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Review Article

BACTERIOCIN PRODUCED BY LACTIC ACID BACTERIA: A PROBIOTIC

BARNALI MANDAL*

Department of Chemical Engineering, Rajabajar Science College, University of Calcutta, 92, Acharyya Prafulla Chandra Road, Kolkata-700009, West Bengal, India

***Corresponding author: B. Mandal; *Email: bmchemengg@caluniv.ac.in**

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ABSTRACT

Chemical preservatives, usually used during the long period, to protect the food materials by controlling undesirable bacteria and harmful spoiler, have been proved as toxic to human health. Conscious consumers have serious awareness to purchase safe foods without chemical additives. In the recent years, bio-preservation is gained increasing attention to harmonize consumer demands along with standard food quality. Various attempts are growing on the use of micro-organisms or their antimicrobial metabolites for the protection of food products. The bacteriocins produced by lactic acid bacteria (LAB) have a relatively broad antimicrobial spectrum against variety of food-borne pathogenic and spoilage bacteria. Bacteriocin-producing lactic acid bacteria or bacteriocins can be used in foods as bio-preservatives. The review is focused on bacteriocin produced by lactic acid bacteria.

Keywords: Bacteriocin, Lactic acid bacteria, Bio-preservative, Antimicrobial spectrum

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INTRODUCTION

Natural micro-biota is traditionally used in the preservation of foods through occurring fermentations over the millennia. Lactic acid bacteria (LAB) have long been employed as starter cultures for the preservation of foods in the history of mankind [1]. These are well known as 'food grade' microorganisms and widely used as protective cultures for the industrial processing of fermented dairy, meat, vegetables and cereal products [2]. The probiotic starter cultures are able to produce antimicrobial metabolites. Bacteriocins are antimicrobial peptides or proteins produced by different genera of LAB, have a relatively broad antagonistic activity against variety of microorganisms. The use of LAB or its bacteriocin as bio-preservative is a green ecological alternative strategy of extending shelf life and food safety through the inhibition of spoilage and pathogenic bacteria without altering the nutritional quality of raw materials and food products. The bacteriocins are nontoxic, generally recognized as safe substances, usually pH and heat-tolerant, become inactivated by digestive proteases [3, 4].

Lactic acid bacteria

LAB produce lactic acid as the major end-product during the fermentation of carbohydrates. These are abundant in nature. The microorganisms are found in milk, meat, green plants, grains and fermenting vegetables. LAB have been isolated from mucosal surface of animals [5], sourdoughs [6], vacuum-packaged refrigerated beef [7] and traditional Indian fermented foods such as appam batter and vegetable pickle [8]. LAB are included in diverse genera of organisms [9]; those are *Lactobacillus, Pediococcus, Lactococcus, Carnobacterium, Enterococcus, Lactosphaera, Leuconostoc*, *Melissococcus, Oenococcus*, *Streptococcus, Tetragenococcus, Vagococcus, Weissella* and *Bifidobacterium* itc. These are the most important probiotic known to have beneficial effects on human gastrointestinal (GI) tract. LAB can be effective in preventing gastrointestinal disorders like diarrhea [10, 11]. The bacteria cause lowered blood cholesterol, increased immune response. Some LAB strains are even associated with anti-carcinogenic action and tumor control [12]. *Lactobacillus* species may colonize on the mucosal surface of duodenum and stomach [13].

Probiotics

The term "probiotics", which literally means "for life", has been introduced to describe health-promoting bacteria [14]. Probiotics defined as 'live microorganisms that beneficially affect the host's health by improving its microbial balance. The adaptations of useful microbes are possible in human intestine [15].

Nowadays, with the resurgence of infectious disease, physicians, researchers and public are reconsidering the effective role of probiotics as an alternative supplement of antibiotic-dominated therapies [16, 17]. Probiotic bacteria have been targeted as potential therapeutic agents. Examples include LAB, *bifidobacteria* [18], *saccharomyces* [19], enterics [20], streptococci [21].

There are over 400 types of microbes present in human intestine that may be either harmful or beneficial. The beneficial ones assist in the breakdown of food and also manufacture vitamins that essential to the body. The microbes can break down and destroy some toxic chemicals that may have been ingested with the food. Under both healthy and sick conditions, several types of bacteria compete or fight with each other to establish dominance in the warm and moist environment of the alimentary canal that serves as an ecosystem for their survival and propagation. Potential probiotics species differ in terms of their bioavailability, metabolic activity and mode of action. In addition, probiotics must survive the transition to the target niche and protect the host against infection by pathogenic microorganisms [22].

Over the few past years, the research has been rapidly focused on the use of probiotic bacteria as supplements in food medicine with a growing commercial interest [23, 24]. Probiotics have been incorporated into a wide range of foods, including dairy products (cheese, yogurt and ice cream) and non-dairy products (chocolate, juices and cereals) [25]. For use in foods, probiotics microorganisms should be capable of surviving passage through the digestive tract, serving to protect the host against infection by pathogenic microorganisms. The organism must be resistant to gastric juices and be able to grow in the presence of bile under conditions in the intestines [22].

A large range of microorganisms are considered as probiotics must be non-pathogenic and non-toxic such as LAB (e. g. *Lactococcus lactis*, *Pediococcus acidilactici*, *Enterococcus faecium*, etc.), non-lactic acid bacteria (e. g. *Escherichia coli*) and some yeasts (e. g. *Saccharomyces boulardii*, *Saccharomyces cerevisiae* etc.). The organisms such as *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus casei* subsp. *rhamnosus, Lactobacillus fermentum, Lactobacillus reuteri*, *Lactococcus lactis* subsp. *lactis, Lactobacillus bulgaricus, Lactobacillus plantarum*, *Streptococcus thermophilus, Enterococcus faecium, Enterococcus faecalis, Bifidobacterium bifidum,*

Bifidobacterium infantis, Bifidobacterium adolescentis, Bifidobacterium longum, Bifidobacterium breve etc. have been recognized as probiotic species [26].

