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MINIREVIEW

Characteristic of Bacteriocines and their Application

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Abstract

Bacteriocines are small peptides with anti-bacterial properties. They are produced both by Gram-positive and Gram-negative bacteria. Until now, a few hundred bacteriocines were described. Classification of bacteriocines undergoes continuous alterations, as new developments regarding their structure, amino acid sequence and recognised mechanism of their action are available. Some of bacteriocins (lantibiotics) contain atypical amino acids, such as lantionine (Lan), methyllantionine (MeLan), dehydroalanine (Dha), dehydrobutyrine (Dhb), or D-alanine (D-Ala). The best recognized bacteriocines are produced by lactic acid bacteria, including nisine produced by strains of *Lactococcus lactis*. These bacteriocines have been recognized to be fully safe for humans. At present, nisine is used in food industry, as a preserving agent. Other lactic acid bacteria bacteriocines and probiotic preparations provide an alternative for antibiotics, and are used in food and in animal feed.

Key words: *Lactobacillus* sp., antimicrobial peptides, bacteriocines, enterocines, lactic acid bacteria, lantibiotics

1. Introduction

Bacteriocines include low molecular weight peptides exhibiting anti-bacterial properties, which are targeted at species closely related to their producer (Casaus *et al*., 1997; Cintas *et al*., 1998). They are produced both by Gram-positive (*Lactobacillus*, *Lactococcus*, *Streptococcus*, *Enterococcus*, *Leuconostoc*, *Pediococcus*, *Propionibacterium*), and by Gram-negative bacteria (*Escherichia coli*, *Shigella*, *Serratia*, *Klebsiella*, *Pseudomonas*) (Cintas *et al*., 1998; Nes *et al*., 2007; Oppegård *et al*., 2007; Cascales *et al*., 2007). Due to their function and structural similarity bacteriocines belong to the group of anti-bacterial compounds, which also includes defensins (produced by mammals), tionines (produced by plants), mangaines (secreted by frogs) or mellitin (present in bee venom). Until now, a few hundred bacteriocines were described (Bactibase, 2013; Bagel, 2013). Interest in bacteriocines reflects potential application of the metabolites and bacteriocine-forming microbes as natural food preserving agents (Delves-Broughton *et al*., 1996; de Carvalho *et al*., 2010).

2. Bacteriocines of Gram-positive bacteria

Bacteriocines produced by Gram-positive bacteria were classified for the first time by Klaenhammer in 1993 (Klaenhammer, 1993). Classification of bacteriocines, including enterocines, undergoes continuous alterations, linked to studies on their structure, amino acid sequence and recognised mechanism of their action. The purpose of this review is to present recent classification of bacteriocines, taking into account, their molecular weight, presence of the YGNGVXC motif, disulphide bridges, activity towards *Listeria* sp., and sensitivity to temperature (Jack *et al*., 1995; van Belkum and Stiles, 2000; Franz *et al*., 2007; Nes *et al*., 2007).

Class I of bacteriocines produced by Gram-positive bacteria encompasses lantibiotics or thermostable peptides of molecular weight below 5 kDa. They undergo postranslational modification and contain atypical amino acids, such as lantionine (Lan), methyllantionine (MeLan), dehydroalanine (Dha), dehydrobutyrine (Dhb), or D-alanine (D-Ala) (Nissen-Meyer *et al*., 2009). Lantibiotics are divided into two groups: lantibiotics of type A and of type B, each group manifesting distinct structural and functional properties. Type A lantibiotics groups elongated molecules, acting by permeabilization of cytoplasmic membrane in sensitive cells while lantibiotics of type B include globular molecules of a variable manner of action.

The best recognized bacteriocine of class I is nisine (Fig. 1), produced by certain strains of *Lactococcus lactis*. Nisine manifests a broad range of anti-bacterial activity directed against Gram-positive bacteria, such as *Enterococcus*, *Leuconostoc*, *Lactococcus*, *Lactobacillus*,

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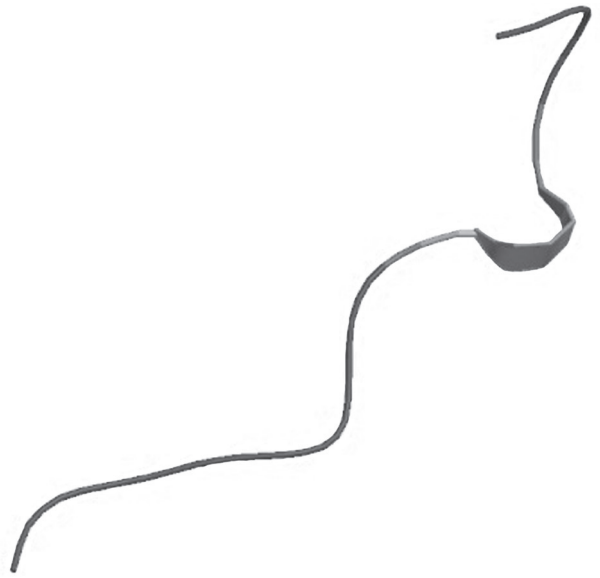

Fig. 1. Tertiary structure of nisine A
(the model generated using I-TASSER server, 2012)

Staphylococcus, *Micrococcus*, *Pediococcus*, *Listeria*. It prevents also against formation of spores and inhibits development of vegetative bacterial cells of *Bacillus* and *Clostridium* genera (Delves-Broughton *et al*., 1996; Cintas *et al*., 1998; Cheigh and Pyun, 2005).

