Bacteriocins: Promising Natural Antimicrobials

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Bacteriocins are described as ribosomally synthesized small poly peptides that exert antimicrobial effects against closely or non-closely related bacteria. The major producer group for bacteriocins is lactic acid bacteria (LAB) that contain a great variety of microorganisms described as "generally recognized as safe (GRAS)" by the US Food and Drug Administration. Due to this accredited safety potency of their origin and the wide-range effectiveness on pathogenic or spoilage bacteria, bacteriocins have attracted great research interest as natural antimicrobial agents, thereby allowing the design of new technologies for combating microbial pathogens in many industrial applications. For example, bacteriocins play a crucial role in maintaining the food safety and several bacteriocin preparations are commercially available for wide-range applications in the industry.

On the other hand, although many research efforts have been successfully done up to date, it is remarkable that there are still several gaps in this subject. Filling these gaps fundamentally requires a clear understanding on the nature of bacteriocins and carefully considered research strategies. Thus, the present study will include general information about bacteriocins such as definition, origin, nature and more complicated issues including effect mechanisms, application and development strategies.

Keywords bacteriocins; natural antimicrobials; effect mechanism; biopreservative agents

1. Introduction

Bacteriocins are generally defined as ribosomally synthesized peptides produced by bacteria that have bacteriostatic or bactericidal activity against other related and unrelated microorganisms [1-9]. The first bacteriocin isolation study was achieved by using a Gram-negative bacterium *Escherichia coli* and the isolated molecules were named as colisins in 1925. Up to date, colisins of *E. coli* has been one of the most studied groups of bacteriocins and the related studies showed that these molecules constitute a diverse group of antibacterial peptides, which exert bactericidal effects on closely related bacteria by various mechanisms including inhibition of cell wall synthesis, permeabilization of the target cell membrane, or inhibition of RNase or DNase activity [2, 3, 5, 6, 9]. On the other hand, many of recent studies emphasize that bacteriocin production is not restricted by Gram-negative bacteria. In this manner, Gram-positive lactic acid bacteria (LAB), a group of phylogenetically diverse microorganisms characterized by some morphological, metabolic and physiological properties, comprise an arsenal for various bacteriocins that have a great potential for industrial or medicinal applications due to the GRAS status (generally recognized as safe bacteria) of LAB. In addition, the bacteriocins from Gram-positive bacteria show a special inhibitory effect that is not directed against only bacteria within the same species as the bacteriocin producer but also against other species and/or genera different from of the producer. Thus, the bacteriocins produced by Gram-positive bacteria seem to possess a broader range of susceptible organisms and it makes these types of molecules more suitable for technological processes [1, 4, 5].

Bacteriocins are often confused in literature with antibiotics or other types of peptides with antimicrobial activity. This confusion is the most important legal standpoint to limit their use in industrial applications [9]. When they are compared, bacteriocins have ribosomally synthesized nature, while antibiotics are produced by multi-enzyme complexes. Many times bacteriocins show bactericidal or bacteriostatic effects on a narrow spectrum of bacteria, but traditional antibiotics have a broader spectrum. Moreover, most bacteriocins are more effective against their target bacteria than antibiotics at lower concentrations. There are also slight differences between bacteriocins and antibiotics in terms of host cell immunity, mechanism of target cell resistance or tolerance, interaction requirements, mode of action, toxicity and side effect mechanisms [2, 3, 5, 9]. Some bioactive peptides originated from prokaryotic or eukaryotic cells also have antimicrobial activity but these molecules and bacteriocins should be considered as different antimicrobial compounds. Bioactive peptides are encrypted in the polypeptide chain and released via proteolysis. The final yield of this process generally contain 3-20 amino acids and such bioactive peptides interact with the related receptor after releasing and cause hormone-like activity in their effect mechanism. This maturation pathway distinguishes bioactive peptides from all of the bacteriocins [1, 5, 8].

Recent concerns about arising microbial populations with antibiotic resistance and undesirable toxic properties of several bioactive peptides attract attention to the bacteriocins as promising natural antimicrobials in combating pathogens and spoilage microorganisms. Achieving this task requires a clear understanding about the nature of these molecules. Thus, this review is organized to critically discuss fundamental issues about bacteriocins including definition, origin, classification, mode of action, technological applications and recent perspectives in developmental strategies.

2. An Outlook for the History

Bacteriocins were first discovered in 1925 by Gratia, who observed inhibition of *Escherichia coli* S by *E. coli* V almost 100 years ago. They were initially named as colicins and then their proteinaceous nature were resolved in 1946 by Fredericq, who also demonstrated that the inhibitory activity of bacteriocins was depended on the presence of specific receptors on the surface of sensitive cells. His findings are also valuable to explain why bacteriocins have a limited effect spectrum on specific species or strains. Colicins and other types of the bacteriocins produced by Gram-negative bacteria dominated the research studies from these years to the near past. Indeed the colicins of *E. coli* are the most studied member of the bacteriocin family [2, 3, 5, 6, 9].

