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Bacteriocins of Lactic Acid Bacteria as Potent Antimicrobial Peptides against Food Pathogens

Parveen Kaur Sidhu and Kiran Nehra

Abstract

An ever-growing demand for food products with minimal chemical additives has generated a necessity for exploring new alternatives for food preservation. In this context, more recently, bacteriocins, the peptides having antimicrobial property, synthesized ribosomally by numerous bacteria have been attracting a lot of attention. They are known to possess the potential to restrict the growth of microorganisms causing food spoilage without causing any harm to the bacteria themselves owing to the presence of self-defensive proteins. In particular, the bacteriocins of lactic acid bacteria have been considered harmless and safe for consumption and are indicated to evade the development of unwanted bacteria. Use of bacteriocins as biopreservatives has been studied in various food industries, and they have been established to elevate the shelf life of minimally processed food items by exerting killing mechanism. They restrict the growth of undesirable bacteria by breaking the target cell membrane and finally resulting into pore formation. The current article provides an insight on bacteriocins of lactic acid bacteria, their biosynthesis, mechanism of action, and promising applications of these antimicrobial peptides in the food sector.

Keywords: antimicrobial peptides, bacteriocins, food-preservatives, food spoiling pathogens, lactic acid bacteria

1. Introduction

Most of the commercially available food preservatives are synthesized chemically, causing a lot of toxic effect on human health. The increase in the consumption of packed food which require preservatives for long-term storage has created a need for the production of minimally processed food free of any chemical additives. The present-day food industry is therefore looking for natural substitutes that have no adverse effect on consumers and on the surroundings to replace the existing chemical preservatives. Lactic acid bacteria (LAB) have been known since ages for their use in traditional fermented foodstuff owing to their capability to bring enviable changes in flavor, taste and for inhibiting food spoiling pathogenic microorganisms, thus making them an attractive natural biopreservative [1]. LAB are in general considered to be food grade microorganisms and assumed to be secure for human consumption as they get degraded when they come in contact with human gut by the action of proteases; hence, also contemplated as generally regarded as safe (GRAS)

organisms. These are known to show preservative effect owing to their capability to produce hydrogen peroxide, organic acids, diacyls, and bacteriocins. Among all these, the antimicrobial compounds, bacteriocins, have received a greater attention as natural preservatives because nearly all of them are heat tolerant up to a particular temperature range and are amenable to proteolytic inactivation [1].

The bacteriocins are known to be produced by both positively and negatively Gram stained bacteria, however, the highest number of bacteriocins studied and identified are reported to be the antimicrobial peptides of Gram positive bacteria. A freely available database, BACTIBASE, which is totally dedicated to bacteriocins, consists of almost 177 sequences of bacteriocins out of which 156 belong to Gram positive bacterial strains, and the remaining 18 belong to Gram negative [2]. Production of bacteriocin depends on their genetic determinants; genes for bacteriocin production are reported to be localized either on plasmid or chromosomes [3]. These antibacterial peptides are synthesized on ribosomes and are known to show a bactericidal activity against identical or approximately related species [1]. Bacteriocins confer their bactericidal mode of action by creating a pore in the target cell, thus helping in combating the food pathogens.

2. Bacteriocins: antimicrobial peptide derivatives of lactic acid bacteria

During exponential growth, a huge number of both Gram positive and Gram negative bacteria produce peptides with antimicrobial activities. A universal term “bacteriocin” is used for these protein-like substances with bactericidal activity restricted to related species [4]. However, bacteriocins derived from Gram positive bacteria possess a moderately broader spectrum of antimicrobial activity. These proteinaceous compounds are degraded in the gastrointestinal tract of humans by protease digestion; hence, they become inactive in the human gut and do not pose any harmful effect. Production of bacteriocins is considered as an advantage by the food producers as they are efficient in killing or restricting pathogenic bacteria that struggle for the same habitat in a sufficient amount [5, 6].

Although several bacterial species produce bacteriocins, but LAB group of bacteria include some of the most important genera responsible for an elevated amount of bacteriocin production effective in the food industry [7]. LAB are considered as a heterogeneous cluster of Gram positive, non-aerobic but aero-tolerant, non-sporulating, catalase-negative, acid-tolerant, bacteria having low GC-content, which produce lactic acid by fermentation of sugars. They are recognized to be obtained from an array of different sources, for instance, meat, milk products, vegetables [6], grains, plants [8, 9] mucosal surface of animals, beverages, and from various fermented foods [10, 11]. LAB produce various metabolic products with antimicrobial properties, but current research is more focused on the production of bacteriocins which are toxic proteinaceous compounds and are known to exhibit a strong bactericidal activity against closely-related species; even small doses of bacteriocins are reported to be highly efficient in eradicating food spoiling bacteria [12–14].

2.1 Bacteriocins: classification

Bacteriocins produced from LAB were earlier categorized in four general classes on account of their characteristics by Klaenhammer et al. [12]. However, a more recent modified scheme of classification of LAB has been formulated by Alvarez-Sieiro et al. [13] which is now more acceptable (**Figure 1**). It includes only three major classes: Class I which includes lantibiotics, Class II which includes non-lantibiotics and class III which are basically large peptides (**Table 1**).