Class II groups non-lantibiotic bacteriocines, which contain no lantionine. They are thermostable bacteriocines of molecular weight below 10 kDa. Bacteriocines of this class do not undergo posttranslational modification. Differences in their structure permitted to distinguish four subclasses. The subclass IIa includes pedicine-like bacteriocines with strong activity against bacteria of *Listeria* genus. They carry a hydrophilic cationic region with a conserved Tyr-Gly-Asn-Gly-Val-X-Cys (YGNGVXC) motif and two cysteins linked by a disulphide bridge (van Belkum and Stiles, 2000; Franz *et al*., 2007). The bacteriocines of this subclass exhibit high sequence homology (38–80% identity of amino acid sequences), particularly within the N-terminal region. On the other hand, the C-terminal region is more hydrophobic and differentiated (Casaus *et al*., 1997; Feng *et al*., 2009). Common characteristic of subclass IIa bacteriocins is their strong inhibitory activity against the *L. monocytogenes* (Nishie *et al*., 2012).

The subclass IIb groups dipeptide bacteriocines. They contain a single disulphide bridge, may contain the N-terminal sequence of Tyr-Gly-Asn-Gly-Val-X-Cys (van Belkum and Stiles, 2000) or be devoid of it (Franz *et al*., 2007). Within the subclass IIb investigators distinguish bacteriocines, such as lactococcin G from *L. lactis*, lactacin F from *Lactobacillus johnsonii*, and lactocin 705 from *Lactobacillus casei,* that require the presence of both peptides for the activity, since separately neither of them manifests antibacterial activity, *e.g.* (Nissen-Meyer *et al*., 1992; Allison *et al*., 1994; Cuozzo *et al*., 2000; Garneau *et al*., 2002). The second subgroup of IIb includes bacteriocines in which a single or both peptides manifest activity although their combination increases the activity, *e.g.* thermophilin 13 from *Streptococcus thermophilus*, and ABP-118 from *Lactobacillus salivarius* (Marciset *et al*., 1997; Flynn *et al*., 2002).

The subclass IIc groups bacteriocines that are secreted *via* the Sec pathway, termed the sec-dependent bacteriocines. They contain a single disulphide bridge but they carry no N-terminal sequence of Tyr-Gly-Asn-Gly-Val-X-Cys (van Belkum and Stiles, 2000; Franz *et al*., 2007).

The subclass IId encompasses bacteriocines which are distinct in their structure, secretion mechanism and manner of action from bacteriocines classified in subgroups of IIa-IIc. Their example involves enterocines L50 (EntL50A and EntL50B), produced by *Enterococcus faecium* L50. The EntL50 system resembles dipeptide bacteriocines since the two peptides act synergistically although their sequence shows no similarity to bacteriocines of subclasses IIa-IIc, and they are secreted from their producer with no involvement of the signal peptide (Cintas *et al*., 1998; Cintas *et al*., 2000). The subclass IId contains also bacteriocines activated by thiol groups, such as lactococcin B (Venema *et al*., 1993).

Class III includes bacteriocines of molecular weight above 30 kDa. They are thermolabile and are produced mainly by Gram-positive bacteria (van Belkum and Stiles, 2000). The large bacteriocins of Gram-positive bacteria can be further subdivided into two distinct groups: group of the bacteriolytic enzymes (or bacteriolysins), which facilitate the killing of sensitive strains by cell lysis *e.g.* lysostaphin produced by *Staphylococcus aureus* and enterolysin A produced by *Enterococcus faecalis* (Thumm and Gotz, 1997; Nilsen *et al*., 2003), and group of the non-lytic antimicrobial proteins *e.g.* helveticin J, produced by *Lactobacillus helveticus* (Joerger and Klaenhammer, 1986).

Class IV includes bacteriocines which for full activity require presence of a lipid portion or a carbohydrate portion of their molecule (Jack *et al*., 1995).

Principal characteristics of selected bacteriocines (other than enterocines) are presented in Table 1.

2.1. Bacteriocines of lactic acid bacteria

Lactic acid bacteria (LAB) form a non-uniform group with the common property of the ability of anoxic saccharide fermentation. The bacteria include Gram-positive cocci and rods belonging to, *Lactobacillus, Lactococcus*, *Bifidobacterium*, *Streptococcus*, *Leuconostoc* or *Pediococcus* genera. The milk fermentation bacteria are able synthesize several antimicrobial substances. In line with bacteriocines, they produce high

Table I
Basic characteristics of selected backteriocines of Gram-positive bacteria (excluding enterocines)