On the other hand, the studies focused on the bacteriocins produced by Gram-positive bacteria were formerly fall behind. However, the broad antimicrobial activity spectrum and more advantageous properties of these bacteriocins spurred the associated researches. Thus, studies on the bacteriocins of Gram-positive bacteria have come to dominate the bacteriocin-related literature in the past three decades [1, 3, 5].

Recently, the bacteriocins produced by lactic acid bacteria, include a great variety of Gram-positive bacteria, have been the most popular group due to the characteristics of their producers that have GRAS property and versatile usefulness in many industrial applications [1-5, 7, 9].

3. Microbial Origin

As mentioned before, bacteriocins are referred as ribosomally synthesized antimicrobial peptides from microorganisms and there is a great variation in their producers fundamentally divided in three groups: Archaea, Gram-negative and Gram-positive bacteria.

3.1. Bacteriocins of Archaea

The Archaea synthesize their own distinct family of bacteriocin-like antimicrobial peptides named as archaeocins. The halocin S8 from halobacteria, a short hydrophobic peptide with 36 amino acids, is the first discovered member of the archaeocin family. These molecules are produced as the cells enter stationary phase. When resources are limited by microorganisms, the producer strain lyses the target cells by secretion of archaeocins and reduces the competition in the local environment [3, 6].

3.2. Bacteriocins of Gram-negative Bacteria

As mentioned before, bacteriocins are initially isolated from Gram-negative bacteria. A colicin from *E. coli*, identified as an antimicrobial protein by Gratia in 1925, was the first described one for the bacteriocin family and dominated many of the related studies up to the recent past. Then, following researches pointed out that bacteriocin producer strains are not only restricted by *E. coli* but also the fact that many species of Gram-negative bacteria have production ability for colicin-like proteins. Klebicins of *Klebsiella pneumonia*, marcescins of *Serratia marcescens*, alveicins of *Hafnia alvei*, cloacins of *Enterobacter cloacae* and pyocins of *Pseudomonads* are important representative examples for bacteriocins of other Gram-negative bacteria.

Most bacteriocins of this group are relatively large and consequently heat-labile peptides. An exception, microcins such as microcin V of *E. coli* breaks this rule. It characteristically contains only a few peptides and shows heat-stable property.

The narrow antimicrobial activity spectrum is the main disadvantage for the bacteriocins of Gram-negative bacteria that limits their industrial-scale uses. This property calls attentions towards to the more suitable types of bacteriocins produced by Gram-positive bacteria [2, 3, 5, 6, 9].

3.3. Bacteriocins of Gram-positive Bacteria

Gram-positive bacteria also produce a wide variety of bacteriocins. Their non-toxic property on eukaryotic cells and much broader inhibitory spectra make Gram-positive bacteriocins a unique useful tool for many industrial and medicinal applications. In this respect, lactic acid bacteria (LAB), a group of phylogenetically diverse Gram-positive bacteria characterized by some common morphological, metabolic and physiological properties, have attracted much interest due to their GRAS (generally regarded as safe) potential for human consumption [1-5, 7, 9].

LAB are characterized by production of lactic acid in their fermentation pathway, thereby earning the name “lactic acid bacteria”. In this process, a member of LAB converts at least 50% of the carbon from sugars into two isomers of lactic acid. This group of bacteria shows a great variety depending on many physiological and morphological properties. Members of LAB can be cocci, bacilli or coccobacilli shaped Gram-positive bacterial strains with various physiological characteristics. Due to their safe nature and valuable metabolic products (such as organic acids, diacetyl, acetoin, hydrogen peroxide, reuterin, reutericyclin, antifungal peptides, and bacteriocins), these have a great importance

in medicinal and food applications. Especially various types of bacteriocins have attracted much interest [1-5, 7, 9]. Thus, some important bacteriocin types and producer LAB strains are shown in Table 1.

Table 1 Some important bacteriocin examples of lactic acid bacteria.

