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Review Article

Classification of Antimicrobial Peptides Bacteriocins, and the Nature of Some Bacteriocins with Potential Applications in Food Safety and Bio-Pharmaceuticals

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Abstract

Bacteria have mechanisms to compete for nutrients and space in their habitat. One of these mechanisms is the acquisition of defense system by the production of antimicrobial peptides (AMPs), that is also known by the name bacteriocins.

Bacteriocins are classified by different methods, including producing bacteria strains, peptides chemical structure, mechanism of actions, and their common resistance mechanisms. Antimicrobial peptides (AMPs) are ribosomal synthesized peptides of less than 70 amino acids chain with a narrow to wide antimicrobial spectrum against Gram-positive bacteria.

Different Gram-positive bacteria including several of lactic acid bacteria (LAB) produce bacteriocins with a broad spectrum of inhibition against the growth of both food spoilage and foodborne pathogen bacteria.

These Lactic acid bacteria species producing bacteriocins offers potential applications in food preservation/safety as a natural bio preservative that help reducing the addition of chemical preservatives or physical treatments such as the intensity of heat treatments during food processing. Application of bacteriocins as natural bio preservatives in food processing result in food products richer in organoleptic, less acidic, lower in salt content and higher in nutritional values. In addition, since food safety has become an increasingly important international concern, bacteriocins from lactic acid bacteria (LAB) that are capable to target foodborne pathogens without toxic or other adverse effects have received great attentions.

In addition to the potential application of bacteriocins in food processing, there are many other applications for bacteriocins in various industries such as animal/poultry feeds, bio pharmaceuticals, and cosmetics industries. These bacteriocins can also be applies as antimicrobial film in packaging materials for foods, pharmaceuticals, and cosmetics products to extend products shelf life and expiration date.

In recent years the frequency of antibiotics-resistant bacteria is emerging causing serious health problems for both human and animals. Antimicrobial peptides (AMPs) including bacteriocins exert their bactericidal activity that are different from antibiotic mechanisms of actions. These AMPs have potential applications as alternative or a supplement to traditional antibiotics against emerging antibiotics resistant microbial pathogens to treat patients and animals infected with these antibiotic resistant pathogens such as methicillin-resistant *Staphylococcus aureus* and others.

Keywords: *Antimicrobial Peptides (AMPs); Bacteriocins; Nisin; Mersacidin; Pediocin PA-1; Lactococcin G; Enterocin AS-48; Aureocin A53; Lysostaphin; Helveticin J; Foodborne Pathogens; Antibiotic Resistant Strains; Tumor Cells; Anti-Cancer Peptides*

Introduction

Antimicrobial peptides (AMPs) are generally, positive charge peptides found in a wide range of live organisms from microorganisms to mammalians [1]. These peptides demonstrated capabilities to kill pathogenic and nonpathogenic bacteria, fungi, envelop viruses, and even transformed or cancerous cells with different mechanisms [2] such as destabilize host cell membrane, forming channels in host cell transmembrane, or enhancing host immunity by functioning as immunomodulators (Figure 1).

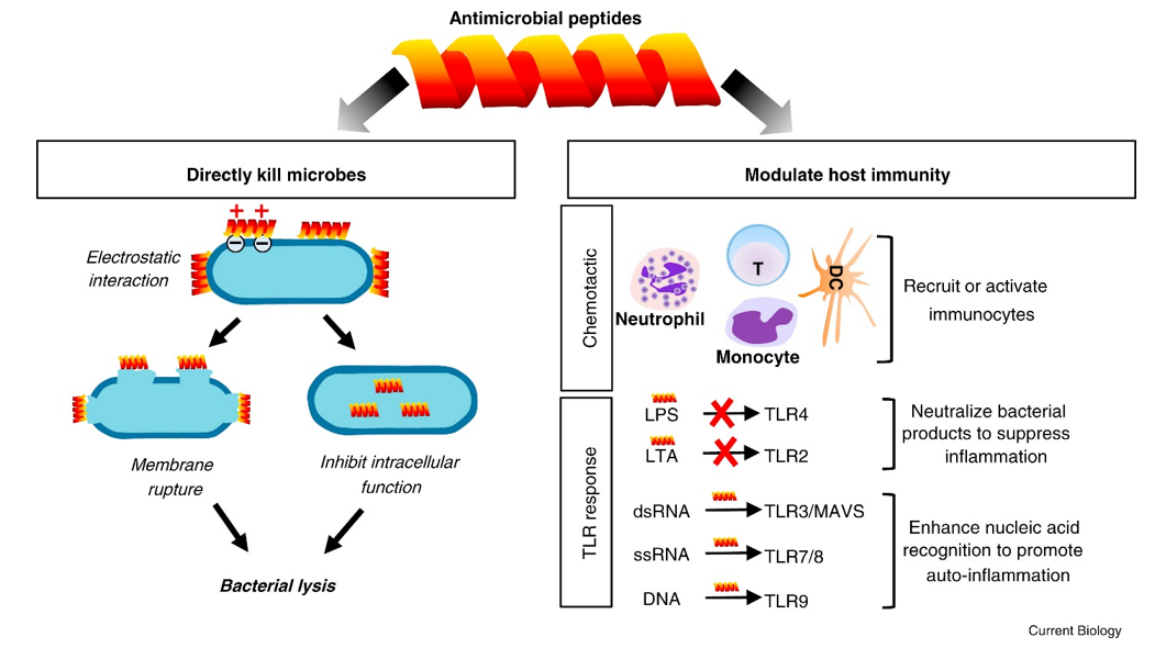

Figure 1: *Antimicrobial peptides function directly in killing microbes and in modulating host immunity. (a): AMPs exhibit a net positive charge and hydrophobic amino acids, allowing them to bind to negatively charged bacteria cell membranes leads to intracellular inhibition or disruption and death. (b): AMPs also modulate host immunity by recruiting/activating monocytes or influencing Toll-Like Receptor (TLR) to recognize microbial products to suppress inflammation or recognize microbial nucleic acids to promote auto-inflammation. DC*(dendritic cell); LPS* (lipopolysaccharide); LTA* (lipoteichoic acid); MAVS*, (mitochondrial antiviral) signaling protein.*

Insects [3], plants [4] and mammalians [5] are producing AMPs, as an antibiotic for the protection against potential pathogenic microorganisms. In these eukaryotic organisms AMPs are part of innate immunity system and can be referred to as 'host defense peptides', due to their additional mechanism as immunomodulatory activities. Microorganisms as being prokaryotic also produce AMPs to defend their environmental niche from other microorganisms and are referred to bacteriocins. Bacteriocins that are produced from nonpathogenic Gram-positive bacteria have potential applications in food products against foodborne pathogens for food safety and against spoilage microorganisms for food preservation [6].

The majority of AMPs are short chain amino acids generally between 12 to 70 amino acids with a net cationic charge, these peptides contains two or more positively charged residues provided by arginine, lysine, and over 50% hydrophobic amino acids residues. It is important to highlight that some AMPs with net neutral or anionic charge have been recently reported [5]. The secondary structures of these cationic AMPs are generally classified into four groups based on amino acids composition [7]. One group is extended peptide chain

forming amphipathic α-helical structure, second group is peptide chain arranged in β-sheet structure with internal two or more disulfide bonds, third group is extended linear peptide chain structure, and the fourth group is mixed peptide chain structure in a loop structure that is formed via a single internal disulfide bond (Figure 2). Many of these antimicrobial peptides (AMPs) are unstructured in free solution and folded into their proper configuration upon partitioning into the host cell membranes.

