Bacteriocins from Latic Acid Bacteria: An Overview

[1]Kumari Luri Sethi, [1]Twinkle Jangde, [1]Somesh Kumar Sahay, [1]Shreyansh Verma, *Megha Chaturvedi

Department of Biotechnology, Faculty of Science, Kalinga University, Naya Raipur, Chhattisgarh

E-mail Id- megha.chaturvedi@kalingauniversity.ac,in

Abstract- Bacteriocins are antimicrobial peptides produced by lactic acid bacteria (LAB) bacteria are commonly found in fermented foods and beverages. In recent years, Among the various sources of bacteriocins, lactic acid bacteria (LAB) have attracted significant attention due to their potential as natural alternatives to conventional antibiotics in various domains, including food preservation, healthcare, and agriculture. Several classes of bacteriocins have also been identified, having unique structural and functional characteristics which provides insights into their potential applications and strategies for optimizing their efficacy. The applications of bacteriocins are not limited to food preservation but also extend to healthcare settings, where they can be used as bio-preservatives for medical devices or as therapeutic agents in the treatment of infections. Moreover, bacteriocins have been shown to have immunomodulatory properties and to enhance the efficacy of existing antibiotics, suggesting their potential as adjuvants for clinical use. This review paper aims to provide a comprehensive overview of bacteriocins, focusing on their mechanisms of action, applications, and future perspectives.

Keywords: Bacteriocins, antimicrobial peptides, LAB

DOI:10.48047/ecb/2023.12.7.295

INTRODUCTION

Bacteriocins are antimicrobial peptides produced by ribosome synthesis that are heat stable. In the late-exponential to the early-stationary growth phases, both Gram-positive and Gram-negative bacteria, as well as archaea, emit antimicrobial peptides extracellularly (Zheng et al., 2014). One of such bacteriocins is lactic acid bacteria (LAB). Lactic acid bacteria" (LAB) is a group of organisms that are meticulous, do not produce spores, are catalase-negative, are shaped like cocci or rods, and are highly tolerant of low pH. (Van Geel et al.,1998; De Vuyst & Leroy.,2007). LAB is some of the most crucial bacteria that are utilized in food fermentations as well as to improve the flavour and texture of fermented food items. (Hati S.et al.,2013). LAB also exhibits essential antimicrobial qualities in context with food preservation and safety and are capable of suppressing a variety of bacteria in a food environment. Additionally, it has been demonstrated that some LAB strains have remarkable health-promoting qualities. One of these probiotics qualities is their ability to fight against gastrointestinal pathogenic bacteria like Helicobacter pylori, e-coli, and Salmonella. (De Vuyst & Leroy.,2007) Numerous studies have shown that LAB inhibits the growth of harmful microorganisms, degrades mycotoxins, and has a probiotic effect (Mokoena M.P.,2017). LAB are widely distributed in nature and interact symbiotically with higher creatures. They have been removed from dairy products, meat, fruits, and vegetables, among other sources. They

can also be found in plants, wastewater, soil, and manure, as well as in the mucous membranes of the respiratory, gastrointestinal, and other anatomical regions of both humans and animals (Liu W. et al., 2014). LAB has been utilised as starter cultures and bacteriocins as food preservatives. To characterize and find new LAB strains with stronger antimicrobial activity, it is crucial to make use of the modern technologies that are currently available. In order to learn more about the characteristics of LAB isolates and their bacteriocins, as well as their ability to inhibit uropathogens, and ultimately lessen the need for antibiotics. (Juan et al., 2021)

