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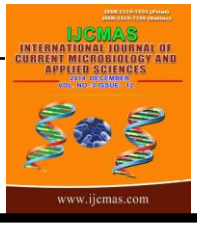

Review Article

Applications of bacteriocins in food, livestock health and medicine

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A B S T R A C T

Increase of bacterial antibiotic resistance is a major cause for animal and public health stresses globally. Many bacteriocins and bacteriocins producing probiotic bacteria show potential for biotechnological, food and agro-industrial applications. The current global response to these useful bacteriocins needs to be improved by genetic or metabolic engineering. Due to the alarming rise in antibiotic resistance and adverse effects provoked by a number of antibiotics, bacteriocins have been applied in several fields: human health, food industry, animal health, and medicine, in particular as a substitution for the traditional growth promoters, antibiotics. The use of bacteriocins became an universal trend well over in 50 countries since their first discovery. Lactic Acid Bacteria (LAB) bacterocins are likely used because of their "safe" (GRAS) status, especially in food industry as bio-preservatives. Among these LAB bacteriocins, commercially marketed, nisin groups produced by *Lactococcus lactis* subsp. *lactis* and pediocins produced by *Pediococcus* sp. are the most characterized by their antilisterian property. Despite the widespread use in foods, their applications in livestock and medicine have been largely limited and further investigations are necessary.

Introduction

Antibiotics have been used as therapeutic and prophylactic treatments to control a variety of bacterial infections in livestock since their discovery in the half of 19th century. Therefore, the continuous uses of these antibiotics led to the emergence of antibiotic-resistance in many bacteria relevant for animal and public health stresses (Diez-Gonzalez 2007; Mantovani et al. 2011). Several alternative approaches using probiotic bacteria were undertaken to control animal and foodborne pathogenic bacteria in livestock, but many of the beneficial effects of probiotics and the

mechanisms are not fully elucidated (Fuller and Tannock 1999). However, many bacteriocins show potential for biotechnological and agro-industrial applications. Some bacteriocins show desirable properties for in vivo application, such as stability to low pH and heat, simple production and extraction processes and little, if any, inhibitory activity towards eukaryotic cells. Therefore, bacteriocins have been evaluated as the most promising class of antimicrobial peptides to be used as antibiotic substitutes in the field of animal and human medicine or in designing and production of new antimicrobials (Sahl and Bierbaum 2008). Particularly on animal trials, bacteriocin and bacteriocin-producing bacteria may be useful to improve animal nutrition and health through the manipulation of ruminal fermentation, the control of animal infections and the inhibition of enteric pathogens (Patra 2012). Although current applications of antibiotics in the farm environment are apparently not available, estimates are as high as 10.5 million pounds annually in the United States for the poultry production (Mellon et al. 2001). The efficacy and cost-effectiveness of many of these compounds are at the root of their popularity, but looming or already imposed restrictions or prohibitions on the use of antibiotics as growth promoters have drawn attention to possible alternatives (Bedford 2000; Wierup 2000), Doyle 2001). In contrast to the currently used antibiotics, bacteriocins are often considered more natural than common antibiotics because they are thought to present in many of the fermented foods eaten since ancient times (Cleveland et al. 2001).

Bacteriocins have long attracted the interest of food sector as potential natural food preservatives against spoilage and pathogenic bacteria (Kumar et al. 2011). Nisin, pediocin and other bacteriocins produced by lactic acid bacteria (LAB) have received a great deal of attention because of their beneficial effects to human health and to food production as well as the replacement of chemical preservatives that are being continuously questioned with regard of safety (Zendo 2013). Thus, this potential offers a logical explanation for the expanding trend of applications of LAB in the food industry (Papagianni and Anastasiadou 2009). In addition, no side effects and no development of resistant bacteria have been reported in the practical use of LAB bacteriocins (Zendo 2013). The administration of bacteriocin-producing bacteria rather than the bacteriocins themselves might be a more cost-effective approach, but significant progress in developing suitable producer strains will have to be made before such an approach will be feasible (Joerger 2003).

In this review, current trends and perspectives on the applications of two most known LAB bacteriocins: Nisin (lantibiotic) and Pediocin (non-lantibiotic) in food industry, livestock health, aquaculture as well as medicine are discussed.

Bacteriocins

Bacteriocins are proteinaceous toxins produced by bacteria and some archaea members (Table 1) to inhibit the growth of similar or closely related bacterial strain(s). The inhibitory spectrum of bacteriocins can be narrow and confined to closely related species, or it can be relatively broad, inhibiting a range of target organisms (Mantovani et al. 2011). The bacteriocin family is the most abundant and diverse group of bacterial defenses (Riley 2009). The application of bacteriocins in livestock to control or/and to maintain intestinal microflora of animals by feeding bacteriocin-producing strains has been

largely achieved (Diez-Gonzalez 2007; Papavassiliou 1961; Riley 2009). Novel alternative strategies to reduce or eliminate animal pathogens have also been tested by different research groups. The alternatives include bacteriocins, probiotic micro-organisms and bacteriophages (Bedford 2000; Joerger 2003). Lactic acid bacteria (LAB) can act antagonistically against a wide range of food-borne pathogens and spoilage organisms such as *Salmonella* (El-Khatiband El-Rahman 1987; Guptaand Savaliya 2012). Among LAB bacteriocins, nisin is the most extensively characterized and used (Mohanasirivasan et al. 2012).

Bacteriocins of Gram Positive Bacteria

Bacteriocins of Gram-positive bacteria are as abundant and even more diverse as those found in Gram-negative bacteria. The Gram-positive bacteriocins resemble many of the antimicrobial peptides produced by eukaryotes; they are generally cationic, amphiphilic, membrane-permeabilizing peptides, approximately 2–6 kDa in size (Riley 2009). Bacteriocins produced by Gram-positive and Gram-negative bacteria differ into several ecological and evolutionary aspects. In Gram-positive bacteria, the biosynthesis of bacteriocins is self-regulated and bacteriocin production is not a lethal event. In addition, the spectrum of antimicrobial activity is broader than the peptides from Gram-negative species and bacteriocin release is controlled by specific regulatory mechanisms (Mantovani et al. 2011). Additional roles have been proposed for some bacteriocins produced by Gram-positive bacteria, such as chemical mediators in quorum sensing and communication molecules in bacterial consortia (Gillor 2007; Gobbetti et al. 2007). *Quorum sensing* is one of well-studied systems involved in bacteriocin gene control. *Quorum sensing* is a cell-density dependent regulatory system in which autoinducing signal molecule mediates cell-to-cell communication (Wang et al. 2013). By using this system, each bacterial cell senses the number of cells of same species or same strain and adjusts the timing of expression of certain genes. LAB often use *quorum sensing* for the control of bacteriocin expression in which LAB attack the competitor only when the concentration of the bacteriocin producers is high enough to suppress the growth of competitive strain. A landmark observation in the investigation of bacteriocins of Gram-positive bacteria was the documentation in 1947 that some of the inhibitory activity of lactococci (group N streptococci) toward other lactic acid bacteria (LAB) are due to a molecule characterized as a proteinaceous antimicrobial called “group N inhibitory substance”, or nisin (Heng et al. 2007). Also this name has been suggested, partly on the basis of their mode of action, that bacteriocins of Gram-positive bacteria differ from those of the Gram-negative bacteria (Reeves 1965).