Classes of bacteriocines	Bacteriocine	Molecular weight	Producing strain	Activity against bacteria
Class I	Nisin A (Delves-Broughton *et al*., 1996; Cintas *et al*., 1998; McAuliffe *et al*., 2001)	5963 Da	*Lactococcus lactis* subsp. *lactis*	*Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Listeria*, *Staphylococcus*, *Micrococcus*, *Pediococcus*, *Clostridium*, *Bacillus* (genera)
	Nisin Z (Mulders *et al*., 1991)	5940 Da	*Lactococcus lactis* subsp. *lactis*	*Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Listeria*, *Clostridium*
	Nisin U (Wirawan *et al*., 2006)	5863 Da	*Lactococcus uberis*	*Streptococcus pyogenes, S. uberis, S. agalactiae, S. dysgalactiae, S. mitis, Staphylococcus simulans, S. cohnii, Lactococcus lactis, Lactobacillus acidophilus*
	Mutacin B-Ny266 (Mota-Meira *et al*., 1997)	2425 Da	*Streptococcus mutans*	*Gram-positive bacteria*
	Salivaricin A (Ross *et al*., 1993; Wescombe *et al*., 2006)	2315 Da	*Streptococcus salivarius*	*Gram-positive bacteria*
Class II Subclass IIa	Lactococcin MMFII (Ferchichi *et al*., 2001a; 2001b)	4145 Da	*Lactococcus lactis*	*Enterococcus*, *Lactobacillus*, *Lactococcus*, *Listeria* (genera)
	Mesentericin Y105 (Héchard *et al*., 1992; Fremaux *et al*., 1995)	6548 Da	*Leuconostoc mesenteroides*	*Lactobacillus, Leuconostoc, Pediococcus*, *Listeria* (genera)
	Ubericin A (Heng *et al*., 2007)	7681 Da	*Streptococcus uberis*	*Listeria* sp., *Enterococcus faecalis, E. hirae, Streptococcus bovis, Lactococcus lactis*
	Leucocin A (Hastings *et al*., 1991)	3932 Da	*Leuconostoc gelidum*	*Lactobacillus* sp., *Listeria monocytogenes*
	Curvacin A (Tichaczek *et al*., 1993)	4327 Da	*Lactobacillus curvatus*	*Lactobacillus*, *Listeria*, *Enterococcus faecalis* (genera)
	Pediocin PA-1 (Lozano *et al*., 1992; Rodriguez *et al*., 2002)	4647 Da	*Pediococcus acidilactici*	*Pediococcus*, *Lactobacillus*, *Leuconostoc*, *Listeria*, *Bacillus*, *Enterococcus*, *Staphylococcus* (genera)
Class II Subclass IIb	Lactobin-A (De Vuyst *et al*., 2004)	6537 Da	*Lactobacillus amylovorus*	*Lactobacillus* sp.
	Lactacin-F (Alisson *et al*., 1994; Contreras *et al*., 1997; Mollet *et al*., 2004)	6250 Da	*Lactobacillus johnsonii*	*Lactobacillus* sp., *Enterococcus faecalis*
	Lactocin-705 (Vignolo *et al*., 1996)	3376 Da	*Lactobacillus paracasei*	*Lactobacillus*, *Listeria*, *Streptococcus* (genera)
	Plantaricin F (Diep *et al*., 1995)	3722 Da	*Lactobacillus plantarum*	*Lactobacillus*, *Pediococcus* (genera)
Class II Subclass IIc	Carnobacteriocin-A (Worobo *et al*. 1994; Holck *et al*., 1994)	7041 Da	*Carnobacterium piscicola*	*Carnobacterium* sp., *Enterococcus* sp., *Listeria monocytogenes, Clostridium perfringens*
	Subtilosin A (Shelburne *et al*., 2007)	5813 Da	*Bacillus subtillis*	*Bacillus subtillis*, *Enterococcus faecalis*, *Escherichia coli*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Porphyromonas gingivalis*, *Enterobacter aerogenes*, *Shigella sonnei*
	Uberolisin (Wirawan *et al*., 2007)	7086 Da	*Streptococcus uberis* strain 42	*Enterococcus faecalis*, *E. hirae*, *Lactococcus lactis*, *Micrococcus luteus*, *Listeria* sp., *Staphylococcus aureus*, *Streptococcus*
	Acidocin B (Leer *et al*., 1995)	5773 Da	*Lactobacillus acidophilus* M46	*Listeria monocytogenes*, *Lactobacillus* sp., *Clostridium sporogenes*
Class III	Helveticin J (Joerger and Klaenhammer, 1986)	37512 Da	*Lactobacillus helveticus*	*Lactobacillus bulgaricus*, *Lactococcus lactis*
Class IV	Glycocin F (Venugopal *et al*., 2011)	7002 Da	*Lactobacillus plantarum*	no data

amounts of organic acids (*e.g.*, lactic acid, acetic acid) and other compounds of antimicrobial action, *e.g.* H_2O_2 (Szkaradkiewicz and Karpiński, 2013). LAB are broadly used for production of fermented food, and are responsible for a specific taste and aroma of the products. In parallel, due to production of bacteriocines they protect food from infection by other, often harmful and pathogenic bacteria. The preserving properties of lactic acid bacteria have been known for thousands of years and are broadly applied in food industry (Libudzisz, 2002).

Due to their metabolic activity, lactobacilli form an unfavourable environment for pathogenic bacteria, by producing pH-lowering compounds and bacteriocines in alimentary tract and inhibiting growth of the neighbouring bacteria (Fuller, 1989). Because of their properties, lactobacilli are frequently used in probiotic preparations. The strains of *Lactobacillus* sp. with confirmed probiotic properties usually belong to the species of *Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus helveticus*, *Lactobacillus salivarius* and *Lactobacillus plantarum* (Słońska and Klimuszko, 2010; Klewicka *et al*., 2011). Due to they probiotic properties, they inhibit growth of several pathogenic microbes, can reduce incidence of traveller's diarrhoea, alleviate the course and shorten duration of some bacterial and viral diarrhoeas (*e.g.* those induced by *Clostridium difficile, Shigella, Salmonella,* enterotoxic strains of *Escherichia coli* or rotaviruses), prevent manifestation or relieve course of post-antibiotic diarrhoeas (Salminen *et al*., 1998; Pathmakanthan *et al*., 2000; Rolfe, 2000; Sanders, 2000).