OVERVIEW OF BACTERIOCINS

Bacteriocins are a varied class of hydrophobic, cationic, and antimicrobial peptides made up of 20–60 amino acids. Bacteriocin synthesis is carried out by the ribosomal machinery. Amino acid modification, bacteriocin export and regulation, and self-immunity proteins are all thought to be regulated by a number of genes. (Riley et al., 2002) The operons that contain the genes that code for bacteriocins can be found on chromosomes, plasmids, or other mobile genetic components. These operons are often inducible and necessitate the secretion and extracellular buildup of bacterial peptides for induction. Bacteriocins are secreted extracellularly and have effects that are either bactericidal or bacteriostatic on species that are closely related to the generating strain as well as on other genera, phyla, and even domains (Zimina M et al.,2020). The bacteriocins that lactic acid bacteria produce is anticipated to be secure antibacterial substances. Although nisin A, the most researched LAB bacteriocin, is frequently employed as a food preservation, numerous novel bacteriocins are needed to more effectively suppress undesirable bacteria (*Zendo T., 2013*). A quick screening technique that assesses the bacteriocins produced by recently isolated LABs based on their antibacterial spectra and molecular weights is created in order to identify new bacteriocins at an early stage of the screening process. Using this technique, several new bacteriocins have been discovered, including the nisin variant lactococcin Q, the two-peptide lactococcin Q, the leaderless lacticin Q, and the ring lactocyclic Q. Additionally, it is discovered that a few LAB isolates produce a variety of bacteriocins. Their structure, modes of action, and biosynthetic mechanisms have all been described. Applications for the novel LAB bacteriocins and their biosynthesis pathways include peptide engineering and food preservation.

Bacteriocins, which are bacterial proteins or peptides, are being looked at as potential novel antibacterial agents (*Blinkova et al., 2007*). From the perspective of the molecular basis of their generation and action, the examination of the characteristics of naturally occurring and genetically modified bacteriocinosis is presented. The majority of bacteriocins have a constrained range of inhibitory activity. The C- and N-ends of several broad-spectrum bacteriocins are connected by a peptide bond, giving rise to a ring shape. The protein's ability to bind to various receptors on the surface of target cells is caused by the fixed location of the protein's ends. It is possible for alien cells, even eukaryotic cells, to express the genes responsible for producing bacteriocins and related proteins (*Blinkova et al., 2007*). A large number of bacteriocins have been identified up to this point (Karpiński et al.,2013). As new information on bacteriocins structure, amino acid sequence, and understood mode of action emerges, the classification of these substances is constantly changing. Atypical amino acids like lanthionine (Lan), methylanthionine (MeLan), dehydroalanine (Dha), dehydrobutyrin (Dhb), or D-alanine (D-Ala) are found in some bacteriocins (lantibiotics). Nisin, which is produced by strains of Lactococcus lactis, is one of the most well-known bacteriocins produced by lactic acid bacteria (Egorov et al., 1999). These bacteriocins are known to be 100 percent safe for use on people. Currently, the food sector uses nisin as a preservative.

CLASSIFICATION OF BACTERIOCINS FROM LACTIC ACID BACTERIA (LAB)

Bacteriocins are categorized according to their genetic makeup, post-translational alterations, molecular weights, and basic structural components. However, there isn't a LAB classification system that is widely used. Though there are minor variations in the descriptions of the sub-classes among the many authors, authors have recently revised the four classes that were initially recognized into three.

Class I: RiPPs (less than 10 kDa)

This class encompasses all the peptides that undergo enzymatic modification during biosynthesis, which provides molecules with uncommon amino acids and structures that have an impact on their properties (e.g., lanthionine, heterocycles, head-to-tail cyclization, glycosylation). They consist of a leader peptide which serves for enzyme recognition, transport, and keeping the peptide inactive, which is fused to a core peptide (Arnison et al. 2013).

Class Ia. Or lanthipeptides (types I, II, III, and IV)

Lanthipeptides undergo PTMs, and generally the genes involved in the maturation process are in the same operon. Based on the PTM enzymes involved in the maturation process, lanthipeptides can be divided into four types, but only types I (LanBC-modified) and II (LanM-modified) can be considered lantibiotics (Knerr and van der Donk 2012). The nisin precursor is modified by the dehydratase NisB which dehydrates Ser and Thr via glutamyl-tRNA-dependent glutamylation and elimination (Garg et al. 2013; Ortega et al. 2015).

Class Ib. Or head-to-tail cyclized peptides

Head-to-tail cyclized bacteriocins are a group of RiPPs whose N- and C-termini are linked by a peptide bond, thereby rendering a circular molecule (Fig. 1). All of them contain only alpha helical segments (either 4 or 5) and share a similar structure with a saposin folding (Montalbán-López et al. 2012a; Lohans et al. 2013; Acedo et al. 2015; Himeno et al. 2015)

Class Ic. Or sactibiotics

Sactipeptides (also referred to as sactibiotics when they possess antimicrobial activity) are Sulphur-to-α-carbon-containing peptides (Arnison et al. 2013; Mathur et al. 2015). To the best of our knowledge, there has been no sactipeptide from a LAB characterized so far and only putative clusters have been identified in silico (Table 1) (Table S1) (Murphy et al. 2011), awaiting further study.