Nisin

Nisin was first discovered in the late 1920s and early 1930s when it was described as a toxic substance (Delves-Broughton et al. 1996) produced by *Lactococcus lactis*, subsp *lactis.* Approved by the US Food and Drug Administration (FDA) for food applications, nisin received GRAS status in 1988 (FDA 1988) and was authorized for food preservation in the European Union by Directive 95/2/EC in 1995 under the code E234. The status as GRAS for use as an anti-microbial agent on cooked meat and poultry products was affirmed in 2001 by the FDA (FDA 2011). Nisin is a small peptide of 34 amino acids with a molecular mass 3354 kDa ribosomally synthesized and post-translationally modified peptide

contains five lanthionine rings, which can be divided into two parts. The N-terminal half including three rings (A, B, and C) is more hydrophobic than the C-terminus containing two rings (D and E) in Fig.1. The rigid ring structures are separated by a flexible hinge region (Diez-Gonzalez 2007; Takala 2005) including one Dhb, two Dha one lanthionine, and four methyllanthionine residues (form the five lanthionine rings) in its structure. The rigid ring structures are separated by a flexible hinge region (Delves-Broughton et al. 1996). The ring structures give nisin a screw-like conformation that possesses amphipathic characteristics. In water its solubility and stability increases with decreasing pH, showing maximum solubility 57 mg/ml at pH 2 (Liu and Hansen 1990), and maximum stability at pH 3 (Davies et al. 1998). Nisin belongs to the lantibiotic class of bacteriocins, cationic and hydrophobic peptide. Nisin provides a paradigm for studies of lantibiotic structure, biosynthesis, and mode of action of antimicrobial peptides, and is often referred to as the "prototypical" lantibiotic (Mantovani et al. 2011; Nolan and Walsh 2009).

Pediocin

Pediocins belong to the Class II of unmodified bacteriocins which subdivided into the groups of the pediocin-like bacteriocins and the two-peptide bacteriocins (Fig. 2). This class comprises over 50 members with diverse origins. They are generally small (<5 kDa) and are heat-stable membrane-active and cationic peptides with similar primary structures. Their activity is retained at a wide pH range. They are sensitive to most proteases. The pediocin-like bacteriocins (36–48 residues) are produced by many lactic acid bacteria and share a 40–60% amino acid sequence similarity (Heng et al. 2007; Papagianni 2003; Papagianni and Anastasiadou 2009; Zacharof and Lovitt 2012). In general, class IIa bacteriocins have a rather narrow spectrum of activity (Drider et al. 2006). The peptides of this group are known as "antilisterian" or "Listeria-active" peptides and they are characterized by a -YGNGV-N-terminus (Papagianni and Anastasiadou 2009). The positively charged residues in class IIa bacteriocins are located mostly in the hydrophilic N-terminal region. It has been shown for pediocin AcH/PA-1 that electrostatic interactions and not the -YGNGV- motif, govern the binding of the pediocin and its fragments to phospholipids vesicles (Chen et al. 1997). Lys11 and His12: that are part of the cationic patch in the N-terminal β-sheet-like region of pediocin AcH/PA-1; are of special importance for the electrostatic interactions and subsequent mutagenesis studies, in charged residues of pediocin AcH/PA-1, and in sakacin P. Earlier research confirmed these two amino acids were replaced by neutral residues (Kazazic et al. 2002; Miller et al. 1998b; Uteng et al. 2003). The C-terminal region is important in determining the target cell specificity for class IIa bacteriocins (Drider et al. 2006).This has been shown by combining N- and C-terminal regions from different class IIa bacteriocins (hybrid bacteriocins), which displayed target cell specificities similar to the bacteriocins from which the C-terminal was derived (Fimland et al. 1996). Further works carried out with pediocin AcH/PA-1 also showed the inhibition of the bactericidal activity of the pediocin by cleaving the area from residue 20 to residue 34. This is an indication of a role for the C-terminal in recognition of target cells (Fimland et al. 1998).

Mode of Action

Different mechanisms of action have been

proposed for bacteriocins: alteration of enzymatic activity, inhibition of spore germination and inactivation of anionic carriers through the formation of selective and non-selective pores (Abee 1995; Martinez and de Martinis 2006).

LAB bacteriocins can work via different mechanisms to exert an antimicrobial effect, but the cell envelope is generally the target. The initial electrostatic attraction between the target cell membrane and the bacteriocin peptide is thought to be the driving force for subsequent events. (Deegan et al. 2006). The first step in the mechanism of action of nisin is considered to be the binding of the peptide to the cytoplasmic membrane of target bacteria. (van Kraaij et al. 1999). Nisin has different antimicrobial activities based on both high-affinity targets and low-affinity membrane interactions (Pag and Sahl 2002). The C-terminal region of nisin containing 4 out of the 6 positively charged residues of nisin A (Lys-22, His-27, His-31, Lys-34) was shown to play a dominant role in the membrane-binding step. This part of the molecule inserts into the cell membrane (Hsu et al. 2002) while nisin's N-terminus binds with high affinity to the Lipid II molecule, a hydrophobic carrier for peptidoglycan monomers, using this compound as a specific receptor to integrate into the bacterial membrane and to form pores that increase membrane permeability; nisin-Lipid II interaction compromises the incorporation of precursor units, blocking the biosynthesis of bacterial cell wall (Breukink et al. 1997; Brötz et al. 1998; Mantovani et al. 2011; Wiedemann et al. 2001). The final pore structure is believed to have a stoichiometry of eight nisin and four Lipid II molecules. Nisin's pore-forming ability induces the loss of membrane integrity and passive efflux of small intracellular metabolites through the lipid bilayer. Because of the loss of ions (potassium, phosphate), amino acids and ATP, the proton-motive force is reduced or dissipated and the cell dies (Breukink et al. 1997; Hasper et al. 2004). Nisin can also promote the release of certain enzymes, such N-acetylmuramoyl-L-alanin amidase and N-acetylglucosaminidase, which hydrolyze the cell wall by binding to teichoic, teichuronic and lipoteichoic acids (Héchard and Sahl 2002). Nisin also inhibits the outgrowth of bacterial spores, by uncoupling the establishment of oxidative metabolism or membrane potential and the shedding of external spore structures (Gut et al. 2008).