Studies documenting antagonism of probiotic bacteria towards *Helicobacter pylori* (Coconnier *et al*., 1998; Andrzejewska and Szkaradkiewicz, 2007) are also of interest. At present, it is known that bacteria of *Lactobacillus* genus manifest also antagonistic effects toward periodontopathogens, such as *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia* and *Porphyromonas gingivalis*. Presence of H_2O_2-producing strains of *Lactobacillus* in periodontal pockets prevents against development of chronic periodontitis (Szkaradkiewicz and Stopa, 2008; Szkaradkiewicz *et al*., 2011; Andrzejewska and Szkaradkiewicz, 2012).

LAB are capable of binding nitrosoamines and certain other mutagenic bacteria, *e.g.*, azo dyes, mycotoxins or amino acid pyrolysates, which corroborates their antineoplastic activity (Rafter, 1995; Burns and Rowland, 2000).

Probiotic bacteria producing bacteriocines are used in dairy industry for the production of cheeses, icecream, yoghurts, kefirs and other fermented soft drinks (Garde *et al*., 1997; Beshkova and Frengova, 2012). The best known bacteriocine used in food industry is nisine, produced by some strains of *Lactococcus. lactis*. Nisine, the only bacteriocine of the GRAS status (**g**enerally **r**ecognized **a**s **s**afe) is used in over forty countries as a conserving agent under the name E234, in meat and dairy products, vegetable and fruit preserves, fish and eggs products (Schillinger *et al*., 1999). Nisine is easily digested by trypsin and, therefore, it is non-toxic for higher organisms and humans (Piard and Desmazeaud, 1992). Along nisine**,** some other bacteriocines such as pediocine, bawaricine, piscicoline, jensenine, curvaticine, lacticine and sacacine are of technological/industry significance. In general,bacteriocines synthesized by strains of lactic fermentation bacteria such as *Lactococcus* sp., *Lactobacillus* sp., *Pediococcus* sp., *Carnobacterium* sp. and *Leuconostoc* sp. are regarded as safe to use in food preparation. In food products high biostatic activity of bacteriocines is observed in food of low pH values. This relates to fermented milk products, such as acidic-chymosin cottage cheese, yoghurts and ripening chymosin cottage cheese (Steinka, 2009).

2.2. Enterocines

Enterocines represent bacteriocines produced by bacteria of *Enterococcus* genus. Enterocines exhibit an extensive variability and broad manifestation among isolated obtained from various sources. (Klaenhammer, 1993; Gálvez *et al*., 1998; Nes *et al*., 2007). It is suggested that variability of enterocines is a result of genetic exchange between various genera of bacteria, which seems to be confirmed by, *e.g.*, similarity of sequences between enterolysine and staphylococcal lysostaphine or enterocine AS-48 (Fig. 2) and circularine produced by *Clostridium beijerinckii* (Franz *et al*., 2007). Enterococci are well known for the presence of multiple mobile genetic elements such as plasmids, or conjugative and non-conjugative transposons. Mechanism of gene transfer may induce a rapid and effective transfer of enterocine encoding genes between enterococci. An excellent example of mobile bacteriocines of clinical significance can be demonstrated by pheromone-inducible conjugative plasmids (Clewell, 1990). On the described plasmids genes encoding cytolysine, bacteriocine 31, enterocine EK97 and enterocine AS-48 were found (Tomita and Clewell, 2000; Tomita *et al*., 2008). The pheromone-inducible conjugative plasmids may also carry antibiotic resistance genes. Production of bacteriocines may also play a role in colonization of food products by enterococci, dairy and meat products in particular. Several enterocines manifest a broad spectrum of antibacterial activity towards bacteria of *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Staphylococcus*, *Listeria* or *Clostridium* genera (Franz *et al*., 2007; Nes *et al*., 2007). Because of this broad target, including *Listeria monocytogenes* and *Clostridium tyrobutyricum*, bacteriocine-producing enterococci, as well as isolated bacteriocines, are extensively studied. The goal of these

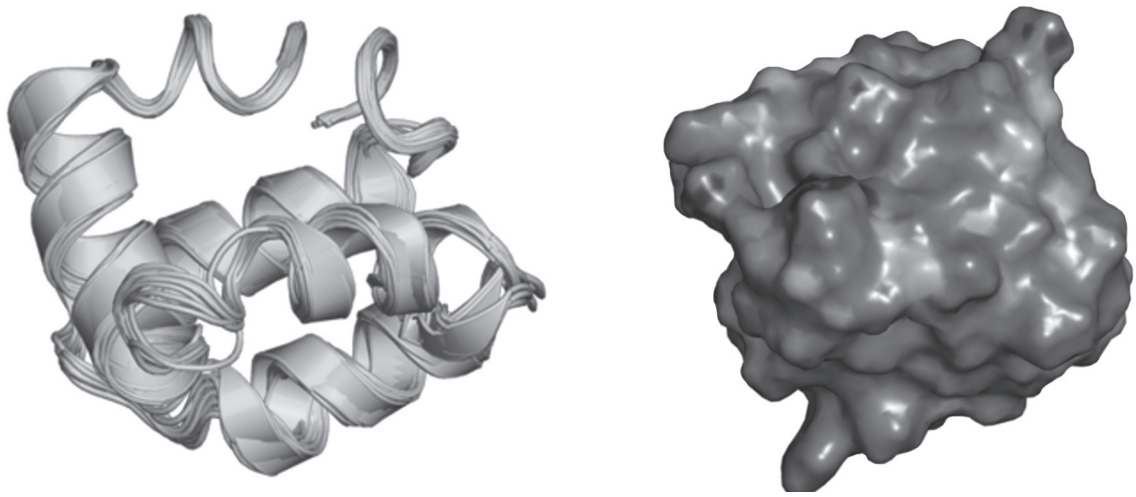

Fig. 2. Tertiary structure of enterocine AS-48 (models generated using the I-TASSER server, 2012)

investigations is mostly related to their application in production of cheese and in fermentation processes (Franz *et al*., 2007). Table II presents basic characteristics of selected enterocins.

