

Bacterial Antagonist Mediated Protein Molecules

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Abstract

Bacterial antagonism mediated by ribosomally synthesised peptides has gained considerable attention in recent years because of its potential applications in the control of undesirable microbiota. These peptides, generally referred to as bacteriocins, are defined as a heterogeneous group of ribosomally synthesised, proteinaceous substances (with or without further modifications) extracellularly secreted by many Gram-positive and some Gram-negative bacteria. Their mode of activity is primarily bactericidal and directed against closely related strains and species. These peptides are nearly all cationic and very often amphiphilic, which is reflected in the fact that many of these peptides kill their target cells by accumulation in the membrane causing increasing permeability and loss of barrier functions. Bacteriocins have been explored primarily as natural food preservatives, but there is much interest in exploring the application of these therapeutic peptides as antimicrobial agents since many of them exhibit antimicrobial activity against various important human pathogens. The suitability of bacteriocins such as pharmaceuticals is explored through measures of cytotoxicity, effects on the natural microbiota, and *in vivo* efficacy in mouse models. Bacteriocins are promising therapeutic agents.

Keywords: Bacteria; Protein; Veterinary; Human medicine

Introduction

Antimicrobial resistance of bacteria is a pivotal health concern worldwide in Human, as well as Veterinary Medicine. Undoubtedly, the excessive and often empiric antimicrobials for the treatment of different clinical situations has led to changes in the bacterial ecology, leading to fatal consequences for public health. Scientists say that the community-acquired sepsis should be distinguished from nosocomial sepsis (nosocomial). As it is known, their differences are the main sources of infection, the predominant bacteria and the sensitivity to the antimicrobial. The process is well known and studied of bacterial resistance becomes larger in the hospital environment, where there have been very aggressive microbes that spread easily from patient to patient. The bacteria acquire the ability to resist the action of antibiotics through several mechanisms such as genetic variability, the modification of the permeability of the inner membrane, extraction of the compound and enzyme inhibition, as well as modification of the target ribosomal or altering the composition and content of glycoproteins of the bacterial wall [1]. This resistance is transferred between organisms of the same genus (horizontal transmission) and between organisms of different genus (vertical transmission). Even more, the fact that there is limited data on antibiotic susceptibility and resistance surveillance in all countries (in either, Veterinary and Human Medicine), must be added. Many foods of animal origin are often reservoirs of bacteria carrying resistance genes. These bacteria into the gastrointestinal tract may transfer their resistance genes to the intestinal microbiota being the consequence the follow resistance sequence transfer animal-animal, animal-human, human-human [2].

Antimicrobial Peptides

The scientific work on bacterial antagonism-mediated by protein molecules was sourced on the 80's being now a significant area of research, whose results are reflected in the description of a large family of antimicrobial substances, known as antimicrobial peptides (AMPs). These peptides are produced by many cell types in a variety of life forms found in protozoa, prokaryotes, plants and animals [3-17]. Some of them are produced constitutively and others are synthesized in response to microbial attack [4-25]. Probably one of the attractions has been considered that such molecules represent an ancestral defense mechanism still not explored [20]. It will constitute an alternative to

today's predicament posed by the emergence of resistance to antibiotics [19-23]. Among the identified proteins and peptides is a great diversity of primary structures, but in most cases are cationic molecules ribosomal synthesis-mediated [9]. These molecules, often amphiphilic [24], direct its action to the bacterial membrane, interacting with the negatively charged structures leading to its permeabilization [7-25]. Nowadays, its known that not only AMPs' produce permeabilization of bacterial membranes, but also have other role such as inhibition of protein synthesis or DNA, the antitumor activity, and stimulation of cell proliferation or angiogenesis [25]. Target organisms of antimicrobial peptides are very diverse (enveloped viruses, bacteria, fungi, trypanosomes, protozoa, parasites and cancer cells) but they all have in common the possession of a negatively charged surface membrane, low concentration of cholesterol and high transmembrane electric potential [26,27].

There is no correlation between the activity of AMPs and its isoelectric point, molecular weight or length. However, it has been shown to possess residues Lys and Arg helps peptides to reach the bacterial membranes, although the mechanism involved in permeabilization. Two factors that determine the permeability activity of antimicrobial peptides are amphipathic and hydrophobicity [19]. It has recently been seen some AMPs insert their propellers obliquely to promote permeabilization membrane [28].