Pediocins are bactericidal to sensitive Gram-positive bacteria (Ray 1995).The cytoplasmic membrane of Gram-positive bacteria is the target of pediocins (Papagianni 2003). All the class IIa bacteriocins, whose modes of action have been studied, permealize the cytoplasmic membrane through pore formation by insertion of the C-terminal regions into the membrane (Drider et al. 2006). Being hydrophobic molecules, they destabilize the cytoplasmic membrane when they come in contact with it. This action includes loss of the permeability barrier and loss of the membrane potential in strains that possess an autolytic system, resulting in cell lysis. However, the specific role of the YGNGV motif of the pediocins has not clarified yet (Ray 1995). They kill sensitive bacteria by punching holes in their cell membranes, causing a disruption in their trans-membrane potential and destroying the delicate balance of which the organisms maintain between themselves and their environment (Chikindas et al. 1993). Higher concentration of pediocin effectively released higher molecular weighted substances. They frequently adopt conformations where polar and non-polar residues are segregated properly resulting in a typical amphipathic structure that exhibits

more peptide internalization and membrane perturbation. Trans-membrane potential (negative inside) in bacteria acts as a potential driving force for insertion and internalization of the antimicrobial peptides promoting AMP interaction (Melo et al. 2009). For example, Pediocin PA-1 exerts bactericidal or bacteriolytic effect depending on the species of the sensitive cells (Bhunia et al. 1991). Pediocins also act on some sensitive bacterial strains in bacteriostatic manner and thus retard further proliferation of the sensitive cells (e.g. Pediocin ST18, Pediocin CP2) (Mashal 2007).

Bioengineering of LAB Bacteriocins

In last two decades, there have been significant advances in functional genomic analysis of LAB and their biochemical characterization of bacteriocins. Considerable efforts have been made to functionally characterize bacteriocin operons and to express them in heterologous systems (Coderre and Somkuti 1999; Miller et al. 1998a; Osmanağaoğlu et al. 2000; Tominaga and Hatakeyama 2007).

The genes responsible for bacteriocin production are frequently associated with mobilisable elements, or in the chromosome in association with transposons or plasmids (Belkum et al. 1998). The low-molecular-weight bacteriocins of Gram-positive bacteria generally appear to be translated as pre-peptides that are subsequently modified to form the mature biologically active (bactericidal) molecules (Buchman et al. 1998). Specific auxiliary functions required by bacteriocin-producing cells include mechanisms for extracellular translocation of the bacteriocin and for self-immunity to the bactericidal activity of the molecule (Jack et al. 1995). As is the case for most bacteriocins, the lantibiotics are initially synthesized with an N-terminal leader peptide. In general, the pre-peptide is modified by the action of other proteins encoded by the bacteriocin gene cluster before export (Deegan et al. 2006).

Biosynthesis of nisin: The genes involved in biosynthesis of the model lantibiotic nisin are located on a 70 kb conjugative transposon (Rauch et al. 1991). Biosynthesis of nisin is encoded by a cluster of 11 genes (Fig. 3) of which the first gene, nisA, encodes the precursor of nisin (Mierau and Kleerebezem 2005). The first gene of the nisin gene cluster, nisA, encodes the 57 amino acid nisin precursor, consisting of a N-terminal leader, sequence followed by the propeptide, from which nisin A is matured. The structural gene is followed by ten other genes i.e. nisB, nisT, nisC, nisI, nisP, nisR, nisK, nisF, nisE, nisG, encoding regulatory proteins, proteases, transport proteins and immunity proteins (van Kraaij et al. 1999). The proteins that are encoded by these genes have been found to be homologous to gene products of the gene clusters of other lantibiotics, such as those of subtilin, epidermin and Pep5 (van Kraaij et al. 1999). Thus, as a result of their gene encoded nature, lantibiotics have been the focus of bioengineering with a view in elucidating structure function relationships (Cortés et al. 2009; Cotter et al. 2005; Field et al. 2010; Lubelski et al. 2008). The majority of works that lead to enhanced peptides have resulted as a consequence of manipulation of the hinge region (Rouse et al. 2012). The hinge comprises residues 20 (Asn), 21 (Met) and 22 (Lys) (Fig. 1), which are thought to permit the movement of the N- and C-termini relative to one another during pore formation. The first success in this regard related to the creation of nisin derivatives, N20K and M21K, with enhanced anti-microbial activity against Gram-negatives (Yuan et al. 2004). Subsequent investigations have further highlighted the

benefits of manipulating the hinge and finally resulted in the identification of nisin derivatives, such as nisin N20P, M21V, K22T and K22S, which possess enhanced specific activity against Gram-positive pathogens (Field et al. 2008). Such activity has been highlighted with the enhanced specific activity of nisin M21V (or nisin V) in foodborne and clinical purpose (Field et al. 2010).

Biosynthesis of pediocin

Characteristically, class IIa bacteriocins like other low-molecular-mass bacteriocins are first formed as ribosomally synthesized precursors or pre-peptides, which appear not to be biologically active and contain a N-terminal extension or leader sequence. Subsequent cleavage of the pre-peptide at a specific processing site removes the leader sequence from the antimicrobial molecule concomitantly with its export to the outside of the cell (Håvarstein et al. 1994). The leader peptide's removal during trans-membrane translocation is accomplished by the same protein that is associated with the bacteriocin transport (Håvarstein et al. 1994; Nes et al. 1996).

The amino acid sequence of a number of class-IIa-bacteriocin leader peptides, which vary in length from 18 up to 27 residues. One important feature of the majority of these leaders is the presence of two glycine residues in the C-terminus at positions 32 and 31 relative to the processing site, though this is not distinctive of the class IIa. These leaders are believed to serve as signal peptides for the processing and the secretion of class IIa bacteriocins, independently of the GSP, by a dedicated transport system involving two distinct proteins: an ABC-type translocator and an accessory protein. The two conserved glycine residues may serve as a recognition signal for this sec-independent transporter system (Ennahar et al. 2000; Håvarstein et al. 1994; Klaenhammer 1993; Nes et al. 1996).

In the case of pediocin PA-1/AcH the four genes needed for bacteriocin production and secretion are located in one operon [35]. The four genes are 1) the structural bacteriocin gene, encoding a prebacteriocin; 2) the immunity gene, encoding an immunity protein that protects the bacteriocin producer from its own bacteriocin; 3) the gene encoding the ABC transporter for secretion; and 4) a gene encoding a complementary protein of unknown function (Ennahar et al. 2000). It has been shown that the four genes cluster of pediocin AcH/PA-1 contain common promoter and terminator sequences (Bukhtiyarova et al. 1994; Marugg et al. 1992; Motlagh et al. 1994). PedA encodes a 62 amino acids long pre-pediocin PA-1. Eighteen residue long leader sequences from N-terminal of pre-pediocin are removed during processing and export of pediocin through producer cell membrane. Mature pediocin carries 44 amino acid residues and two intra-molecular disulphide bridges at cys9-cys14 and cys24-cys44 positions (Henderson et al. 1992; Miller et al. 1998a; Neetoo et al. 2008). PedB immunity gene is located downstream to pedA and encodes a protein of 112 amino acid residues. PedC a 174 amino acid long amphiphilic protein involved along with pedD protein in facilitating/accelerating the trans-membrane export (Henderson et al. 1992). PedD gene specifies a polypeptide of 724 amino acid residues. Deletion analysis and site specific mutagenesis of pedD resulted in complete loss of pediocin production, showing its essentiality for secretion in *E. coli* (Marugg et al. 1992). Its sequence shows a very high homology to members of ATP dependent transport proteins and also to a group of eukaryotic proteins involved in multidrug resistance (Kumar et al. 2011; Marugg et al. 1992). Figure 4 shows the suggested

machinery for production of class IIa bacteriocins (Ennahar et al. 2000).