3. Bacteriocines of Gram-negative bacteria

Extracellular antibacterial cytotoxins produced by *E. coli* which reduce competition from other bacterial strains are named colicins and microcins. Spectrum of activity manifested by bacteriocines of Gram-negative bacteria is more narrow than those produced by Gram-positive bacteria. Most frequently both the producer and the sensitive strains belong to the same family or to the same species (Šmarda and Šmajs, 1998). Principal characteristics of selected bacteriocines produced by Gram-negative bacteria are presented in Tables III.

The largest group is formed by colicines. They are synthesized by over half of *E. coli* strains and also by *Yersinia pestis* (pesticins), *Serratia marcescens* (marcescins) and by bacteria of genus: *Shigella*, *Klebsiella* (klebicins) and *Pseudomonas* (pyocins) (Cascales *et al*., 2007). Colicines are large peptides, with molecular weight of 25–80 kDa. All colicines are encoded by plasmids Col and their synthesis may be induced using UV rays or mitomycin C. Colicines exhibit antimicrobial activity targeted at closely related bacterial strains, which carry colicin-binding receptor on cell surface and produce no resistance proteins, capable of inactivating colicines (Braun *et al*., 2002).

The bactericidal action of colicines involves formation of ion channels in the cytoplasmic membrane of sensitive cells, which leads to depolarization of the membrane. Also degradation of peptidoglycan of the cell wall or inhibition of its synthesis may take place. Synthesis and export of colicines are lethal for the producer cells and result in their lysis. The group of genes responsible for colicine activity consists of a gene encoding the toxic protein, resistance-coding gene and, in most of colicines, the gene coding for a protein facilitating colicine export from the cell and inducing lysis of the cell (Šmarda and Šmajs, 1998; Gwiazdowska and Trojanowska, 2005; Cascales *et al*., 2007). Synthesis of colicines remains under control of a few mechanisms. The principal mechanism involves the SOS system, forming a proportion of gene expression control system involved in DNA repair. In standard conditions synthesis of colicines is switched off in majority of cells and becomes mobilized in stress conditions (Braun *et al*., 2002).

Microcines, the low molecular weight peptides, manifesting thermostability and a hydrophobic character, form a separate class of bacteriocines produced by Gram-negative bacteria. Microcines are synthesized by *E. coli* and by a single strain of *Klebsiella pneumoniae* identified so far (de Lorenzo and Pugsley, 1984; Pons *et al*., 2002). Based on the mechanism of their action, structure and genetic criteria two classes of microcines can be distinguished. The first class includes peptides of molecular weight < 5 kDa, which undergo posttranslational modifications and which attack mainly intracellular structures. The other class encompasses peptides of molecular weight ranging between 7 and 10 kDa, which do not undergo posttranslational modifications and which lead to damage and destruction of cell membrane of target cells (Pons *et al*., 2002; Gwiazdowska and Trojanowska, 2005). In contrast to colicines, synthesis of microcines is not lethal for their producers and is not controlled by the SOS system (Kolter and Moreno, 1992). Microcines are secreted to medium in the late logarythmic phase of growth, except of microcine Mcc E492, which is produced in the early logarythmic phase (de Lorenzo and Pugsley, 1984; Hetz *et al*., 2002).