Bacteriocin

Bacteriocins are ribosomally synthesized peptides or proteins produced by different genera of bacteria. Bacteriocins offer several desirable properties that make them suitable for the preservation of food. These are nontoxic, generally recognized as safe substances, usually pH and heat-tolerant, become inactivated by digestive proteases; show a bactericidal mode of action, usually acting on the bacterial cytoplasm membrane [3, 4].

Bacteriocins are extracellular proteinaceous compound produced by different LAB species. These have antibacterial activity against undesirable microorganisms, specifically closely related species of Gram-positive bacteria [27]. About 100 y ago, a bacteriocin was first identified by Gratia as colicin, produced by *Escherichia coli* V [28]. Colicin-producing strain *E. coli* is Gram Gram-negative bacteria. Both Gram negative and Gram-positive bacteria produce bacteriocins [29, 30]. *E. coli* strains produce another bacteriocin, known as microcins, which is smaller than colicins and has more similar properties with the bacteriocins produced by Gram-positive bacteria [31, 32]. Besides *E. coli,* other bacteriocins producing Gram-negative bacteria are *Salmonella enterica*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Citrobacter freundii*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, and *Hafnia alvei* [30, 33].

Bacteriocins from Gram-positive bacteria have lower molecular weight than colicins have a much broader range of antimicrobial activity against target bacteria [34]. Usually, these are hydrophobic, cationic and membrane-permeabilizing small peptides in the range of size from 2 to 6 kDa [29, 35], although there are exceptions [36]. The bacteriocins produced by LAB are potential peptides which can kill or inhibit pathogenic bacteria that compete for the same ecological niche or nutrient pool [37, 38]. These are very active against food-borne pathogens such as *Listeria monocytogenes*, *Clostridium botulinum*, *Staphylococcus aureus* and spoilage microorganisms, including *Bacillus* sp. and *Enterococcus faecalis* [39]. Moreover, the use of bacteriocins are considered as the great advantage for food and feed producers since these are non-toxic, active even at low concentrations and generally regarded as safe (GRAS status)[38]. So the bacteriocins produced by LAB have received most considerable attention as antagonistic natural biopreservativs to inhibit the survival of pathogens in foods and to enhance food safety [27]. The bacteriocins are considered to be safe bio-preservatives since they are easily degraded by proteases present in gastrointestinal tract [40]. These are effectively used as natural preservatives in meat and milk [15]. Only bacteriocin, namly nisin produced by *Lactococcus lactis*, is approved as a commercially available food additive in most major food-producing countries [40, 41]. Another important bacteriocin is pediocin that attracts research interest and will likely be the next to be used in the food industry [42], which has anti-listerial property [43, 44], produced by *Pediococcus* strains. Nisin (Nisaplin™) and pediocin (Alta™) are used commercially as food additives to improve quality and safety by means of a natural ingredient. Apart from nisin and pediocin, other bacteriocins, such as lactocin S (produced by *Lactobacillus sake* L45) and curvacin A (produced by *Lactobacillus* curvatus), achieve bacterial killing [45]. The limitation of bacteriocins from Gram-positive bacteria is that these are not active against Gram-negative bacteria. Because the outer membrane of Gram-negative bacteria acts as an impermeable barrier for the cells [46].

Other reported bacteriocins are Plantaricin NC8 produced by *Lb. plantarum* NC8 [47], Enterocin 1071A and Enterocin 1071B produced by *Enterococcus faecalis* BFE 1071 [48], Pentocin L and S produced by *Pediococcus pentosaceus* L and S [49] and Lactococcin 972 produced by *Lactococcus lactis* [50].

The bacteriocins of Gram-positive bacteria are generally produced in log phase to stationary phase. The production of bacteriocin is growth-associated because production occurs during the mid-exponential phase and increase to reach a maximal level at the end of the exponential phase or the beginning of the early-stationary phase [51]. For example, nisin production starts in the mid-log phase and increases to a maximum as the growth of cells enter stationary phase [52].

The antibiotic therapy for some illnesses destroys the microbial flora (both the useful and the targeted harmful microbes) present in the digestive tract; where bacteriocin have no cross-resistance with antibiotics without affecting harmless microbiota. Bacteriocins are promising substitute for therapeutic antibiotics. The introduction of probiotic bacteria to the gastrointestinal tract is an important concern regarding the potential use of bacteriocin-producing strains, which will produce bacteriocins. Bacteriocins differ from most of conventional antibiotics that these are ribosomally synthesized peptides and have a relatively narrow killing spectrum [46, 53] where antibiotics are secondary metabolites, have broad range of inhibitory activity. In addition, bacteriocins, proteinaceous and easily digested by proteases in the human digestive tract. Although some antibiotics are enzymatically synthesized are composed of amino acids, such as Vancomycin [40]. Bacteriocins possess antibiotic properties, but these are not termed as antibiotics. Only therapeutic antibiotics can potentially illicit allergic reactions in humans and other medical problems in humans [54].

Lantibiotics and pediocin-like bactericins can able to kill a broad spectrum of Gram-positive bacteria, including important pathogens. The commercially available bacteriocins are nisin and pediocin PA-1/AcH. The main differences between bacteriocins and antibiotics are summarized in table 1.

Table 1: Comparison of bacteriocins and antibiotics

Characteristic	Bacteriocins	Antibiotics	References
Application	Food	Clinical	
Synthesis	Ribosomal (primary metabolites)	Secondary metabolite	
Activity	Narrow spectrum	Varying spectrum	
Host cell immunity	Yes	No	[40]
Mechanism of target	Usually, adaptation affecting	Usually a genetically	
Cell resistance or tolerance	Cell membrane composition	Transferable determinant affecting different sites depending the mode of action	
Interaction requirements	Sometimes docking molecules	Specific target	
Mode of action	Mostly pore formation, but in a few cases possibly cell wall biosynthesis	Cell membrane or intracellular targets	
Toxicology/side effects	None known (rapidly digested by proteases in the human digestive tract)	Yes	

Nisin

Nisin produced by *Lactococcus lactis* subsp. *Lactis* is a lantibiotic with a small peptide (molecular weight < 5 kDa). *L. lactis* strains are regarded as safe (food-grade). The bacteriocin exhibits antimicrobial activity towards a wide range of Gram-positive bacteria like *Listeria* sp and *Micrococcus* sp, especially prevents heat-resistant spore-forming spoilage like *Bacillus* and *Clostridium* [55]. It is suitable as a food preservative since it is natural, toxicologically safe and quickly digested by proteases in

GI tract. In 1969, nisin was approved as food additive (234) by the Joint FAO/WHO Expert Committee. The bacteriocin is permitted for use as a safe natural food preservative in food in more than 50 countries, including the US and Europe. Nisin has been sold under the trade name of Nisaplin®, which contains approximately 2.5% nisin, the balance consisting of milk and milk solids derived from the fermentation of a modified milk medium by nisin-producing strains of *L. lactis*. The product is standardized to an activity of one million international units per gram. The assay method in most common use involves measuring zones of inhibition in agar seeded with the test organism [56, 57]. It is predominantly used in canned foods and dairy products, processed and natural cheeses [38].