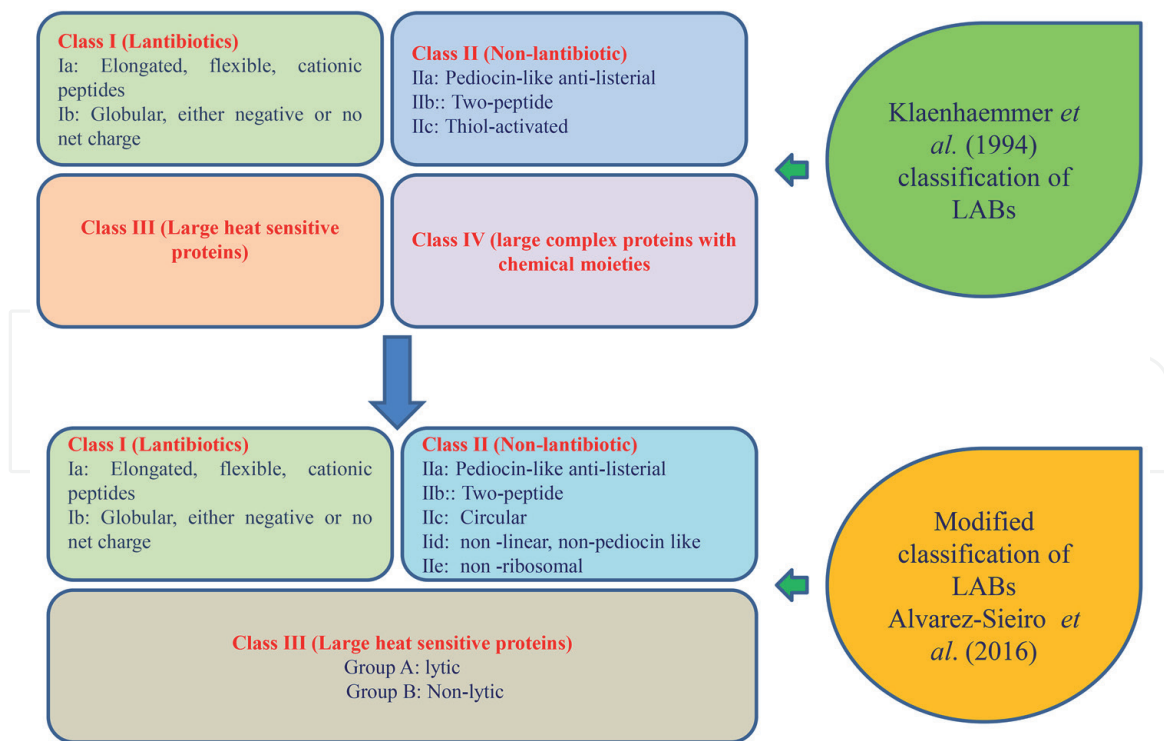


Figure 1.
 Classification of bacteriocins produced by lactic acid bacteria.

Among all the three classes discussed in **Table 1**, the bacteriocins of class I and II have caught the attention of researchers; since these are more abundant and have been reported to have potential industrial applications including application in the food sector [15]. However, till date, only Nisin (class I) and Pedicon PA-1 (class II) are marketed commercially as a food additive. Nisin (marketed as Nispalin) is commercially approved to be used as a preservative in many food items in almost 50 countries in the world and Pediocin PA-1 (commercialized as Alto®2341) is authorized for its use in meat products [4].

2.1.1 Important commercialized bacteriocins: nisin and pediocin

Nisin is a 34 amino acid polypeptide having a molecular mass of 3354 Daltons. Synthesis of nisin is intricate, involving transcription, followed by post-translational modifications, secretion and final processing. It is synthesized as a pro-pre-peptide of 57 amino acid residues, where few residues located at terminal end function as the amino-terminal signal sequence of nisin molecule [1]. The other end of the nisin (carboxyl-terminal region of 34 residues) contains threonine, serine, and cysteine which are involved in the generation of reformed amino acids such as lanthionine, methyllanthionine, dehydroalanine and dehydrobutyrine, which are present in fully matured nisin [1] (**Figure 2a**). Nisin generally occurs in the form of a dimer (7 kDa), but may be present as a tetramer (14 kDa) at times. Nisin has two variants namely, nisin A and nisin Z. The difference between these two variants is because of a difference of one amino acid residue at the 27th position, histidine and asparagine being the 27th amino acid for nisin A and nisin Z, respectively. Nisin is predominantly used in dairy products and in canned food, and is particularly efficient when used in the production of cheese, restricting the growth of heat-tolerant sporulating strains [19]. It is also reported to be effective against mastitis-causing Gram positive organisms [20]. *Lactococci*, producer of nisin occur naturally in cheese and raw milk. Apart from

Class	Subclass	Characteristic features	Major representatives	References
I (Lantibiotics)	Small, heat-tolerant, and post-translationally modified peptides.		Nisin A, Enterocin W	[6, 15]
	Ia	Elongated, flexible, cationic peptides that generally perform their activity via pore formation and disruption of cell membrane.		
	Ib	Normally compact, with globular structures, either having negative charge or no net charge. These are enzyme inhibitors, immunologically active and act by interrupting the essential enzymatic reactions in the target species.		
II (Non-lantibiotics)	Heat-resistant antimicrobial peptides, devoid of any modified amino acid residues.		Pediocin PA-1/Ach Sakacin A Carnobacteriocin X	[13, 16, 17]
	IIa	Pediocin-like, active against <i>Listeria</i> spp., also known as listeria-active peptides.		
	IIb	It consists of complex of two different inactive peptides, activated by complex formation of these two inactive peptides.		
	IIc	Mostly circular peptides, N-terminal and C-terminal covalently linked to each other to form stable structure.		
	II d	Non-pediocin, one-peptide, non-linear, sec-dependent bacteriocins.		
	IIe	Non-ribosomal having post-translational modifications at serine-rich C-terminal region.		
III	Large in size, heat-sensitive, usually multi-domain with catalytic properties and have domain-type structure. Different domains in their domain structure function in different manner: i. binding to the receptor, ii. translocation, and iii. antimicrobial activity.		Enterolysin A	[13, 18]
	Group A	lytic enzymes that act by causing cell wall lysis.		
	Group B	Non-lytic proteins.		
			Caseicin 80	

Table 1.
Classification of bacteriocin produced by lactic acid bacteria.