Table II
Basic characteristics of selected enterocines

Classes of bacteriocines	Enterocine	Molecular weight	Producing strain	Activity against bacteria
Class I	Cytolysin ($CylL_{S''}$)	2031 Da	*Enterococcus faecalis*	*Enterococcus faecalis*, *Streptococcus*, *Staphylococcus aureus*, *S. epidermidis*, *Lactobacillus fermentum*, *L. plantarum*, *Bacillus cereus*, *Clostridium difficile*, *C. perfringens*, *Micrococcus* (Cox *et al*., 2005; Coburn and Gilmore, 2003; Coburn *et al*., 2004)
	Cytolysin ($CylL_{L''}$)	3437 Da	*Enterococcus faecalis*	
Class II Subclass IIa	Avicin A (Birri *et al*., 2009)	4288 Da	*Enterococcus avium*	*Carnobacterium* sp., *Enterococcus avium*, *E. faecalis*, *E. maldoratus*, *Lactobacillus rhamnosus*, *L. sakei*, *Leuconostoc lactis*, *L. mesenteroides*, *Listeria innocua*, *L. monocytogenes*, *Pediococcus acidilactici*, *P. pentosaceus*
	Enterocin A (Aymerich *et al*., 1996)	4851 Da	*Enterococcus faecium*	*Enterococcus faecalis*, *E. faecium*, *E. hirae*, *Lactobacillus plantarum*, *L. sakei*, *Lactococcus lactis*, *Bacillus coagulans*, *B. subtilis*, *Listeria innocua*, *L. monocytogenes*, *Pediococcus* sp.
	Enterocin P (Cintas *et al*., 1998)	4649 Da	*Enterococcus faecium*	*Lactobacillus sakei*, *Enterococcus faecium*
Class II Subclass IIb	Enterocin I (L50A) (Cintas *et al*., 1998; Basanta *et al*., 2008)	5209 Da	*Enterococcus faecium*	*Clostridium* sp., *Propionibacterium*, *Listeria monocytogenes*, *Lactobacillus sakei*, *Enterococcus faecium*, *Pediococcus acidilactici*, *P. pentosaceus*
	Enterocin Q (Basanta *et al*. 2008)	3970,31 Da	*Enterococcus faecium*	*Lactobacillus sakei*, *Enterococcus faecium*
	Enterocin Xalfa (Hu *et al*., 2010)	4420 Da	*Enterococcus faecium*	*Enterococcus faecalis*, *E. faecium*, *E. hirae*, *Lactobacillus plantarum*, *L. sakei*, *Lactococcus lactis*, *Listeria innocua*
	Enterocin Xbeta (Hu *et al*., 2010)	4068 Da	*Enterococcus faecium*	*Enterococcus faecalis*, *E. faecium*, *E. hirae*, *Lactobacillus plantarum*, *L. sakei*, *Bacillus circulans*, *B. coagulans*, *B. subtilis*, *Listeria innocua*
Class II Subclass IIc	Enterocin B (Casaus *et al*., 1997)	5484 Da	*Enterococcus faecium*	*Enterococcus faecalis*, *E. faecium*, *E. hirae*, *Lactobacillus plantarum*, *L. sakei*, *Bacillus coagulans*, *B. subtilis*
	Hiracin JM79 (Sánchez *et al*., 2007)	5093 Da	*Enterococcus hirae* DCH5	*Lactobacillus helveticus*, *L. curvatus*, *L. bulgaricus*, *L. sakei*, *Pediococcus pentosaceus*, *Enterococcus faecium*, *E. faecalis*, *Propionibacterium acidipropionici*, *Clostridium tyrobutyricum*, *Listeria monocytogenes*, *L. ivanovii*, *L. seeligeri*, *L. welshimeri*, *L. grayi*, *Staphylococcus aureus*
	Durancin TW-49M (Hu *et al*., 2008)	5247 Da	*Enterococcus durans* QU 49	*Enterococcus faecalis*, *E. faecium*, *E. hirae*, *Lactobacillus alimentarius*, *L. kimchii*, *L. plantarum*, *L. sakei* ssp, *Lactococcus lactis*, *Geobacillus stearothermophilus*, *Bacillus subtilis*, *B. coagulans*, *B. circulans*
	Enterocin 96 (Izquierdo *et al*., 2009)	5494 Da	*Enterococcus faecalis*	*Enterococcus faecalis*, *E. faecium*, *E. hirae*, *E. pseudoavium*, *E. sulfureus*, *E. saccharolyticus*, *E. columbae*, *Lactobacillus plantarum*, *L. acidophilus*, *L. sakei*, *L. paracasei*, *Lactococcus lactis*, *Leuconostoc mesenteroides*, *Bacillus subtilis*, *B. cereus*, *Listeria innocua*, *L. monocytogenes*, *Staphylococcus xylosus*, *S. aureus*, *Salmonella* Typhimurium, *Klebsiella pneumoniae*, *Serratia liquefaciens*, *Proteus vulgaris*, *Enterobacter cloacae*, *Escherichia coli*

Table II continued

Classes of bacteriocines	Enterocine	Molecular weight	Producing strain	Activity against bacteria
Class III	Enterolisin A (Nilsen *et al*., 2003	34525 Da	*Enterococcus faecalis*	*Lactobacillus sakei*, *L. brevis*, *L. curvatus*, *Lactococcus cremoris*, *L. lactis*, *Pediococcus pentosaceus*, *P. acidilactici*, *Enterococcus faecium*, *E. faecalis*, *Listeria innocua*, *L. ivanovii*, *Bacillus subtilis*, *B. cereus*, *Staphylococcus carnosus*, *Propionibacterium ensenii*
Unclassified	Enterocin AS-48 (Sánchez-Barrena *et al*., 2003; Sánchez-Hidalgo *et al*., 2011)	7187 Da	*Enterococcus faecalis*	*Bacillus subtilus*, *B. cereus*, *B. circulans*, *Corynebacterium glutamicum*, *C. bovis*, *Mycobacterium phlei*, *Nocardia corrallina*, *Micrococcus luteus*, *M. lysodeikticus*, *Staphylococcus aureus*, *Enterococcus faecalis*, *E. faecium*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus inconstans*, *Salmonella* Typhimurium, *Shigella sonnei*, *Pseudomonas fluorescens*, *P. aeruginosa*

Table III
Basic characteristics of selected bacteriocins of Gram-negative bacteria