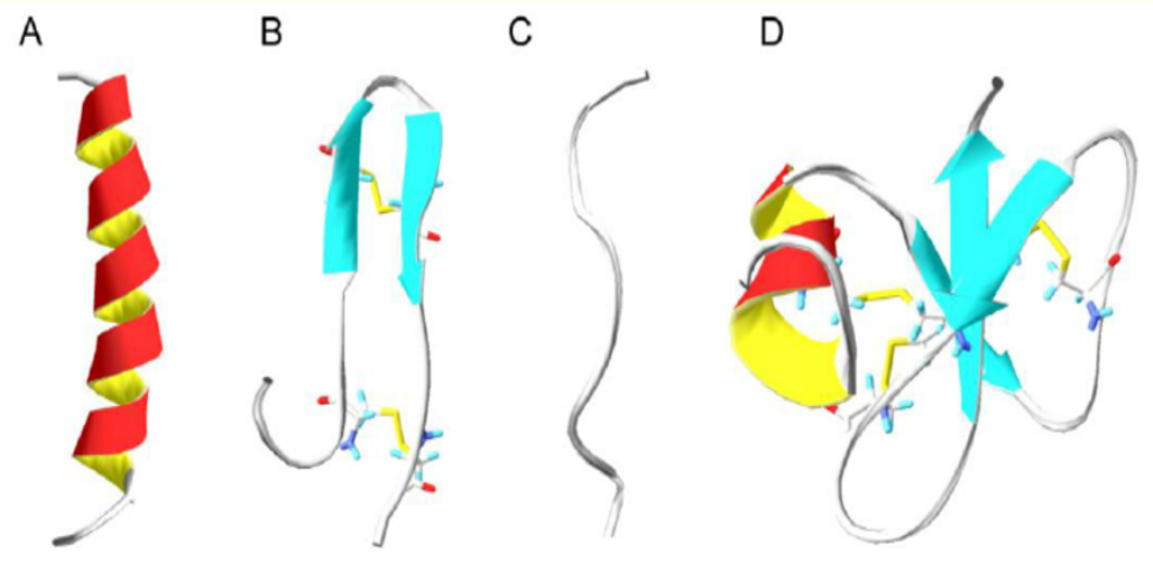

Figure 2: *Structural classes of antimicrobial peptides. (A) Extended peptide chain forming amphipathic a-helical structure, (B) peptide chain arranged in β-sheet structure with internal two or more disulfide bonds, (C) extended linear peptide chain structure, (D) mixed peptide chain structure in a loop structure that is formed via a single internal disulfide bonds.*

Food preservation and safety

Food preservation prevents the growth of spoilage microorganisms such as bacteria, mold, and yeast that spoil foods and reduce food products shelf life, Food safety prevent the presence of foodborne pathogens in food products that cause illness, hospitalization and death. These foodborne pathogens are Gram-positive and Gram-negative bacteria, such as *Listeria monocytogenes*, *Staphylococcus aureus, Clostridium perfringens, Campylobacter jejuni*, *Escherichia coli O157:H7* and *Salmonella sp*. Other foodborne pathogens are viruses such as norovirus. The cost of foodborne illness associated with these foodborne pathogens is between $6.5 and $34.9 billion/year and Centers for Disease Control and Prevention (CDC) in United States estimated that there are about 76 million cases of food borne illness in United States resulted with an estimated of 5,000 death per year. Due to international concern from foodborne illness and death, food safety become the major responsibility of food manufacturers to protect consumers health and safety. Thermal process to destroy viable microorganisms for food preservation and safety is generally applied, this traditional thermal process triggers biochemical reaction that effect nutritional values, flavor, and taste. Therefore, number of nontraditional technologies are developed to ensure food safety and in the same time maintaining foods nutritional values, and taste. One of these nontraditional technologies is the application bacteriocins to extend foods shelf life (food preservation) and to kill foodborne pathogens that have effects on consumers health (food safety).

Bacteriocins

Bacteriocins are antimicrobial peptides produced by different group of bacteria to inhibit or kill the growth of similar bacteria strains or closely related bacteria. Many lactic acid bacteria (LAB) are the producer of these bacteriocins that are ribosomal-synthesized peptides or proteins with narrow or wide spectrum antimicrobial activity [8]. A number of bacteriocins have been discovered and their diverted structures, mode of actions, mechanisms of biosynthesis, and genes regulation have been reported. These bacteriocins that are produced

from lactic acid bacteria are considered to be Generally Recognized AS Safe (GRAS) with potential applications for both food preservation and safety against both of spoilage microorganisms and against foodborne pathogens respectively. These bacteriocins also have other applications in pharmaceuticals, cosmetics, and other industries.

Gram-positive bacteria of lactic acid bacteria (LAB) produce wide variety of bacteriocins of different sizes, structures, properties, and inhibitory spectrum. These wide varieties of bacteriocins are generally classified into three classes according to their post-translational modification (peptides biosynthesis). These three classes are class I, class II, and class III (Figure 3). Class I bacteriocins are highly modified peptides made of 20-30 amino acids residue named lantibiotics because peptides chemical structure in this class contains intramolecular thioether rings formed by lanthionine and 3-methyllanthionine (Figure 4). This class I bacteriocins are subdivided into subclass I A and subclass I B. Class II bacteriocins are larger peptides non-lantibiotics with about 30 - 70 amino acids residue and subdivided into subclass II a, subclass II b, subclass II c,and subclass II d. Class III are higher molecular weight protein size produced by both Gram-positive and Gram- negative bacteria. It is important to highlight that class III have mode of action against target microorganisms different than class I and class II and are not usually included in the antimicrobial peptides (AMPs) family.

Class	Subclass	Representative AMPs	Producing bacteria
I Lantibiotic	I A	Nisin	*Lactococcus lactis*
I Lantibiotic	I B	Mersacidin	*Bacillus* spp.
II Non lantibiotic	IIa	Leucocin A	*Leuconostoc gelidum*
II Non lantibiotic	IIb	Lactococcin G	*L. lactis*
II Non lantibiotic	IIc	AS-48 enterocin	*Enterococcus faecalis*
II Non lantibiotic	IId	Lactococcin A	*L. lactis*
III Proteins		Helveticin J	*L. helveticus*

Figure 3: *Classification of bacteriocins produced by Gram-positive bacteria. Class I (IA and IB), Class II (IIa, IIb, IIc, and IId), and Class III (IIIa and IIIb).*

Lantibiotics antimicrobial peptides (bacteriocins Class I)

The name lantibiotics are referred to lanthionine-containing antimicrobial peptide [9]. Lantibiotics antimicrobial peptides produced by a large number of Gram-positive bacteria such as *Streptococcus spp*. that are capable to kill other Gram-positive bacteria. This class I bacteriocins are divided into two subclasses of type- I A lantibiotic, and type I B lantibiotic. Both types are cationic peptides and bactericidal. Type 1 A lantibiotic include Nisin, and Type I B include Mersacidin. These lantibiotic bacteriocins are will studied because of its large applications in food industry specially in dairy products, and for its potential applications in bio-pharmaceuticals, cosmetics, and agriculture industries.