Bacteriocin	Producer Organism	Reference(s)
Nisin A	*Lactococcus lactis*	[10]
Nisin Z	*Lactococcus lactis*	[10]
Nisin U	*Streptococcus uberis*	[5]
Lactococcin DR	*Lactococcus lactis* ADRIA 85L030	[11]
Lacticin 481	*Lactococcus lactis* CNRZ481	[12]
Lacticin 3147 (LtnA1 and LtnA2)	*Lactococcus lactis* DPC3147	[13]
Estreptococcin A-FF22	*Streptococcus pyogenes* FF22	[14]
Salivaricin A	*Streptococcus salivarius* 20P3	[15]
Cytolysin (CylL1 and CylL2)	*Enterococcus faecalis*	[16]
Carnocin U149	*Carnobacterium piscicola* U149	[17]
Lactocin S	*Lactobacillus sakei* L45	[18]
Pediocin PA1	*Pediococcus acidilactici* PAC-1.0	[19]
Pediocin AcH	*Pediococcus acidilactici* H	[20]
Leucocin A-UAL187	*Leuconostoc gelidum* UAL187	[21]
Mesentericin Y105	*Leuconostoc mesenteroides* Y105	[22]
Mesentericin 52B	*Leuconostoc mesenteroides* FR52	[23]
Mesentericin B105	*Leuconostoc mesenteroides* Y105	[24]
Acidocin A	*Lactobacillus acidophilus* TK9201	[25]
Bavaricin A	*Lactobacillus bavaricus* MI401	[26]
Curvacin A	*Lactobacillus curvatus* LTH1174	[27]
Sacacin A	*Lactobacillus sakei* LB706	[28]
Sacacin P	*Lactobacillus sakei* LTH673	[27]
Sacacin 674	*Lactobacillus sakei* LB674	[29]
Carnobacteriocin BM1	*Carnobacterium piscicola* LB17B	[30]
Carnobacteriocin B2	*Carnobacterium piscicola* LV17B	[30]
Divercin V41	*Carnobacterium divergens* V41	[31]
Enterocin A	*Enterococcus faecium* CTC492	[32]
Lactococcin M (LcnM and LcnN)	*Lactococcus cremoris* 9B4	[33]
Lactococcin G (LcnGα and LcnGβ)	*Lactococcus lactis* LMG2081	[34]
Acidocin J1132 (α,β)	*Lactobacillus acidophilus* JCM1132	[35]
Lactacin F (LafA and LafX)	*Lactobacillus johnsonii* VPI11088	[36]
Plantaricin S (Plsα and Plsβ)	*Lactobacillus plantarum* LCPO10	[37]
Plantaricins EF (PlnE and PlnF)	*Lactobacillus plantarum* C11	[38]
Plantaricins JK (PlnJ and PlnK)	*Lactobacillus plantarum* C11	[38]
Leucocin H (α and β)	*Leuconostoc* sp. MF215B	[39]
Termophilin 13 (ThmA/ThmB)	*Streptococcus thermophilus* SPi13	[40]
Acidocin B	*Lactobacillus acidophilus* M46	[41]
Divergicin A	*Carnobacterium divergens* LV13	[42]
Bacteriocin 31	*Enterococcus faecalis* YI17	[43]
Enterocin P	*Enterococcus faecium* P13	[44, 45]
Lactococcin 972	*Lactococcus lactis* IPLA972	[46]
Lactococcins A and B	*Lactococcus cremoris* 9B4	[47]
	Lactococcus cremoris LMG2130	[48]
	Lactococcus lactis WM4	[49]
Diacetin B	*Lactococcus lactis* subsp. *diacetylactis* UL720	[50]
Acidocin 8912	*Lactobacillus acidophilus* TK8192	[25]
Peptide A	*Lactobacillus acidophilus* LF221	[51]
Peptide B	*Lactobacillus acidophilus* LF221	[51]
Lactobin A	*Lactobacillus amylovorous* LMG P-13139	[52]
Lactocin 705	*Lactobacillus casei* CRL 705	[53]
Gassericin B3	*Lactobacillus gasseri* HCM2124	[54]
Plantaricin 1.25α	*Lactobacillus plantarum* TMW1.25	[55, 56]
Plantaricin 1.25β	*Lactobacillus plantarum* TMW1.25	[55, 56]
Divergicin 750	*Carnobacterium divergens* 750	[57]
Carnobacteriocin A (¥)	*Carnobacterium piscicola* LV17A	[58]
Piscicolin 61 (¥)	*Carnobacterium piscicola* LV61	[59]
Leucocin B-TA33a	*Leuconostoc mesenteroides* TA33a	[60]
Enterocin B	*Enterococcus faecium* T136	[44]
Enterocins L50 (EntL50A and EntL50B)	*Enterococcus faecium* L50	[61]
Enterocin Q	*Enterococcus faecium* L50	[62]
Enterolysin A	*Enterococcus faecalis* LMG 2333	[63]
Helveticin J	*Lactobacillus helveticus* 481	[64]
Caseicin 80	*Lactobacillus casei* B80	[65]

*Table 1 adapted from Cintas et al., 2001 with some minor modifications [1].