AMPs Produced by Bacteria

Antimicrobial peptides produced by bacteria are also called bacteriocins, and defined as "a heterogeneous group of ribosomal synthetic peptides with or without further modifications, which are secreted extracellularly and have a bactericidal mechanism of action

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against related strains” [29,30-32]. However, that some bacteriocins in Gram-positive have a broader spectrum [33,34] and in some cases may extend beyond the borders of bacteria and include protozoa, yeasts, fungi, and virus [35]. Bacteriocin differ from eukaryotes antimicrobial peptides in the high self-toxicity showing the second, as is the case of defensins produced by human neutrophils that are cytotoxic at high concentrations to the producing cell itself [36]. AMPs from bacteria differ basically from traditional antibiotics in: a) molecular structure, b) chemicals nature, c) mode and range of action, and d) absence of toxicity and induced resistance mechanisms [37]. Like bacteriophages, the bacteriocins can specifically target a particular subset of bacterial strains or species. However, unlike viruses, some bacteriocins were found to be safe for human consumption by the Food and Drug Administration [38].

Its importance lies in the fact that these inhibitors have been described in virtually all lineages Domain Bacteria, and frequently the production of various types of bacteriocins from strains of the same species [30-41]. The bacteriocin family may be divided into two Gram-negative and Gram-positive’s bacteria main groups [42,43]. Bacteriocins have primarily been characterized in Gram-negative bacteria, in which is described the colicins produced by *Escherichia coli* [44-46], and the microcin generated by members of the Enterobacteriaceae family [47,48].

AMPs Obtained from Gram-Positive Bacteria

Bacteriocins of Gram- positive are abundant and more diverse than those described at the present for Gram-negatives [29-31]. The Gram-positive bacteriocins resemble many of the antimicrobial peptides produced by eukaryotes. They are generally cationic, amphiphilic, membrane permeabilizing peptides ranged in size from 2 to 6 kDa [43]. They also differ from bacteriocins of Gram-negative bacteria in

two elementary ways according [49]. Firstly, the bacteriocins produced by Gram-positive bacteria are not necessarily lethal to the producing cell. This pivotal difference is because the transport mechanisms Gram-positive bacteria encode the release of the bacteriocin-toxin. Typically, their biosynthesis is self-regulated with specifically dedicated transport mechanisms facilitating release, although some employ the Sec-dependent export pathway [50-52]. Secondly, the Gram-positive bacteria have evolved bacteriocin-specific regulation, whereas bacteriocins of Gram-negative bacteria rely solely on host regulatory networks [53].

The last twenty years of research has focused primarily on the study of bacteriocins produced by Lactic Acid Bacteria (LAB) on feasibility of using them as natural food preservatives in order to increase the lifetime and improve the hygienic quality of them. According to the structural and biological characteristics of LAB’s bacteriocins, [54] established four classes of bacteriocins, in which the first three are still recognized today. The discovery and characterization of new bacteriocins has become necessary to amend this classification, especially for class II [37-58]. Table 1 shows the classification of bacteriocins described by Diep et al. [32] and Cotter et al. [58] as follows: Class I: named lantibiotics, because they are post-translationally modified. These substances contain amino acids such as lanthionine and β-methyl lanthionine, and many dehydrated amino acids [59,60]. Based on the structural characteristics and mode of action, lantibiotics have been subdivided into two subgroups: A and B. Type A lantibiotics inhibit depolarization-sensitive cells of the cytoplasmic membrane [61,62] these are larger than type B lantibiotics and their size varies between 21 and 38 amino acids. The best bacteriocin studied of Gram-positive bacteria [63]. Nisin has a dual mode of action: (1) They bind to lipid II, the main transporter of peptidoglycan subunits from the cytoplasm to the cell wall, and therefore prevent correct cell wall synthesis, leading