Class IA: is polycyclic antimicrobial peptide ribosomally synthesized by Gram- positive lactic acid bacteria (LAB) during fermentation process. One of class 1A bacteriocins is Nisin that is produced from *Lactococcus lactis*. Nisin has 34 amino acid residues including uncommon amino acids of lanthionine (Lan), methyllanthionine (MeLan), didehydroalanine (Dha), and didehydroaminobutyricacid (Dhb) (Figure 5). These uncommon amino acids are incorporated in Nisin peptide chain via post-translational modification of precursor peptides [10]. Nisin has a wide broad-spectrum of inhibition against Gram-positive bacteria associated with food spoilage such as lactic acid bacteria, and against foodborne pathogens such as *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus* and *Clostridium botulinum.* Nisin also showed effectiveness against microbial spores [11]. Nisin was awarded Generally Regarded as Safe (GRAS) status in the year 1988 and is being approved as a natural food bio-preservative in the United States and in more than forty countries. In Europe Nisin in known by the E number name of E234. Nisin is soluble in water, very effective at wide range of pH from 3.5 to 8.0, and at concentration levels from 1 to 25 ppm, depending on food type and regulatory. Nisin is currently used in thermal processed foods, especially in dairy products, canned foods, juices, beer, cured meat and fermented foods without showing change in finish products color, flavor, odor, and taste [12]. Nisin is also used in food packaging materials manufacturing to serve as a food preservative by controlled release onto the packaged food surface from the polymer packaging [13]. In addition to food processing Nisin is used as a selective agent in microbiological media for the isolation of Gram-negative bacteria, yeast, and molds. Several research studies have been demonstrated that Nisin can prevent the growth of drug-resistant bacterial strains, such as methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococci* and *Clostridium difficile* [14]. Plus, there are increasing evidence indicates that Nisin can inhibit the growth of tumors and can exhibit selective cytotoxicity towards cancer cells [15]. Other research studies demonstrated that Nisin can work synergistically in combination with conventional therapeutic drugs [16]. In summary, Nisin has wide range of potential applications. These research studies demonstrated potential applications of Nisin in bio-pharmaceutical industries as well.

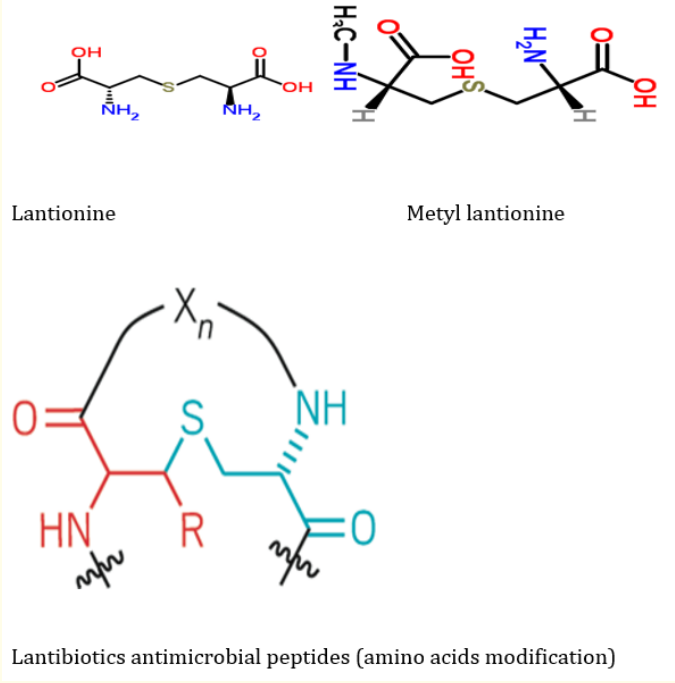

Figure 4: *Lantibiotic polypeptides formed by cyclization of serine or threonine (red) with a cysteine (blue) to form lanthionine (R = H) or methyllanthionine (R = CH3), which bridges a section of the polypeptide (Xn) [66].*

Class 1B: is tetracyclic lantibiotics with antimicrobial activity against Gram- positive bacteria including pathogenic bacteria and have no activity against Gram-negative bacteria or fungi. Class IB such as Mersacidin is produced from *Bacillus species* at the late stage of logarithmic growth phase and in stationary phase. It is a polycyclic antimicrobial peptide with 19 amino acids residues including the modified amino acid beta-methyl lanthionine (Figure 6). Mersacidin is not received Generally Recognized As Safe (GRAS) status from Food and Drugs Administration (FDA) in United States and is not approved for food applications as food bio-preservation. Pharmaceutical research studies demonstrated that Mersacidin comparing to Nisin and to antibiotics is strongly induce cell wall stress response against *Staphylococcus aureus* even at very low concentrations. This unique Mersacidin mode of action against the pathogenic bacteria of *Staphylococcus aureus* qualified Mersacidin for potential application against antibiotic methicillin-resistant of *Staphylococcus aureus* and against other Gram-positive pathogenic bacteria [17]. Currently, researchers are working in developing modified mutant peptide of Mersacidin with high antimicrobial activity toward developing an alternative to novel antibiotic with efficacy against conventional antibiotics-resistant strains of pathogenic bacteria [21].

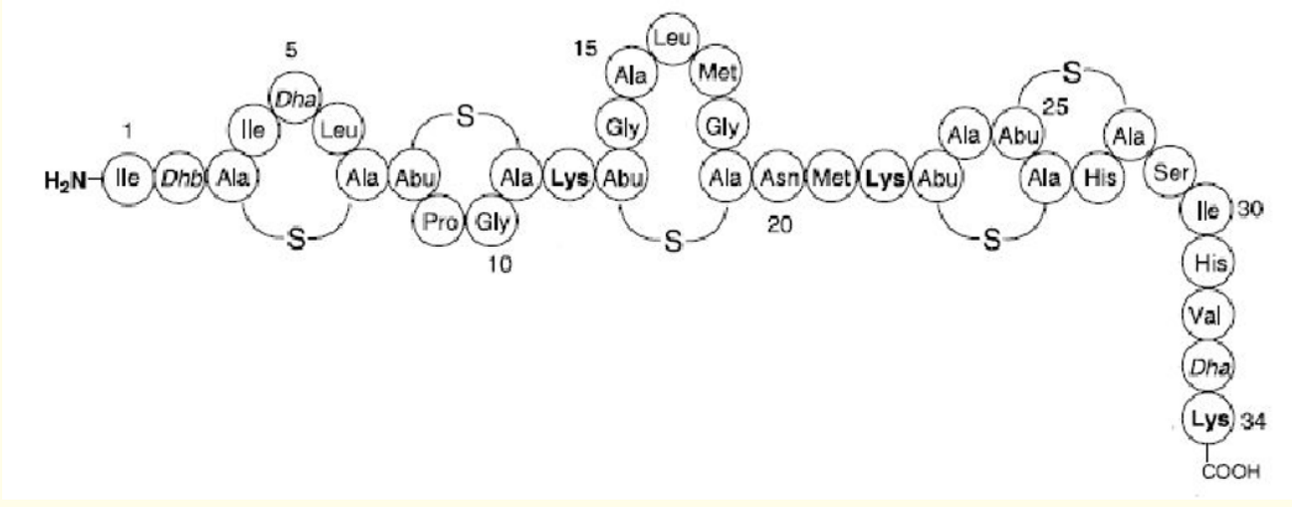

Figure 5: *Antimicrobial peptide Nisin. Primary structure of class I-A lantibiotic Nisin composed of hydrophobic and hydrophilic amino acids regions, divided into N-terminal and C-terminal respectively, and five lanthionine rings of modified amino acids: Dha (dehydro-alanine); Dhb (dehydrobutyrine); Ala-S-Ala (lanthionine); Abu-S-Ala (β-methyl-lanthionine).*