Class Ie. Or glycocins

Glycocins are bacteriocins containing glycosylated residue(s) (Arnison et al. 2013). Glycocin F from Lactobacillus plantarum was the first glycocin described in LAB (Stepper et al. 2011). Glycocin F is arranged as two alpha helices held together by disulfide bonds (Venugopal et al. 2011).

Class I f. Or lasso peptides

Lasso peptides are a group of RiPPs that show as a main characteristic the presence of an amide bond between the first amino acid in the core peptide chain and a negatively charged residue in positions +7 to +9 generating a ring that embraces the C-terminal linear part of the polypeptide (Fig. 1) (Arnison et al. 2013; Hegemann et al.

2015). Moreover, lasso peptides display diverse activities which range from antimicrobial to putative antiviral or anticancer (Maksimov et al. 2012)

Class II: unmodified bacteriocins (less than 10 kDa)

This class groups bacteriocins that do not contain unusual modifications. Thus, they do not require enzymes for their maturation other than a leader peptidase and/or a transporter

Class IIa. Or pediocin-like bacteriocins

The pediocin-like class IIa bacteriocins are broad spectrum antimicrobials particularly active agains Listeria (Kjos et al. 2011). The structure of peptides of class IIa can be divided in two different regions separated by a flexible hinge

(Haugen et al. 2008). Class IIa bacteriocins are subdivided into eight groups on the basis of their primary structures (Nissen-Meyer et al. 2009). However, the first and the most extensively studied representative of this class is pediocin PA-1

Class IIb. Or two-peptide bacteriocins

Class IIb bacteriocins consist of two very different peptides, and full activity requires the presence of both peptides in about equal quantities (Nissen-Meyer et al. 2010). In some cases, such as lactococcin G from L. lactis (Nissen-Meyer et al. 1992), antimicrobial activity requires the presence of both peptides.

Class IIc. Or leaderless bacteriocins

Leaderless bacteriocins are unique as they are synthetized without an N-terminal leader peptide, which usually functions as a recognition sequence for secretion and modification and maintains the bacteriocin inactive inside the producer cell (Liu et al. 2011; Masuda et al. 2012).

Class IId. Or non-pediocin-like, single-peptide bacteriocins

Class IId is a heterogeneous group of unrelated single linear peptide bacteriocins with different structures, mechanisms of secretion, and manners of action such as lactococcin 972, lactococcin A, and enterocin B (Franz et al. 2007).

Class III: unmodified bacteriocins (larger than 10 kDa)

These are unmodified bacteriocins with bacteriolytic or non-lytic mechanism of action. Class III bacteriocins are large molecular weight (>30 kDa), heat unstable proteins. Class III can be further subdivided into two distinct groups. Group A bacteriocins are the bacteriolytic enzymes which killing the sensitive strains by lysis of the cell well, such as Enterolisin A (Nilsen et al., 2003). Group B bacteriocins are non-lytic proteins such as Caseicin 80 (Müller and Radler, 1993) and Helveticin J (Joerger and Klaenhammer, 1986). Class III bacteriocins are large-molecular-weight and heat-labile antimicrobial proteins usually composed of different domains. For instance, based on sequence analysis, enterolysin A consists of an N-terminal endopeptidase domain and a C-terminal substrate recognition domain similarly to zoocin A (Nilsen et al. 2003; Lai et al. 2002). Zoocin A, a D-alanyl-L-alanine endopeptidase, is one of the best-characterized LAB bacteriolysins (Simmonds et al. 1996). Millericin B is a murein hydrolase. Its production depends on the expression of three genes encoding millericin B precursor (MilB), immunity protein (MilF), and transporter protein (MilT) (Beukes et al. 2000). Similarly, enterolysin A cleaves within the peptidoglycan of target cells between L-alanine and D-glutamic acid of the stem peptide and

between L-lysine of the stem peptide and D-aspartic acid of the interpeptide bridge (Khan et al. 2013). Non-lytic bacteriocins exhibit their bactericidal mode without causing concomitant cell lysis. For instance, dysgalacticin from *S. pyogenes* binds to the glucose- and/or Man-PTS, resulting in the inhibition of the sugar uptake, and also causes a membrane leakage of small molecules (Swe et al. 2009).