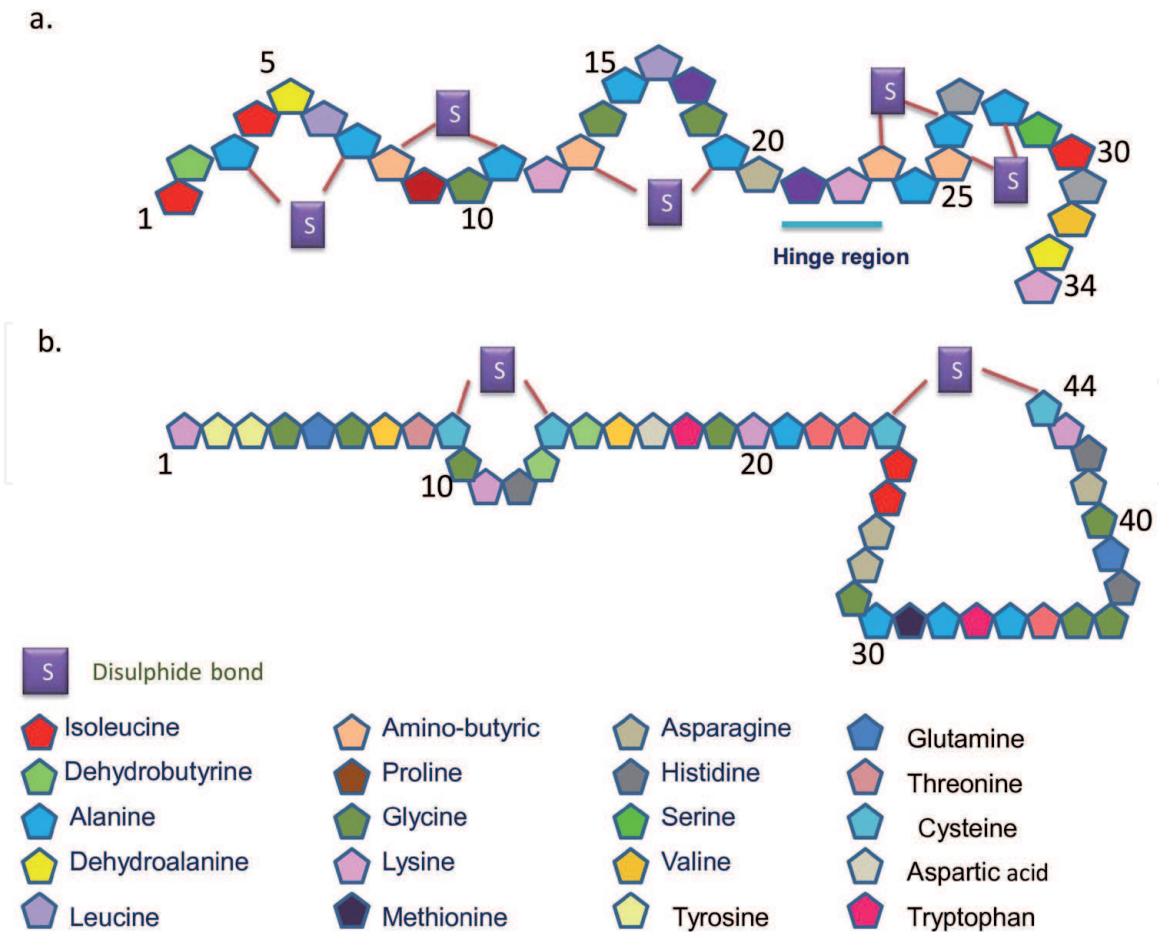


Figure 2.
 Structure of (a) Nisin, showing the existence of post-translationally modified amino acids and (b) Pediocin PA-1.

nisin, other bacteriocins produced from genus *Lactococcus* are also of economic importance. Lacticin 3147 is an example of bacteriocin derived from *Lactococcus spp.* which works efficiently in a broad array of pH and comprises a wide antimicrobial action spectrum over Gram positive bacteria [5].

In contrast, Pediocin PA-1 is derived from the genus *Pediococcus* which is naturally found in many plant sources [8]. Strains of *Pediococcus* have been used since a long time as inoculum for the manufacture of fermented foods of natural sources [19]. Pediocin PA-1 shows an inhibitory response against few Gram positive bacteria but is reported to show strong antimicrobial activity against *Listeria monocytogenes* which is one of the chief food spoiling bacteria [4]. Pediocin PA-1 comprises of 44 amino acids with no post-translational modifications and has a molecular weight is 4646.95 Daltons (**Figure 2b**). The genes responsible for pediocin PA-1 biosynthesis are positioned on a 3.5 kb DNA segment of plasmid, and comprise four genes; (i) pedA (ii) pedB (iii) pedC and, (iv) pedD.

Although, nisin is approved by the Food and Drug Administration (FDA) for use as a food preservative, its use is limited to acidic foods only, because of its low solubility and constancy at high and neutral pH. This was the major reason for the search for bacteriocins from other species which led to the discovery of bacteriocins from *Pediococcus* species [21]. These bacteriocins are more effectual than nisin in inhibiting food spoiling pathogens, but their antibacterial spectrum is not as broad as nisin [22, 23]. Thus, although both nisin and pediocin play a significant role as a biological preservative in the food processing industry, their glaring limitations have caused the rise of research on bacteriocins from other classes as well.

3. Bacteriocins: genetics and biosynthesis

Bacteriocins produced from LAB are synthesized by genes encoded by either chromosomes or plasmids. For example, Plantaricin 423 [24] is plasmid encoded, while genes for enterocin A, sakacin P, divercin V41 and carnobacteriocin B2 and BM1 [25, 26] are localized on bacterial chromosomes. Plasmids concerned with the production of bacteriocins differ significantly in size. Some of them have been identified to carry the genetic determinants for numerous bacteriocins [3, 27].

3.1 Genetic constitution of bacteriocin operons

The genes accountable for synthesis of bacteriocin are often localized in single or multiple operons and are individually transcribed [28]. Most commonly, two types of genes are involved in production of bacteriocins: (i) structural genes and (ii) genes which encode for immunity protein. However, in some cases, apart from these two genes, other specific export machinery and regulatory genes are also required, thus making the bacteriocin operon much more intricate [29, 30].

3.1.1 Class I bacteriocin operon

Class I bacteriocin operon can be localized either on the bacterial chromosome or the plasmid. Few examples of lantibiotics with plasmid genetic determinants include: lactacin 481 [31] encoded by genes localized on 70 kb plasmid and the two-component lactacin 3147 [32] encoded on 63 kb plasmid, both of which are produced by *Lactobacillus lactis*. Class I bacteriocins are considered to be more complex than class II non-lantibiotics as they require supplementary enzyme encoding genes for post-translational modifications. The biosynthesis of lantibiotics involves the translation of pre-peptide which undergoes few modifications, and then the modified pre-peptide moves onto the other side of the membrane, and the amino-terminal signal peptide is cleaved via proteolytic enzymes present in the cytoplasm. The best described lantibiotic is nisin, whose genetic determinants are reported to be localized on conjugative transposon Tn5276 contained by the bacterial chromosomes. Genes which aid in nisin production and immunity are transferred conjugally and it is reported to be situated in a nucleotide segment of size 8.5 kb. The gene cluster of nisin is designated as nisABTCIPRKFEG, and contains eleven genes which include structural genes, immunity protein encoding self-defensive genes, transporter genes and response regulator genes [3, 30]. Biosynthesis of nisin involves following steps: (a) firstly nisin A undergoes translation to form pre nisin A (b) The partially formed nisin A is then changed to form precursor nisin A via the proteins encoded by both nisB and nisC and (c) lastly, the precursor nisin is transported extracellularly by the nisT and nisP gene products by cleaving the leader peptide at the same time to obtain the end product, Nisin A (**Figure 3a**) [3, 33].