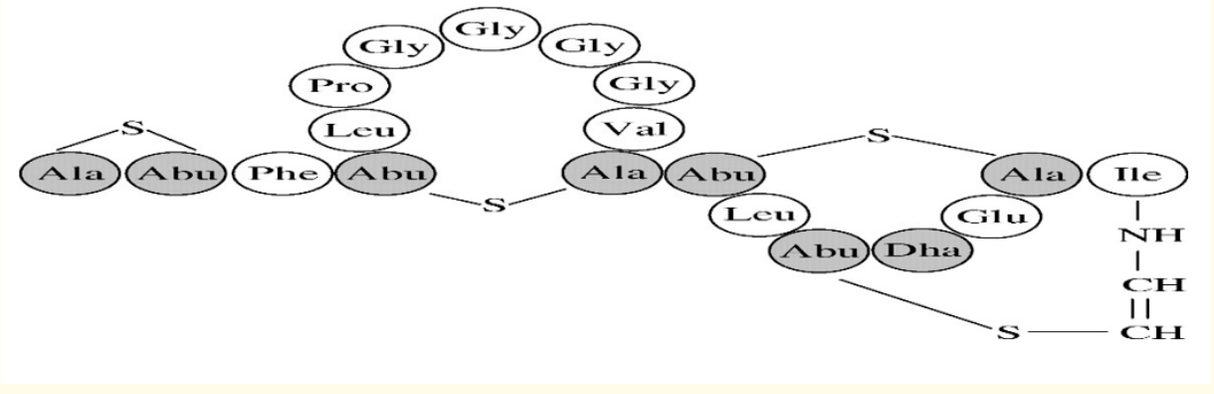

Figure 6: *Antimicrobial peptide Marsacidin. Primary structure of the class I-B lantibiotic Mersacidin contains post-translational modifications amino acid residues; Abu—S—Ala (3-methyllanthionine); and Dha (dehydroalanine).*

In general, mechanism of action of Lantibiotics class I bacteriocins showed substantial specificity for some components in bacterial cell membranes especially for lipid II expressed on target Gram-positive bacteria (Figure 7). In summary, class I type A lantibiotics such as Nisin and class I type B lantibiotics such as Mersacidin at lower concentrations are capable to kill target microorganisms by pore formation in target cell membrane, and by the inhibition of cell wall peptidoglycan biosynthesis in the target cell wall [18].

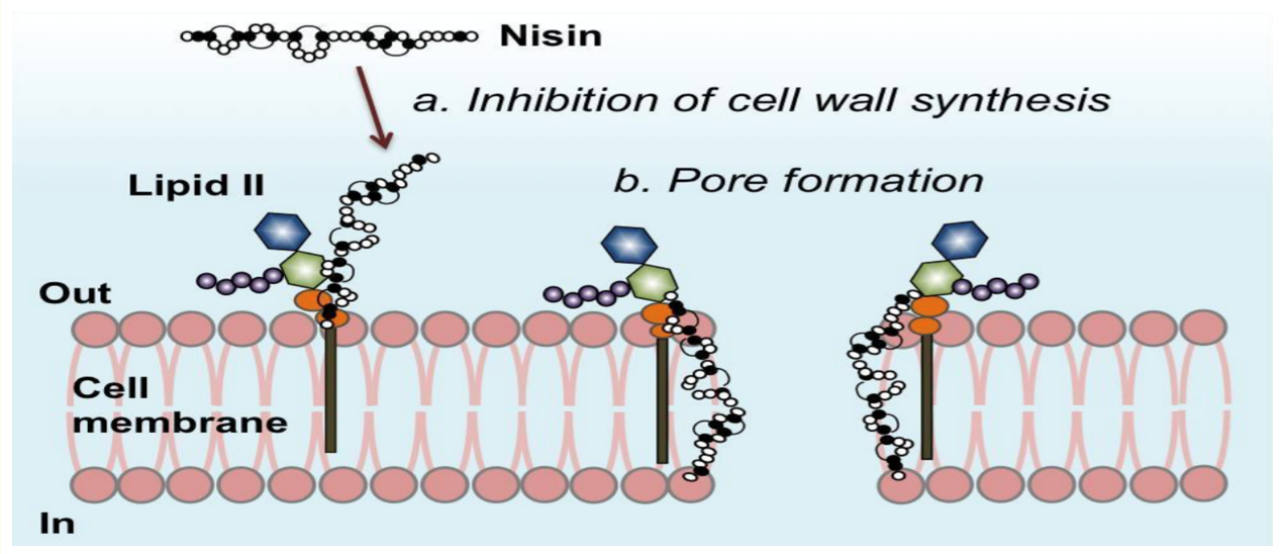

Figure 7: *Nisin and or Mersacidin mechanism of action against Gram positive bacteria. a. Bind to lipid II causing bacteria cell wall synthesis inhibition, and cell death. b. Insert in bacteria cell causing pore formation, and cell death.*

Non-lantibiotics antimicrobial peptides (bacteriocins class II)

Class II bacitracins are small peptides about 30 to 70 amino acids residue produced by lactic acid bacteria (LAB). They are cationic neutral pH peptides, contains hydrophobic and /or amphiphilic regions. Mode of action of this class II is on the cell membrane of target Gram-positive bacteria causing cells damage and death [19]. Large numbers of class II bacteriocins are produced by lactic acid bacteria such as *Pediococcus acidilactici* that produce the bacteriocin Pediocin PA-1, *Leuconostoc mesenteroides* that produce Masentericin Yqo5, *Lactobacillus sakei* that produce Sakacin P., *Leuconostoc gelidum* that produce Leucocin A, and *Lactobacillus curvatus* that produce Curvacin. These Class II bacteriocins are subclassified according to their amino acids sequences similarities, mode of action, target specificity and the number of peptides that constitute the antimicrobial peptide (bacteriocin). These subclasses are type IIa, type IIb, type IIc, and type IId.

Class IIa: Frequently referred to one-peptide pediocin-like-bacteriocins and are expanded into more than 15 different known bacteriocins including Pediocin PA-1, Pediocin AcH, Lactococcin A, Lactococcin B, Sakacin A, and others. All are cationic peptides, contains between 37 - 48 amino acids residue long, with similarities in amino acids sequence [20].

Pediocin PA-1 is the most studied one from all these one peptide pediocin-like bacteriocins (class IIa). It is produced from the Gram-positive bacteria *Pediococcus acidilactici* and has been sufficiently well characterized to be used as a food bio-preservative [21]. It is low molecular weight cationic peptide with hydrophilic *N*-terminal containing the pediocin box of amino acids motif YGNGYV (tyrosine, glycine, asparagine, glycine, tyrosine, and valine respectively), and a hydrophilic or amphiphilic *C*-terminal (Figure 8). Pediocin PA-1

mechanism of action is on target Gram-positive bacteria cytoplasmic membrane causing pores formation and cell death (Figure 9). It has unique properties such as thermostability, activity at wide range of pH, and resistance to some proteolytic enzymes [22]. Pediocin PA-1 has inhibition activities against food spoilage bacteria and against foodborne pathogens such the genus of *Listeria*, *Bacillus*, *Clostridium* and *Staphylococcus.* Pediocin PA-1 showed potential applications in foods processing such as meats, and dairy products specially for food safety against foodborne pathogen *Listeria monocytogenes* [21].