Mechanism of Action Bacteriocins

Mechanism of Action Bacteriocins exert their antimicrobial activity by targeting the cell membrane or cell wall of susceptible bacteria. The mode of action of bacteriocins varies depending on their class. Lantibiotics such as nisin bind to lipid II, a precursor of peptidoglycan synthesis, thereby inhibiting cell wall biosynthesis. Pediocin-like bacteriocins such as pediocin PA-1 bind to the mannose phosphotransferase system, resulting in the dissipation of the proton motive force and cell death. Two-peptide bacteriocins such as lactococcin G and enterococcin FS-59 bind to different targets in the cell membrane, resulting in the formation of pores and cell death.

Applications

Bacteriocins have the potential to be used as natural preservatives in food products. LAB-derived bacteriocins have been shown to inhibit the growth of foodborne pathogens such as Listeria monocytogenes, Escherichia coli, and Salmonella enterica. The use of bacteriocins as natural preservatives in food products can reduce the need for synthetic preservatives, which are often associated with health concerns. Furthermore, the use of bacteriocins as natural preservatives can improve the shelf life and safety of food products.

The main product of LAB is lactic acid. Hetero-fermentative lactic acid bacteria produce equimolar amounts of lactic acid, acetic acid/ethanol and carbon dioxide (CO2) during fermentation. The antimicrobial activity of lactic acid at low concentrations is not high, especially at neutral pH. Acetic acid is a stronger inhibitor than lactic acid for bacteria, mold and yeast (Reis et al., 2012). Un-dissociated forms of acids diffuse through the wall of the microbial cell due to their hydrophobic nature and then dissociate inside the pathogen cell. From the mixture of acids produced by LAB, lactic acid mainly reduces intracellular pH and inhibits various metabolic functions, while acetic acid also interferes with cell membrane potential maintenance, inhibits active transport, and damages the cell membrane of pathogens (Ross et al., 2002)

Challenges and Future prospects

Despite the potential applications of bacteriocins in food preservation, there are several challenges associated with their use. One of the main challenges is the limited spectrum of activity of bacteriocins. Bacteriocins produced by LAB are often only active against closely related bacteria, limiting their use in food preservation. Another challenge is the potential for the development of resistance to bacteriocins by target bacteria. Furthermore, the production of bacteriocins by LAB can be expensive and time-consuming, limiting their commercial viability.

Conclusion

Bacteriocins produced by LAB have the potential to be used as natural preservatives in food products. The antimicrobial activity of bacteriocins can inhibit the growth of foodborne pathogens, thereby improving the safety and shelf life of food products. However, there are several challenges associated with the use of bacteriocins, including their limited spectrum of activity, the potential for the development of resistance, and the cost of

production. Further research is needed to overcome these challenges and to fully realize the potential of bacteriocins as natural preservatives in food products.