Applications of Bacteriocins in Food

Although several methods other than bacteriocins are employed for the preservation of food and beverages, an increasingly health conscious public may seek to avoid foods that have undergone extensive processing or which contain chemical preservatives. Bacterial fermentation of perishable raw materials has been used for centuries to preserve the nutritive value of food and beverages and to extend shelf-life. Among bacteriocins produced by many Gram-positive and Gram-negative species, those produced by LAB are of particular interest to the food industry, since these bacteria have generally been regarded as safe. The production of bacteriocins by LAB is advantageous for survival of the producing bacteria in a competitive ecological niche; therefore they could be exploited by the food industry as a tool to control undesirable bacteria in a food-grade and natural manner, which is likely to be more acceptable to consumers (Deegan et al. 2006; Parada et al. 2007).

Many lactic acid bacteria produce a high diversity of different bacteriocins and several have been patented for their applications in foods (Schöbitz et al. 2006). *Listeria monocytogenes* is a pathogenic bacterium that has been involved in several foodborne outbreaks worldwide and causes special concern with regard to food safety due to its psychrotropic and ubiquitous characteristics. The presence of this pathogen in fermented sausages and in vacuum-packaged meat products (Chung and Hancock 2000) is of particular interest for food safety, as these two groups of meat are frequently eaten without reheating (Vignolo et al. 1996). This pathogen has shown to survive at pH as low as 3.6 in foods and in salt concentration of up to 10%, in the presence of surfactants, sanitizers and after several cycles of freezing and thawing (Martinez and de Martinis 2006), being a serious risk.

Several possible strategies for the application of bacteriocins in the preservation of foods may be considered: i) inoculation of the food with LAB as starter or protective cultures that produce the bacteriocin in the product (production *in situ*); ii) addition of the purified or semi-purified bacteriocin as a food preservative, and iii) use of a product previously fermented with a bacteriocin-producing strain as an ingredient in food formulation (Jeevaratnam et al. 2005).

Bacteriocin production *in situ* by starter cultures has a good chance of finding applications in fermented foods. In non-fermented refrigerated products, such as minimally processed meats or prepackaged vegetable salads, only those strains producing sufficient and potent amounts of bacteriocin but no other metabolic compounds, at levels detrimental to the sensory quality product, can be applied. The direct addition of purified bacteriocins obviously provides a more controllable preservative tool in such products (Jeevaratnam et al. 2005).

The use of nisin in foods and foodborne is the most expected use of this bacteriocin. There is an enormous amount of information about its application to inhibit a variety of pathogenic and spoilage bacteria in many food products (Delves-Broughton et al. 1996). Nisin is suitable for use in a wide range of foods (liquid or solid), canned or packaged, chill or warm ambient storage. Based on target microorganisms, its usage falls into three broad categories: i) to

prevent spoilage by Gram-positive endospore formers (especially in heat processed food), ii) to prevent spoilage by LAB and similar organisms like *Brocothrix thermosphacta*, and iii) to kill or inhibit Gram-positive pathogens such *Listeria monocytogenes*, and *Clostridium botulinum*. It was demonstrated that nisin is best added as an aqueous solution. Usually, it serves as the liquid portion of a product during its processing. It can also be added as a powder, but it is essential to ensure uniform dispersal throughout the food matrix in both ways. The best time to add nisin is at the last practical stage before heat processing (if this is a part of the manufacturing process). In the manufacture of processed cheese, for instance, nisin is usually added to the heated cheese at the same time as the melting salts. Nisin can also be used at high concentrations as a spray or dip for surface decontamination. The level of nisin addition depends on the type of food, severity of heat process, pH, storage conditions and the required self-life. Nisin is often used in acidic foods, but is effective in products across a wide range of pH values 3.5-8.0. It is used in variety of products including pasteurized, flavored and long-life milks, aged and processed cheeses, and canned vegetables and soups (Delves-Broughton et al. 1996; Jeevaratnam et al. 2005). Nisin has utilized to inhibit undesirable LAB in wine and beer (Daeschel et al. 1991; Jeevaratnam et al. 2005; Ogden et al. 1988). Nisin has also been used in conjunction with other preservative measures to enhance product safety or quality. In canned foods such vegetables, soups and puddings, nisin has been applied in conjunction with heat to successfully counter heat-resistant spores of flat-sour thermophilic bacteria (Chung and Hancock 2000; Smid and Gorris 1999).

In seafood industry, studies of nisin indicated that it delayed growth of *L. monocytogenes* in cold-smoked salmon (Bakkal et al. 2012). There has also been encouraging research into nisin-coated packaging. The effect of nisin-coated plastic films on the survival of *L. monocytogenes* on vacuum-packed cold smoked salmon (Neetoo et al. 2008) showed that nisin-coated plastic films reduced the number of *L. monocytogenes* by 3.9 log CFU/cm^2 at 4^{o}C and 10^{o}C after 56 and 49 days of incubation, respectively. This study also showed that nisin-coated plastic films suppressed the growth of other aerobic and anaerobic spoilage microorganisms in a concentration-dependent manner. A combination of nisin and some lactates has been demonstrated to be more active against *L. monocytogenes* due to synergistic action (McEntire et al. 2003; Nykänen et al. 2000). A combinatory treatment of nisin and listeriophage was found to be effective in controlling *L. monocytogenes*, while it was not effective in model food systems which reflect the complexity of natural system (Dykes and Moorhead 2002).

Despite of few studies reported on the applications of pediocins, pedioci PA-1/AcH has been demonstrated to effectively reduce populations of listeria strains in ice cream mix, sausage mix, fresh and ground beef and whole milk (Motlagh et al. 1994). It has been found to be effective against many strains of sub-lethally stressed Gram-positive and Gram-negative bacteria. Such injured bacteria can be present in foods that have an acid pH (below 6), water activity below 0.9, or have been given low heat treatment, subjected to hydrostatic pressure, or stored at low temperature, including long-term storage at refrigerated temperature. Incorporation of pediocins as preservatives in such foods can help in killing the normally sensitive and resistant but injured cells of spoilage and pathogenic bacteria and ensure longer product shelf-life and greater consumer safety (Jeevaratnam et al. 2005).

Pediocin PA-1/AcH has a specific application to control *L. monocytogenes* in the production of certain fermented foods, especially in controlled fermentation where specific strains of starter cultures are used. Many refrigerated, vacuum-packaged processed food products from meat, dairy, fish and vegetable groups contain normally psychotropic Gram-positive bacteria strains such *Leuconostoc*, *Lactobacillus*, *Carnobacterium*, *Brochothrix* and *Clostridium*. By incorporating pediocin PA-1/AcH during the formulation of the raw product, spoilage problems in the final product could be reduced (Breukink et al. 1997; Ennahar et al. 1998; Yang and Ray 1994). Researchers in several countries have recognized its potential as a food preservative, especially for use in certain specific foods. Pediocins are also commercially available but are marketed as fermentates of lactic acid bacteria (LAB) having GRAS status (Gálvez et al. 2008).