Classes of bacteriocines	Bacteriocine	Molecular weight	Producing strain	Activity against bacteria
Colicins	Colicin B (Schramm *et al*., 1987; Kolter and Moreno, 1992)	54863 Da	*Escherichia coli*	*Enterobacteriaceae*
	Colicin U (Šmajs *et al*., 1997; Šmarda and Šmajs, 1998)	66289 Da	*Schigella boydii*	*Enterobacteriaceae*
	Colicin E2 (Lau *et al*., 1984; Cole *et al*., 1985)	61629 Da	*Escherichia coli*	*Enterobacteriaceae*
	Colicin E8 (Uchimura and Lau, 1987; Toba *et al*., 1988)	23198 Da	*Escherichia coli*	*Enterobacteriaceae*
	Colicin M (Ölschläger and Braun, 1987)	29505 Da	*Escherichia coli*	*Enterobacteriaceae*
Microcins	Microcin B17 (Baquero and Moreno, 1984; Vizán *et al*., 1991)	3274 Da	*Escherichia coli*	*Enterobacteriaceae*
	Microcin J25 (Salomon and Farias, 1992; Rintoul *et al*., 2001)	2144 Da	*Escherichia coli*	*Enterobacteriaceae*
	Microcin H47 (Rodriguez *et al*., 1999; Azpiroz *et al*., 2001)	4883 Da	*Escherichia coli*	*Enterobacteriaceae*
	Microcin E492 (Lorenzo and Pugsley, 1984; Lagos *et al*., 1993)	7906 Da	*Klebsiella pneumoniae*	*Enterobacteriaceae*

4. Mechanisms of bacteriocine action

Most of bacteriocines exerts a bactericidal effect on sensitive cells. The first contact of bacteriocine with a sensitive cell takes place due to electrostatic interactions between a positively charged, hydrophobic bacteriocine molecule and negatively charged phospholipids in cytoplasmic membrane of a sensitive cell (Chen *et al*., 1997). The mechanism of bacteriocines action involves formation in the cytoplasmic membrane of sensitive bacteria of transient pore and ion channel complexes. This is accompanied by a passive outflow of small molecules, such as potassium, magnesium and phosphorus ions, amino acids and ATP. This causes a disturbance in membrane potential, pH gradient and function of the proton pump becomes inhibited. The low level of ATP and ion deficit in the cell results in inhibition of DNA, RNA, protein and polysaccharide synthesis, and finally leads to death of the bacterial cell (Moll *et al*., 1999; Rodriguez *et al*., 2002). Such mechanism was described for *L. monocytogenes* under effect of sakacine P, produced by *Lactobacillus sakei* subsp. sakei 2a, or pediocin PA-1, produced by *Pediococcus acidilactici* (Rodriguez *et al*., 2002; de Carvalho *et al*., 2010).

Another mechanism of bacteriocines activity involves their ability to induce lysis of bacterial cells. The process is linked to interaction of bacteriocines with teicholic, lipoteicholic and teichuronic acids, representing coponents of cell wall. This results in a release and activation of autolytic enzymes, linked to the cell, which results in cell autolysis. Such activity was described for plantaricine C produced by *L. plantarum* LL441 and bacteriocines produced by *L. delbrueckii* subsp. *bulgaricus* LMG 13551 strain (Gonzáles *et al*., 1994). Bacteriocines belonging to lantibiotics class may additionally interrupt processes of cell wall biosynthesis. They inhibit synthesis of peptidoglycan at the transglycosylation stage, which is not accompoanied by a disturbed biosynthesis of DNA,

RNA or protein (Moll *et al*., 1999). The lantibiotics inhibiting peptidoglycan synthesis include mersacidin that inhibits peptidoglycan synthesis through a specific interaction with the peptidoglycan precursor lipid II. The sequestering of lipid II prevents its utilization by the transpeptidase and transglycosylase enzymes that install the crosslinked network of the bacterial cell wall. Mersacidin appears to bind to a different portion of lipid II than does vancomycin, indicating that this bacteriocin may prove to have important chemotherapeutic applications (Brotz *et al*., 1995; Brotz *et al*., 1997).

Mechanism of cell-targeted activity manifested by bacteriocines produced by Gram-negative bacteria include depolarization of cell membranes (*e.g.*, colicin E1), damage to DNA (*e.g.*, colicin E2, acting as a non-specific endonuclease) or inhibition of protein synthesis by inactivation of ribosomal RNA (colicin E3 and cloacin DF13). Colicin E1 is coded by a set of genes representing 'colicin casette' in ColE1 plasmid. As mentioned above, the produced colicin is lethal for the host since its release to the environment results in cell lysis, for which product of kil gene is responsible. In normal conditions the entire system is located on a plasmid in a repressed condition, which results from blocking of the principal promoter (Pcol) by the repressor – cellular protein of LexA. Cells which at a given moment do not produce colicin even if they contain the ColE1 plasmid, are protected from action of exogenous colicin due to function of *imm* gene product while the related bacteria containing no such plasmid become eliminated from the environment. All situations resulting in destruction of the LexA protein, and, thus, inducing the cellular SOS system mobilize in paralel colicin production by the entire population of bacteria carrying the plasmid (Riley and Gordon, 1999; Włodarczyk, 2002; Cascales *et al*., 2007).

Bacteriocines, as molecules of low molecular weight and usually a hydrophobic character, tend to form aggregates, which reduces their activity (Karpiński, 2012). The example includes propionicin (PLG-1), which a small molecule of around 10 kDa and forms aggregates of molecular weight above 100 kDa (Lyon and Glatz, 1993). On the other hand, lactacin B tend to form macromolecular complexes with lipid and carbohydrate components of culture media (Barefoot and Klaenhammer, 1984). Activity of bacteriocines may be increased by destruction of the aggregates and an increase in numer of active molecules using mild detergent such as Triton X100. For example, antibacterial activity of cerein 7 increases after TritonX100 tratment, most probably due to desaggregation of larger molecules (Oscáriz and Pisabarro 2000). The ability to disintegrate bacteriocine aggregates was also shown for urea, which, induces a 200-fold increase in activity of lactacin B (Barefoot and Klaenhammer, 1984).

