A review of pediocins and pediocin-like bacteriocins (PLBs)

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ABSTRACT Bacteriocins are widely used in the food industry due to their bio-preservative potential and antimicrobial properties. Despite the large number of identified LAB bacteriocins, nisin, and pediocin PA-1 are the only ones that have been thoroughly studies in food system application studies. Genetic engineering of pediocins is an interesting open research area that could lead to the development of pediocins with enhanced properties. The aim of this review is to explain the general molecular structure of pediocin and pediocin-like bacteriocins (PLBs) produced by *Pediococcus* spp. and compare their structural advantages. Another goal is to identify what changes can be made to the molecular structures of pediocins and PLBs. In doing so, we hope to shed light on the potential applications of pediocins and PLBs in the food industry.

KEYWORDS Class IIa bacteriocins; Mechanism of action; Molecular structure; Pediocin; *Pediococcus* spp.

1. Introduction

Bacteriocins are ribosomally synthesized antagonistic substances with a protein structure that have bactericidal or bacteriostatic activity against a limited number of bacteria, especially species which are close to the bacteriocin producing bacteria (Jack et al., 1995; Piva and Headon, 1994; Ennahar et al., 2000; Karpiński and Szkaradkiewicz, 2016). Although the first bacteriocin, colicin, isolated in 1953 primarily as an extracellularly secreted bioactive peptide with a low molecular weight from Gram-negative bacteria, *Escherichia coli*, bacteriocins are generally known to be related to Gram-positive bacteria and directly associated with specific immune mechanisms of the producer strain (Balandin et al., 2019). Bacteriocins first gained attention as biopreservative bioactive peptides due to their strong antibacterial properties. Recently, bacteriocins have been shown to play a critical role in the antimicrobial activities of some bacteria, primarily those belonging to the lactic acid bacteria (LAB) group.

Bacteriocins secreted by LAB are divided into four groups. Peptides that undergo post-translational modifications are classified as Class I bacteriocins. Bacteriocins in this class include lantibiotics, lasso peptides, sactibiotics, and thiopeptides, etc. Bacteriocins classified as Class II have minor post-translational modifications such as cyclization, formation of disulfide bonds, and N-terminal methionine formulation. Class III bacteriocins are peptides with a molecular weight greater than 30 kDa and generally defined as heat-labile peptides. Class IV bacteriocins are peptides that are covalently bound to glycolipids. Furthermore, five subgroups of Class II bacteriocins have been identified: iia) pediocin-like bacteriocins (PLBs), iib) cyclic bacteriocins, iic) bipeptide bacteriocins, iid) linear bacteriocins not belonging to the other sub-classes, and iie) microcin E492-like bacteriocins (Cotter et al., 2013; Alvarez-Sieiro et al., 2016; Balandin et al., 2019).

The most studied bacteriocin, nisin, has been legally confirmed to be safe (Punyauppa-path and Phumkhachorn, 2015; Ibarra-Sánchez et al., 2020). Nisin is a cationic bacteriocin with a wide antibacterial spectrum against Gram-positive bacteria (Colas et al., 2007; de Arauz et al., 2009; Punyauppa-path and Phumkhachorn, 2015). Pediocins and PLBs are probably the most studied bacteriocins after nisin due to their wide antimicrobial spectrum against pathogens that can cause both human and animal infections (Wang et al., 2015).

Within the scope of this review, an overview of pediocin and pediocin-like bacteriocins (PLBs), class IIa bacteriocins has been viewed and the importance of these

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peptides, their usage areas, and their structural superiority have been examined.

2. The use of bacteriocins

Bacteriocins and other metabolites produced by LAB have been used in the food industry, as well as other fields, as the safe, healthy, long shelf-life and minimally processed food products are demanded by consumers. Bacteriocins have been reported to be used to improve the quality of food components due to properties such as stability and antimicrobial activity (Carr et al., 2002; Cotter et al., 2005). In the dairy industry, bacteriocins can be used safely as an alternative to chemical preservatives (Silva et al., 2018).

The use of LAB bacteriocins as antimicrobial additives makes them significantly important for food industry. The development of new antimicrobial agents has grown in importance due to their potential for use against antibiotic resistant bacteria as well as their lack of side effects caused by chemical preservatives. The use of bacteriocins as preservatives in the treatment of infections and their role as food additives, has led to an increased interest in them (Kuipers et al., 1996; Gillor et al., 2005; Pag and Sahl, 2002).

In general, LAB bacteriocins have an inhibiting effect on Gram-positive bacteria (Osmanagaoglu and Lu, 2001). Many LAB bacteriocins have been shown to have the potential to increase food spoilage time and inhibit pathogen bacteria such as *Listeria monocytogenes*, *Bacillus cereus*, *Staphylococcus aureus*, and *Clostridium botulinum*. However, there are very few LAB bacteriocins that inhibit Gram-negative bacteria. Bacteriocins produced by some strains of the *Lactococcus*, *Enterococcus*, *Lactobacillus* genera and *Leuconostoc* spp. have been shown to be effective against Gram-negative and Gram-positive bacteria (Lee and Paik, 2001; De Kwaadsteniet et al., 2005; von Mollendorff et al., 2006). Factors such as the limited antimicrobial spectrum of most LAB bacteriocins and the protective effect of food composition limit the use of bacteriocins as food preservatives (Mazzotta and Montville, 1997).