Applications of Bacteriocins in Livestock Health

The application of bacteriocins in livestock has been largely achieved by feeding bacteriocin-producing strains. Feeding purified bacteriocins to humans for control of diarrhea was reported in a few publications during the 1900's (Papavassiliou 1961), but very little evidence exists in administering of bacteriocins alone to livestock. Because of lack of evidence, the use of bacteriocins in livestock is largely based on those studies that reported feeding or applying bacteriocin-producing bacteria (BPB) (Diez-Gonzalez 2007).

The application of BPB for improvements in productivity has not been limited to cattle, as several researchers have explored the use of probiotic strains capable of producing bacteriocins to increase the growth rate of swine. In poultry, the use of BPB has been mainly targeted for the control salmonella (Rodriguez et al. 2003). The utilization of BPB as a pre-harvest food safety strategy is considered as one of the most viable interventions for reducing the gastrointestinal colonization of livestock by foodborne pathogens (Callaway et al. 2004; Gillor et al. 2004; Renter and Sargeant 2002). The BPB can easily be administered to animals by mixing dried or wet cultures with feed or drinking water, and depending on the ability of the particular probiotic strain to colonize the gastrointestinal tract they could be fed sporadically or continuously. The feeding of BPB can have a direct effect on reducing the existing populations of foodborne pathogens such as salmonella and *Escherichia coli*, and long-term colonization with BPB would prevent further re-introduction of the pathogenic bacteria (Diez-Gonzalez 2007).

Many different types of LAB bacteriocins have been studied and characterized, but the most widely known are: nisin, lacticin, enterocin, pediocin, and plantaricin. These have been extensively studied for their application in foods, but just a few of them have been used in livestock (Ray and Bhunia 2013). The well-known, most and likely use among of them is nisin. One of the most promising applications of nisin is on the control of *Listeria monocytogenes* in ready-to-eat meats (Ariyapitipun et al. 2000). Nisin has also successfully been used to control respiratory tract infection by *Staphylococcus aureus* in animal model (De Kwaadsteniet et al. 2008). One of the major disease in dairy cattle is 'bovine mastitis' (Ruegg 2003) induced by *Staphylococcus aureus* that is the one of the most pathogen agent implicated in clinical and subclinical mastitis infections (Kerro et al. 2002). Several bacteriocins including nisin have

been tested against the causative bacteria of bovine mastitis. The positive results have been reported for *in vivo* studies performed with intra-mammary formulations containing bacteriocins like germicidal preparation for cow's teats (Sears et al. 1992; Wu et al. 2007). Therapeutic formulations containing nisin reduced considerably the viability of *S. aureus* and *E. coli* at 3.9 and 4.2 log cycles, respectively (Sears et al. 1992). Other studies using treatment with nisin Z have shown a significant increase in cure rates of infections caused by *S. agalactiae*, *S. aureus*, and other mastitis pathogens (90.1 %, 50 % and 65.2 %). Moreover, after 48 hours of treatment, no bacteriocin residue was detected in milk (Wu et al. 2007).

Nisin was able to decrease the methane production *in vitro* in ruminal fermentation. For instance, the reduction of methane emissions in sheep had been reported with the combinations of this bacteriocin with nitrate (Sar et al. 2005). Nisin has shown an inhibitory effect against common rumen anaerobes (Kišidayová et al. 2003; Mantovani and Russell 2001). *In vitro*, this bacteriocin affected ruminal fermentation in the similar way to monensin, the most common ionophore used as feed additive in cattle rations (Callaway et al. 1997). Moreover, the introduction of nisin into an artificial rumen system brought some changes in fermentation parameters, such as an increase in hemicellulose degradation and acetate and propionate production, which contributed to the improvement of microbial balance in this environment. (Jalc and Lauková 2001; Santoso et al. 2006; Zendo 2013).

Applications of Bacteriocins in Aquaculture

Aquatic cultures are facing with the same problems with animal farming. They are continuously exposed to a wide range of microorganisms, some of which are pathogenic (Reilly and Kaeferstein 1998). Many efforts were undertaken to prevent and control this dilemma: husbandry techniques and the use of vaccines (Corripio-Miyar and Mazorra de Quero) and antibiotics (Smith 2007). These methods can create several negative problems. They cannot prevent disease (husbandry techniques). Laborious, costly, and highly stressful to the animals (vaccines) and especially the selection for antibiotic-resistant bacteria and active residues of the drugs remain long after use (Lauková et al. 2003; Matyar 2007; Zhou and Wang 2012).

An alternative approach to disease prevention in aquaculture is the use of bacteriocin-producing bacteria, BPB (Lauková et al. 2003). It means use these bacteria as probiotic because in aquaculture, aquatic animal and microorganisms share the same ecosystem in the aquatic environment and it suggested that the interaction between the microbiota, including probiotics, and the host is not limited to the intestinal tract (Zhou and Wang 2012). Many works reported that the administration of BPB as probiotic exclude competitively pathogenic bacteria through the production of inhibitory compounds, improve water quality, enhance the immune response of host species, and enhance the nutrition of host species through the production of supplemental digestive enzymes (Taoka et al. 2006; Wang 2007). Most probiotics used in aquaculture belong to the lactic acid bacteria, of the genus *Bacillus*, to the photosynthetic bacteria or to the yeast, although other genera or species have also been mentioned. Many studies have reported promising results using a single beneficial bacterial strain as probiotic in the culture of many aquatic species (Zhou

and Wang 2012)but it is important to consider the possibility of using different species. The effect of probiotics, photosynthetic bacteria (*Rhodobacter sphaeroides*) and *Bacillus* sp. (*B. coagulans*), on growth performance and digestive enzyme activity of the shrimp, *Penaeus vannamei*, was investigated and the results showed that the effects were related with supplementation concentrations of probiotics and thus use of a 10g/kg (wet weight) supplement of probiotics in shrimp diet was recommended to stimulate productive performance (Wang 2007).

Some study showed that nutrient and water enrichment with commercial BPB, designated Alchem Poseidon™ (a mixture of *Bacillus subtilis*, *L. acidophilus*, *Clostridium butyricum*, and *Saccharomyces cerevisiae*) significantly improved lysozyme activity, lowered levels of mucosal proteins and also improved survival after bacterial immersion challenge with *Vibrio anguillarum* (Taoka et al. 2006). BPB has the potential to serve as an efficacious long-term solution, as the administered bacteria become established in the host and/or the aquatic environment.

Early attempts to use probiotic species in aquaculture usually employed BPB developed for terrestrial animals, which contained the facultative or obligate Gram-positive anaerobes found in the GI tract, specifically of the genera *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* (Callaway et al. 2004; Gatesoupe 2007; Gatesoupe 1999). Production of BPB specifically for the use in aquaculture is now a more popular approach, as these strains are more likely to establish in aquatic communities (Irianto and Austin 2002). Bacteriocin producing strains should be developed to be more effective for aquaculture than the regular probiotic strains in the future.