CLASS	SUBCLASS	EXAMPLES	REFERENCE
Class I Lantibiotics < 5 KDa	<i>Ia: Cationic linear peptides.</i>	Nisin Epidermin	[154] [123]
	<i>Globular peptides without charge or net charge negative.</i>	Lactacin 3147 Mersacidin	[156] [95]
Class II Bacteriocins heat-stable unmodified < 10 kDa	<i>Ila: Anti-Listeria bacteriocins similar to pediocin.</i>	Pediocin PA-1 Enterocin A	[11]
	<i>Ilb: Heterodimeric Bacteriocins.</i>	Lactacin F Lactococcin G	
	<i>Ilc: Sec-dependent Bacteriocins.</i>	Bacteriocin 31 Enterocin P	[52]
	<i>Ild: Bacteriocins without leader peptide.</i>	EJ97 Enterocin L50 AS-48	[37,41,76]
	<i>Ile: Cyclical Bacteriocins.</i>	Circularin A Gassericin A	[11]
Class III Large heat-labile proteins (Bacteriolisins) * > 30 Kda	<i>Ilf: Nonclustered Bacteriocins.</i>	Lactococcin A Enterocin B	[54]
		Helveticin J Enterolisins A	

Table 1: Classification of bacteriocins based on classifications proposed by Diep et al. [23,32,53] and Cotter et al. [58,68]. Class IV (non-protein motifs bacteriocins) is not included because it has not demonstrated the existence of members of this class. * It is suggested that this class is not considered as bacteriocins.

to cell death, and (2) they employ lipid II as a docking molecule to initiate a process of membrane insertion and pore formation that leads to rapid cell death [64]. The type B lantibiotics are more globular secondary structure and do not exceed the 19 amino acids long. The type B lantibiotics works through enzyme inhibition. An example is the mersacidin, which interferes with cell wall biosynthesis [65]. The other well studied lantibiotic, Lacticin 3147, consists in two lantibiotic peptides that synergistically display antimicrobial activity [66,67]. It was shown that the dual activities could be distributed across two peptides: While one resembles type B lantibiotic mersacidin, which depolarizes the membrane, the other one is more similar to the type A lantibiotic class pore formers [68]. Bacteriocins of LAB class II are also small, ranging in size from 30 to 60 amino acids, are heat stable and contain no lanthionine in peptides [69]. These are further classified into 6 subgroups: Class IIa: are potent inhibitors of *Listeria* species, showing activity at low nanomolar concentrations. These bacteriocins are heat-stable and not post-translationally modified beyond the proteolytic removal of a leader peptide and the formation of a conserved N-terminal disulfide bridge (although some members contain an additional C-terminal disulfide bridge). The N-terminal region contains a characteristic YGNGV amino acid sequence, although variants with the alternate YGNGL sequence have been classified in class IIa. Briefly, class IIa bacteriocins kill susceptible bacteria by forming pores in their membranes. Initially, the bacteriocins are attracted by electrostatic interaction and then inserted in the membrane forming pores. This mechanism of action is dependent on a complex protein Mannose-Phosphotransferase (MPT) found in the membranes of susceptible organisms, but the exact nature [70]. Class IIb bacteriocins, act forming pores in the membranes of their target cells and are composed of two proteins that function complementarily. The subgroup IIc consists of bacteriocins that are sec-dependent. The subgroup IId is not leader peptide Bacteriocins and transport systems used are typical of the bacteriocin (specific). The subset IIe are Cyclic Bacteriocins and finally the subgroup consisting of Bacteriocins IIIf not clustered in the above classifications. Class III bacteriocins are large proteins and heat sensitive. The proposed additional class of bacteriocins (IV) is characterized by incorporating groups such as carbohydrates or lipids in the molecule to be active. Little is known about the structure and function of this class, some examples include leuconocin S [71] and lactocin 27 [72].

Several reports described the *Enterococcus*’ production of bacteriocins, also named enterocins. Most studies have been conducted on the species *E. faecalis* and *E. faecium* [73-75]. The best enterocin characterized from the genetics and biochemistry viewpoint is AS-48,

