). Supernatant → ammonium sulfate (20–80%) precipitation, dialyzed, gel permeation chromatography, filter-centrifuged (cut off: 10 kDa), and lyophilized	Tricine SDS-PAGE: 20.5 kDa	Bacteriocin was active against <i>L. monocytogenes</i> , <i>Micrococcus luteus</i> , <i>Ps. aeruginosa</i> , methicillin-resistant <i>Staph. aureus</i> , <i>Bacillus cereus</i> , <i>E. coli</i> , <i>Ent. faecalis</i> , <i>Aspergillus terreus</i> , and <i>A. flavus</i> . Also, exhibited low cytotoxicity against NIH/3T3 fibroblast cells: 60–90% cell viability in presence of 40–160 µg/mL	[77]
Mongolian fermented hard cheese	<i>Lact. plantarum</i> KLDS1.0344	BLIS	LAB grown in MRS (37 °C, 24 h). Supernatant → ammonium sulfate precipitation (60%), dialyzed (1200 Da)	SDS-PAGE analysis: 12 to 45 kDa	Active against <i>Salmonella typhimurium</i> , <i>E. coli</i> O157: H7, <i>L. monocytogenes</i> and <i>Staph. aureus</i>	[78]
Traditional Armenian naturally fermented salted cheese	<i>Lact. rhamnosus</i> BTK 20–12	BCN 1 and BCN 2	LAB grown in MRS (37 °C, 24 h). Supernatant → ion-exchange chromatography, gel-filtration Sephadex G 25, HPLC	MS ESI: BCN 1 (1427 Da) BCN 2 (602.6 Da)	BCNs attack pathogenic <i>B. subtilis</i> G 17–89 and <i>Salmonella typhimurium</i> G 38. BCN 2 2%, acts against multidrug-resistance pathogenic (20–100% sensitivity): <i>Staph. aureus</i> , <i>Ps. aeruginosa</i> , <i>Klebsiella</i> sp., <i>Proteus mirabilis</i> , <i>Pr. vulgaris</i> , <i>Salmonella</i> sp., <i>E. coli</i> , isolated from blood, feces, urine, saliva, and wound	[29]
Artisanal Brazilian cheese (Viçosa, Minas Gerais state)	<i>Ped. pentosaceus</i> (4 strains)	Pediocin	LAB grown in MRS and MRS with modifications (37 °C, 18–24 h). Supernatant → ammonium sulfate precipitation, SepPak C18	Amplicon sequencing confirmed pediocin PA-1 SDS-PAGE: molecular weight between 3.5–6.5 kDa	<i>Ped. pentosaceus</i> 63, at t = 24 h, produced an antilisterial activity of 25,600 AU/mL, in modified MRS with 20 g/L maltose	[40]
Traditional Qinghai yak cheeses	<i>Lact. plantarum</i> SLG1	Plantaricin SLG1	LAB grown in MRS (37 °C, after 24 h). Supernatant → magnetic liposome adsorption combined with RP-HPLC	MS: 1083.25 Da N-sequencing: Tyr-Gly-Asn-Gly-Val-Phe-Ser-Val-Ile-Lys. Analyses by CD spectra and predicted 3D structure suggested that maintains a well-defined conformation	SEM: mode of action was bactericidal against <i>Staph. aureus</i> CICC10384, <i>E. coli</i> CICC 10,302, and <i>Saccharomyces cerevisiae</i> CICC 1002. Also was active against other 37 strains of food-borne spoilage and pathogenic bacteria, and some fungi	[59]

Table 2 (continued)