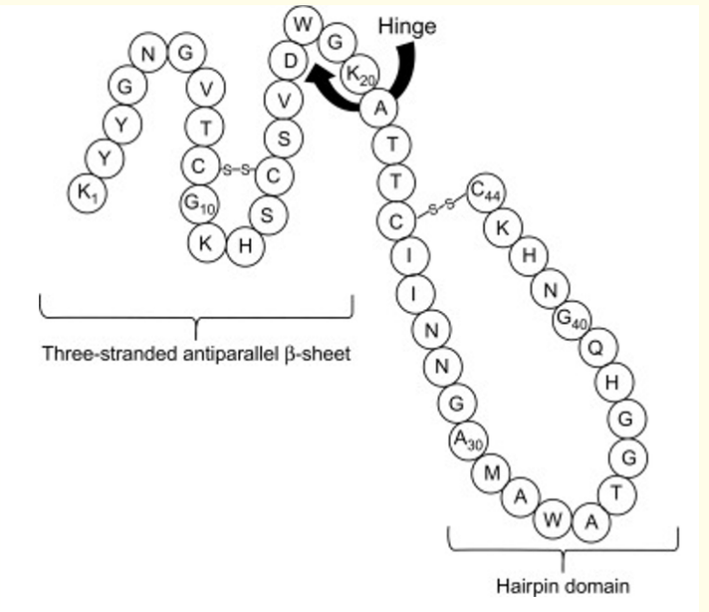

Figure 8: *Antimicrobial peptide Pediocin PA. Primary structure class IIa non-lantibiotic Pediocin PA-1 contain two domains: cationic N-terminal β-sheet domain that mediates binding to the target bacteria cell surface and hydrophobic C-terminal hairpin-like domain that penetrates into the hydrophobic part of the target bacteria cell membrane. The two domains are joined by a hinge, which enables movement these two relative to each other.*

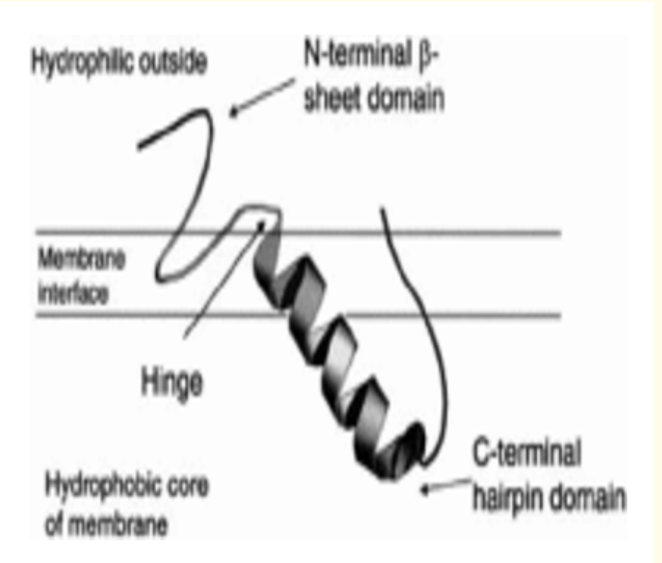

Figure 9: *Pediocin PA-1 mechanism of action. Pediocin bind to the target bacteria cytoplasm membrane, insertion of pediocin molecule in the cell membrane and forming the proration complex leading to cell death.*

Class IIb: Also know by the name two- peptide bacteriocins because this class consisting of two complementary cationic peptides and its antimicrobial activity is obtained when both peptides are present in equal amount [23]. This class IIb includes the two bacteriocins of Lactococcin G, and Enterocosins. Lactococcin G was the first one from these two-peptides bacteriocins (class IIb) to be isolated, and identified, and the most studied one. It is produced from Gram-positive bacteria *Lactococcus lactic* strains and consists of two unmodified peptides of Lcn-α (39 amino acids), and Lcn-ß (35 amino acids). Both are cationic peptides contains hydrophobic and/or amphiphilic regions (Figure 10). Lactococcin G inhibit the growth of spoilage bacteria of Lactic acid bacteria (LAB), and spore former Gram-positive bacteria such as *Clostridium spp*. Lactococcin G mechanism of action against target bacteria depends on the combination of Lnc-α and Lcn-ß in forming transmembrane pores in target bacteria causing ion imbalance inside target cells due to rapid release of potassium ions. This mechanism of action of class IIb is bactericidal due to the formation of potassium -selective channels in the target bacteria membrane by the Lnc- α and Lnc- ß peptides of Lactococcin G [24].

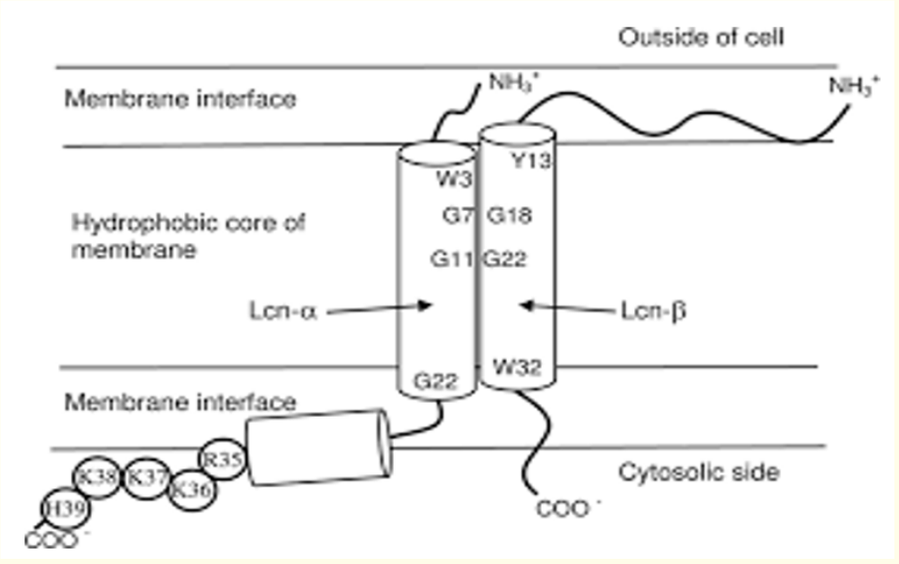

Figure 10: *Lactococcin G structure and mechanism of action. Class II b non-lantibiotic consist of two cationic peptides Lcn-a- and Lcn-ß. Both form a transmembrane helix-helix structure in the target microbial cell, with tryptophan-rich N-terminal end of the two Lcn (a and ß)-positioned in the outer membrane. The positively charged C-terminal end of the Lcn-a is forced through the membrane of the negative charge of target cell trans-membrane, leading to cell death.*