Pediocin

The bacteriocin produced by *Pediococcus* species is known as pediocin that shows broad inhibition activity against pathogenic and food spoilage bacteria such as *Listeria monocytogenes*, *Enterococcus faecalis, Staphylococcus aureus* and *Clostrium perfringes* [3]. Pediocin is small, heat-stable, non-lantibiotic peptide. Its molecular weight is approximately 3.5 kDa and is resistant to heat treatment at 121 °C for 10 min [58]. *Pediococcus acidilactici* MM33 is the first pediocin-producing strain reported and could be used as probiotic in human to prevent enteric pathogen colonization [59]. Pediocin like bacteriocins are sakacin P, leucocin A, and curvacin A [60, 61]. Various reported bacteriocins from *Pediococcus* species are shown in table 2.

Table 2: Various types of pediocin produced by pediococcus strains

Pediocin	Producer strain	References
Pediocin	*Pediococcus acidilactici* MM33	[59]
Pediocin PA-1	*Pediococcus parvulus*	[60]
Pediocin PA-1	*Pediococcus acidilactici* PAC1.0	[62]
Pediocin PA-1	*P. acidilactici* UL5	[63]

Determination of bacteriocin activity

The antimicrobial activity of bacteriocin is usually determined against test organism by agar plate diffusion assay [64]. The inhibition zone in agar medium is measured by the inhibited growth of indicator strain. The activity is expressed in arbitrary units (AU) ml^{-1}. One AU was defined as the reciprocal of the highest serial two-fold dilution, showing a clear zone of growth inhibition of the indicator strain [65].

Classification of bacteriocins

Bacteriocins produced by Gram-positive bacteria are divided in four classes on the basis of physico-chemical properties such as antimicrobial activity, molecular weight, stability, immunity, mode of action etc [55, 66].

Class I

Class I is comprised of modified bacteriocins, known as lantibiotics (lanthionine-containing peptides antibiotic), generally produced by LAB [67, 68]. Lantibiotics are ribosomally synthesized compounds that target a broad range of Gram-positive bacteria. Class I bacteriocin is being further subdivided into two classes, namely, Ia and Ib. Class Ia bacteriocins, such as nisin, are relatively elongated, flexible, cationic and hydrophobic peptides (2–5 kDa). Generally, they act through the formation of pores in the cytoplasmic membrane of target bacteria [69]. Class Ib bacteriocins, which are globular peptides, such as mersacidin [68], have no net charge or a net negative charge; antimicrobial activity is related to the inhibition of specific enzymes [38, 70]. Examples of Class I bacteriocins are summarized in table 3.

Table 3: Examples of class I bacteriocins (lantibiotics)

Class	Bacteriocin	Producer strain	References
Class Ia	Nisin A	*Lactococcus lactis* NIZOR5, 6F3,NCFB894	[66]
	Nisin Z	*Lactococcus lactis* N8, NIZO22186	
	Lacticin 481	*Lactococcus lactis* CNRZ481, ADRIA85LO30	
	Lacticin 3147	*Lactococcus lactis* DPC3147	
	Lactocin S	*Lactobacillus sake* 145	
	Lactococcin	*Lactobacillus lactis* ADRI85L030	
Class Ib	Mersacidin	*Bacillus subtilis*	
	Cinnamycin	*Streptomyces cinnamoneus*	
	Ancovenin	*Streptomyces ssp.*	
	Actagardin	Actinoplanes ssp.	
Class Ic	Salvaricin A	*Streptococcus salvarius* 20P3	
	Cytolysin	*Enterococcus faecalis* DS16	
	Carnocin U149	*Carnobacterium pisicola*	
	Streptococcin	*Streptococcus pyrogens* FF22	
	Variacin 8	*Micrococcus varians* MCV8	

Class II

Small (<10 kDa), heat-stable, non lantibiotics are contained in class II [71, 72]. These bacteriocins are classified into three subgroups.

Class IIa are distinguished by inhibitory activity against food-borne pathogen like, *Listeria monocytogenes* [73]. The most extensively studied class IIa bacteriocins are pediocins. They inhibit a wide range of organisms, including *Actinomyces*, *Bacillus*, *Clostridium*, *Corynebacterium*, *Enterococcus*, *Gardnerella*, *Lactococcus*, *Micrococcus*, *Mycobacterium*, *Propionibacterium*, *Streptococcus*, and *Staphylococcus* [74]. The bacteriocins of this group are also active against a number of Gram-negative bacteria, including *Campylobacter*, *Haemophilus*, *Helicobacter*, and *Neisseria* [75]. Examples of class IIa bacteriocins are shown in table 4.

Table 4: Class IIa bacteriocins bacteriocins produced by LAB

Bacteriocin	Producer strain	References
Pediocin PA-1/AcH	*Pediococcus acidilactici*	
Sakacin A	*Lactobacillus sake* LB 706	
Sakacin P	*Lactobacillus sake* LTH 673	
Curvacin A	*Lactobacillus curvatus* LTH 1174	

Bacteriocin	Producer strain	References
Divercin V41	*Carnobacterium divergen* V41	[73]
Enterocin A	*Enterococcus faecium* CTC 492/T136	
Enterocin P	*Enterococcus faecium* P13	
Bavaricin A	*Lactobacillus sake* MI401	
Bavaricin MN	*Lactobacillus sake* MN	
Piscicocin 126	*Carnobacterium piscicola* JG126	
Piscicocin V1b	*Carnobacterium piscicola* V1	
Mesentericin Y105	*Leuconostoc mesenteroides* Y105	
Mundticin	*Enterococcus mundtii* AT06	
Carnobacteriocin B2	*Carnobacterium piscicola* LV17A	

Class IIb bacteriocins composed by a complex of two distinct peptides, have little or no activity form pores in the membrane of their target cells [76]. Examples of class IIb bacteriocins are shown in table 5.