4. Classification

Bacteriocins have been grouped into various classes based on the different criteria such as producer organisms, molecular sizes, physical properties, chemical structures and mode of actions. However, there is no certain classification. Initially, bacteriocins were divided into four classes by Klaenhammer in 1993 [66]. In this classification, the class I is lantibiotics characterized by thermostable properties, very low molecular weight (<5 kDa), presence of lanthionine and its derivatives. Nisin can be given as an example for the members of this class. The class II contains small thermostable peptides without lanthionine derivatives and up to 10 kDa molecular weight. It also includes three subclasses as IIa (pediocin and enterocin), IIb (lactocin G) and IIc (lactocin B). The class III, represented by helveticin J, gathers high molecular weight (>30 kDa) thermolabile peptides and the class IV contains large peptides combined with carbohydrates or lipids [9, 66]. A contradiction in 2001, Cleveland et al. proposed that the complex structures of class IV are artifacts of partial purification and not a new class of bacteriocins [67]. Later, Cotter et al. suggested a new classification in 2005. There were two classes in this concept: the class I (lantibiotics) and the class II (other peptides without lanthionine). High molecular weight thermolabile peptides were excluded from the bacteriocin classes and separately grouped as bacteriolysins. The authors also suggested that the class IV of the initial classification should be extinguished [68]. In 2006, Drider et al. finally divided bacteriocins in three main classes by using their genetic and biochemical characteristics [69]. Table 2 shows basic features of this classification and the present context will follow its contents.

Table 2 Classification of bacteriocins.

Classification	Features	Subcategories	Examples
Class I (Lantibiotics)	Lanthionine or peptides containing β-lanthionine	Type A (linear molecules) Type B (globular molecules)	Nisin, subtilin, epidermine Mersacidin
Class II	Heterogeneous class of small thermostable peptides	Subclass IIa (antilisterial-pediocine bacteriocins type) Subclass IIb (composed of two peptides) Subclass IIc (other bacteriocin)	Pediocin, enterocin, sakacin Plantaricin, lactacin F Lactococcin
Class III	Large thermolabile peptides		Helveticin J, millericin B

*Table 2 adapted from Drider et al., 2006 and Balcianus et al., 2013 [9, 69].

4.1. Class I

Members of the class I bacteriocins, also called as lantibiotics, are small (19-38 amino acid residues) and thermostable peptides. Previous studies refer to that lanthionine or β lanthionine in the structure of the molecules may be responsible for the thermostability [9].

Nisin is the most well-known example for this group. Several strains of *Lactococcus lactis* subsp. *lactis* are natural producers of this bacteriocin and it contains 34 amino acid residues in its molecular structure. The two variant of nisin are nisin A and nisin Z. Both of them have the same molecular pattern except only one amino acid, but show similar antimicrobial activity. Besides, there is a new variant of nisin isolated from *Streptococcus uberis* and named as nisin U with 78% similarity to nisin A [5, 9].

Many research efforts showed that nisin exhibits a broad-range spectrum antimicrobial effect on various pathogens and LAB species including *Listeria monocytogenes*, *Staphylococcus aureus* and *Bacillus cereus*. In its mode of action mechanism, nisin affects the target cell wall and membrane via a dual action mechanism, resulting pore formation, outflow of essential compounds (K^+ ion, amino acids and ATP) through the pores, changes in permeability and finally the target cell death [9].

Its broad range antimicrobial activity makes nisin a valuable tool for technological applications. Indeed, nisin is the only bacteriocin approved for food applications being considered to be safe by the Food and Agriculture Organization/World Health Organization (FAO/WHO) in 1969. Moreover, it is also accepted as biopreservative ingredient in the European Union countries and assigned the number E234 [9].

4.2. Class II

This class of bacteriocins constitutes a large and diverse group of ribosomally synthesized antimicrobial peptides, while class II bacteriocins are structurally simpler than lantibiotics because they do not have post-translational modifications in the peptide chain such as lanthionine or β-lanthionine. This class includes thermostable small (<10 kDa) peptides with an amphiphilic helical form. The structural conformation of the class II bacteriocins leads to their insertion in the cytoplasmic membrane of the target cell. Finally, this process causes membrane depolarization and cell death.

Class II bacteriocins can be divided in three subclasses as subclass II-A, subclass II-B and Subclass II-C [9].

4.2.1. Subclass II-A

The members of the subclass II-A are characterized by showing high antilisterial activity. These bacteriocins also include 37-48 amino acid residues in their molecular structure. The N-terminal portion of the compound has a pleated sheet configuration and the C terminal portion contains one or two α-helices. In the mode of action mechanism, a bacteriocin from the subclass II-A falls into the cell membrane of the target cell by the C terminus. This promotes pore formation and consequent dissipation of proton motive force that cause high ATP consumption and consequently death. Pediocin, enterocin and sakacin are the most well-known examples of subclass II-A [9].