Class IIc: is circular cationic peptides [25] produced by Gram-positive bacteria. These circular property of bacteriocins enhanced antimicrobial activity and stability compared to other classes of linear antimicrobial peptides (bacteriocins). This antimicrobial activity and stability (mechanism of action) is due to the insertion of class IIc circular backbone into the cytoplasmic membrane of target bacteria cells, causing pore formation, and cell death (Figure 11). Currently, several circular antimicrobial peptides bacteriocins have been identified including Enterocin AS-48 produced from *Enterococcus faecalis.* The bacteriocin Enterococin AS-48 is a circular peptide contains 70 amino acids residue chain circularized by a head and tail peptide bond (Figure 12). Enterocin AS-48 has wide inhibitory spectrum against Gram-positive bacteria in addition to inhibition activity against Gram-negative bacteria in combination with chemical preservatives or physical treatment to destabilize the target Gram-negative cell outer-membrane of lipopolysaccharides (LPS) [26]. Potential applications of Enterocin AS-48 as a food bio-preservative have been demonstrated activity against foodborne pathogens of *Listeria monocytogenes*, *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella enterica* [27]. In addition, Enterocin AS-48 demonstrated activity against spoilage bacteria of *Alicyclobacillus acidoterrestris*, *Bacillus spp*., and lactic acid bacteria. The efficacy of Enterocin AS-48 against the Gram-negative bacteria of *Escherichia coli* and *Salmonella enterica,* are increased in combination with chemical preservatives, such as essential oils and phenolic compounds, or in combination with physical treatments such as sublethal heat, high-intensity pulsed-electric fields or high hydrostatic pressure [28].

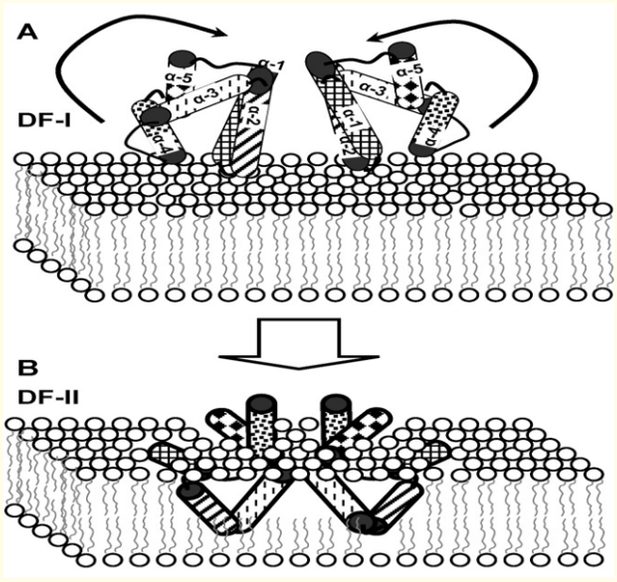

Figure 11: *Class II c such as Enterocin AS-48 mechanism of action. Class IIc bacteriocins are cyclic cationic peptide bound and inserted in the target bacteria cell membranes causing cell membrane permeabilization that lead to target cell death.*

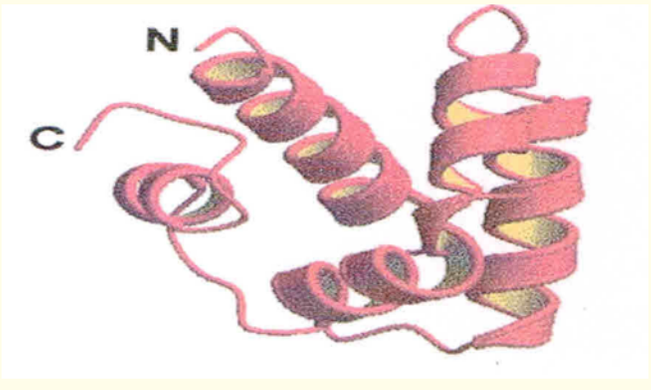

Figure 12: *Antimicrobial peptide Enterocin AS-48. Class IIc non-lantibiotic Enterocin AS-48 contains 70 amino acid-residue chain circularized by a head-to-tail peptide bonds arranged into five alpha-helices with a compact globular structure.*

Class IId: This class of bacteriocins have great diversity in their primary structures and mode of actions against target Gram-positive bacteria. They are stable antimicrobial peptides (bacteriocins) under high acidity and high temperature conditions plus are stable against protease enzymes. The best example from this class IId bacteriocins is Aureocin A53 [29]. Aureocin A53 is produced by *Staphylococcus aureus* A53. It is cationic peptide of 51amino acids containing ten lysine and five tryptophan. Its peptide structure in aqueous solution consisting of helical and ß-sheet confirmation (Figure 13). Aureacin A53 interacted with neutral and acidic membranes of target cells and it is likely to cause membrane permeabilization through membrane disruption rather than through membrane pores formation [29]. Aureacin A53 exhibits a broad-spectrum of antimicrobial activity against multidrug-resistant strains of *Staphylococcus spp*. [30] and exhibits antimicrobial activity against foodborne pathogen *Listeria monocytogenes* even in food matrix. Aureacin A53 has potential applications in food processing as food preservative and in pharmaceutical biotechnology as alternative or a supplement to traditional antibiotics to treat patients and animals infected with antibiotic resistant pathogens such as methicillin-resistant *Staphylococcus aureus.*

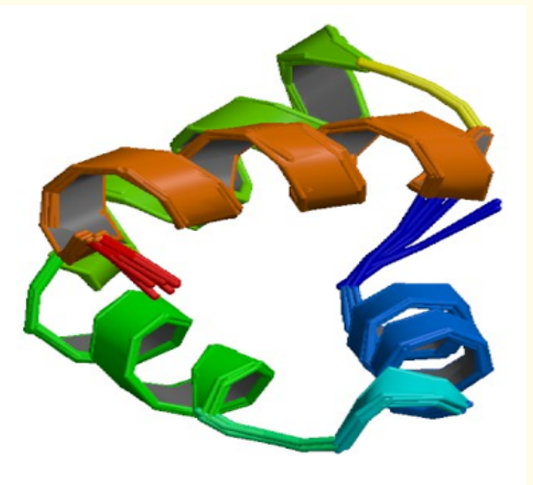

Figure 13: *Antimicrobial peptide Aureocin A53. Class IId non lantibiotic Aureocin A53 consist of four α-helices that are very similar compact, globular overall fold with a highly cationic surface and a hydrophobic core.*

Antimicrobial protein (Class III bacteriocins)

Class III bacteriocins are heat unstable large proteins with > 30 kDa molecular weights and are subdivided into two subgroups of class IIIa and class IIIb bacteriocins [31].

Class IIIa: Such Lysostaphin is a proteolytic enzyme that kill target Gram-positive bacteria by degrading the peptidoglycan in the cell wall structure [32]. Lysostaphin is capable to cleave the crosslinking pentaglycine bridges present in the cell wall peptidoglycan for certain species of the Gram-positive bacteria such as *Staphylococcus spp.* (Figure 14). Lysostaphin is 27kDa protein enzyme produced from the Gram-positive bacteria *Staphylococcus simulans*. It is highly effective against *Staphylococcal* infection from both *Staphylococcus aureus* and *Staphylococcus epidermidis* [33]. Both bacteria have the ability to form biofilm on implantable devices and became antibiotic resistant. Studies demonstrated that Lysostaphin has the ability to disrupt biofilms (growth) formed by *Staphylococcus aureus* and *Staphylococcus epidermidis* on implanted devices compared to commonly used antibiotics such as vancomycin [34]. In addition, Lysostaphin demonstrated effectiveness against methicillin resistant bacteria of *Staphylococcus aureus* (MRSA).