Table 5: Class IIb bacteriocins and their producer strains

Bacteriocin	Producer strain	References
Lactacin F (LafX and LafA)	*Lactobacillus johnsonii* VPI11088	
Lactocin 705 α and β	*Lactobacillus casei* CRL505	
Lactocoocin Gα and β	*Lactococcus lactis* LMG2081	
Lactocoocin M and N	*Lactococcus lactis subsp. cremoris* 9B4	
Lacticin 3147 A1 and A2	*Lactococcus lactis* DPC3147	[76]
Thermophilin 13 A and B	*Streptococcus thermophilus* SFi13	
Plantaricin E and F	*Lactobacillus plantarum* C-11	
Plantaricin J and K	*Lactobacillus plantarum* C-11	
Plantaricin Sα and β	*Lactobacillus plantarum* PLCO10	
Plantaricin Wα and β	*Lactobacillus plantarum* LMG2379	
Enterocin 1071A and 1071B	*Enterococcus faecalis* BFE1071	
Enterocin L50A and L50B	*Enterococcus faecium* L50	
ABP118 (Abp 118 α and β)	*Lactobacillus salivarius* UCC118	

Class IIc has been proposed as *sec*-dependent secreted bacteriocins [35, 77]. Two types of bacteriocins can be found within this group: (a) antibiotics with one or two cysteine residues (thiolbiotics and cystibiotics) and (b) bacteriocins without cysteine (lactococcin A and acidocin B). Examples of class IIc bacteriocins are shown in table 6.

Table 6: Class IIc bacteriocins

Bacteriocin	Producer strain	References
Acidocin B	*Lactobacillus acidophilus* M46	
Lactococcin A	*Lactococcus lactis* LMG 2130	[78]
Lactococcin B	*Lactococcus lactic* WM4	
Enterocin B	*Enterococcus faecium* CECT 492	
Cerein 7/8	*Bacillus cereus* Bc7	
Divergicin A	*Carnobacterium divergens* LV13	

Class III

The class III bacteriocins are heat-labile proteins of large molecular weight larger than 30 kDa [78, 79]. They are usually produced by bacteria of *Lactobacillus* [73, 78], e. g. helveticin J, acidophilucin A, lacticin A and B, caseicin80 [80, 81]. Examples of Class III bacteriocins are given in table 7.

Class IV

This group is comprised of complex bacteriocins carrying an undefined mixture of proteins, lipids or carbohydrates [29, 82]. Examples include lactocin 27, leuconocin S, Plantaricin S, Leuconocin S etc. [83, 84].

Mode of action

The cytoplasmic membrane of Gram-positive bacteria is the primary target for the action of bacteriocins [85]. Bacteriocins are generally positively charged molecules with hydrophobic patches, where, Gram-positive bacteria have a high content of negatively charged lipids (phosphate groups) in the cytoplasmic membrane. Hydrophobic patches of bacteriocins electro-statically interact with the hydrophobic membrane of target cell. The hydrostatic portion easily inserts into the membrane and forms discrete pores [40, 86]. Pores in the cytoplasmic membrane dissipate proton motive force (PMF) and clearly affect the essential energy source of the cell. The PMF, which is composed of a chemical component (the pH gradient: ΔpH) and an electrical component (trans-membrane potential; Δψ), drive ATP synthesis and the accumulation of ions and other metabolites through PMF-driven transport systems in the membrane. Collapse of the PMF, induced by bacteriocin action, leads to cell death through cessation of energy-requiring reactions [87]. All class I bacteriocins (lantibiotics), particularly nisin dissipate the proton motive force (PMF) to kill target cells by forming pores in the membrane in the leakage of cellular materials [88].

Gram-negative bacteria are generally insensitive to bacteriocins from LAB strains because of their outer membrane providing them with a permeability barrier. The sensitivity of Gram-negative bacteria can be increased by sub-lethal injury of the cells, using for instance high hydrostatic pressure and pulsed electric field as non-thermal methods of preservation [89]. Bacteriocin affects Gram-negative bacteria when their outer membrane is impaired [90].

Immunity

Bacteriocin producer strains can protects themselves against their own antimicrobial substances is referred as immunity [71]. The resistance of *P. acidilactici* H to pediocin AcH/PA-1 has been reported as specific immunity of strain [90]. The composition of membrane lipid and the constitution of cell wall are responsible for the protection of cell against bacteriocin action [91]. The inhibitory activity of bacteriocin depends on species of different genera, growth cultures and environmental conditions [92].

Table 7: Class III bacteriocins produced by LAB

Bacteriocin	Producer strain	References
Acidophilucin A	*Lactobacillus acidophilus*	
Caseicin 80	*Lactobacillus casei* B80	[86]
Helviticin J/V-1829	*Lactobacillus heviticus*	
Lacticin A/B	*Lactobacillus delbrueckii*	

CONCLUSION

Application of LAB or bacteriocin as bio-preservative is a great strategy for preservation of functional food through killing of pathogenic and spoilage microorganisms. Variety of foods, especially dairy products supplemented with probiotics have been reported broadly. The beneficial microbes stimulate the human intestine flora as well as immunity through regular consumption of the food products. Another effort is going on to incorporate bacteriocin in packaging matrix. Bioactive packaging is able to extend shelf life and protect food with nutritional quality. The design of edible antimicrobial film or coatings is also developed for safety of food products. Some bioactive compounds are combined with bacteriocin to enhance the inhibition of bacteria.