3.1.2 Class II bacteriocin operon

The genes encoding for structural proteins of class II bacteriocins are mostly localized on plasmids, for example, pediocin PA-1 and pediocin AcH [4] extracted from *Pediococcus acidilactici* strains. Bacteriocins belonging to class II usually require 2 to 8 genes for their production. The genes concerned with their production, secretion and immunity are: structural gene, immunity gene, ATP-binding cassette (ABC) protein encoding genes and its accessory proteins. Pediocin AcH, the bacteriocin representing class IIa is organized in a gene segment of 3500 bp

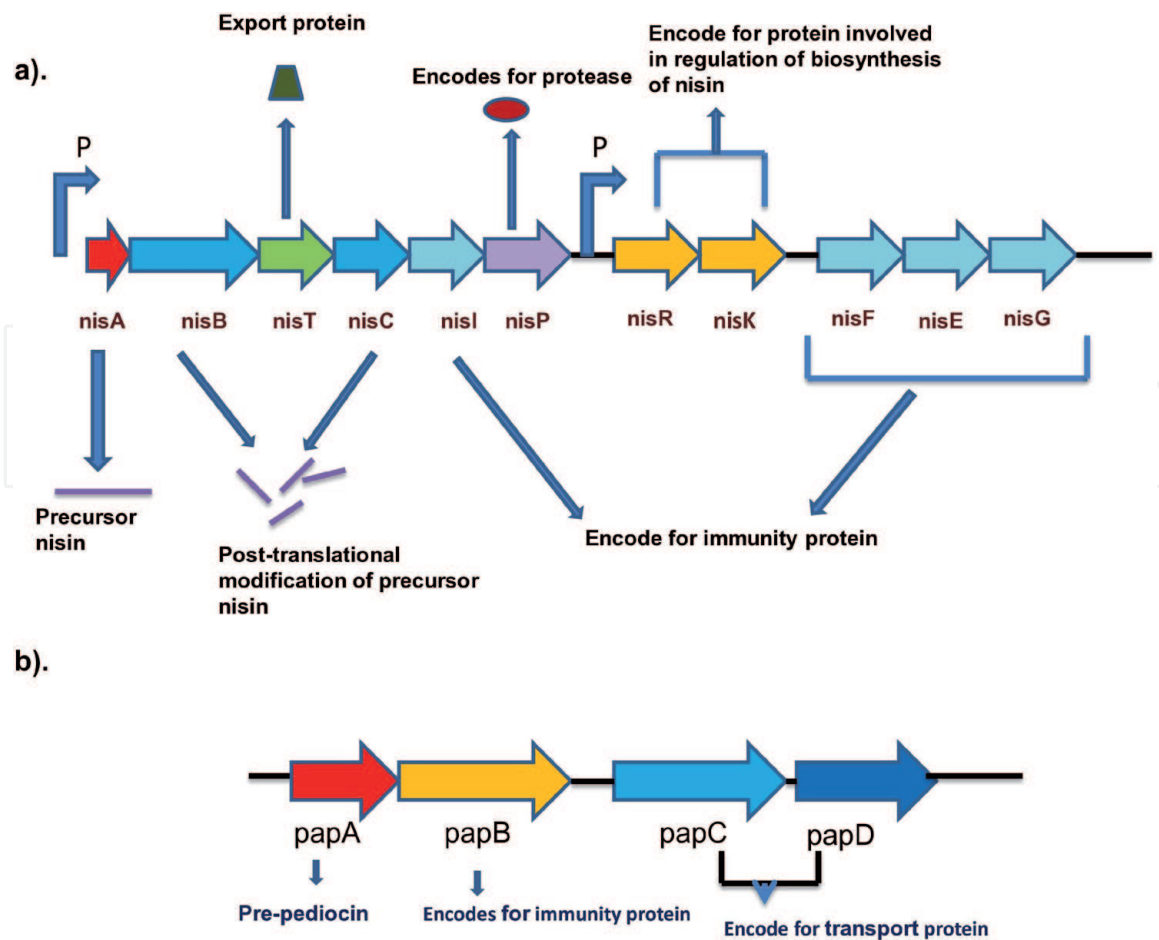


Figure 3. Schematic structure of genes concerned with the synthesis of bacteriocins. (a) Nisin operon (b) Pediocin AcH operon. P: Promoter region.

having four genes designated as (i) *papA*, (ii) *papB*, (iii) *papC* and (iv) *papD* [3] (Figure 3b).

The genes involved in synthesis generally produce inactive pre-pro peptide having an amino-terminal leader peptide [29, 34]. The gene which imparts immunity is transcribed in parallel, along with the bacteriocin precursor. The ABC transporter and its accessory proteins which aid in the export of bacteriocins are encoded by a group of genes typically localized on operon present in closer proximity to immunity genes [3, 12, 29]. The leader peptide sequence of nearly all the bacteriocins of class IIa is of double glycine-type (GG-type), though, several of them have also been found to possess a sec-type amino-terminal signal sequence, for example, bacteriocin 31, listeriolysin 743A, and enterocin P [35]. These bacteriocins are understood to be released out by sec-dependent exporting system. The ABC transporters are assumed to aid in the recognition of GG-type leader peptides [29]. ABC transporters during transmembrane translocation consequently remove the GG-leader sequence and the fully active bacteriocin is afterwards secreted. Class IIa bacteriocin can be expressed heterologously through another secretion system by exchanging the leader peptide [29].