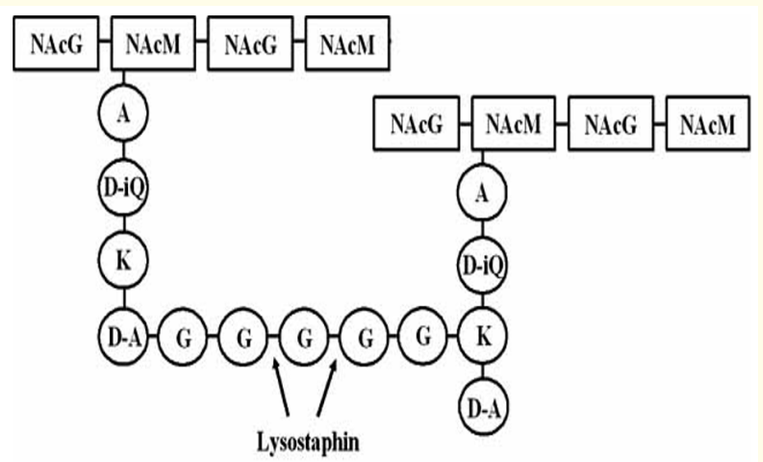

Figure 14: *Peptidoglycan chemical structure for Gram -positive bacteria and lysostaphin mechanism of action. Site of hydrolysis of lysostaphin on the staphylococcal peptidoglycan [NacG= N-acetylglucosamine; NacM = N-acetylmuramic acid; A= L-alanine; D-iQ= D-isoglutamine; K= L-lysine; D- A= D-alanine; G= L-glycine].*

Class IIIb: Such as Helveticin J is > 37 kDa non-lytic protein produced from the Gram-positive bacteria *Lactobacillus Helveticas* [35]. Helveticin J is antimicrobial protein with activity against closely-related species of *Lactobacillus* at neutral pH under aerobic or anaerobic conditions [36]. Helveticin J is sensitive to proteolytic enzymes and sensitive to high temperature (deactivated at 100^0C in 30 minutes exposure). It is capable to disrupts the target Gram-positive bacteria cell wall and the cytoplasmic inner membrane causing the leakage of cell contents and also, capable to disorganize the outer membrane of target Gram-negative bacteria cells leading to cell death.

In addition to the above three classes of bacteriocins (class I, class II, and class III), a fourth class IV has been identified. This class IV of bacteriocins are defined as complex bacteriocin containing lipid or carbohydrate moieties. In this class IV two bacteriocins of Sublancin and Glycocin F have been investigated, both are classified in separate subclasses. Sublancin is glycopeptide produced from the Gram-positive spore former bacteria of *Bacillus subtilis* 168. Sublancin reported to has antimicrobial activity against strains of *Staphylococcus aureus* and can be used as an alternative to conventional antibiotics [37]. Glycocin F is 43-amino acid bacteriocin contains two beta-linked *N*-acetylglucosamine moieties, attached via side chain linkages to a serine (Ser18) via oxygen, and to a cysteine (Cys43) via sulfur and produced by *Lactobacillus plantarum.* This bacteriocin Glycocin F, demonstrated to has bactericidal activity against wide range of Gram-positive bacteria [38].

Discussion

Antimicrobial peptides (AMPs) are a diverse classis of natural molecules produced by monocellular and multicellular organisms as a first line of defense. These antimicrobial peptides (AMPs) plus some identified antimicrobial proteins (APPs) are demonstrated to have biological activity to kill bacteria, yeasts, fungi, viruses and even cancer cells. Insects and plants secrete AMPs primarily as antibiotics to protect themselves from the potential microbial infection. AMPs produced by higher eukaryotic organisms including human are referred to as 'host defense peptides due to their immunomodulatory activities [39]. In some instances, the inappropriate expression of AMPs by human, can induce autoimmune diseases [40]. AMPs produced by bacteria (prokaryotic) are referred to bacteriocins and are produced by bacteria to defend their environmental niche against the competition by other related bacteria. Chemical structures of all these diversities of AMPs are generally, cationic peptides with 10 to 70 amino acids, and contains basic amino acids including hydrophobic residues to form structures that are positively charged and hydrophobic. These positive charges peptides with high ratio of hydrophobic amino acids allowing AMPs to bind to target selectivity specific species of negatively charged bacteria cell membranes leading to non-enzymatic cell disruption and death [41]. This specific selectivity is due to differences in the membrane composition of different bacteria and cell types.

Antimicrobial peptides (AMPs) can be classified into groups based on their secondary structure into α-helical; β-sheet; extended linear peptides, and mixed peptide chains. As an example, amphipathic α-helical AMPs such as frog magainin [42] and human cathelicidin peptide LL37 [43] exhibit little secondary structure in aqueous solution but they are amphipathic α-helical structure when enter a non-polar environment such as the target bacteria cell membrane [44]. Other examples are bactenecins and defensins [45], both peptides are characterized by two or more β-sheets that are stabilized by disulfide bonds.

A great number of nonpathogenic Gram-positive bacteria such as lactic acid bacteria (LAB) produce polypeptides that have antimicrobial activities with potential applications in foods as bio-preservatives against food spoilage bacteria and against foodborne pathogens. It is important to highlight that few pathogenic Gram-negative bacteria also produce polypeptides that have antimicrobial activities as well such as Colicin [46] and Microcins [47]. Both Colicin and Microcin are produced from pathogenic Gram-negative bacteria *Escherichia coli.* Antimicrobial peptides produced by pathogenic Gram-negative bacteria such as *Escherichia coli* are not acceptable for foods applications as bio- preservatives or for other applications due to health safety concerns.

Antimicrobial peptides produced from bacteria are called bacteriocins and are not refer to antibiotics. The major difference between bacteriocins and antibiotics are bacteriocins generally have narrow spectrum antimicrobial activities and are restricted to bacteria strains related to the same producing bacteria species. Antibiotics in other hands have wide spectrum antimicrobial activities and does not show

preferential effects on closely related to antibiotics producing bacteria strains. Other differences, Bacteriocins (antimicrobial peptides) are synthesized in producing bacteria ribosomes by translation process as primary metabolites. While antibiotics synthesized in producing bacteria as secondary metabolites [48].

Bacteriocins are classified by several methods based on producing bacteria strains, mechanism of action against target bacteria, molecular weight, chemical structure, and the presence of modified amino acid in peptide chains. Bacteriocins that contains modified amino acid lanthionine as part of their peptide chains are referred to Lantibiotics. Bacteriocins that does not contain modified amino acids are referred to non-Lantibiotics. In general, bacteriocins are classified into class I, class II, class III, and class IV. Some researchers exclude class III, and class IV from bacteriocins classification because these last two classes are protein with high molecular weight and are not polypeptides with a total of 10 to 70 amino acids chain as in the case of class I and class II bacteriocins.

Gram-Positive bacteria of lactic acid bacteria from the genus of *Lactobacillus* are the focus for bacteriocins production for the application in food processing as a natural bio- preservative because they are nonpathogenic and present naturally in fermented foods. These bacteriocins produced by lactic acid bacteria have the GRAS status (Generally Recognized As Safe) from Foods and Drugs Organizations (FDA) in United States and from other worldwide Health Organizations.