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REFERENCES

1. Ross RP, Morgan S, Hill C. Preservation and fermentation: past, present and future. Int J Food Microbiol. 2002;79(1-2):3-16. doi: 10.1016/s0168-1605(02)00174-5, PMID 12382680.
2. McKay LL, Baldwin KA. Applications for biotechnology: present and future improvements in lactic acid bacteria. FEMS Microbiol Rev. 1990;7(1-2):3-14. doi: 10.1111/j.1574-6968.1990.tb04876.x, PMID 2271224.
3. Bhunia AK, Johnson MC, Ray B. Purification, characterization and antimicroial spectrum of a bacteriocin produced by *Pediococcus acidilactici*. J Appl Bacteriol. 1988;65(4):261-8.
4. Cintas LM, Rodriguez JM, Fernandez MF, Sletten K, Nes IF, Hernandez PE. Isolation and characterization of pediocin L50, a new bacteriocin from *Pediococcus acidilactici* with a broad inhibitory spectrum. Appl Environ Microbiol. 1995;61(7):2643-8. doi: 10.1128/aem.61.7.2643-2648.1995, PMID 7618877.
5. Lindgren SE, Dobrogosz WJ. Antagonistic activities of lactic acid bacteria in food and feed fermentations. FEMS Microbiol Rev. 1990;7(1-2):149-63. doi: 10.1111/j.1574-6968.1990.tb04885.x, PMID 2125429.
6. Messens W, De VL. Inhibitory substances produced by *Lactobacilli* isolated from sourdoughs-a review. Int J Food Microbiol. 2002;72(1-2):31-43. doi: 10.1016/s0168-1605(01)00611-0, PMID 11843411.
7. Sakala RM, Hayashidani H, Kato Y, Kaneuchi C, Ogawa M. Isolation and characterization of *Lactococcus piscium* strains from vacuum-packaged refrigerated beef. J Appl Microbiol. 2002;92(1):173-9. doi: 10.1046/j.1365-2672.2002.01513.x, PMID 11849342.
8. Jamuna M, Jeevaratnam K. Isolation and characterization of lactobacilli from some traditional fermented foods and evaluation of the bacteriocins. J Gen Appl Microbiol. 2004;50(2):79-90. doi: 10.2323/jgam.50.79, PMID 15248146.
9. Axelsson L. Lactic acid bacteria: classification and physiology. In: Salminen S, von Wright AV, Ouwehand A, editors. Lactic acid bacteria: microbiological and functional aspects. 3rd ed. Vol. 67. New York: Marcel Dekker, New York; 2004. p. 656. doi: org/10.1201/9780824752033.
10. Marteau PR, de Vrese M, Cellier CJ, Schrezenmeir J. Protection from gastrointestinal diseases with the use of probiotics. Am J Clin Nutr. 2001;73(2)Suppl:430S-6S. doi: 10.1093/ajcn/73.2.430s, PMID 11157353.
11. Guandalini S, Pensabene L, Zikri MA, Dias JA, Casali LG, Hoekstra H, Kolacek S, Massar K, Micetic Turk D, Papadopoulou A, De Sousa JS, Sandhu B, Szajewska H, Weizman Z. *Lactobacillus GG* administered in oral rehydratation solution to children with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr. 2000;30(1):54–60. doi: 10.1097/00005176-200001000-00018, PMID: 10630440.
12. Marteau P, Rambaud JC. Therapeutic applications of probiotics in humans. In: leeds AR, Rowland IR, editors. Gut flora and Health. Past, present and future. Vol. 47. London: Royal society of medicine press Ltd; 1996. p. 56.
13. Adachi S. Lactic acid bacteria and the control of tumours. In: Wood BJB, editor. Lactic acid bacteria in health and disease. London: Elsevier; 1992. p. 233-61.
14. Lilly DM, Stillwell RH. Probiotics: growth-promoting factors produced by microorganisms. Science. 1965;147(3659):747-8. doi: 10.1126/science.147.3659.747, PMID 14242024.
15. Metchnikoff E. Prolongation of life: optimistic studies Mitchell PC, translator. New York: Putnam; 1908.
16. Saavedra JM. Clinical applications of probiotic agents. Am J Clin Nutr. 2001;73(6):1147S-51S. doi: 10.1093/ajcn/73.6.1147S, PMID 11393193.
17. Senok AC, Ismaeel AY, Botta GA. Probiotics: facts and myths. Clin Microbiol Infect. 2005;11(12):958-66. doi: 10.1111/j.1469-0691.2005.01228.x, PMID 16307549.
18. Picard C, Fioramonti J, Francois A, Robinson T, Neant F, Matuchansky C. Bifidobacteria as probiotic agents-physiological effects and clinical benefits. Aliment Pharmacol Ther. 2005;22(6):495-512. doi: 10.1111/j.1365-2036.2005.02615.x, PMID 16167966.
19. Czerucka D, Piche T, Rampal P. Yeast as probiotics-saccharomyces boulardii. Aliment Pharmacol Ther. 2007;26(6):767-78. doi: 10.1111/j.1365-2036.2007.03442.x, PMID 17767461.
20. Sartor RB. Targeting enteric bacteria in treatment of inflammatory bowel diseases: why, how, and when. Curr Opin Gastroenterol. 2003;19(4):358-65. doi: 10.1097/00001574-200307000-00006, PMID 15703577.
21. Meurman JH, Stamatova I. Probiotics: contributions to oral health. Oral Dis. 2007;13(5):443-51. doi: 10.1111/j.1601-0825.2007.01386.x, PMID 17714346.
22. Klaenhammer TR, Kullen MJ. Selection and design of probiotics. Int J Food Microbiol. 1999;50(1-2):45-57. doi: 10.1016/s0168-1605(99)00076-8, PMID 10488843.
23. Morelli L. Probiotics: clinics and/or nutrition. Dig Liver Dis. 2002;34:S8-S11. doi: 10.1016/S1590-8658(02)80156-6.
24. Scarpellini E, Cazzato A, Lauritano C, Gabrielli M, Lupascu A, Gerardino L. Probiotics: which and when? Dig Dis. 2008;26(2):175-82. doi: 10.1159/000116776, PMID 18431068.
25. Anal AK, Singh H. Recent advances in microencapsulation of probiotics for industrial applica-tions and targeted delivery. Trends Food Sci Technol. 2007;18:240-51. doi: 10.1016/j.tifs.2007.01.004.
26. Conway PL. Selection criteria for probiotic microorganisms. Asia Pac J Clin Nutr. 1996;5(1):10-4. PMID 24394458.
27. Klaenhammer TR. Bacteriocins of lactic acid bacteria. Biochimie. 1988;70(3):337-49. doi: 10.1016/0300-9084(88)90206-4, PMID 3139051.
28. Gratia A. Surun remarquable exemple d'antagonisme entre deux souches de colibacille. Comt Rend Soc Biol l. 1925;93:1040-2.
29. Gratia JP. Andre gratia: a forerunner in microbial and viral genetics. Genetics. 2000;156(2):471-6. doi: 10.1093/genetics/156.2.471, PMID 11014798.
30. Heng NCK, Wescombe PA, Burton JP, Jack RW, Tagg JR. The diversity of bacteriocins in Gram-positive bacteria. In: Riley MA, Chavan MA. editors. Bacteriocins: ecology and evolution. Vol. 4.