Applications of Bacteriocins in Medicine

Bacteriocins have interest in medicine because they are made by non-pathogenic bacteria that normally colonize the human body. Loss of these harmless bacteria following antibiotic use may allow opportunistic pathogenic bacteria to invade the human body. As the narrow spectrum of bacteriocins produced by LAB represent an important limitation for the application of these bacteriocins as clinical drugs or as food preservatives (Acuña et al. 2012), some examples of bacteriocins and their pharmaceutical applications are (a) the use of microcins derived from enterobacteria to control Gram negative bacteria (Duquesne et al. 2007).

Similarly to pediocin-like bacteriocins, microcins belonging to class IIa such as microcin V are linear polypeptides, and the removal of the leader peptide is the unique posttranslational modification that they undergo before being secreted by the cells. In order to obtain a peptide with a broader antimicrobial spectrum, recent works fused by asymmetrical PCR the required portions of genes encoding enterocin CRL35 and microcin V, namely munA and cvaC.

The hybrid bacteriocin purified from *E. coli* extracts, named Ent35eMccV, showed inhibitory activity against enterohemorrhagic *E.coli*, *L. monocytogenes*, and other pathogenic Gram-positive and Gram-negative bacteria (Acuña et al. 2012). In this field, several lantibiotics are used in pharmaceutical applications (van Kraaij et al. 1999). Some have been used in dental caries treatment (mutacin-producing strain) (Hillman et al. 2000; Hillman 2002) used to control vaginal microbiota with significantly reducing the adherence of the urogenital pathogen *Staphylococcus aureus* (Zárate and Nader-Macias 2006). So far,

nisin is the most promising in this medical field. The intravenous use of nisin has not been further developed since nisin shows a low stability at physiological pH. However, several protein-engineered derivatives of nisin Z have been generated in recent years that show improved stability and these or others may extend the medical application of nisin (Kuipers et al. 1991, (Severina et al. 1998).

Nisin was also applied in the treatment of respiratory tract infections. Some study reported the capacity of nisin to develop resistance in respiratory tract to prevent growth of resistant *Staphylococcus aureus* or *Streptococcus pneumonia* (De Kwaadsteniet et al. 2009). Also, recent work reported that Nisin F inhibits *Staphylococcus aureus* in the nasal cavities of immunosuppressed rats (De Kwaadsteniet et al. 2009). Many studies report the efficiency of nisin against several diseases responsible in digestive tract especially *Clostridium* species that can induce diarrhea: *C. botulinum*, *C. tyrobutyricum* and *C. difficile* (De Carvalho et al. 2007; Delves-Broughton et al. 1996; Irianto and Austin 2002) and gastric ulcers: *Helicobacter pylori (Delves-Broughton et al. 1996; Kim et al. 2003).*

Recently, the study of the therapeutic properties of nisin F in mice infected by *S. aureus* Xen 36 appeared to be promising to control the disease (Brand 2013). The resistance of spontaneous mutants to bacteriocins have also been reported, that may be related to changes in membrane and cell wall, such as alterations in the electrical potential, fluidity, membrane lipid composition and load or cell wall thickness or even a combination of all factors. These changes may occur following cell exposure to low concentrations of bacteriocins or as part of an adaptive response to some other stress.

The resistance of *L. monocytogenes* to nisin is related to variation in fatty acid composition of cell membranes, reducing the concentration of phospholipids, hindering the formation of pores. The mechanism of resistance to subclass IIa bacteriocins appears to be linked to reduced expression of mannose permease of the phosphotransferase system (Vadyvaloo et al. 2002).

Commercial Production of Bacteriocins

Several bacteriocin-producing bacteria have been patented, but to the end of 2005 none of them were at the commercialization stage (Brown et al. 1999; Shotts Jr and Wooley 2000), the only commercially produced bacteriocins are the group of nisin produced by *Lactoccocus lactis* (Jones et al. 2005) and pediocin PA-1 by *Pediococcus acidilactici* (Gálvez et al. 2008). Nisin is the most commercially important member of a large class of bacteriocins produced by bacteria that can kill or inhibit the growth of other bacteria.

This phase of the Nisin Market Study analyzes the characteristics of the current market for nisin and competing bacteriocins in four main sections highlighting: (1) the general market characteristics for antimicrobial preservatives; (2) current producers and sellers of commercial grade nisin; (3) current users of nisin and competing bacteriocins; and (4) implications for the market opportunities for nisin production in the U.S.

The global leader in the antimicrobial preservatives industry is Danisco A/S, a Danish company, with Royal DSM (Netherlands), and Kerry Bio-Sciences (Ireland) considered being their peer competitors in the bio-preservatives sector (Jones et al. 2005). Danisco's Nisaplin™ is

generally considered to be the most commercially available form of nisin for food preservative uses. Danisco's strategic focus for their nisin product line is the U.S. meat and deli food sector in order to take advantage of the FDA approval status of nisin as a natural ingredient. Other players in the global nisin market include Rhodia, S.A. (France) along with numerous producers and providers of various antimicrobial products based in China. Some of these Chinese sources are in joint ventures or alliances with European-based corporate entities.

Bacteriocin preservatives are part of the $22 billion global food additives market that has grown at 2-3% per annum through 2007 to $24 billion. The Genencor division of Danisco has manufacturing locations in the United States, Finland, Belgium, China, and Argentina (http://www.genencor.com). More than half of Genencor's $410 million yearly sales are outside the United States (Law 2005). Key competitors to Genencor have been identified as Diversa, Novo Nordisk, and DSM (Royal DSM NV) (www.hoovers.com). Several attempts have also been tried to express and secrete pediocin PA-1 in other *L. lactis* hosts, resulting in the enhanced production of pediocin PA-1 and to coproduce the lantibiotic nisin A and pediocin PA-1 and develop novel expression system for large-scale production and purification of recombinant class IIa bacterions and its application to Piscicolin (Gibbs et al. 2004). More recently the bacteriocin sakacin A (SakA) and two SakA-derived expressed as chimeras in lactic acid bacteria (LAB) and the yeast *Pichia pastoris* and *Kluyveromyces lactis* (Jiménez et al. 2013).

Concluding remarks

Lactic acid bacteria have been recognized as safe, and bacteriocins produced by these microorganisms have been a good model to use in food industries. Bacteriocins may further be a good solution to the problem of resurgence of resistant strains to antibiotics. It is now evident that the bacteriocin-like products of Gram-positive bacteria, especially those with a relatively broad anti-bacterial spectrum, will continue to be an active area of applied research.

The potential for either the discovery or genetic engineering of novel peptides with commercially desirable antibacterial activities offers an irresistible lure (Jack et al. 1995; Jones et al. 2005; Liu and Hansen 1990).