References

1. Alvarez-Sieiro, Manuel Montalbán-López, Dongdong Mu & Oscar P. Kuipers. Bacteriocins of lactic acid bacteria: extending the family Patricia Applied Microbiology and Biotechnology volume 100, pages2939–2951 (2016)
2. Blinkova L.P., Al'tshuler M.L., Dorofeeva E.S., Gorobest O.B. (2007) Molecular basis of production and action of bacteriocins (In Russian) J. Microbiol. Epidemiol. Immunobiol. 2007; 2:97–104.
3. Cotter, P. D., Ross, R. P., & Hill, C. (2013). Bacteriocins—A viable alternative to antibiotics. Nature Reviews Microbiology, 11(2), 95-105.
4. Cui Y, Zhang C, Wang Y, Shi J, Zhang L, Ding Z, Qu X, Cui H (2012) Class IIa bacteriocins: diversity and new developments. Int J Mol Sci 13:16668–16707. doi:10.3390/ijms131216668
5. De Kwaadsteniet M, Fraser T, Van Reenen CA, Dicks LMT (2006) Bacteriocin T8, a novel class IIa sec-dependent bacteriocin produced by Enterococcus faecium T8, isolated from vaginal secretions of children infected with human immunodeficiency virus. Appl Environ Microbiol 72:4761–4766. doi:10.1128/AEM.00436-06
6. De Vuyst L., Leroy F. (2007) Bacteriocins from lactic acid bacteria: Production, purification and food applications. J. Mol. Microbiol. Biotechnol.; 13:194–199. doi: 10.1159/000104752.
7. Diep DB, Myhre R, Johnsborg O, Aakra A, Nes IF (2003) Inducible bacteriocin production in Lactobacillus is regulated by differential expression of the pln operons and by two antagonizing response regulators, the activity of which is enhanced upon phosphorylation. Mol Microbiol 47:483–494. doi:10.1046/j.1365-2958.2003. 03310.x
8. Diep DB, Skaugen M, Salehian Z, Holo H, Nes IF (2007) Common mechanisms of target cell recognition and immunity for class II bacteriocins. Proc Natl Acad Sci U S A 104:2384–2389. doi:10.1073/pnas.0608775104
9. Dobson A, Cotter PD, Ross RP, Hill C (2012) Bacteriocin production: a probiotic trait? Appl Environ Microbiol 78:1–6. doi:10.1128/AEM.05576-11
10. Drider, D., & Rebuffat, S. (2011). Antimicrobial peptides: discovery, design and novel therapeutic strategies. Advances in microbial physiology, 58, 1-21.
11. Dunbar KL, Melby JO, Mitchell DA (2012) YcaO domains use ATP to activate amide backbones during peptide cyclodehydrations. Nat Chem Biol 8:569–575. doi:10.1038/nchembio.944
12. Egorov N.S., Baranova I.P. (1999) Bacteriocins. Formation, properties, application. Antibiot. Chemother; 6:33–40.
13. Ennahar S, Sonomoto K, Ishizaki A (1999) Class IIa bacteriocins from lactic acid bacteria: antibacterial activity and food preservation. J Biosci Bioeng 87:705–716. doi:10.1016/S1389-1723(99)80142-X
14. Ennahar, S., Sashihara, T., Sonomoto, K., & Ishizaki, A. (2000). Class IIa bacteriocins: biosynthesis, structure and activity. FEMS microbiology reviews, 24(1), 85-106.
15. FAO/WHO (2001) Report on joint FAO/WHO expert consultation on evaluation of health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria.
16. Flühe L, Burghaus O, Wieckowski BM, Giessen TW, Linne U, Marahiel MA (2013) Two [4Fe-4S] clusters containing radical SAM enzyme SkfB catalyze thioether bond formation during the maturation of the sporulation killing factor. J Am Chem Soc 135:959–962. doi:10.1021/ja310542g