which presents the most unusual feature of being a circular protein, having a broad spectrum of action. For this reason, Kemperman et al. [76] and Maqueda et al. [77], proposed to include the enterocin AS-48 in a new class (class V) of circular bacteriocins. LAB’s bacteriocins enterococci have certain general characteristics [78,79]: a) can be readily isolated from fermented foods, are stable to the action of heat (up to 70-100°C 5 min), b) retain activity in a wide pH range (pH 4-8), c) have important biological activity on *Listeria* spp. and bactericidal activity (*Listeria*, *Clostridium*, *Staphylococcus*). The most notorious enterocins characterized are shown in Table 2. Other enterocins have been discovered and characterized at the present, such as AP-CECT7121 isolated from a strain of *E. faecalis* recovered from corn silage [80]. This antimicrobial peptide have a broad spectrum of inhibitory activity against Gram-positive bacteria such as *Listeria* spp., other species of *Enterococci*, *S. aureus*, *Streptococcus* spp., *Bacillus* spp. and *Clostridium* spp. and some Gram-negative like *E. coli* and *Shigella* spp. [81,82]. It has also been reported *in vivo* antiparasitic activity [83], immunomodulation properties [84,85], antitumor action [86] and food biopreserver [80]. AP-CECT7121 is stable at a pH range of 4.0-8.0. This enterocin belong to in the group II of the classification of [87]. When the bacteriocin AP-CECT7121 was studied against Gram-positive and Gram-negative a broader spectrum of inhibition was observed compared with other bacteriocins [31,88,89]. The fact that the enterocin maintain inhibitory activity at different pH from 4 to 8, gives this potential use in fermented food which is subject to variations in pH during processing and maturation [90]. The action mechanism of this peptide would involve the formation of pores in the cytoplasmic membrane and the output of cellular material, as observed with enterocin 100 and AS-48 [91,92]. Other studies conducted “*in vitro*” showed the effectiveness of this peptide against a broad range of bacteria resistant Gram-positive aerobic and anaerobic conditions many of which were associated with multidrug resistance to conventional antibiotics [82]. Also the AP-CECT7121 enterocin has shown activity *in vitro* on common bacteria that produce mastitis in cattle [81]. Studies performed with the plasmid CECT7121 enterocin indicate that the plasmid contains genes encoding both its production and immunity. The broad spectrum of inhibitory activity, its stability in a wide range of pH and temperature (heat resistant, inactivation occurs at 15 minutes at 121°C) make the AP-CECT7121 enterocin is a molecule to be studied as a preservative food, as well as therapy of common infectious diseases refractory produced in human and veterinary medicine.

Applications of Bacteriocins in Food

A wide range of bacteriocins produced by BAL have been intensively

Microorganism	Bacteriocin	Type	Mass Da)(aminoacids)
<i>E. faecalis</i>	Cytolysin	Class I two-peptide	3,458 (38), 2,032 (21)
<i>E. faecium</i>	Enterocin A	Class IIa Pediocin-like	4,829 (47)
<i>E. faecium</i>	Enterocin P	Class IIa Pediocin-like	4,493 (44)
<i>E. faecium</i>	Bac 32	Class IIa Pediocin-like	7,998 (70)
<i>E. faecium</i>	Bacteriocin GM-1	Class IIa Pediocin-like	4,630 (44)
<i>E. faecalis</i>	Bac 31	Class IIa Pediocin-like	(43)
<i>E. mundtii</i>	Mundticin ATO6, Mundticin KS	Class IIa Pediocin-like	4,287 (43)
<i>E. faecalis</i>	Enterocin SE-K4	Class IIa pediocin-like	5,356.2 (43)
<i>E. faecium</i>	Bacteriocin T8	Class IIa pediocin-like	5,090 (44)
<i>E. faecium</i>	Enterocin B	Class IIa	5,479 (53)
<i>E. faecalis</i>	Enterocin 1071A, enterocin 1071B	Class IIb two-peptide	4,285 (39), 3,897 (35)
<i>E. faecalis</i>	MR10A MR10B	Class IIc, leaderless	5,202 (44), 5,208 (43)
<i>E. faecium</i>	Enterocin L50; L50A, L50B	Class IIc, leaderless	5,190 (44), 5,178 (43)
<i>E. faecium</i>	Enterocin Q	Class IIc, leaderless	3,980 (34)
<i>E. faecalis</i>	Enterocin EJ97	Class IIc, leaderless	5,328 (44)
<i>E. faecium</i>	Enterocin RJ-11	Class IIc, leaderless	5,049 (44)
<i>E. faecalis</i>	AS-48	Class IIId circular bacteriocin	7,166 (70)

Table 2: Classification of enterocins described from Nes et al., 2007.

investigated enabling detailed chemical characterization [93]. Because BAL has been used for centuries to fermented foods, they are generally regarded as safe by the FDA (Food and Drug Administration). Nisin was the first bacteriocin isolated and approved in 1988 by FDA, for using in foods specifically to prevent the outbreak of *Clostridium botulinum* spores in cheese spread in England [94]. The use of nisin has a long history and is currently used as a safe food preservative in about 48 different countries [93]. The attention of bacteriocin researchers were focused on the bacterium *Listeria monocytogenes*, the causative agent of listeriosis, because the frequency of outbreaks of infection combined with increased natural resistance of the causative agent. Furthermore, the study of this bacterium was interesting because of its ability of growing at refrigerated ion temperatures close to that used for traditional food preservation. This led to the isolation of a large number of Class IIa bacteriocins, which are highly active against *L. monocytogenes* [95]. Bacteriocins have also been used in cured meat, milk, cheese and soybean meal [49].