Germany: Heidelberg, Germany; 2007. p. 92. doi: 10.1007/978-3-540-36604-1_4.

31. Gordon DM, Oliver E, Littlefield Wyer J. The diversity of bacteriocins in gram-negative bacteria. In: Riley MA, Chavan M, editors. Bacteriocins. Ecology and evolution. Berlin: Springer; 2007. p. 5-18.
32. Gillor O, Nigro LM, Riley MA. Genetically engineered bacteriocins and their potential as the next generation of antimicrobials. Curr Pharm Des. 2005;11(8):1067-75. doi: 10.2174/1381612053381666, PMID 15777256.
33. Pons AM, Lanneluc I, Cottenceau G, Sable S. New developments in non-post translationally modified microcins. Biochimie. 2002;84(5-6):531-7. doi: 10.1016/s0300-9084(02)01416-5, PMID 12423797.
34. Riley MA, Goldstone CM, Wertz JE, Gordon D. A phylogenetic approach to assessing the targets of microbial warfare. J Evol Biol. 2003;16(4):690-7. doi: 10.1046/j.1420-9101.2003.00575.x, PMID 14632232.
35. Riley MA. Molecular mechanisms of bacteriocin evolution. Annu Rev Genet. 1998;32:255-78. doi: 10.1146/annurev.genet.32.1.255, PMID 9928481.
36. Nes IF, Holo H. Class II antimicrobial peptides from lactic acid bacteria. Biopolymers. 2000;55(1):50-61. doi: 10.1002/1097-0282(2000)55:1<50::AID-BIP50>3.0.CO;2-3, PMID 10931441.
37. Joerger MC, Klaenhammer TR. Cloning, expression, and nucleotide sequence of the lactobacillus helveticus 481 gene encoding the bacteriocin helveticin. J Bacteriol. 1990;172(11):6339-47. doi: 10.1128/jb.172.11.6339-6347.1990, PMID 2228964.
38. Tagg JR, Dajani AS, Wannamaker LW. Bacteriocins of gram-positive bacteria. Bacteriol Rev. 1976;40(3):722-56. doi: 10.1128/br.40.3.722-756.1976, PMID 791239.
39. Deegan LH, Cotter PD, Hill C, Ross P. Bacteriocins: biological tools for bio-preservation and shelf-life extension. Int Dairy J. 2006;16(9):1058-71. doi: 10.1016/j.idairyj.2005.10.026.
40. Delves Broughton J. Nisin and its uses as a food preservation. Food Technol. 1990;44:100-10.
41. Cleveland J, Montville TJ, Nes IF, Chikindas ML. Bacteriocins: safe, natural antimicrobials for food preservation. Int J Food Microbiol. 2001;71(1):1-20. doi: 10.1016/s0168-1605(01)00560-8, PMID 11764886.
42. Li C, Bai J, Cai Z, Ouyang F. Optimization of a cultural medium for bacteriocin production by *Lactococcus lactis* using response surface methodology. J Biotechnol. 2002;93(1):27-34. doi: 10.1016/s0168-1656(01)00377-7, PMID 11690692.
43. Turcotte C, Lacroix C, Kheadr E, Grignon L, Fliss IA. A rapid turbidometric microplate bioassay for accurate quantification of lactic acid bacteria bacteriocins. Int J Food Microbiol. 2004;90(3):283-93. doi: 10.1016/s0168-1605(03)00315-5, PMID 14751683.
44. Simon L, Fremaux C, Cenatiempo Y, Berjeaud JM. Sakacin g, a new type of antilisterial bacteriocin. Appl Environ Microbiol. 2002;68(12):6416-20. doi: 10.1128/AEM.68.12.6416-6420.2002, PMID 12450870.
45. Guyonnet D, Fremaux C, Cenatiempo Y, Berjeaud JM. Method for rapid purification of class IIa bacteriocins and comparison of their activities. Appl Environ Microbiol. 2000;66(4):1744-8. doi: 10.1128/AEM.66.4.1744-1748.2000, PMID 10742275.
46. Cintas LM, Casaus P, Fernandez MF, Hernandez PE. Comparative antimicrobial activity of enterocin L50, pediocin PA-1, nisin a and lactocin S against spoilage and foodborne pathogenic bacteria. Food Microbiol. 1998;15(3):289-98. doi: 10.1006/fmic.1997.0160.
47. Riley MA, Wertz JE. Bacteriocin diversity: ecological and evolutionary perspectives. Biochimie. 2002;84(5-6):357-64. doi: 10.1016/s0300-9084(02)01421-9, PMID 12423779.
48. Maldonado A, Ruiz Barba JL, Jimenez Diaz R. Purification and genetic characterization of plantaricin NC8, a novel coculture-inducible two-peptide bacteriocin from lactobacillus plantarum NC8. Appl Environ Microbiol. 2003;69(1):383-9. doi: 10.1128/AEM.69.1.383-389.2003, PMID 12514019.
49. Balla E, Dicks LM, Du Toit M, Van Der Merwe MJ, Holzapfel WH. Characterization and cloning of the genes encoding enterocin 1071A and enterocin 1071B, two antimicrobial peptides produced by *Enterococcus faecalis* BFE 1071. Appl Environ Microbiol. 2000;66(4):1298-304. doi: 10.1128/AEM.66.4.1298-1304.2000, PMID 10742203.