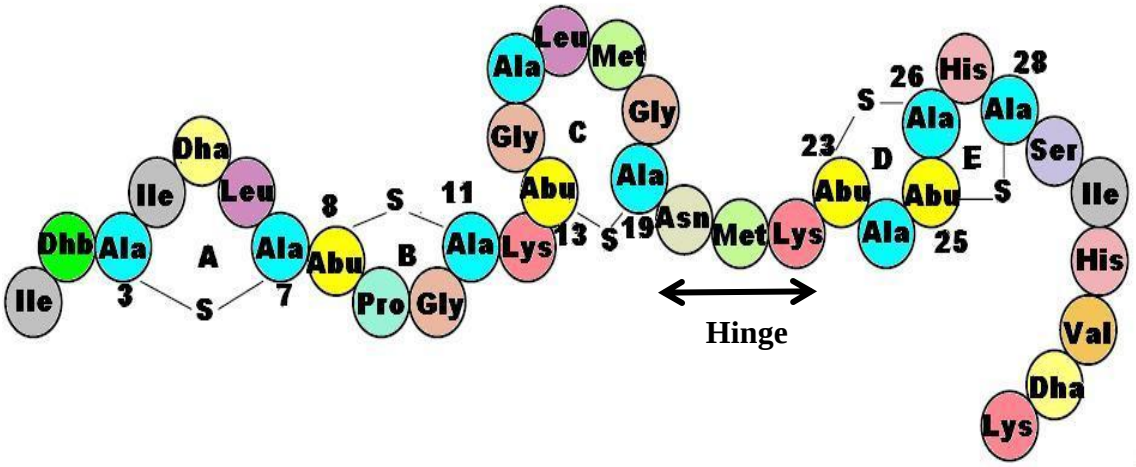
The utilization of bacteriocins or bacteriocin-producing bacteria in livestock is a field with enormous possibilities for both research and commercialization, but it has been very limited research in this area. As more countries develop antibiotic-limiting policies, the need for alternative antimicrobial will probably be the main driving force to continuously identifying novel bacteriocins and testing existing ones.

Because of the relative specificity of bacteriocins as compared with antibiotics, it can be anticipated that the identification of broader spectrum bacteriocins will be an active research endeavor. Novel LAB bacteriocins and their bioengineering will be useful in applications, but more details of their actions mechanisms and biosynthetic mechanisms must be determined for further application in food and livestock health. On the other hand, other techniques such as screening must further be undertaken to discover novel bacteriocins. This could help in the control of undesirable bacteria and in designing more powerful and more selective antimicrobial peptides.

Table.1 Bacteriocins of bacteria and archea (Bakkal et al. 2012)

	Bacteriocins	Bacteriocin Types /Class	Size (kDa)	Examples	References
Gram-negative bacteria	Colicins	Pore Formers Nucleases	20-80	Colicins A, B Colicins E2, E3	(Cascales et al. 2007)
	Colicin-like	NA	20-80	S-pyocins Klebicins	(Michel-Briand and Baysse 2002)
	Phage-tail like	NA	> 80	R and F pyocins Microcin C7	(Gillor et al. 2004)
	Microcins	Post-translationally modified Unmodified	< 10	Microcin B17 Colicin V	(Reeves 1965)
Gram-positive bacteria	Class I	Type A-positivelycharged and linear Type B-uncharged or negatively charged globular Type C-synergistic	< 5	Nisin Mersacidin Lacticin 3147	(Heng et al. 2007)
	Class II	Class IIa-antilisterial Class IIb-synergisti	< 10	Pediocin PA1 Carnobacteriocin B2	(Zacharof and Lovitt 2012)
	Class III	Type IIIa-Bacteriolytic enzymes Type IIIb-Nonlytic peptides	> 10	Lysostaphin Helveticin	(Field et al. 2007)
	Class IV	Cyclic peptides	< 10	Enterocin AS-48	(Maqueda et al. 2004)
Archea	Halocins	Microhalocins Protein halocins	< 10 > 10	Halocin A4, C8, G1 Halocin H1, H4	(Shand and Leyva 2007) (O'Connor and Shand 2002)
	Sulfolobicin	NA	~20	Sulfolobicin	(Ellen et al. 2011) (Sun et al. 2005)

Figure.1 Structure of nisin (hu.wikipedia.org)



ABU = Amino butyric
DHA = Dehydroalanine
ALA-S-ALA= Lanthionine
DHB = Dehydrobutyrine (β-Methyldehydroalanine)
ABU-S-ALA = β-Methyl lanthionine

Figure.2 Structure of Pediocin PA-1 (Desriac et al. 2010)

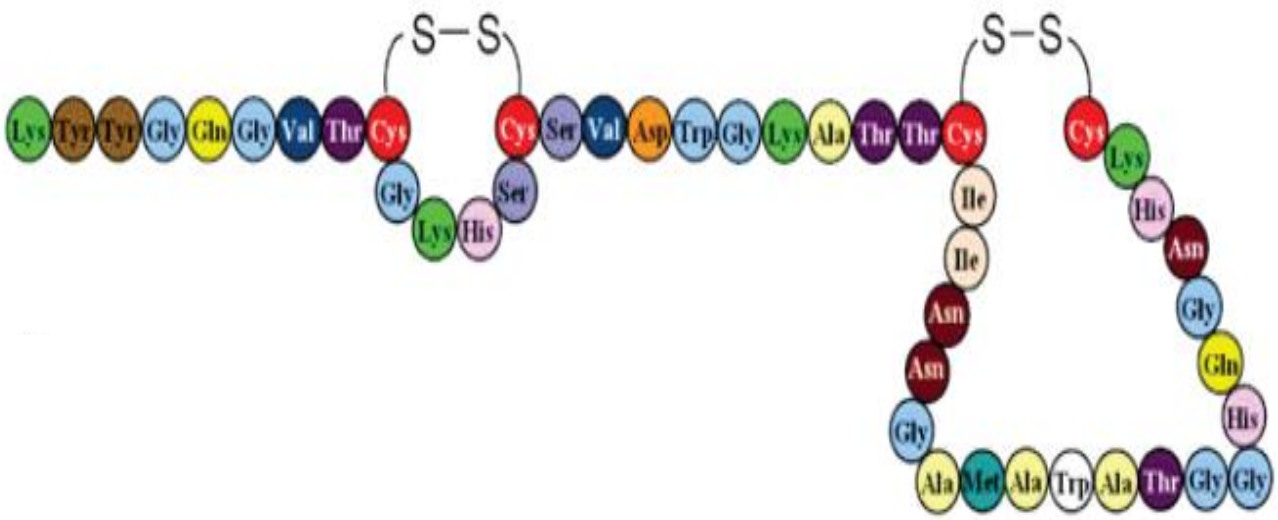


Figure 3. Model for the biosynthesis of nisin. The nisin precursor is modified by the putative enzymes NisB and NisC and translocated across the membrane by the exporter NisT. The precursor is extracellularly processed by NisP, resulting in the release of mature nisin. NisK senses the presence of nisin in the medium and autophosphorylates. The phosphate-group is transferred to NisR, which activates transcription of the genes nisABTCIP and nisFEG. NisI, F, E, and G protect the cell from the bacteriocidal activity of nisin. P: promoter region, P*: nisin-regulated promoters (Van et al.2009).