Pediocin, is a class IIa bacteriocin made by lactic acid producing bacteria. A pediocin producing strain has also been added to sausages finding a reduction in bacterial numbers approximately 10 000 times compared to untreated sausage number [96]. In addition, the active pediocin was found in the inlays two months after cooling. Another example of a bacteriocin that could be used in the food industry is the piscicolin, a bacteriocin from another lactic acid producing bacteria [96]. The piscicolin has already been patented and will soon be used in meat products and to wash salad greens [96]. The Acidocin LCHV is another antimicrobial peptide produced by *Lactobacillus acidophilus* n.v. Er 317/ 402 strain Narine, probiotic bacteria widely used as a supplement to dairy milk [97]. A number of other bacterially derived AMPs are also used as food preservatives [98,99]. AP-CECT7121 is a peptide with potential application in the food industry, for its broad spectrum of antimicrobial activity, its stability to different temperatures and pH range [80]. A study in dry sausages was undertaken to evaluate its performance as biopreservative, showing good peptide activity against food pathogens with the advantage of not affecting the growth of *Lactobacillus* spp. [80].

One concern about the use of bacteriocins for food preservation is the selection of resistant strains. BAL studies have shown the generation of resistant strains of bacteriocin activity after having exposed the sensitive strain at 25 cycles of continuous growth in the presence of the bacteriocin [100]. Treatment with a combination of bacteriocins, such as nisin could theoretically reduce the incidence of resistance [101,102]. An additional concern is whether the resistance to a class of bacteriocin BAL may result in cross-resistance with other kinds of bacteriocin [101]. However, the diverse chemical nature of bacteriocins suggest different modes of action, which leads to believe that cross-resistance is more difficult to obtain, although, it has been reported some cross-resistance between different bacteriocins within the class IIa [103]. Interestingly, at the present there are not described disadvantages of using of bacteriocins in food.

In Vivo Utilization of Bacteriocins and Biomedical Applications

Bacteriocins have been primarily explored as natural food preservatives, but there is much interest in exploring the application of these peptides as therapeutic antimicrobial agents. Several bacteriocins possess antimicrobial activity against several important human pathogens. The use of bacteriocins *in vivo* has been focused on the introduction of probiotic bacteria in the gastrointestinal tract. Fewer

studies have been conducted by administering the purified bacteriocin itself in animals. The use of probiotic strains could be beneficial as a prophylactic, but the use of purified bacteriocins seems to be higher to offset an established infection. This has been demonstrated by administration of PA-1 pediocin *Pediococcus acidilactici* UL5, a producer of pediocin PA-1, to mice infected with *L. monocytogenes* [104].

A major concern regarding the use of antibiotics is the effect on the body's microbiota. The presence of commensal bacteria provides a barrier of great value for infection by opportunistic pathogens. Ideally, an antimicrobial agent should have specific activity on pathogenic bacteria with minimal impact on the natural microbiota. PA-1 pediocin has been tested *in vitro* against human intestinal bacteria such as bifidobacteria and at the concentrations tested, no antagonistic activity was observed. In contrast, in similar studies, lantibiotics such as nisin class I A and nisin Z, showed inhibition against most of the Gram-positive strains tested [105,106].