50. Yin LJ, Wu CW, Jiang ST. Bacteriocins from *Pediococcus pentosaceus* L and S from pork meat. J Agric Food Chem. 2003;51(4):1071-6. doi: 10.1021/jf025838f, PMID 12568574.
51. Martinez B, Rodriguez A, Suarez JE. Lactococcin 927, a bacteriocin that inhibits septum formation in lactococci. Microbiol. 2000;146:949-55. doi: 10.1099/00221287-146-4-949, PMID 10784053.
52. Cheigh CI, Choi HJ, Park H, Kim SB, Kook MC, Kim TS. Influence of growth conditions on the production of a nisin-like bacteriocin by *Lactococcus lactis* subsp. *lactis* A164 isolated from kimchi. J Biotechnol. 2002;95(3):225-35. doi: 10.1016/s0168-1656(02)00010-x, PMID 12007863.
53. Breukink E, de Kruijff B. The lantibiotic nisin, a special case or not? Biochim Biophys Acta. 1999;1462(1-2):223-34. doi: 10.1016/s0005-2736(99)00208-4. PMID 10590310.
54. Saavedra JM, Abi-Hanna A, Moore N, Yolken RH. Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety. Am J Clin Nutr. 2004;79(2):261-7. doi: 10.1093/ajcn/79.2.261, PMID 14749232.
55. Deraz SF, Karlsson EN, Hedstrom M, Andersson MM, Mattiasson B. Purification and characterisation of acidocin D20079, a bacteriocin produced by *Lactobacillus acidophilus* DSM 20079. J Biotechnol. 2005;117(4):343-54. doi: 10.1016/j.jbiotec.2005.02.005, PMID 15925717.
56. Gonzalez Martinez C, Becerra M, Chafer M, Albors A, Carot JM, Chiralt A. Influence of substituting milk powder for whey powder on yoghurt quality. Trends Food Sci Technol. 2002;13(9-10):334-40. doi: 10.1016/S0924-2244(02)00160-7.
57. Vandenbergh PA. Lactic acid bacteria, their metabolic products and interference with microbial growth. FEMS Microbiol Rev. 1993;12(1-3):221-37. doi: 10.1111/j.1574-6976.1993.tb00020.x.
58. Delves Broughton J, Blackburn P, Evans RJ, Hugenholtz J. Applications of the bacteriocin, nisin. Antonie Leeuwenhoek. 1996;69(2):193-202. doi: 10.1007/BF00399424, PMID 8775979.
59. Green G, Dicks LM, Bruggeman G, Vandamme EJ, Chikindas ML. Pediocin PD-1, a bactericidal antimicrobial peptide from *Pediococcus damnosus* NCFB 1832. J Appl Microbiol. 1997;83(1):127-32. doi: 10.1046/j.1365-2672.1997.00241.x, PMID 9246779.
60. Millette M, Cornut G, Dupont C, Shareck F, Archambault D, Lacroix M. Capacity of human nisin-and pediocin-producing lactic acid bacteria to reduce intestinal colonization by vancomycin-resistant enterococci. Appl Environ Microbiol. 2008;74(7):1997-2003. doi: 10.1128/AEM.02150-07, PMID 18245231.
61. Motlagh AM, Bhunia AK, Szostek F, Hansen T, Johnson MC, Ray B. Nucleotide and amino acid sequence of pap-gene (pediocin AcH production) in *Pediococcus acidilactici* H. Lett Appl microbiol. 1992;15(2):45 –8. doi: 10.1111/j.1472-765x.1992, PMID 1368421.
62. Bukhtiyarova M, Yang R, Ray B. Analysis of the pediocin AcH gene cluster from plasmid pSMB74 and its expression in a pediocin-negative pediococcus acidilactici strain. Appl Environ Microbiol. 1994;60(9):3405-8. doi: 10.1128/aem.60.9.3405-3408.1994, PMID 7944372.
63. Gonzalez CF, Kunka BS. Plasmid-associated bacteriocin production and sucrose fermentation in *Pediococcus acidilactici*. Appl Environ Microbiol. 1987;53(10):2534-8. doi: 10.1128/aem.53.10.2534-2538.1987, PMID 16347470.
64. Daba H, Lacroix C, Huang J, Simard RE, Lemieux L. Simple method of purification and sequencing of a bacteriocin produced by *Pediococcus acidilactici* UL5. J Appl Bacteriol. 1994;77(6):682-8. doi: 10.1111/j.1365-2672.1994.tb02819.x, PMID 7822227.
65. Tagg JR, McGiven AR. Assay system for bacteriocins. Appl Microbiol. 1971;21(5):943. doi: 10.1128/am.21.5.943-943.1971, PMID 4930039.
66. Van Reenen CA, Dicks LM, Chikindas ML. Isolation, purification and partial characterization of plantaricin 423, a bacteriocin produced by lactobacillus plantarum. J Appl Microbiol. 1998;84(6):1131-7. doi: 10.1046/j.1365-2672.1998.00451.x, PMID 9717299.