4.2.2. Subclass II-B

This subclass includes heterodimeric bacteriocins which consist of two peptides. Members of this subclass of the bacteriocins meet three criteria: (i) full antimicrobial activity needs both peptides and the individual peptides show little or no activity, (ii) one immunity protein is sufficient to get immunity, and (iii) the genetic organization of the bacteriocin system includes two sequential bacteriocin structural genes encoding the individual peptides and a single immunity gene. Lactococcin G is the first discovered bacteriocin of this group and its antimicrobial activity depends on both α- and β-peptides. Plantaricin and lactacin F are also other important representative examples for two-peptide bacteriocins. Their mechanism of action involves the dissipation of membrane potential and a decrease in the intracellular ATP concentration [1-3, 5, 9] .

Although the presence of both peptides is required to obtain full antimicrobial activity, the individual peptides can act as residual antimicrobials with a modest effect in some cases.

4.2.3. Subclass II-C

Bacteriocins of this subclass uniquely have a circular structure associated with a covalent bond between C and N terminals that cause head to tail cyclic shape of the peptides. The main representative and the most studied example of this subclass is AS-48 from *E. faecalis*. In its mode of action mechanism, AS-48 permeabilizes the cytoplasmic membrane of the target cells, resulting in dissipation of the proton motive force and eventually cell death [9].

4.3. Class III

This class includes large thermolabile bacteriocins with more than 30 kDa molecular weight. An important criterion for members of this group is that Class III bacteriocins have complex activity and protein structure that provide a totally different action mechanism from other bacteriocins, in which they induce lysis of the cell wall of the target microorganism. In the mode of action process, N-terminal portion of the molecule acts as an endopeptidase and C-terminal portion recognizes the target cell [9].

5. Biological Features

As biological products of microorganisms, all bacteriocins have certain characteristics that compile in or distinguish these molecules from other types of biologically synthesized molecules. These characteristics establish biological properties of bacteriocins that include synthesis, mode of action, immunity and resistance mechanisms.

Due to their proteinaceous nature, all bacteriocins are synthesized by the ribosomes of the producer microorganisms. The required information is supplied from the genetic code which may be occasionally placed on plasmids, the main chromosome or mobile elements such as transposons [1-3]. Genetic organization of bacteriocin gene clusters comprises a functional operon, which generally includes the structural gene, the gene codifying immunity protein, the genes responsible for processing and transport of the bacteriocin, and, in some cases, the genes codifying some enzymes for posttranscriptional modifications. Moreover, bacteriocin operons also include the gene encoding the preinduction factor (IF), the histidine protein kinase (HPK) gene, and the gene(s) codifying the response regulator (RR) [2].

Firstly, the structural gene is activated in the beginning of the bacteriocin production and it produces biologically inactive precursors or prepropeptides also called as preprobacteriocins. Then, other related parts of the bacteriocin operon sequentially become operational and the process consequently results in the releasing of the mature bacteriocins with antimicrobial activity [1].

The exact regulation mechanism for the biosynthesis of bacteriocins is not completely understood. On the other hand, many studies emphasizes that the competition among the members of microflora in an environment with limited substrates or nutrients plays a key role in the regulation of bacteriocin production. Recent studies have also pointed out that the induction factors (IF or pheromone), bacteriocin-like peptides with 19-26 amino acid residues length, low-molecular weight and cationic nature, have a great importance in the regulation mechanism [1, 3, 5, 9]. In 1996, Nes et al. reviewed the role of IFs and proposed two models to explain bacteriocin induction. The first one was the quorum sensing model, which refers that the IF is constitutively produced and accumulated in low concentrations during bacterial growth. Then, induction of the bacteriocin genes occurs when IF concentration reaches the threshold for IF autoinduction level. Therefore, this model relies on a control mechanism depending on the cell density of the cultures

[1, 70]. According to the second model, an alternative for the quorum sensing model, the IF concentration never reaches the threshold by itself and requires unidentified environmental signals or modification in environmental conditions such as changes in nutrient levels or physicochemical growth conditions [1, 70]. Besides, more recent studies pointed out that the regulating system is composed of three components in many cases: an inducing peptide (or pheromone-activating factor), the transmembrane histidine kinase (pheromone receptor) and a response regulator. Apart from these, it is also known that regulation of the production of lantibiotics such as nisin and plantaricin is directly controlled by the bacteriocin itself, which acts as a pheromone inducing their production at high levels [5, 9].

In the mode of action, all types of bacteriocins show their effects on the target cell surface via various mechanisms as mentioned in the classification section. This generally results in deficiencies in the cell wall synthesis, changes in the membrane permeability and/or formation of pores causing the death of the target cells. As an example, lantibiotics inhibit target cells by forming pores in the membrane, depleting the transmembrane potential ($\Delta\psi$) and/or the pH gradient, resulting in the leakage of cellular materials. In this phenomenon, a positively charged bacteriocin molecule with hydrophobic patches binds to negatively charged phosphate groups on target cell membranes via electrostatic interactions. Thus, hydrophobic portion of the bacteriocin inserts into the membrane, causes pore formation and consequently cell death [2, 9].