Relationship between Administration Route and Efficacy

In vivo studies in mouse model pediocin PA-1 had no effect on the intestinal microbiota [107] unlike conventional antibiotics such as penicillin and tetracycline [106]. Other studies undertaken in mice infected with *L. monocytogenes*, reported the use of two different routes of administration of the bacteriocin: intravenous [108,109] and intragastric [104]. Piscicolin 126, RV41 divercin recombinant (DvnRV41) and structural variants of DvnRV41 were administered intravenously to mice immediately before infection with *L. monocytogenes* [108,109]. Injection of both bacteriocins was effective in 15 minutes pre-challenge and 30 minutes after challenge. However, administration of 126 piscicolin 24 hours after challenge showed no significant reduction in the count of *Listeria*. Both of these experiments used only 2 g of purified bacteriocin. The fact that *Listeria* is an intracellular pathogen may explain the lack of sensitivity observed after administration of bacteriocin 24 hours after challenge [110]. One concern with the intravenous administration of peptides is the possibility of generate immune response. To corroborate the latter, pediocin ACH was introduced intraperitoneally in mice and rabbits to determine its antigenic properties, showing no effect on antibody response, appearing to be not immunogenic [111].

The intragastric administration of bacteriocins has also been studied on Class IIa bacteriocins, which are susceptible to common digestive proteases. However, IIa bacteriocins tend to be relatively stable to acidic conditions, and pediocin PA-1 was stable at pH 2.5 for at least two hours [112]. The stability of bacteriocins in the gastrointestinal tract has been examined by passing purified pediocin PA-1 through an artificial system mimicking the human stomach and small intestine [113]. Pediocin PA-1 activity retained after 90 minutes in artificial gastric conditions, whereas all activity was lost once the sample was in the duodenal compartment. It was suggested that pancreatin in the duodenum was responsible for cleaving the end of PA-1 pediocin, while a combination of pepsin and low pH may be responsible for the decrease of the activity observed in the gastric chamber [107]. However, intragastric administration of PA-1 pediocin has proven effective to reduce the load *L. monocytogenes* in a mouse model [104]. Moreover, different pharmacothechnic strategies for protecting bacteriocins have been assayed. The peptide encapsulation may preserve the power in the bacteriocin gastrointestinal tract, although this has not been reported for IIa bacteriocins. However, the nisin's liposome encapsulation has shown some success in other studies [114,115]. Intragastric administration of PA-1 pediocin in mice

infected with *L. monocytogenes* has been examined by Dabour et al. [104], were 250 µg of treatment with PA-1 pediocin daily for three consecutive days resulted in a 2 log reduction in fecal *Listeria* account. *L. monocytogenes* in general comes through the epithelium barrier, after entering the small intestine and then extending the system of liver, spleen and central nervous systems [110]. This bacteriocin treatment was found to decrease the amount of *L. monocytogenes* reaching the liver and spleen [104].

Current and Potential Applications in Veterinary and Human Medicine

The lack of toxicity of bacteriocins to humans and animals and the activity to pathogenic bacteria became these peptides in potential therapeutic alternatives.

Treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE) in pre-clinical trials

It has been demonstrated in pre-clinical trials that Mersacidin, a lantibiotic produced by *Bacillus* sp. strain HIL Y-85 54728 [116], inhibits *in vivo* the growth of MRSA strains in murine model [117]. The mechanism of action of mersacidin is through the inhibition of the cell wall synthesis, being its efficacy similar to the antibiotic vancomycin [118,119]. Other peptide, Lacticin 3147, which is a bacteriocin isolated from *Lactococcus lactis* subsp. *Lactis* also inhibits *in vitro* the growth of *S. aureus*, MRSA and VRE [120]. Other potential peptide named AP-CECT7121 (bacteriocin isolated from *Enterococcus faecalis* CECT7121) [80] has shown *in vitro* efficacy against some strains of enterococcal and streptococcal, hospitalary and community-acquired methicillin-resistant *S. aureus* [82].

Treatment of skin infections

Mersacidin is also active against *Propionibacterium acnes* having a potential use in the treatment of acne [121-124]. Epidermin, lantibiotic isolated from *Staphylococcus epidermidis* is also effective in treating skin infections [123]. This peptide is active against *P. acnes* and *Micrococcus flavus* [121,125]. Gallidermin, lantibiotic isolated from *Staphylococcus gallinarum*, has also proven effectiveness against skin infections [123]. This peptide is also active against *P. acnes*, *Staphylococcus simulans* and *Micrococcus flavus* [121,125].

Prevention of tooth decay and gingivitis

Nisin has been included in mouthwashes as antimicrobial activity against bacteria that produce plaque and gingivitis [126]. Lacticin 3147 inhibits the growth of *Streptococcus mutans* associated with dental caries [120]. Salivaricin A2 and B, isolated from *Streptococcus salivarius* inhibit bacteria associated with bad breath [127]. Mutacin 1140, bacteriocin isolated from *Streptococcus mutans* is active against bacteria from caries [128].