3.2 Biosynthesis of bacteriocins

Bacteriocins or antimicrobial peptides are primarily biosynthesized as pre-peptides which are biologically non-active, having amino-terminal signaling peptide which remains linked to carboxyl-terminal pro-peptide [13, 36]. This pre-pro-peptide is encoded by the structural genes. The pre-peptide is directed towards the maturation

and transportation of the protein by the signal peptide which behaves as recognition spot and keeps the producing strain protected by being in an inactive state within the bacterial cells. Additionally, the signal peptide interacts with pro-peptide domain to make sure that it is in the proper state for further interface with modification machinery [24, 32]. The structural genes play an important role in bacteriocin biosynthesis and are generally succeeded by the immunity genes.

To defend the bacteriocin producing strains from the killing action of their self- bacteriocins, a self-defensive system known as immunity has been evolved by these bacteria. The protection from bacteriocins is gained via production of specific immunity proteins via immunity genes. These genes encoding immunity protein lie closer to the structural and accessory genes of bacteriocins [19]. Dissimilarity in expression and presence of these genes accounts for huge disparity in sensitivity demonstrated by LAB for bacteriocins. The size of immunity proteins lie in the range of 51 to 150 amino acids. An immunity gene encodes the immunity protein which lies downstream to the structural protein coding genes usually in the same operon. In the bacterial cell, transcription of both the bacteriocins and their immunity genes are regulated in parallel as defensive system can be stopped concurrently. Immunity of LAB depends on the definite immunity protein, Lan I [19], which basically remains bound to the exterior side of the plasma membrane. It grants protection to the producer strains by shutting off the membrane pores formed by the bacteriocin molecules and transferring them to the neighboring medium, hence, regulating the amount of bacteriocin present on the cell surface upto a critical level.

Bacteriocins are transported extracellularly with the aid of transporter proteins, which are basically from ABC transporter family. In prokaryotic and eukaryotic organisms, ABC transporters assist in the oozing of an ample range of products. These transporters include (i) bacterial importers, which aid in transportation of vitamins, oligopeptides, sugar, phosphate, amino acids and metallic ions, (ii) eukaryotic exporters, which enable the transportation of lipotropic drugs, pigments and peptides, and (iii) bacterial exporters, which carry large toxic protein, polysaccharides, heme molecules, and high and low molecular weight antibiotics [34]. The bacteriocin ABC transporters facilitate the exclusion of substrate from the signal peptide and its transportation across the cytoplasmic membrane hence, performing dual functions. This aids in effectively preventing the active and fully formed bacteriocins from enduring inside the cytoplasm.

The bacteriocin synthesis is regulated via multi-component regulatory system that involves (i) a signal peptide (ii) a cell surface bound receptor to which signal peptide binds and (iii) a response regulator. The signal peptide binds with histidine-kinase receptor and the binding leads to phosphorylation, signaling surge that finally targets the phosphate residue towards the response regulator that then induces the gene expression and production of bacteriocins by binding with the promoter region [34].

4. Bacteriocins: mode of action

Bacteriocins are recognized for restraining the growth of pathogenic microorganisms by forming pores in the cell envelope, and are known to be highly effective against Gram positive bacteria. Their activity against Gram negative bacteria is reported to be very less because of the outer wall of bacteria, which might possibly block the site of bacteriocin action [37]. Bacteriocins are proposed to exert their inhibitory effect using different mechanisms which include (i) a change in enzymatic activity (ii) restricting spore germination (iii) anionic carrier inactivation and (iv) with the aid of selective and non-selective pore formation in cell

membrane [14, 37]. However, most of the bacteriocins follow the fourth model and act by targeting the cell envelope.

The primary interface connecting the bacteriocins and the target cell membrane involves either of the following two mechanisms: (a) attachment of bacteriocin to the membrane bound receptor molecule and/or (b) interface amidst the positively charged amino acids of bacteriocins and negatively charged phospholipid molecules on the cell membrane [29, 38]. In the first mechanism, the bacteriocins often need a receptor molecule on the surface of the target organism which varies among different species and sub-species [39]. The second mechanism involves three basic steps for the bactericidal action: binding, insertion and pore formation. In the binding and insertion step, when the bacteriocins come in contact with the target membrane, their C-terminal consisting of hydrophobic amino acids penetrates the hydrophobic region of the bacterial membrane and binds with the mannose phosphotransferase permease which ultimately leads to the leakage of the membrane. The interactions among phospholipids (negatively charged) in the target cell membrane and groups of amino acids (positively charged) in the bacteriocin are chiefly involved in the binding and insertion step. The bacteriocin finally creates pore in the target cell and allows the outflow of rather large molecules. Formation of pores eventually leads to the ionic imbalance, disturbing nucleic acid content and leakage of inorganic phosphates [19, 40]. The preliminary interruptions stimulate the dispersion of the proton motive force (PMF) that ultimately leads to the disturbance of pH and transmembrane potential of the cell. But this mode of action does not work for negatively stained bacteria as their bacterial membrane consists of lipopolysaccharide as an outer membrane which differs from Gram positive bacteria. Some researchers have reported that when bacteriocins are combined with compounds that have the capability to disrupt the outer membrane such as surfactants like Triton X-100 or EDTA, they can be rendered active against Gram negative bacteria [5].

Formation of pore in the cell membrane induced by the bacteriocins has been expected to take place by three models [38]: (i) a wedge-like model (ii) a barrel-stave like model and (iii) carpet model. A wedge-like model involves insertion of nisin and lipids via proton motive force. In barrel-stave like model, upon insertion in the membranes, bacteriocins arrange themselves to make a bunch of α helical peptides. The interior wall of the pore is formed by the inner hydrophilic faces of these peptides and the outer hydrophobic surface faces the membrane lipids. On the other hand, in carpet model, the pore is induced by peptides. In this model, an individual peptide might get assembled analogous to the cell surface and hinders the bilipid organization of the cell membrane and hence results in transient permeability due to strong phospholipid mobilizing activity [41]. For the induction of pore formation, class I bacteriocins are thought to act by means of wedge-like model, while in bacteriocins belonging to class II, pore formation may be either permitted via barrel-stave like model, or the carpet model [38]. Pore formation in class IIa bacteriocins is induced through barrel-stave like model probably because of the putative transmembrane helices in the peptide structure of these bacteriocin molecules (**Table 2**) [5, 29].