The immunity mechanism of the bacteriocin producer strain to its own product makes a certain distinction between bacteriocins and antibiotics. In this phenomenon, a producer strain offers self-protection the toxicity of its own bacteriocins by a special mechanism depending on a variety of bacteriocin-specific immunity proteins. These proteins are encoded by the related gene sequences, in close genetic proximity to other bacteriocin structural/processing genes and commonly located on the same operon. The characteristics of the immunity proteins are their small sizes (51-154 amino acid residues), high isoelectric point (pI) values (7-10) and putative transmembrane α-helices. These characteristics facilitate binding the immunity proteins to the cytoplasmic membrane of the host cell [1, 2].

On the other hand, the bacteriocin resistance mechanism is completely different from the immunity. In this respect, resistant strains are mainly arisen from spontaneous or induced mutations that cause changes in membrane and cell wall, such as alterations in the bacteriocin receptors, electrical potential, fluidity, membrane lipid composition and load or cell wall thickness [1, 2, 9]. Although exact mechanism of the bacteriocin resistance has not understood yet, Van Schaik et al. underlined that the mutational changes on the cell surface of the resistant strain may occur following cell exposure to low concentrations of bacteriocins as part of an adaptive response to some other internal or external stress factors [9, 71].

6. Technological Applications

The use potential of bacteriocins in various technological applications is fundamentally depending on their antimicrobial effects and a clear understanding on the value of this activity is required to develop innovative strategies. In this regard, the rapid rise and spread of multi-resistant bacterial pathogens state expressly the importance of the research studies purposing to find alternative methods combating of infections. Bacteriocins with broad-scale antimicrobial activity can be thought as promising natural antimicrobials for many industrial applications in this manner. Especially, human health and food industries have been dominated the related studies and many prosperous improvements have been done up to date [1-9].

6.1. Bacteriocins and Human Health Applications

Modern medicine is faced with a drastic increase in the count of antibiotic-resistant pathogens. On the other hand, undesirable effects of new-generation antibiotics with highly toxic features have forced the consideration of alternative methods. Bacteriocins have a great potential in human health applications when compared to the traditional antibiotics. Their low-toxicity, high target-specific affect mechanism, presence of various types in nature and effectiveness at nanomolar concentrations are the main advantages of bacteriocins [3, 9]. In this regard, many efforts have been done and some promising examples of pharmaceutical applications are shown in Table 3.

Table 3 Examples of some bacteriocins and their pharmaceutical applications in human health.

Group of Bacteriocins	Pharmaceutical Applications
Lantibiotics	Blood pressure treatment, Inflammations and allergies treatment, Skin infections treatment, Mastitis infections treatment, Herpes treatment, Dental carries treatment, Peptic ulcer treatment.
Colicins	Hemolytic uremic syndrome treatment, Urogenital infection treatment, Hemorrhagic colitis treatment.
Microcins	Antimicrobial agent, Salmonellosis treatment.

*Table 3 adapted from Balcianus et al., 2013 [9].

6.2. Bacteriocins and Food Applications

Although modern advances in technology have been developing day by day, the preservation of food is still a debated issue, resulting in economic losses due to food spoilage and undesirable effects on human health. In this respect, many chemical preservatives have been identified and successfully applied in various food processing applications. However, the growing awareness of consumers and the health concerns regarding chemical food additives make natural antimicrobials more attractive. Bacteriocins, especially produced by LAB, have a great potential to meet this request in the food industries [1, 2, 4, 5, 7-9].

In food preservation, the bacteriocins produced by LAB: (i) are generally recognized as safe substances (GRAS property), (ii) are not active and non-toxic on eukaryotic cells, (iii) become inactivated by digestive proteases, having little influence on the gut microbiota, (iv) are usually pH and heat-tolerant, (v) have a relatively broad antimicrobial spectrum, against many food-borne pathogenic and spoilage bacteria, (vi) show a bactericidal mode of action, usually acting on the bacterial cytoplasmic membrane: no cross resistance with antibiotics, and (vii) their genetic determinants are usually plasmid-encoded, facilitating genetic manipulation [4].

The related studies indicates that the applications of bacteriocins with these features in food industries can extend shelf life of foods, provide extra protection during temperature abuse conditions, decrease the risk for transmission of food-borne pathogens through the food chain, ameliorate the economic losses due to food spoilage, reduce the application of chemical preservatives, permit the application of less severe heat treatments without compromising food safety: better preservation of food nutrients and vitamins, as well as organoleptic properties of foods, permit the marketing of novel types of foods [4].