Infections caused by contaminated biomedical implant devices

Nisin adsorbed to surfaces silanized, prevent the growth of *Listeria monocytogenes* [129]. Other study carried out on PVC tracheotomy tubes coated with Nisin, indicated that Nisin prevent the colonization of *S. aureus*, *S. epidermidis*, and *Streptococcus faecalis* [130].

Upper respiratory tract infections

Nisin inhibited the growth of *S. pneumoniae* associated with

otitis media in *in vivo* trials [131]. Nisin may also inhibit the growth of *P. aeruginosa* when used in combination with polymyxin E and clarithromycin [132]. ST4SA peptide, a class II bacteriocin, showed efficacy against Gram-positive bacterial pathogens of the middle ear compared with other antimicrobial agents [133]. Bcn5 bacteriocin showed *in vivo* efficacy against *Mycobacterium tuberculosis* in a murine model of experimental infection, but it was less effective than the clinically used antibiotic, rifampicin [134]. Nisin F showed *in vivo* efficacy against *S. aureus* in the respiratory tract of immunosuppressed rats when administered intranasally [135].

Systemic Infections

Pediocin PA-1 produced by *Pediococcus acidilactici*, is active against various strains of *L. monocytogenes* [136,137]. Furthermore, Pediocin PA-1 has the advantage of not inhibiting other intestinal bacteria when administered intragastrically, compared to Nisin A and Nisin Z [106]. Also, it has been demonstrated that Piscicolin126 was active against *Listeria monocytogenes* in various tissues in murine model [108]. A similar effect has been reported for Abp118, a bacteriocin produced by *Lactobacillus salivarius* UCC118 and for Divercin V41 [109-138]. Nisin inhibits *Clostridium botulinum* [139], *Clostridium tyrobutyricum* [140] and *Clostridium difficile* [141]. AS-48 bacteriocin produced by *Enterococcus faecalis*, inhibits the growth of *Salmonella choleraesuis* [142]. Enterocin 012 isolated from *Enterococcus gallinarum* 012, is active against *Salmonella typhimurium* [143]. The peptide AP-CECT7121 inhibits *in vitro* the growth of *Clostridium perfringens* and *C. difficile* [82].

Stomach ulcers

Interestingly, it has been reported that Nisin, Lacticins A164 and BH5 inhibit *in vitro* the growth of *Helicobacter pylori* and therefore would have potential application in treating stomach ulcers [139-144]. However, no *in vivo* studies have been reported at the present.

Inflammation and allergy

It has reported that Duramycin B and C, and Cinnamycin are lantibiotics, which act indirectly by inhibiting phospholipase A2, sequestering the substrate phosphatidylethanolamine [145,146] have potential as anti-inflammatory drugs [126].

Treating high blood pressure

Cinnamycin and Ancovenin are two lantibiotics that inhibit angiotensin converting enzyme [121-147], so they would have potential for treating high blood pressure [148].

Infections of the urogenital tract

Subtilisin A, originally isolated from wild-type *B. subtilis* 168 by [149] and recently found in *B. amyloliquefaciens* [150] is active against *Gardnerella vaginalis* and offers the advantage of not inhibit *Lactobacillus* part of the natural microflora in the vagina [150].

Spermicidal activity and potential contraceptive

Nisin also showed contraceptive activity [151] and protective vaginal animal studies [35]. Subtilisin also showed potent spermicidal activity *in vitro* studies with human sperm [152] and also *in vivo* studies in animals [153].

Bovine bacterial mastitis

Nisin is effective in the treatment of bovine mastitis, being approved by FDA by intramammary administration in dairy cattle [154,155].

Other bacteriocins, like Lacticin 3147 have shown inhibition against streptococci and staphylococci causing bovine mastitis [156]. LFB112, bacteriocin produced by *Bacillus subtilis*, also inhibited the growth of *S. aureus* associated with mastitis [157]. Macedocin ST91KM, bacteriocin produced by *Streptococcus gallolyticus* subsp. *macedonicus* could also be considered an alternative in treatment of mastitis coil since this peptide inhibits *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *dysgalactiae*, *Streptococcus uberis*, *Staphylococcus aureus* and *Staphylococcus epidermidis*, including resistant strains methicillin and oxacillin [158-159]. Other peptide named AP-CECT7121 has also shown *in vitro* efficacy against *Staphylococcus aureus*, *Streptococcus dysgalactiae*, *S. uberis*, *S. agalactiae* strains isolated from dairy cattle with mastitis [81].