Cheese	Isolated LAB	Bacteriocins	Production and Purification methods	Characterization/size/amino acid composition/genes	Assayed antimicrobial activity/ other relevant results	Reference
A French-origin Tomme-de-Savoie, a 2- to 4-month ripened raw, skimmed cow's milk cheese	<i>Lact. plantarum</i> B391	Bacteriocin B391	LAB grown in MRS (30 °C, 18 h). Supernatant → ammonium sulfate (40%) precipitation, SepPack C18 cartridge	Tricine-SDS-PAGE: Approx. 6000 Da DNA analysis	Active against <i>Clostridium perfringens</i> NCTC 13,170, <i>Ent. faecalis</i> NCTC 775, and <i>L. monocytogenes</i> (3 strains)	[45]
Traditional Cotija cheese from Michoacán, México	Halotolerant <i>Ped. acidilactici</i> QC38	Pediocin	LAB grown in MRS (37 °C, 24 h). Supernatant → adjusted to pH 6.5, treated with catalase and filtered	Tricine-SDS-PAGE: 3.4–6.5 kDa	Active against some Gram-positive and Gram-negative food-borne pathogens: <i>E. coli</i> , <i>L. monocytogenes</i> , <i>L. innocua</i> , <i>Staph. aureus</i> , <i>Salm. Typhimurium</i> , <i>Vibrio vulnificus</i> , <i>V. cholera</i> (2 strains) LAB was able to grow in 1–9% NaCl concentration and harbored a plasmid that contains a gene for a pediocin (PA-1)	[48]
Chinese Tibet cheese	<i>Ent. faecium</i> T1	Enterocin T1	LAB grown in MRS (37 °C, 24 h). Supernatant → Sepharose fast flow cation-exchange chromatography, obtained antimicrobial activity-fractions were analyzed by RP-HPLC	LC-ESI/MS: 4629 Da After acid hydrolysis, the derivatized amino acids were analyzed by RP-HPLC. Enterocin T1 contains 3 basic amino acids (His, Arg) and 7 acidic amino acids (Glu, Asp) and 19 hydrophobic amino acids (Ala, Val, Met, Ile, Leu, Phe, Pro)	<i>Pseudomonas</i> spp. (4 species) <i>E. coli</i> <i>Salm. Typhimurium</i> <i>Shigella</i> spp. (2 species) <i>Staph. aureus</i> <i>L. monocytogenes</i> Novel bacteriocin with the potential to be used as a bio-preservative to control <i>Pseudomonas</i> spp. in food	[58]
Mold-ripened Camembert cheese made with unpasteurized milk	<i>Carnobacterium maltaromaticum</i> CPN	Maltarinin CPN	LAB grown in MRS at pH 8.0 (20 °C, 24 h). Supernatant → cation exchange chromatography, RP-HPLC	MS ESI: 4427.29 Da Amino acid sequence (Edman degradation): Similar to class IIa bacteriocins (YGNGL N-terminal), 44 unmodified amino acids, including 2 cysteine residues at positions 9 and 14 linked by a disulfide bond	Active against: <i>Enterococcus</i> spp. (10 species), <i>Lact. sakei</i> , <i>L. lactis</i> (2 strains), <i>L. monocytogenes</i> (6 strains), <i>L. innocua</i> (2 strains), <i>Staphylococcus</i> spp. (3 species). No activity against Gram-negative	[79]
Brazilian semi-hard Minas cheese	<i>Lact. paraplantarum</i> FT259	Plantarinin	LAB grown in MRS (37 °C, 24 h). Supernatant → gel filtration chromatography, SPE cartridge	SDS-PAGE: 3900 Da. DNA sequencing detected the plantarinin NC8 gene	There was an antilisterial effect in <i>Lact. paraplantarum</i> FT259 on <i>L. monocytogenes</i> co-culture biofilms, reducing approx. 2 log CFU/mL in 2–3 days	[80]
Artisanal raw sheep-milk cheeses	<i>Lact. plantarum</i> LpU4	Plantarinin LpU4	LAB grown in MRS (25 °C, 24 h) trichloroacetic acid, Tricine SDS-PAGE	MALDI-TOF: 4,866.7 Da	<i>Ent. faecalis</i> (7 strains), <i>Staph. aureus</i> (6 strains, including one methicillin resistant), <i>Ent. faecium</i> (2 strains), <i>Lact. plantarum</i> , <i>Leuconostoc citreum</i> , <i>C. divergens</i> , <i>L. lactis</i>	[52]

Table 2 (continued)