Nisin a Lantibiotic bacteriocin is granted safe status in United states and in over 40 Countries worldwide. It was discovered in 1928 and is now used in a variety of food applications. Nisin is produced from *Lactobacillus lactis* a microorganism used in dairy industry for the production of fermented dairy products. It has a bactericidal mode of action under optimum conditions of temperature, pH, and water activity (a_w). Nisin has a wide spectrum activity against many Gram-positive bacteria, including lactic acid bacteria that are commonly associated with food spoilage, and against known foodborne pathogens such as *Listeria monocytogenes, Staphylococcus aureus*, *Bacillus cereus* and *Clostridium botulinum*. In addition, Nisin showed activity against Gram-negative bacteria that are protected by their outer membrane chemical structure of lipopolysaccharides (LPS). The antimicrobial activity of Nisin against Gram-negative bacteria is after heat shock treatment to the target microorganism first or when Nisin is coupled with EDT (Ethylenediaminetetraacetic acid) [49]. The success of Nisin as a bio- preservative in food applications increased the interest for possible Nisin applications as alternative to antibiotics to kill antibiotics resistant pathogens such as methicillin resistant strain of *S. aureus* (MRSA).

Nisin is the only Lantibiotic bacteriocin commercially approved for the applications in food as bio-preservative in replacement to chemical preservatives such as nitrate and sulfur dioxide. It is currently used in foods against foodborne pathogens, and against food spoilage microorganisms. In addition, Nisin is also demonstrated effectiveness against bacterial spore [50]. Other non-Lantibiotic bacteriocin with potential food applications as bio- preservative is Pediocin PA-1 which demonstrated to has bactericidal activity against foodborne pathogen *Listeria monocytogenes* in meat products [51].

Other potential applications of Nisin and other accepted bacteriocins such as Pediocin PA-1 are in food packaging materials [47]. Currently, vacuum packaging and modified atmosphere packaging are used to prevent spoilage of fresh foods and to extend the shelf life of marketed foods. A number of research studies demonstrated that Nisin at the activity of 5000 IU /g sprayed on fresh meats before vacuum packaging followed by refrigeration resulted in the inhibition of the growth of foodborne pathogens *Listeria spp.* Also, the incorporation of Nisin in food package materials demonstrated to be highly effective in controlling food spoilage by Gram-positive bacteria. In addition, Nisin microencapsulation has been developed to prevent Nisin from foods proteolytic enzymes [52]. This microencapsulation technology increased potential applications of Nisin in foods as bio-preservative against spoilage and foodborne pathogen microorganisms. Bacteriocins in food applications can be applied in a crude form or by using bacteriocin producing strains as starter culture in fermented foods [53]. It is important to highlight that the limitation of bacteriocins activity under variable food environmental conditions can be improved by protein engineering strategies [54].

Multiple antibiotics resistance pathogens have become seriously infection diseases, due to the abuse of antibiotics use in medical treatments and due to the addition of antibiotics in animal feed formulations for animal health and meat production [55].

This emerging antibiotic resistance microbes is a public health challenge and Centers for Disease Control and Prevention (CDC) in United States estimated that over 2 million patients suffering from this antibiotic resistant infection and at least 23,000 patient dies every year due to the lack of suffusion treatment [56]. Researchers are working to find treatment(s) to combat this public health threat by investigating numerous antibacterial agents [57] such as bacteriophages, probiotics, non-microbial antimicrobial peptides (AMPs) and microbial antimicrobial peptides (bacteriocins) as an alternative approaches to antibiotics to treat patients infected with these antibiotics resistance microbes such as penicillin resistant *Streptococcus pneumonia,* methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Pseudomonas aeruginosa.* Penicillin resistant *Streptococcus pneumonia* [58] that infect lung causing mild to severe illness to people of all ages, complications of *Streptococcus pneumonia* infection include bacteremia and meningitis. Methicillin resistant *Staphylococcus aureus* [59] is an opportunist pathogen, infecting burn and wound, producing toxins that give rise to toxic shock syndrome leading to fever, and in some cases to death. Other complications caused by *Staphylococcus aureus* include, mastitis (infection of the mammary glands), infections of skin (impetigo), osteomyelitis (infection of bone), endocarditis (infection of the endothelial lining of the heart and valves), and bacteremia [60]. It is important to highlight that *Staphylococcus. aureus* secrete enterotoxin in foods causing food poisoning [61]. *Pseudomonas aeruginosa* [62] is a hospital-acquired infection, especially for immunocompromised patients. In addition, *Pseudomonas* infection is especially prevalent among patients with burn wounds, cystic fibrosis, acute leukemia, organ transplants, and intravenous-drug addiction [63]. The appearance of antibiotic resistant *Pseudomonas aeruginosa* strains is the most serious infection, and if it is not treated properly could lead to these complications and death.

Investigations of antimicrobial peptide including bacteriocins as an alternative for antibiotics showed promising results *in vitro* experiments. As an example, the bacteriocin Nisin, and antimicrobial peptides (AMPs) of Magainin [64], Cecropin [65] and human Cathelicidin LL37 [66], were evaluated against methicillin resistant *Staphylococcus aureus (MRSA). R*esults revealed that these antimicrobial peptides were effective against both antibiotic susceptible and resistant strains of *Staphylococcus aureus* by showing total reduction in bacterial count. When antibiotics were combined separately with these antimicrobial peptides including the bacteriocin Nisin the sensitivity of antibiotics resistant' strain of *Staphylococcus aureus* was increased. Clinical trials, for evaluating potential side effects to patients, and potential emerging antimicrobial peptides resistant pathogen strains are necessary for confirmation before potential application as effective alternative drugs to antibiotics.

In the case of cancer therapy, some researchers demonstrated that antimicrobial peptides including bacteriocins have activity against tumor cells [67]. As an example, research studies demonstrated *in vitro* that bacteriocin Nisin showed capabilities to prevent tumor cell growth. This Nisin and others antimicrobial peptides *in vitro* experiments highlighted that antimicrobial peptides including bacteriocins may have a future potential application as anti-cancer peptides drug in inhibiting and preventing cancer cell growth [68].

Bio-pharmaceutical applications of antimicrobial peptides including bacteriocins or anti-cancer peptides required further investigation including the application of genetically protein engineered technology to develop custom design biosafety and stability peptide's drugs with higher efficacy in treatments [68].

Production scale of such peptide's drugs must be approved after clinical trials, and has to be highly purified and sterile, to meet the United States Pharmacopeia (USP) standard specification and the standard specifications required by other worldwide Health Organizations.

Conclusion

Bacteriocins produced by Gram-positive bacteria showed strong antimicrobial activities against wide range of food spoilage and foodborne pathogens and are now widely used to extend foods and feeds shelf life by suppressing Gram-positive spoilage and pathogenic

bacteria. Ongoing *in vitro* medical research seems to indicate that antimicrobial peptides may have potential applications to treat the infection with antibiotic resistant pathogenic bacteria strains as alternative to conventional antibiotic that lost its efficacy against these antibiotics resistant pathogenic strain, Also ongoing *in vitro* medical research demonstrated that these antimicrobial peptides have potential application as anti-cancer peptides (antitumor peptides) to slow the growth of certain tumors as an alternative to nonspecific antitumor chemicals.

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