Bacteriocins are added into food processing applications as *ex situ* produced preparations, or by inoculation with the bacteriocinogenic strains. Then these antimicrobial agents can be ready to show their specific activity in the food matrix. However, the matrix, the processing steps and the natural microbiota have a fairly complex and non-stable nature in many cases. Thus the bacteriocins have to pass all limiting factors to exert their activity. Gálvez et al. reviewed the limiting factors of bacteriocins for food applications and presented in their paper in 2007 [4]. Table 4 shows these parameters.

Table 4 Bacteriocin efficiency in foods: limiting factors.

Groups	Limiting Factors
Food-related factors	- Food processing conditions - Food storage temperature - Food pH, and bacteriocin unstability to pH changes - Inactivation by food enzymes - Interaction with food additives/ingredients - Bacteriocin adsorption to food components - Low solubility and uneven distribution in the food matrix - Limited stability of bacteriocin during food shelf life
The food microbiota	- Microbial load - Microbial diversity - Bacteriocin sensitivity - Microbial interactions in the food system
The target bacteria	- Microbial load - Bacteriocin sensitivity (Gram-type, genus, species, strains) - Physiological stage (growing, resting, starving or viable but non-culturable cells, stressed or sub-lethally injured cells, endospores, etc. - Protection by physicochemical barriers (microcolonies, biofilms, slime) - Development of resistance/adaptation

*Table 4 adapted from Gálvez et al., 2007 [4].

In another paper published by Galvez et al., in 2008, the potential uses of bacteriocins in food industry applications were elaborated. This paper especially discusses several main topics that include application of bacteriocins in dairy foods, meat and poultry products, fish and sea foods, vegetable foods and drinks, and it can be clearly seen that bacteriocins have been dominating food safety and preservation related studies according to the paper [7].

In this context, Table 5 was designated to summarize the potential bacteriocin applications in food industry and it details these applications in the same time.

On the other hand nisin, the most prominent Class I bacteriocin, is the only one internationally accepted as food biopreservative in certain industrial applications on the contrary to the huge variety of potential applications shown in Table 5. Nisin is commercially named as Nisaplin® and being marketed as lyophilized powder [8, 9].

Recently, pedocin is also another commercially available bacteriocin preparation for food applications and the present studies foresees that the count of these preparations would drastically increase in the near future [8, 72].

Table 5 Some examples for bacteriocins in food applications.

Potential Application	Target Groups	Application Details
Milk and dairy products	Raw material	- Reduction of microbial growth in raw milk - Inactivation of mesophilic bacteria in milk in combination with PEFs or with HHP
	Fermented products	- Inhibition of gas formation by *C.tyrobutricum* on semihard and hard cheeses - Inhibition of pathogenic and toxicogenic bacteria (*L. monocytogenes*, *B. cereus*, *S. aureus*) in cheese and on the cheese surface - Inactivation of mesophilic bacteria and endospore formers in cheese in combination with HHP - Control of over acidification in yogurt and other fermented products - Use of bacteriocin-producer strains as starter or adjunct cultures to inhibit pathogenic and spoilage bacteria in cheese and other fermented milk products - Use of bacteriocin-producing starter cultures to inhibit adventitious nonstarter LAB microflora in cheese - Acceleration of cheese ripening through the increased release of bacterial intracellular enzymes
	Processed products	- Inhibition of endospore formers (mainly, *C. botulinum*) in processed cheese and other processed dairy products - Inhibition of *L. monocytogenes* in dairy products after postprocess contamination
Meat and poultry products	Raw materials	- Decontamination of raw meat (e.g., by spray washing) - Inhibition of spoilage bacteria and shelf-life extension of vacuum-packaged raw meat - Inhibition of *L. monocytogenes* on raw meat surfaces and in minced meat
	Cooked meat products	- Inhibition of spoilage LAB - Shelf-life extension of vacuum-packaged sliced meat products - Reduction of the intensity of HHP treatments applied for inhibition of foodborne pathogens and spoilage bacteria in sliced meat products -Use of bacteriocin-producing LAB as protective cultures against *L. monocytogenes* and spoilage bacteria in vacuum-packaged meats
	Egg and derivatives	- Shelf-life extension - Decreased intensity of thermal treatments - Increased inactivation of pathogenic bacteria in combination with HHP and PEF treatments
	Fermented meat products	- Inhibition of spoilage LAB - Inhibition of foodborne pathogens (*Salmonella*, *L. monocytogenes*, *S. aureus*) - Use of bacteriocin-producing LAB (mainly, *L. sakei* strains) as starters to inhibit *L. monocytogenes* and spoilage bacteria - Enhancement of the predominance of starters during fermentation
Vegetable-based foods and drinks	Raw fruits and vegetables	- Reduction of suppression of *L. monocytogenes* in raw vegetables (sprouts and others) - Reduction of suppression of *L. monocytogenes* and *Salmonella* in fresh-cut produce
	Cooked and pasteurized foods	- Control of endospore formers in pasteurized foods - Control of *B. cereus* in rice-based foods
	Canned foods	- Control of aciduric and nonaciduric endospore-forming spoilage bacteria in canned vegetables - Prevention of spoilage by *C. tyrobutyricum* in canned fruit pulp
	Fruit juices and drinks	- Prevention of spoilage by *Alicyclobacillus* in fruit juices and drinks - Reduction of suppression of *E. coli* O157:H7 and *S. typhimurium* in fruit juices - Inhibition of *L. monocytogenes* and *S. aureus* in soy milk
	Fermented drinks	- Inhibition of beer spoilage bacteria - Inhibition of wine spoilage bacteria and control of wine malolactic fermentation - Reduction of added sulphur dioxide in the wine industry - Inhibition of cider spoilage bacteria
	Fermented vegetables	- Improvement of sauerkraut fermentation by using a paired starter culture - Control of kimchi overripening by adding nisin to partially inhibit *Lactobacillus* sp. - Inhibition of *B. subtilis* in rice miso by using a nisin-producer *L. lactis* subsp. *lactis* as a starter - Control of *L. monocytogenes* in kimchi by a bacteriocinogenic strain of *P. acidilactici* - Improvement of Spanish-style fermentation of table olives by a bacteriocinogenic starter culture of *L. plantarum* producing plantaricins S and T
	Other fermented vegetable foods	- Improvement of sourdough fermentation - Inhibition of rope-forming bacilli in bread - Inhibition of foodborne pathogens in traditional cereal-fermented foods