Cheese	Isolated LAB	Bacteriocins	Production and Purification methods	Characterization/size/amino acid composition/genes	Assayed antimicrobial activity/ other relevant results	Reference
Artisanal raw cow's milk PDO Portuguese cheese	<i>Lact. pentosus</i> B231	Bacteriocin B231	LAB grown in MRS (30 °C, 18 h). Supernatant → ammonium sulfate (40%) precipitation, SepPack C18 SPE cartridge	Tricine-SDS-PAGE: Approx. 5 kDa DNA analysis rendered the presence of plantaricin S gene	Activity against <i>Listeria</i> spp. (3 species, 4 strains)	[46]
Water buffalo mozzarella cheese	<i>Leuc. mesenteroides</i> SJRP55	Mesentericins	LAB grown in MRS (25 °C, 24 h). Supernatant → precipitation with ammonium sulfate (40 and 80% saturation), affinity column blue sepharose, RP Sep-Pak C ₂ SPE cartridge, RP-HPLC	LC-ESI/MS: Mesentericin W-SJRP55 (3,868 kDa) and mesentericin Z-SJRP55 (3,444 kDa) MS-MS, CID, amino acids sequence 100% homology with mesentericin Y105, and mesentericin B105, respectively. DNA analysis rendered 100% homology for mesentericin Y105 and mesentericin B105 genes	Antimicrobial activity against <i>Enterococcus</i> spp. (8 strains), <i>Ent. faecalis</i> (6 strains), <i>Ent. faecium</i> , <i>Leuc. mesenteroides</i> UCV10CET, <i>L. innocua</i> , <i>L. monocytogenes</i> (8 strains)	[81]
Homemade goat feta cheese	<i>Lact. plantarum</i> ST71KS	Bacteriocin ST71KS	LAB grown in MRS (30 °C, 18 h). Supernatant → ammonium sulfate (60% saturation) precipitation, RP Sep-Pak C ₂ SPE cartridge,	Tricine-SDS-PAGE: Approx. 5.0 kDa The LAB harbors 2 bacteriocin genes that encode for plantaricin S and pediocin PA-1	<i>L. monocytogenes</i> (2 strains) Bacteriocin cytotoxicity on monkey kidney Vero cells resulted in low cytotoxicity (i.e., CC ₅₀ > 1200 mg/mL)	[47]
Tulum cheese in Turkey	<i>L. lactis</i> LL171	A new bacteriocin	LAB grown in MRS in a fermentor (35 °C, 24 h). Supernatant → ammonium sulfate precipitation (40, 60, 80 and 100%), dialysis, and HPLC	SDS-PAGE: Approx. 3.344 kDa. Edman degradation indicated the sequence of 29 amino acids: KKIDTRTGKTMEKTEK-KIELSLKNNMKTAT	<i>L. monocytogenes</i> (2 strains), <i>Staph. aureus</i> , <i>B. subtilis</i> , <i>Cl. perfringens</i> , <i>Salm. typhi</i> , <i>Enterobacter aerogenes</i> , <i>M. luteus</i>	[82]
Artisanal Mexican cheese	<i>Ent. durans</i> 41D	Duracin GL	LAB grown in TYL (37 °C, 12 h). Supernatant → column of amberlite XAD-16	SDS-PAGE: ca. 3 kDa	<i>Ent. faecalis</i> , <i>Ent. faecium</i> (2 strains), <i>L. innocua</i> , <i>L. monocytogenes</i> (6 strains)	[49]
“Byaslag”, a traditional cheese in Inner Mongolia of China	<i>Ent. faecium</i> LM-2	Enterocin LM-2	LAB grown in MRS (37 °C, 30 h). Supernatant → ammonium sulfate (80% saturation) precipitation, dialysis, SP-Sepharose cation exchange column	Tricine-SDS-PAGE: two protein bands, approx. 3.5 and 6.4 kDa The LAB harbors the enterocin P gene; also enterocin L50 gene (72% similarity)	<i>Listeria</i> spp. (9 species) including 5 strains of <i>L. monocytogenes</i> , <i>Staph. aureus</i> (4 species), <i>Ent. faecium</i> , <i>M. luteus</i> , <i>Cl. butyricum</i> , <i>Bacillus</i> spp. (3 species), <i>Brochothrix thermosphacta</i> , <i>E. coli</i> 1.90, <i>Salm. CS500</i> , <i>Pseudomonas</i> sp., <i>Candida albicans</i>	[83]

Table 2 (continued)