4.1 Bactericidal mode of class I bacteriocins

Bacteriocins belonging to class I are known to act by dual killing mechanisms, both of which have the same end results. Nisin is most researched antimicrobial peptide of this class. It exerts the bactericidal mode of action since it can diffuse easily through the anionic lipid membrane. It causes pore formation in the target membrane by coming in contact with the lipid II; a peptidoglycan precursor. The

Bacteriocin	Producing strain	Protein sequence	Killing mechanism
<i>Class I bacteriocins</i>			
Nisin	<i>Lactococcus lactis</i> subsp. <i>Lactis</i>	(40 amino acids) ITSISLCTPG CKTGALMGCN MKTATCHCSI HVSK	Dual killing mechanism leading to cell death.
Lacticin 481	<i>Lactococcus lactis</i>	(30 amino acids) KGGSGVIHTI SHECNMNSWQ FVFTCCS	Inhibits peptidoglycan formation.
Lacticin 3147	<i>Lactococcus lactis</i> subsp. <i>lactis</i>	(30 amino acids) TTPATPAISI LSAYISTNTC PTTKCTRAC	Interaction with the cell membrane leads to the pore formation even at minimal concentrations.
Lactocin-S	<i>Lactobacillus sakei</i> L45	(40 amino acids) STPVLASVAV SMELLPTASV LYSDVAGCFK YSAKHHC	Form transmembrane pores in the target bacterial cytoplasmic membrane.
Plantaricin A	<i>Lactobacillus plantarum</i>	(30 amino acids) AYSLQMGATA IKQVKKLFKK WGW	Pore formation by barrel stave model.
Acidocin J1132 β	<i>Lactobacillus acidophilus</i>	(30 amino acids) GNPKVAHCAS QIGRSTAWGA VSGA	Form cell membrane channel by barrel stave mechanism.
<i>Class II bacteriocins</i>			
Plantaricin J	<i>Lactobacillus plantarum</i>	(30 amino acids) GAWKNFWSSL RKGFDGEAG RAIRR	Membrane leakage and cell death.
Acidocin 8912	<i>Lactobacillus acidophilus</i>	(30 amino acids) KTHYPTNAWK SLWKGFWESL RYTDGF	Causes scattering of proton motive force and by pore formation.
Bavaricin-A	<i>Lactobacillus sakei</i>	(50 amino acids) KYYGNGVHXG KHSXTVDWGT AIGNIGNNAA ANXATGXNAG G	Show killing action and inhibit the growth of <i>Listeria monocytogenes</i>
Pediocin PA-1	<i>Pediococcus acidilactici</i>	(50 amino acids) KYYGNGVTCG KHSCSVDWVK ATTCIINNGA MAWATGGHQG NHKC	Pore formation (effective inhibitor of <i>Listeria monocytogenes</i>)

Bacteriocin	Producing strain	Protein sequence	Killing mechanism
Enterolisin A	<i>Enterococcus faecalis</i>	(340 amino acids) MKNILLSILG VLSIVVSLAF SSYSVNAASN EWSWPLGKPY AGRYEEGQQF GNTAFNRGGT YFHDGFDFGS AIYGNQSVYA VHDGKILYAG WDPVGGGSLG AFIVLQAGNT NVIYQEFSRN VGDIKVSTGQ TVKKGQLIGK FTSSHLHLGM TKKEWRSASHS SWNKDDGTWF NPIPILQGGG TPTPPNPGPK NFFTNNVRYGL RVLGGSWLPE VTNFNNTNDG FAGYPNRQHD MLYIKVDKGQ MKYRVHTAQS GWL PWVSKGD KSDTVNGAAG MPGQAIDGVQ LNYITPKGEK LSQAYYRSQT TKRSGWLKVS ADNGSIPGLD SYAGIFGEPL DRLQIGISQS NPF	Cell wall degrading enzyme shows bacteriolytic mode of action.
<i>Class III bacteriocins</i>			
Helveticin J	<i>Lactobacillus helveticus</i>	(330 amino acids) MKHLNETTNV RILSQFDMDT GYQAVVQKGN VGSKYVYGLQ LRGKATTILR GYRSGKINNP ILELSGQAGG HTQTWEFAGD RKDINGEERA GQWFIGVKPS KIEGSKIIWA KQIARVDLRN QMGPHYSNTD FPRLSYLNRA GSNPFAGNKM THAEA AVSPD YTKFLIATVE NNCIGHFTIY NLDTINEKLD EKGNSDEVNL ETVKYEDSFI IDNLYGDDNN SIVNSIQGYD LDNDGNIYIS SQKAPDFDGS YYAHHKQIVK IPYYARSKES EDQWRAVNLS EFGGLDIPGK HSEVESIQII GENHCYLTVA YHSKNKAGEN KTTLNEIYEL SWN	Generally show bactericidal mode of action.

Table 2. General overview of few important bacteriocins belonging to Lactic acid bacteria, their protein sequence and killing mechanism (Data obtained from BACTIBASE database of bacteriocins [<http://bactibase.hamamilab.org>]).