67. And HC, Hoover DG. Bacteriocins and their food applications. Compr Rev Food Sci Food Saf. 2003;2(3):82-100. doi: 10.1111/j.1541-4337.2003.tb00016.x, PMID 33451234.
68. Jack RW, Tagg JR, Ray B. Bacteriocins of gram-positive bacteria. Microbiol Rev. 1995;59(2):171-200. doi: 10.1128/mr.59.2.171-200.1995, PMID 7603408.
69. Twomey D, Ross RP, Ryan M, Meaney B, Hill C. Lantibiotics produced by lactic acid bacteria: structure, function and applications. Antonie Leeuwenhoek. 2002;82(1-4):165-85, PMID 12369187.
70. Broadbent JR, Chou YC, Gillies K, Kondo JK. Nisin inhibits several gram-positive, mastitis-causing pathogens. J Dairy Sci. 1989;72(12):3342-5. doi: 10.3168/jds.S0022-0302(89)79496-0, PMID 2516858.
71. Altena K, Guder A, Cramer C, Bierbaum G. Biosynthesis of the lantibiotic mersacidin: organization of a type B lantibiotic gene cluster. Appl Environ Microbiol. 2000;66(6):2565-71. doi: 10.1128/AEM.66.6.2565-2571.2000, PMID 10831439.
72. Nes IF, Diep DB, Havarstein LS, Brurberg MB, Eijsink V, Holo H. Biosynthesis of bacteriocins in lactic acid bacteria. Antonie Leeuwenhoek. 1996;70(2-4):113-28. doi: 10.1007/BF00395929, PMID 8879403.
73. Oppegard C, Rogne P, Emanuelsen L, Kristiansen PE, Fimland G, Nissen Meyer J. The two-peptide class II bacteriocins: structure, production, and mode of action. J Mol Microbiol Biotechnol. 2007;13(4):210-9. doi: 10.1159/000104750, PMID 17827971.
74. Ennahar S, Sashihara T, Sonomoto K, Ishizaki A. Class IIa bacteriocins: biosynthesis, structure and activity. FEMS Microbiol Rev. 2000;24(1):85-106. doi: 10.1111/j.1574-6976.2000.tb00534.x, PMID 10640600.
75. Mota Meira M, Morency H, Lavoie MC. *In vivo* activity of mutacin B-Ny266. J Antimicrob Chemother. 2005;56(5):869-71. doi: 10.1093/jac/dki295, PMID 16155061.
76. Morency H, Mota Meira M, LaPointe G, Lacroix C, Lavoie MC. Comparison of the activity spectra against pathogens of bacterial strains producing a mutacin or a lantibiotic. Can J Microbiol. 2001;47(4):322-31. doi: 10.1139/w01-013, PMID 11358172.
77. Garneau S, Martin NI, Vederas JC. Two-peptide bacteriocins produced by lactic acid bacteria. Biochimie. 2002;84(5-6):577-92. doi: 10.1016/s0300-9084(02)01414-1, PMID 12423802.
78. Han KS, Kim Y, Kim SH, Oh S. Characterization and purification of acidocin 1B, a bacteriocin produced by *Lactobacillus acidophilus* GP1B. J Microbiol Biotechnol. 2007;17(5):774-83. PMID 18051299.
79. Oscariz JC, Pisabarro AG. Classification and mode of action of membrane-active bacteriocins produced by gram-positive bacteria. Int Microbiol. 2001;4(1):13-9. doi: 10.1007/s101230100003, PMID 11770815.
80. van Belkum MJ, Stiles ME. Nonlantibiotic antibacterial peptides from lactic acid bacteria. Nat Prod Rep. 2000;17(4):323-35. doi: 10.1039/a801347k, PMID 11014335.
81. Joerger RD. Alternatives to antibiotics: bacteriocins, antimicrobial peptides and bacteriophages. Poult Sci. 2003;82(4):640-7. doi: 10.1093/ps/82.4.640, PMID 12710486.
82. Dobson AE, Sanozky Dawes RB, Klaenhammer TR. Identification of an operon and inducing peptide involved in the production of lactacin b by lactobacillus acidophilus. J Appl Microbiol. 2007;103(5):1766-78. doi: 10.1111/j.1365-2672.2007.03417.x, PMID 17953587.
83. Klaenhammer TR. Genetics of bacteriocins produced by lactic acid bacteria. FEMS Microbiol Rev. 1993;12(1-3):39-85. doi: 10.1111/j.1574-6976.1993.tb00012.x, PMID 8398217.
84. Vermeiren L, Devlieghere F, Debevere J. Co-culture experiments demonstrate the usefulness of *Lactobacillus sakei* 10A to prolong the shelf-life of a model cooked ham. Int J Food Microbiol. 2006;108(1):68-77. doi: 10.1016/j.ijfoodmicro.2005.11.001, PMID 16380186.
85. Choi HJ, Lee HS, Her S, Oh DH, Yoon SS. Partial characterization and cloning of leuconocin J, a bacteriocin produced by leuconostoc sp. J2 isolated from the Korean fermented vegetable kimchi. J Appl Microbiol. 1999;86(2):175-81. doi: 10.1046/j.1365-2672.1999.00471.x, PMID 10063614.
86. Garneau S, Martin NI, Vederas JC. Two-peptide bacteriocins produced by lactic acid bacteria. Biochimie. 2002;84(5-6):577-92. doi: 10.1016/s0300-9084(02)01414-1, PMID 12423802.
87. And HC, Hoover DG. Bacteriocins and their food applications. Compr Rev Food Sci Food Saf. 2003;2(3):82-100. doi: 10.1111/j.1541-4337.2003.tb00016.x, PMID 33451234.
88. Moll GN, Konings WN, Driessen AJ. Bacteriocins: mechanism of membrane insertion and pore formation. Antonie Leeuwenhoek. 1999;76(1-4):185-98. PMID 10532378.
89. Okereke A, Montville TJ. Nisin dissipates the proton motive force of the obligate anaerobe *Clostridium sporogenes* PA 3679. Appl Environ Microbiol. 1992;58(8):2463-7. doi: 10.1128/aem.58.8.2463-2467.1992, PMID 1325140.
90. Caplice E, Fitzgerald GF. Food fermentations: role of microorganisms in food production and preservation. Int J Food Microbiol. 1999;50(1-2):131-49. doi: 10.1016/s0168-1605(99)00082-3, PMID 10488849.
91. Abee T, Krockel L, Hill C. Bacteriocins: modes of action and potentials in food preservation and control of food poisoning. Int J Food Microbiol. 1995;28(2):169-85. doi: 10.1016/0168-1605(95)00055-0, PMID 8750665.
92. Koponen O. Studies of producer self-protection and nisin biosynthesis of *Lactococcus lactis* [PhD thesis]. Helsinki, Finland,: University of Helsinki; 2004.
93. Castellano P, Farias ME, Holzapfel W, Vignolo G. Sensitivity variations of *Listeria* strains to the bacteriocins, lactocin 705, enterocin CRL35 and nisin. Biotechnol Lett. 2001;23(8):605-8. doi: 10.1023/A:1010320808989.