Cheese	Isolated LAB	Bacteriocins	Production and Purification methods	Characterization/size/amino acid composition/genes	Assayed antimicrobial activity/ other relevant results	Reference
Overnight-aged milk of a cheese intermediate	<i>Lactococcus</i> sp. QU 12	Lactocycelicin Q (a cyclic bacteriocin)	LAB grown in M17 (30 °C, 18 h). Supernatant → SP Sepharose cation exchange chromatography, hydrophobic interaction chromatography, RP-HPLC	ESI-TOF MS: 6,062.8 Da. Lactocycelicin Q includes 61 amino acids, in a cyclic structure with a peptide bond (i.e., LATAAAIVKHQKAAA-AAW LIDHLGAPRWAVDTILGAIA-VGNLASWVLAALVPGPGW; theoretically, 6080.8 Da). The structural gene encoding lactocycelicin Q was obtained (i.e., lycQ, consisted of 189-bp)	<i>L. lactis</i> (5 strains), <i>L. raffinolactis</i> , <i>Lactobacillus</i> spp. (6 species), <i>Bacillus</i> spp. (4 species), <i>Enterococcus</i> spp. (4 species), <i>Streptococcus</i> spp. (2 species), <i>Pediococcus</i> spp. (4 species), <i>Leuc. mesenteroides</i> , <i>W. cibaria</i> , <i>M. luteus</i> , <i>Listeria</i> spp. (2 species), <i>Staph. aureus</i> , <i>E. coli</i> (2 species)	[70]
Mexican chesses: Queso Fresco and Mennonite	<i>Ent. faecium</i> (5 isolates), <i>Ent. durans</i>	Enterocins	LAB grown in TYL broth (37 °C, overnight). Supernatant → SP Sepharose cation exchange column, RP-HPLC	SDS-PAGE: between 4 and 7 kDa MALDI-TOF-MS: <i>E. faecium</i> H41K, produces enterocin A (4,832 Da) and enterocin B (5,497 Da). Depending on the strains, isolated LAB can harbor the genes encoding Class II enterocins, including A, B, P, Q L50A and L50B	<i>L. monocytogenes</i> and <i>L. innocua</i>	[84]
Traditional domestic Azerbaijan cheeses	<i>Lact. buchneri</i>	BLIS	LAB grown in MRS (37 °C, 24 h). Supernatant → ammonium sulfate (40–80%) precipitation	SDS-PAGE: ≥30 kDa (probably a class 4 bacteriocin)	<i>Lact. bulgaricus</i> , <i>E. coli</i> , <i>Ent. durans</i> , <i>L. innocua</i>	[85]

Abbreviations: *BLIS*, bacteriocin-like inhibitory substance; *CC₅₀*, 50% cytotoxic concentration; *CD*, circular dichroism; *CID*, collision-induced dissociation; *ESI*, electron spray ionization; *HPLC*, high-performance liquid chromatography; *LC*, liquid chromatography; *M17*, complex culture medium; *MALDI*, matrix-assisted laser desorption/ionization; *MRS*, de Man, Rogosa, and Sharpe medium; *MS*, mass spectrometry; *PDO*, protected designation of origin; *RP*, reverse phase; *SDS-PAGE*, sodium dodecyl sulfate–polyacrylamide gel electrophoresis; *SEM*, scanning electron microscopy; *SPE*, solid-phase extraction; *TOF*, time of flight; *TYL*, tryptone-yeast extract-lactose medium

cancer, contraception, bio-nanomaterials, veterinary, oral care, skin care [69]), during the analyzed period, researchers carried out different tests to characterize such bacteriocins, including the spectrum of antimicrobial activity against food borne (i.e., *L. monocytogenes*, *E. coli*) and deterioration microorganisms, as well as some antibiotic-resistant pathogens (i.e., methicillin-resistant *Staph. aureus* (MRSA) and other nosocomial microorganisms); cytotoxicity against some eukaryotic cells (i.e., monkey kidney Vero cells; Madine and Darby bovine kidney cells); molecular size by mass spectrometry (MS) (i.e., ESI (electron spray ionization)–(time-of-flight) TOF–MS; liquid chromatography (LC)–ESI/MS), matrix-assisted laser desorption/ionization (MALDI) (i.e., MALDI-TOF), and sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE); bacteriocin encoding gene sequencing analysis in DNA; and partial or total amino acid sequencing of the functional peptides (Table 2). Also, the activity of the produced bacteriocins is evaluated after adverse treatment conditions of heating (i.e., 100–120 °C for 15–30 min), low temperatures (i.e., –20 °C during several months), pH (i.e., interval 3–10), the enzymatic activity of proteases of pancreatic and gastric origin (i.e., α -chymotrypsin, trypsin, pepsin), fungal (i.e., proteinase K) and bacterial (i.e., pronase E) proteases, and/or other enzymes (i.e., α -amylase, lipase A), among other tests.

Perspectives

The challenge is enormous; the requirement of new and better bacteriocins is a constant demand in the food industry, mainly for the bioconservation of processed foods, but also is the opportunity to be applied within the pharmaceutical industry and in human and animal medicine fields, particularly to combat the antibiotic-resistant pathogens (i.e., MRSA), cancer, and its possible role as gut microbiome modulators, among other potential applications. Here is a plus benefit of traditional cheeses as real mines for the isolation of bacteriocin-producing LAB. Nevertheless, hard work is required for new bacteriocins are commercially available (once appropriate LAB have been isolated), not only concerning the biotechnological process development matters, but particularly fulfilling the requirements of the regulatory agencies like the World Health Organization (WHO), and Food and Agriculture Organization (FAO), as well as the regional agencies involved (i.e., Food and Drug Administration (FDA) in the USA; European Food Safety Authority (EFSA) in Europe), to guarantee the safe use of such bacteriocins.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing Interests The authors declare no competing interests.

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