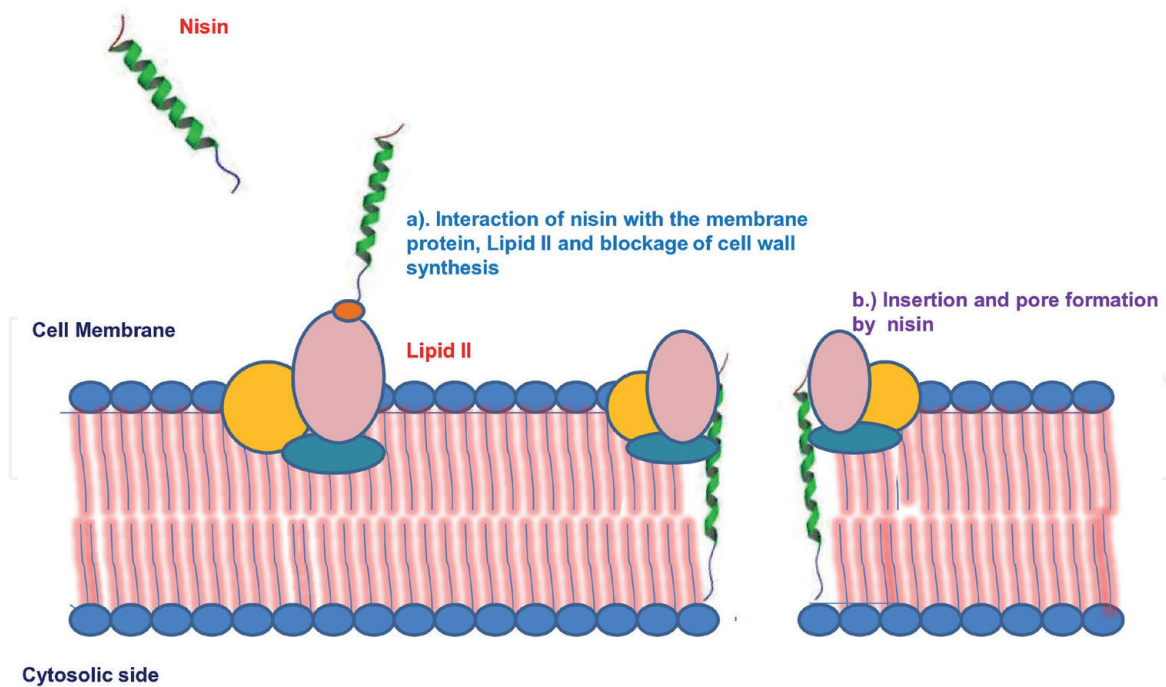


Figure 4. Two-way killing mechanism of class I bacteriocins. (a) Nisin forms complex with the lipid II molecule and halts the synthesis of cell wall. (b) In second mechanism, nisin forms complex with lipid II molecules and initiates formation of pore, ultimately leading to cell death.

existence of lipid II increases nisin activity thereby causing membrane depolarization, disruption of bilayer organization and outflow of limited metabolites like, ions, nucleotides and amino acids, hence halting all the biosynthetic pathways and causing cell death [41]. Nisin is very effective against its target strain and has been reported to show antimicrobial activity even at nanomolar concentrations. When present in lower concentration, nisin gets attached to lipid II molecule and halts cell wall formation by enzyme activity which causes cell death. Furthermore, when nisin is present in higher amount, the nisin- lipid II complex causes sudden cell death by inducing pores in the cell membrane of bacteria (**Figure 4**). Hence, this complex assists in two modes of killing, involving both blockage of cell wall synthesis, and formation of pores (**Figure 4**).

4.2 Bactericidal mechanism of class II bacteriocins

Bacteriocins of class II (non-lantibiotics) show a killing action against related organisms and cause depolarization and cell death by easy insertion into the cell membrane due to their amphiphilic nature. These bacteriocins are capable of disturbing the pH gradient and transmembrane potential of cells which results in scattering of proton motive force; it is reported that this dispersal of proton motive force is believed to be their key action for exerting the fatal activity [42, 43]. The killing mechanism of class II bacteriocins varies among subclasses (**Table 3**) [39]. Class II_d and class II_e mechanisms are still under study and are poorly understood till now.

5. Potential applications of bacteriocins in food sector

Bacteriocins produced by LAB have promising applications in the health, pharmaceutical and food sector. However, this section basically reviews the applications of bacteriocins in food safety. Currently, in food industries, bacteriocins are

S.No.	Subclass	Killing mechanism	References
1.	IIa	<ul style="list-style-type: none"> i. These bacteriocins are highly potent against <i>L.monocytogenes</i>. ii. They act by binding to the mannose phosphotransferase system proteins which are present in the non-polar core of the cell membrane. iii. The conserved amino-terminus and carboxyl-terminus region is accountable for the inhibitory activity against <i>L.monocytogenes</i> and few other desired organisms. 	[28, 42]
2.	IIb	<ul style="list-style-type: none"> i. They are found to exert their killing effect against target organisms only when both the peptides show synergistic activity. ii. Killing mechanism of this subclass involves permeabilization of the target membrane which causes leakage of small cytoplasmic molecules. iii. They create comparatively small and specific pores than bacteriocins of class IIa. 	[44]
3.	IIc	<ul style="list-style-type: none"> i. They show wide antimicrobial spectrum against food pathogens. ii. They act similar to the other bacteriocins in case of mode of action towards target organism, i.e, by causing membrane permeabilization, efflux of ions and leading to cell death. 	[45]

Table 3.
Tabulated overview of Killing mechanism of subclass of class II bacteriocins.

extensively used as biological preservatives. Both Gram positive and Gram negative bacteria are efficient in producing the bacteriocins, but those originating from LAB have a greater importance in the food sector [46]. Bacteriocins produced by LAB apart from being regarded as safe also have QPS (qualified presumption of safety) status, and show deleterious effects against food pathogens even in nanomolar range [47, 48].

Bacteriocins are known to have potential preservative properties either when used alone or when combined with other preservation methods in the form of hurdle technology [4, 30, 36]. Bacteriocins as natural preservatives offer following advantages: (a) extended shelf life of food, (b) protection from economic loss due to food spoilage, (c) preservation of the nutrients and vitamins of food and thus maintenance of the flavor and taste of food (d) satisfaction of consumer demands and (e) stability at variable temperatures and heat. Although, the use of purified form of bacteriocin is the usually applied approach, however, the direct addition of LAB has also been found to be effective [36]. The bacteriocins can be applied by at least three different ways to advance the safety and quality of food, (i) by addition of purified or partially purified preparation of bacteriocins in food items, (ii) by addition of the product formerly fermented with a producer strain [19].

One of the essential applications of bacteriocin is bioactive packaging which protects the food from exterior contaminants. Bioactive packaging generally involves the assimilation of producer strains into the packaging substance that is expected to directly interact with food, thereby, helping to improve the storage life and food safety by restricting the growth of food spoiling organisms, mainly in meat and cheese [49]. The interaction of food surface with the packaging film allows easy diffusion of bacteriocins into the food making this method advantageous over drop-wise addition and sprinkling of bacteriocins on food material; as in the latter cases, the food components may hinder the antibacterial activity of bacteriocins [50–53]. Antimicrobial packaging films are able to be developed by straight-away inclusion of the antimicrobial peptide in the packaging of foodstuff, or by an addition of a packet having bacteriocin in the ready-to-eat packed food, which would be later released in the food product during storage period. Research on nisin coated packaging is increasingly being encouraged since the past few years. Neetoo et al. [54] studied the use of nisin-coated synthetic films on vacuum-packed cold-smoked salmon, and observed that the coating when carried out at a specific storage temperature resulted into a remarkable decrement in the survival rate of *L. monocytogenes*. This method is considered to be better than other methods of bacteriocin application as discussed before the bacteriocins can be deactivated, lose its activity by coming directly in contact with food components [55].