*PEFs, pulsed electric fields and HHP, high hydrostatic pressure

*Table 5 adapted from Gálvez et al., 2008 [7].

Table 5 Some examples for bacteriocins in food applications (continued).

Potential Application	Target Groups	Application Details
Fish and seafood products	General trials	- Addition of purified sakacin P for inhibition of *L. monocytogenes* - Addition of nisin and pediocin combined with CO_2 atmosphere packaging to control *L. monocytogenes* in smoked salmon - Injection of nisin combined with sodium lactate into smoked rainbow trout to control *L. monocytogenes* - Combined treatments of nisin and/or moderate heat treatments/chemical preservatives for inactivation of *L. innocua/L. monocytogenes* in sturgeon caviar and lobster - Addition of bavaricin A or nisin Z for shelf-life extension of brined shrimp - Use of bacteriocinogenic *Carnobacterium* strains as protective cultures against *L. monocytogenes* in cold-smoked salmon and cold-smoked surubim - Use of bacteriocinogenic *Lactobacillus* strains as protective cultures against *L. monocytogenes* in cold-smoked salmon

*Table 5 adapted from Gálvez et al., 2008 [7].

7. Future Perspectives

Bacteriocins seem to have a great potential for filling the gaps in medicine and food industry applications as natural antimicrobial agents in the near future. Besides their conventional use methods, recent research efforts have routed the attentions toward development of different antimicrobial combinations to get more effective responses. Basically, this process is a combination of multiple antimicrobial factors and called as "hurdle technology". To date, more than 60 potential hurdles have been described and the application of bacteriocins as part of this technology has received great attention in recent years. In a hurdle technology application, a bacteriocin may combine with another bacteriocin, other types of natural antimicrobials, chemicals or physical treatments [4].

In this context, the most studied hurdle technology applications of bacteriocins include combinations of bacteriocins with chemical substances (sodium chloride; organic acids and their salts such as acetic acid, sodium lactate and sodium citrate; chelating agents such as EDTA, disodium pyrophosphate, trisodium phosphate, hexametaphosphate; ethanol), natural antimicrobials (essential oils, their active components and phenolic compounds such as carvacrol, eugenol, thymol, terpineol, caffeic acid, *p*-coumaric acid; bacteriocins; non-bacteriocin antimicrobial proteins or peptides) and physical treatments (heat treatments, modified atmosphere packaging, pulsed electric fields, high hydrostatic pressure and other non-thermal treatments). Moreover, many recent efforts have given promising results to develop novel hurdles with high efficiency for the near future [4].

On the other hand, use of computational methods in bacteriocin researches has drastically risen from the near past up to date. BAGEL and BACTIBASE are the most well-known examples for the web-based databases and these provide computational tools for bacteriocin genome mining, similarity search (BLAST, FASTA, SSEARCH), sequence alignment (CLUSTALW, MUSCLE, T-COFFEE), physicochemical profile analysis, hidden markov models and structure prediction [4, 5, 8, 73, 74].

As a consequence, all these perspectives clearly demonstrate that bacteriocin studies will continue their expeditious grow and invention of novel technologies like hurdles or computational methods will determine the fate of these studies in the future.

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