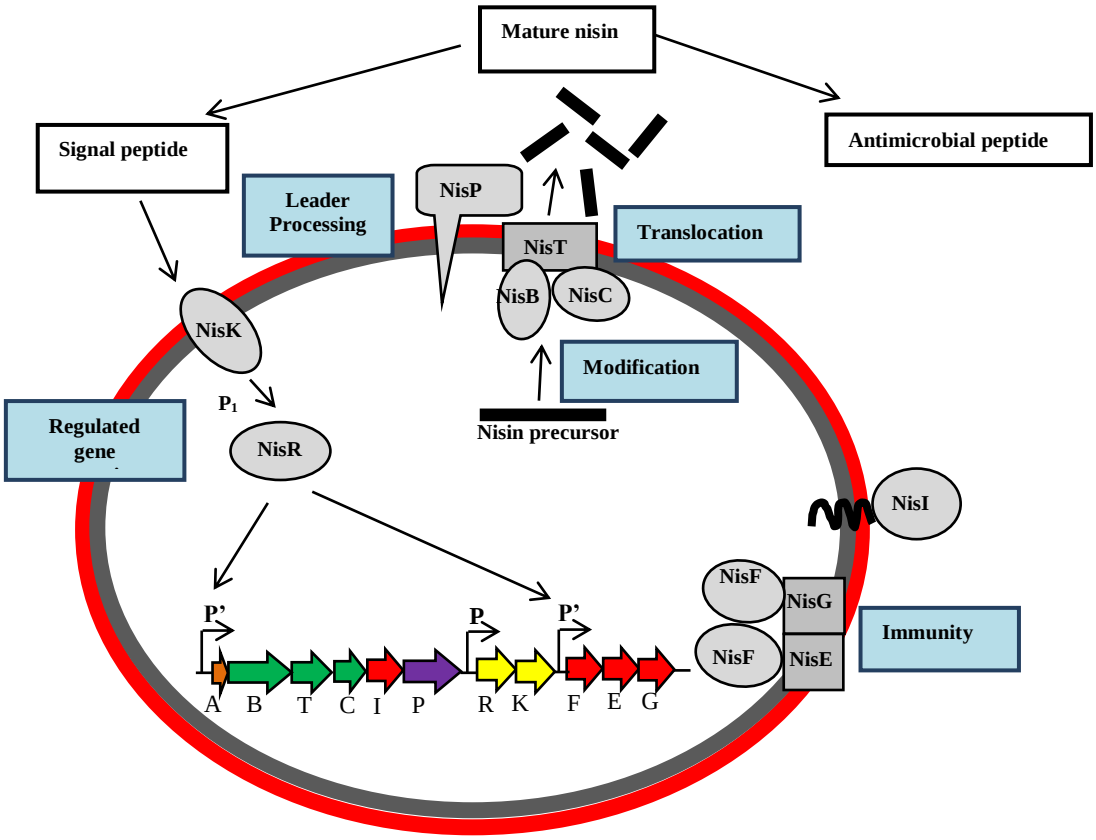
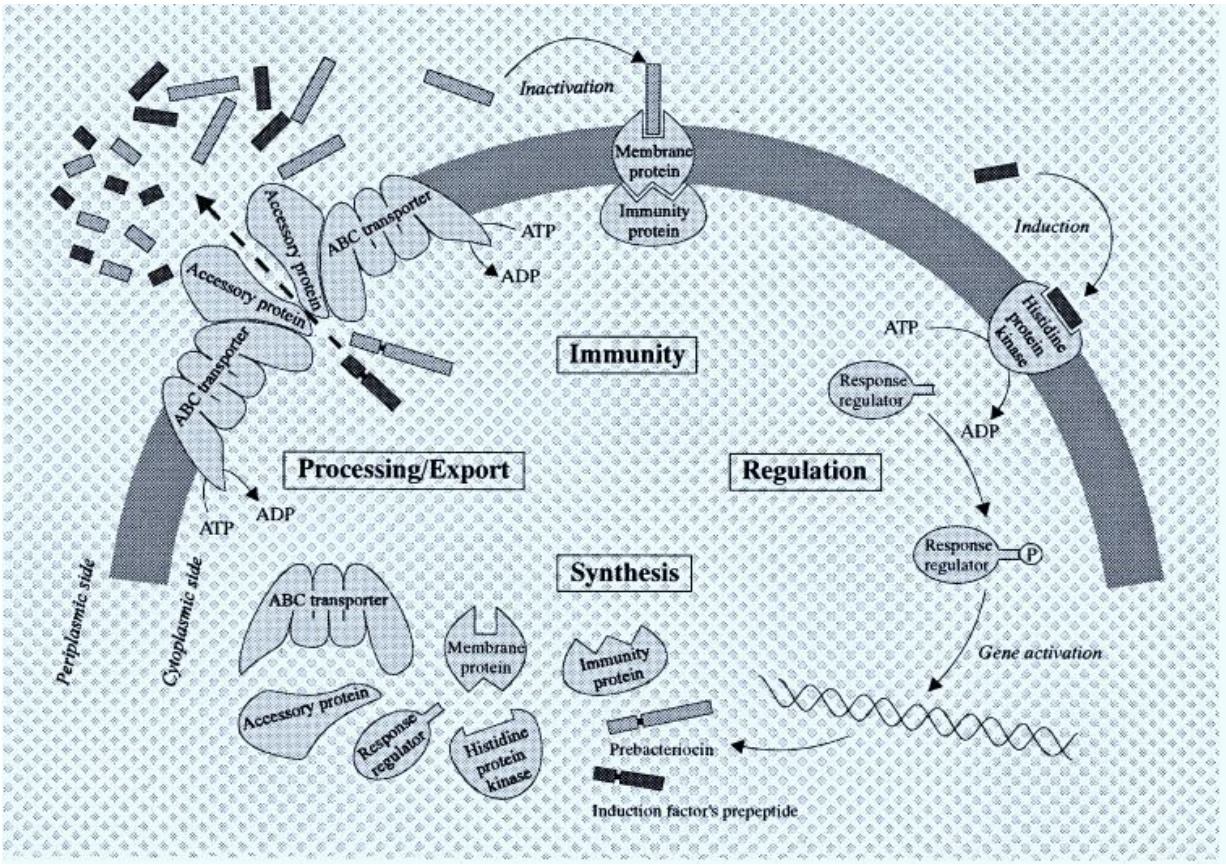


Figure.4 Schematic overview of the suggested machinery for production of class IIa bacteriocins: three-component regulatory system, synthesis, processing, excretion and immunity. Ennahar et al. 2000



Future approaches should consider the application of bacteriocins in combination with treatments enhancing their effectiveness in foods and livestock health together. The evaluation of antibacterial efficiency of the two bacteriocins from LAB, nisin and pediocin PA-1/AcH has revealed that they were more effective antibacterial in combination than they were used alone [160]. The use of more than one LAB bacteriocin as a combination biopreservatives or antimicrobial could be advantageous over a single bacteriocin especially in medical applications.

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