Bacteriocins of LAB are normally found to be potent inhibitors of pathogenic Gram positive bacteria, but when nisin and few other bacteriocins are treated with surfactants, they show wide activity against Gram negative bacteria as well. Nisin is the most researched bacteriocin and has been approved for its commercial production for use in cheese, canned vegetables, egg products etc. [56]. It is often used in acidic foods and also has been used in inhibiting undesirable microorganisms in beer and wine [1]. Nisin is also reported to be conjugated with few other preservative procedures such as heat or other types of bacteriocins. This process/technique is found to be more effective in eradicating food spoiling bacteria due to the increased antimicrobial spectrum. Nisin is preferably applied in aqueous form, as the powder form may have improper dispersal issues. Sea food industry is also being benefited from nisin in restricting the expansion of food spoiling microorganisms. A research by Bakkal et al. [57] showed the delayed growth of *L. monocytogenes* in cold smoked salmon when treated with nisin. A similar study carried out by Pei et al. [58] discussed the inhibitory action by nisin on the spoilage bacteria present in tangerine

wine. Nisin in amalgamation with lactases has been found to be highly competent to restrict the flourishing of *L. monocytogenes*, this may be due to synergistic activity [59]. Use of nisin for non-acidic food and dairy products is very limited; therefore the need arises to identify new bacteriocins having ability to retain stability in different food systems and is also thermally stable.

Comparatively, only a few studies have been carried out on the applications of pediocin in the food industry. Pediocin PA-1/AcH which is accepted for commercial use in meat products has been found to efficiently inhibit the development of *Listeria* species present in ice cream mixture, ground beef and sausage mix [60]. The addition of pediocins as preservatives in the food system aids in efficiently inhibiting the pathogenic food bacteria thereby guaranteeing the extended storage life of food, and safety of consumers [1, 4]. However, only a few bacteriocins have been approved at commercial level. The reason might be that, the newly identified antimicrobial peptides yet remain to be fully characterized, and further studies need to be carried out to gain a complete insight in their molecular mechanism implicated in bacteriocin production.

Bacteriocins are effective in inhibiting several other food spoiling pathogenic bacteria also. Chang and Chang [61] reported the restriction of growth of *Staphylococcus aureus* and *Escherichia coli* by Kimchi made with *Leuconostoc citreum* GJ7, a bacteriocin producing strain. Starter culture of LAB was also found to restrict the *Bacillus cereus* growth in rice fermentation [62] and growth of *Escherichia coli* and *Clostridium perfringens* were also reported to be inhibited by *Lactobacillus plantarum* and *Lactobacillus salivarius* on chicken feed media [63]. These are known to be the major trouble-causers to the food preservation industry. Although the use of bacteriocins has now started becoming popular in the food industry but their full potential has not yet been realized. They still suffer from several limitations as narrow antimicrobial spectrum, high dosage necessity, high production expenditure and low yield. To combat these limitations, research is now-a-days heading in the direction towards combining two or more classes of bacteriocins that aids in checking their efficacy as an improved/better preservative. Additionally, bacteriocins are also being conjugated with nanoparticles to increase their antimicrobial spectrum and for efficient delivery in target cells [30, 40, 64, 65]. These advancements are bound to contribute more towards new inventions and applications in food sector.

6. Future perspective

Bacteriocins have proven themselves to be potent antimicrobials produced by bacteria. Their applications in various sectors encourage for carrying out research for investigating different applications of bacteriocins in diverse areas. Currently, there is a critical need to combat the limitations of bacteriocins, most significantly, the narrow antimicrobial spectrum. For their effective use against various Gram-negative and food-borne pathogens, the already existing techniques need to be supplemented with new methods. There is a need to develop cost-effective methods for purification of bacteriocins and enhancing their production.

Studies conducted using nanotechnology techniques for enhancing antimicrobial spectrum and lowering the dosage requirement of bacteriocins are also encouraged. After that, evaluating the safety of nanoconjugates using various toxicity tests both *in-vivo* and *in-vitro* should be conducted to authorize their use in both food and pharmaceutical sectors. Furthermore, studying the interaction between bacteriocins and nanoparticles can promote the use of bacteriocins in future. Moreover, there is a need to introduce and design new open-access bacteriocin database, having information about newly discovered bacteriocins; their properties structure, and applications.

This will help the researchers to study already characterized bacteriocins in a simpler way. Additionally use of newly developed techniques viz., mass spectroscopy, bioinformatics studies will aid in understanding and characterizing the bacteriocins in more efficient ways.

7. Conclusion

Bacteriocins produced by LAB act as a weapon used by the bacterial cells to fight against other competing bacteria. This property of bacteriocin-producing LAB strains has been exploited by the scientists to combat several issues related to food spoilage and safety in the food sector. The current review is a concerted effort towards exploring in detail the biosynthesis, mechanism of action and existing applications of class I and class II bacteriocins produced by different LAB. However, although several studies describe the emerging and flourishing applications of bacteriocins in the health and food sector, but still, several hurdles limit the realization of their full potential in the commercial sector. Hence, the present research in the area of bacteriocins is getting more targeted towards looking for extraction and purification of more promising novel bacteriocins, and enhancement of antimicrobial spectrum of already existing purified bacteriocins. As an effort in this direction, although several bacteriocins have been studied as well as purified in the last few years, there is still a need as well as huge scope for continuing more dedicated research. A continued effort will surely enable the research fraternity to study and discover novel antimicrobial peptides with more promising properties.

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Conflict of interest


The authors declare no conflict of interest.

Author details

Parveen Kaur Sidhu and Kiran Nehra*
Department of Biotechnology, Deenbandhu Chhotu Ram University of Science and Technology, Haryana, India

*Address all correspondence to: nehrakiran@gmail.com

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