17. Franz CMAP, van Belkum MJ, Holzapfel WH, Abriouel H, Gálvez A (2007) Diversity of enterococcal bacteriocins and their grouping in a new classification scheme. FEMS Microbiol Rev 31:293–310. doi:10.1111/j.1574-6976.2007. 00064.x
18. Gabrielsen C, Brede DA, Hernández PE, Nes IF, Diep DB (2012) The maltose ABC transporter in Lactococcus lactis facilitates high-level sensitivity to the circular bacteriocin garvicin ML. Antimicrob Agents Chemother 56:2908–2915. doi:10.1128/AAC.00314-12
19. Gabrielsen C, Brede DA, Nes IF, Diep DB (2014a) Circular bacteriocins: biosynthesis and mode of action. Appl Environ Microbiol 80:6854–6862. doi:10.1128/AEM.02284-14
20. Gabrielsen C, Brede DA, Salehian Z, Nes IF, Diep DB (2014b) Functional genetic analysis of the GarML gene cluster in Lactococcus garvieae DCC43 gives new insights into circular bacteriocin biosynthesis. J Bacteriol 196:911–919. doi:10.1128/JB.01115-13
21. Galvez, A., Abriouel, H., Lopez, R. L., & Omar, N. B. (2007). Bacteriocin-based strategies for food biopreservation. International journal of food microbiology, 120(1-2), 51-70.
22. Garg N, Salazar-Ocampo LM, van der Donk WA (2013) In vitro activity of the nisin dehydratase NisB. Proc Natl Acad Sci U S A 110:7258–7263. doi:10.1073/pnas.1222488110
23. Gargis AS, O'Rourke AL, Sloan GL, Simmonds RS (2009) Prevalence and acquisition of the genes for zoocin A and zoocin A resistance in Streptococcus equi subsp. zooepidemicus. J Mol Evol 68:498–505. doi:10.1007/s00239-009-9221-x
24. Gavrish E, Sit CS, Cao S, Kandror O, Spoering A, Peoples A, Ling L, Fetterman A, Hughes D, Bissell A, Torrey H, Akopian T, Mueller A, Epstein S, Goldberg A, Clardy J, Lewis K (2014) Lassomycin, a ribosomally synthesized cyclic peptide, kills Mycobacterium tuberculosis by targeting the ATP-dependent protease ClpC1P1P2. Chem Biol 21:509–518. doi: 10.1016/j.chembiol.2014.01.014
25. Gong X, Martin-Visscher LA, Nahirney D, Vederas JC, Duszyk M (2009) The circular bacteriocin, carnocyclin A, forms anion-selective channels in lipid bilayers. Biochim Biophys Acta 1788:1797–1803. doi: 10.1016/j.bbamem.2009.05.008
26. Grande MJ, López RL, Abriouel H, Valdivia E, Ben Omar N, Maqueda M, Martínez-Cañamero M, Gálvez A (2007) Treatment of vegetable sauces with enterocin AS-48 alone or in combination with phenolic compounds to inhibit proliferation of Staphylococcus aureus. J Food Prot 70:405–411
27. Guerra NP, Macías CL, Agrasar AT, Castro LP (2005) Development of a bioactive packaging cellophane using nisaplin as biopreservative agent. Lett Appl Microbiol 40:106–110. doi:10.1111/j.1472-765X.2004. 01649.x
28. Hammami R, Fernandez B, Lacroix C, Fliss I (2013) Anti-infective properties of bacteriocins: an update. Cell Mol Life Sci 70:2947–2967. doi:10.1007/s00018-012-1202-3
29. Hasper HE, Kramer NE, Smith JL, Hillman JD, Zachariah C, Kuipers OP, de Kruijff B, Breukink E (2006) An alternative bactericidal mechanism of action for lantibiotic peptides that target lipid II. Science 313:1636–1637. doi:10.1126/science.1129818
30. Hati S., Mandal S., Prajapati J.B. (2013) Novel starters for value added fermented dairy products. Curr. Res. Nutr. Food Sci.; 1:83–91. doi: 10.12944/CRNFSJ.1.1.09.
31. Haugen HS, Kristiansen PE, Fimland G, Nissen-Meyer J (2008) Mutational analysis of the class IIa bacteriocin curvacin A and its orientation in target cell membranes. Appl Environ Microbiol 74:6766–6773. doi:10.1128/AEM.01068-08
32. Heddle JG, Blance SJ, Zamble DB, Hollfelder F, Miller DA, Wentzell LM, Walsh CT, Maxwell A (2001) The antibiotic microcin B17 is a DNA gyrase poison: characterisation of the mode of inhibition. J Mol Biol 307:1223–1234. doi:10.1006/jmbi.2001.4562