5. Application of bacteriocines

At present, studies continue on application of bacteriocines in food industry and in medicine. Until now, exclusively nisine was commonly used in food industry, as a conserving agent (Schillinger *et al*., 1999).

Nisin and other lanibiotics have been investigated for their potential applications in medicine. The MICs of nisin A and mutacin B-Ny266 were shown to be comparable to those of vancomycin and oxacillin against various bacterial pathogens (Mota-Meira *et al*., 2000). Both lantibiotics were active against vancomycin- and oxacillin-resistant strains of *H. pylori* and *Neisseria* spp. This opens the potential of using lantibiotics in treatment of infections induced by the above mentioned bacteria (Hancock, 1997; Mota-Meira *et al*., 2000). Clinical action of mersacidin was also demonstrated. Mersacidin has been shown to be very effective for the treatment of systemic staphylococcal infections, and in eliminating nasal carriage of *S. aureus* in a mouse rhinitis model (Chatterjee *et al*., 1992; Kruszewska *et al*., 2004). Unfortunately, it was also found that *S. aureus* strains can develop and maintain resistance against nisin A *in vitro*. This suggests that resistance to nisin A and other lantibiotics with similar modes of action would arise in the clinic if these agents are used as chemotherapeutic drugs (Blake *et al*., 2011). Recent studies showed that new bacteriocins – enterocin RM6, produced by *E. faecalis*, and bacteriocin KU24 produced by *L. lactis* KU24, are also active against *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) (Huang *et al*., 2013; Lee *et al*., 2013).

Another bacteriocine – cinnamycin, shows an inhibitory effect on phospholipase A2, the enzyme active in synthesis of prostaglandins and leukotrienes in the human immune system. Its action takes place by the sequestration of its substrate phosphatidylethanolamine. Due to this activity, cinnamycin may prove to have a useful application as an anti-inflammatory and anti-allergy drug (Marki *et al*., 1991).

Bacteria of the *Lactobacillus* genus are frequently employed in probiotic preparations. The main duty of probiotic bacteria involves maintenance of microbiological equilibrium in alimentary tract through interactions with pathogenic bacteria (Słońska and Klimuszko, 2010; Klewicka *et al*., 2011). In addition, probiotic preparations manifest an anti-noeplastic activity (Burns and Rowland, 2000; Sand *et al*., 2007). Moreover, lactic acid bacteria and the produced by them bacteriocines are applied in production of cheeses, yoghurts and other dairy products (Garde *et al*., 1997; Beshkova and Frengova, 2012). In 2012 one of the *S. salivarius* 24SMB strains, deposited as DSM 23307, was selected as a new potential oral probiotic, thanks to its safety assessment, ability to inhibit *Streptococcus pneumoniae*

and the absence of virulence and antibiotic resistance genes (Santagati *et al*., 2012).

Bacteriocines produced by Gram-negative bacteria find application in poultry and cattle breeding. Microcines produced by various *E. coli* strains play a significant role in preventing chicken infections with *Salmonella* since microcins are capable of inhibiting growth of pathogenic *Salmonella* strains (Portrait *et al*., 1999). Colicins and microcins are also used against *E. coli* O157:H7. Microcins and colicins manifest their activity against strains producing shiga toxin, and also against other *E. coli* strains of serotype O. The use of colicin- and microcin-producing bacteria as probiotics may markedly reduce pathogens level in cattle alimentary tract and in this way prevent against infection with pathogenic strains (Walterspiel *et al*., 1992).

The bacteriocin from *Pediococcus acidilactici* K2a2-3 were found to be cytotoxic against human colon adenocarcinoma (HT29) and human cervical carcinoma (HeLa) cells *in vitro*, as determined by MTT assay. Cytotoxicity may be due in part to the high level of hydrophobicity of this bacteriocin (Villarante *et al*., 2011). Whereas, nisin may serve as a potential therapeutic for treating head and neck squamous cell carcinoma. Nisin induces preferential apoptosis, cell cycle arrest, and reduces cell proliferation in squamous carcinoma cells (Joo *et al*., 2012).

Some of bacteriocines may exert a toxic effect and may influence course of infections. Cytolysine produced by strains of *E. faecalis* and *E. faecium* manifest a cytolytic activity inducing β-haemolysis of rabbit, horse and human erythrocytes and, smetimes, of sheep erythrocytes (Archimbaud *et al*., 2002; Coburn *et al*., 2004). Moreover, studies on the course of *E. faecalis* – induced infections in rabbits and mice, demonstrated that strains which produced cytolysine evoked infections of a more severe course and resulting in higher mortality than infections with strains free of this trait (Chow *et al*., 1993; Dupton *et al*., 1998).

In various scientific centres studies continue on bacteriocinogenic strains and the produced by them bacteriocines and on clinical trials of their application. The antibacterial activity of bacteriocines, similarly to that of other substances (silver and gold nanoparticles, plant-derivered products, bacteriophage lytic enzymes) open perspective for their use in medicine (Kurek *et al*., 2011; Wolska *et al*., 2012). This is particularly important due to the increasing antibiotic resistance of pathogenic bacterial species.

6. Summary

Bacteriocines, as peptides of antibacterial properties, manifest high significance for preservation of homeostasis between bacteria. They help humans in preservation of health, they find application in food industry and in medicine. Bacteriocines produced by lactic acid bacteria have been recognized to be fully safe for humans. At present, bacteriocines and probiotic preparations provide an alternative for antibiotics, used as a supplementation of fodder. However, a broader application of bacteriocines requires further studies on their structure, mechanisms of action and their new potential applications.

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