Parasitic infections

AP-CECT7121, bacteriocin isolated from *Enterococcus faecalis* CECT7121 showed antiparasitic activity on *Toxocara canis* through studies *in vitro* and *in vivo* mouse model of experimental infection [83-160].

AMPS Cytotoxicity

Class IIa bacteriocins have been primarily explored as natural food preservatives, but there is much interest in exploring the application of these peptides as therapeutic antimicrobial agents [70]. The suitability of bacteriocins as pharmaceuticals is explored through determinations of cytotoxicity, effects on the natural microbiota, and *in vivo* efficacy in mouse models.

One advantage of bacteriocins from other antimicrobial treatments is their composition. These peptides are metabolized easily to amino acids, which also involves the disadvantage of being shorter in their antimicrobial activity. *In vitro* cytotoxicity studies with bacteriocins have been made. The Cytotoxicity of PA-1 pediocin was tested against simian virus 40-transfected Human colon cells and Vero monkey kidney cells [161], showing cytotoxic effects in both cell lines, with a dose of bacteriocin 700 AU / ml (probably about 10-20 mg / ml) caused a greater reduction 50% viable cell counts. Lower doses also affected the viable cell count, although this was not so dramatic. However, combinations of carnobacteriocins BM1 and B2 at concentrations 100 times greater than required for antimicrobial activity showed no significant cytotoxic effects on human intestinal cell line Caco-2 [162]. The means of production and purification of bacteriocins should also be considered in toxicity studies. As with all antibiotic therapy, development of resistance to bacteriocins in bacterial pathogens is a critical issue to consider. This topic has been the subject of a recent review of Kaur et al. [163]. Of particular concern is that cross-resistance has been observed for the bacteriocins of different classes. For example, a strain of *L. monocytogenes* have shown resistance to Nisin, Pediocin PA-1, and S Leuconocin, bacteriocins of three separate classes [164]. On this basis, the possibility of using multiple bacteriocins to overcome resistant strains may not be entirely feasible. Like other antibiotics, bacteriocins need to be used with caution in order to minimize the spread of resistance phenotypes.

At the present, scarce "*in vivo*" studies had been focused on characterize the side effects of the bacteriocins. The short protease-mediated half life of bacteriocins, which imply its fast degradation, thought the possibility that bacteriocins may have lesser side effects than conventional antibiotics.

Conclusions

Bacteriocins are a promising substitute for conventional antibiotics

for several reasons. Its narrow spectrum towards restricted target specificity (peptides target-design) of some bacteriocins minimizes their impact on commensal microbiota and may decrease the threat of opportunistic pathogens. Furthermore, most bacteriocins are active at lower concentrations, and their degradation products are easily metabolized by the body which probably, lesser side effects compared with conventional antibiotics. With the development of resistance to many important antibiotics, another tool for fighting bacteria is invaluable.

Much of the research on bacteriocins has focused on their application for food preservation. Bacteriocins are active against several important human pathogens. Perhaps most promising is their activity against the foodborne pathogen *Listeria monocytogenes*, the deadliest bacterial source of food poisoning. Up to 30% of foodborne infections by *L. monocytogenes* in high-risk individuals are fatal. Other bacterial foodborne pathogens inhibited by some bacteriocins include *Bacillus cereus*, *Clostridium botulinum*, and *C. perfringens*. Beyond foodborne pathogens, bacteriocins are also active against other human pathogens, such as vancomycin-resistant enterococci and the opportunistic pathogen *Staphylococcus aureus*. Bacteriocins also show other potentially therapeutic properties as antineoplastic and antiviral agents. Although relatively little has been published on the use of bacteriocins *in vivo* to control bacterial infection, what is known is promising. Preliminary experiments have shown that some of these bacteriocins are effective in fighting infection by *L. monocytogenes* in mouse models. Now more is known about the mode of action of bacteriocins, and bacteriocins attempts engineering more power and stability have been successful. The application of bacteriocins as therapeutic agents is a rapidly developing area, and much remains to investigate.

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