33. Hegemann JD, Zimmermann M, Xie X, Marahiel MA (2015) Lasso peptides: an intriguing class of bacterial natural products. Acc Chem Res 48:1909–1919. doi: 10.1021/acs.accounts.5b00156
34. Hillman JD, Brooks TA, Michalek SM, Harmon CC, Snoep JL, Van Der Weijden CC (2000) Construction and characterization of an effector strain of Streptococcus mutans for replacement therapy of dental caries. Infect Immun 68:543–549. doi:10.1128/IAI.68.2.543-549.2000
35. Himeno K, Rosengren KJ, Inoue T, Perez RH, Colgrave ML, Lee HS, Chan LY, Henriques ST, Fujita K, Ishibashi N, Zendo T, Wilaipun P, Nakayama J, Leelawatcharamas V, Jikuya H, Craik DJ, Sonomoto K (2015) Identification, characterization, and three-dimensional structure of the novel circular bacteriocin, enterocin NKR-5-3B, from Enterococcus faecium. Biochemistry 54:4863–4876. doi: 10.1021/acs.biochem.5b00196
36. Holo H, Nilssen O, Nes IF (1991) Lactococcin A, a new bacteriocin from Lactococcus lactis subsp. cremoris: isolation and characterization of the protein and its gene. J Bacteriol 173:3879–3887
37. Hu CB, Malaphan W, Zendo T, Nakayama J, Sonomoto K (2010) Enterocin X, a novel two-peptide bacteriocin from Enterococcus faecium KU-B5, has an antibacterial spectrum entirely different from those of its component peptides. Appl Environ Microbiol 76:4542–4545. doi:10.1128/AEM.02264-09
38. Islam MR, Nishie M, Nagao J, Zendo T, Keller S, Nakayama J, Kohda D, Sahl HG, Sonomoto K (2012) Ring A of nukacin ISK-1: a lipid II-binding motif for type-a(II) lantibiotic. J Am Chem Soc 134:3687–3690. doi:10.1021/ja300007h
39. Juan Carlos Hernández-González, Abigail Martínez-Tapia, Gebim Lazcano-Hernández, Blanca Estela García-Pérez, and Nayeli Shantal Castrejón-Jiménez.(2021) Bacteriocins from Lactic Acid Bacteria. A Powerful Alternative as Antimicrobials, Probiotics, and Immunomodulators in Veterinary Medicine. Animals 11, 979. doi: 10.3390/ani11040979
40. Karpiński T.M., Szkaradkiewicz A.K. (2013) Characteristic of bacteriocines and their application. Pol. J. Microbiol. 2013; 62:223–235. doi: 10.33073/pjm--030.
41. Klaenhammer, T. R. (1993). Genetics of bacteriocins produced by lactic acid bacteria. FEMS microbiology reviews, 12(1-3), 39-85.
42. Liu W., Pang H., Zhang H., Cai Y. (2014) Biodiversity of Lactic Acid Bacteria. In: J.B. Metzler, editor. Lactic Acid Bacteria. Springer; Berlin/Heidelberg, Germany: pp. 103–203
43. Lohans, C. T., & Vederas, J. C. (2012). Development of class IIa bacteriocins as therapeutic agents. International journal of microbiology, 2012.
44. Mokoena M.P. (2017) Lactic Acid Bacteria and Their Bacteriocins: Classification, Biosynthesis and Applications against Uropathogens: A Mini-Review. Molecules.;22:1255. doi: 10.3390/molecules22081255.
45. Montville, T. J., & Chen, Y. (1998). Mechanistic action of pediocin and nisin: recent progress and unresolved questions. Applied microbiology and biotechnology, 50(5), 511-519.
46. Nes, I. F., Diep, D. B., & Holo, H. (2007). Bacteriocin diversity in Streptococcus and Enterococcus. Journal of bacteriology, 189(4), 1189-1198.
47. Riley M.A., Wertz J.E. (2021) Bacteriocins: Evolution, Ecology & application. Annu. Rev. Microbiol.;56:117–137. doi: 10.1146/annurev.micro.56.012302.16102
48. Riley, M. A., & Wertz, J. E. (2002). Bacteriocins: evolution, ecology, and application. Annual review of microbiology, 56(1), 117-137.
49. Sánchez, J., Basanta, A., & Gálvez, A. (2015). Bacteriocins as promising anticancer agents. Current protein & peptide science, 16(8), 668-676.

50. Van Geel-Schuttená G.H., Flesch F., ten Brink B., Smith M.R., Dijkhuizen L. (1998) Screening and characterization of Lactobacillus strains producing large amounts of exopolysaccharides. Appl. Microbiol. Biotechnol.;50:697–703. doi: 10.1007/s002530051353.
51. Zendo T. (2013) Screening and characterization of novel bacteriocins from lactic acid bacteria. Biosci. Biotechnol. Biochem.;77:893–899. doi: 10.1271/bbb.130014.
52. Zheng J., Gänzle M.G., Lin X.B., Ruan L., Sun M. (2014) Diversity and Dynamics of Bacteriocins from Human Microbiome. Environ. Microbiol.; 17:2133–2143. doi: 10.1111/1462-2920.12662.
53. Zimina M., Babich O., Prosekov A., Sukhikh S., Ivanova S., Shevchenko M., Noskova S. (2020) Overview of Global Trends in Classification, Methods of Preparation and Application of Bacteriocins. Antibiotics.;9:553. doi: 10.3390/antibiotics9090553