Bacteriocins can be combined with other antimicrobial agents, such as essential oils to play a more effective biopreservative role. Plant essential oils can help improve medicine properties, such as analgesics, anti-inflammatory agents and local anesthetics due to their bactericidal, fungicidal and virucidal properties. However, as they may be limited by sensory changes, it has been demonstrated that bacteriocins can be combined with plant essential oils to maintain the efficiency with preventing such changes (Burt, 2004; Bakkali et al., 2008; Gutierrez et al., 2008).

Bacteriocins are also known as alternative peptides in anti-cancer strategies. Pediocin PA-1 from *Pediococcus acidilactici* PAC1.0 has been shown to inhibit the growth of human lung carcinoma cell lines and human colorectal adenocarcinoma cell lines. Furthermore, pediocin PA-1, isolated from *P. acidilactici* K2a2-3, has cytotoxicity against the human colon adenocarcinoma cell line (HT29) and the HeLa cell line (Villarante et al., 2011; Kaur and Kaur, 2015).

Bacteriocins have also aided in the protection of gastrointestinal tract in situations where other treatment methods, such as antibiotics, are prohibited, such as in pregnant women (Hammami et al., 2013). Thus, they have been used in the treatment of inflammatory bowel disease, asthma, obesity, cardiovascular disease, and autoimmune conditions (Bull and Plummer, 2014).

3. Class II bacteriocins

PLBs are subgroup IIa bacteriocins that include pediocin PA-1 (AcH), leukosin A, sakacin A, sakacin P and enterocin A. They are characterized by a YGNGV-C sequence located in the N-terminal regions and two cysteine amino acids that form a disulfide bridge in the middle of the peptide which have been preserved throughout the evolutionary process (O'Sullivan et al., 2002). Recent research indicates that bacteriocins of subgroup IIa are more effective as anti-listerial agents when compared to class I bacteriocins, such as nisin. However, this group does not have as broad an activity spectrum as nisin (Schofs et al., 2020).

Subgroup IIb consists of bacteriocins with peptides including lactococcin G, lactococcin F, and lactacin F (Diep et al., 1996; van Belkum et al., 1991). The most important feature of bacteriocins in this group is the need for both peptides to be fully active. While individually, such peptides show very weak inhibitory activity, they become much more active molecules as a result of synergetic interactions when they are communally located in the same environment (Savadogo et al., 2006; Schofs et al., 2020). Since most members of subgroup IIc contain cysteine amino acid residues, these bacteriocins are referred to as "thiobiotics". They are thiol-active bacteriocins that require reduced cysteine amino acid residues for their activity (De Martinis et al., 2002). Subgroup IIc bacteriocins are Gram-positive, catalase-negative, microaerophilic, and cocci-shaped bacteria.

4. Pediocins identified and characterized to date

The antibacterial spectra of a pediocin and a PLB can differ depending on the properties of the preserved N- and varying C-terminal. For example, pediocin PA-1 has antibacterial and bactericidal activity mainly against *L. monocytogenes*, *Clostridium perfringens*, and *Oenococcus oeni* (Ray and Hoover, 1993; Nieto-Lozano et al., 2010; Díez et al., 2012). Altuntaş et al. (2014) also reported that a bacteriocin similar to pediocin PA-1 produced by *P. acidilactici* 13 has anti-listerial activity (Altuntaş et al., 2014). Pediocin SJ-1 has a bactericidal effect against *Lactobacillus plantarum* (*Lactiplantibacillus plantarum*), in addition to *L. monocytogenes* and *C. perfringens* (Schved et al., 1993, 1994). The structural differences between pediocins and PLBs also have an impact on their molecular stability in extreme conditions such as high temperature, and low and high pH values. For example, Pediocin AcM is resistant to extreme pH values varying from 1 to 12, as previously stated, and high temperatures such as 121 °C. It is also antibacte-

rial against *S. aureus*, *L. monocytogenes*, *C. perfringens*, *Bacillus coagulans* (*Weizmannia coagulans*), *B. cereus* and *Aeromonas hydrophila* (Elegado et al., 1997). Pediocin SA-1 can also withstand a temperature of 121 °C up to 60 minutes and has an antibacterial effect against *L. monocytogenes* (Anastasiadou et al., 2008). At high doses (20,000 AU/mL) pediocin NV5 exhibits anti-listerial activity (Mandal et al., 2010) (Table 1). Pediocin L50 is a bacteriocin which is not broadly classified but is synthesized by *Pediococcus* spp. It is highly resistant against pepsin, bile, and low pH values, and inhibits the growth of *L. monocytogenes* and *S. aureus* (Cintas et al., 1995; Chelliah et al., 2020).

5. Pediocins in industry

Bacteriocins can be added directly to foods as starter cultures or through techniques such as starter culture mixes, or they can be applied to the packaging material in which the food is packaged (Ahmad et al., 2017). Pediocins have anti-listerial activity at a wide pH range (2-10) and are stable at 4-25 °C (Khorshidian et al., 2021).

PLBs can be used to inhibit *L. monocytogenes* in raw pork (Woraprayote et al., 2013) and chicken meat (Goff et al., 1996). Since pediocin L50 is thermostable, it can also affect heat-treated meat products. In addition, it differs in that it is effective over a wide pH range but cannot withstand neutral and alkaline pH (Devi and Halami, 2011).

Pediocin PA-1 inhibits *L. monocytogenes* growth in creams, cottage cheese, and cheese sauces and once added to food, it exerts a rapid inhibition on *L. monocytogenes*. The activity of Pediocin PA-1 is not affected by the presence of protein and fat in foods. However, it has been reported that there is a synergistic effect between lactic acid and pediocin PA-1 (Foegeding et al., 1992; Rodríguez et al., 2002). This bacteriocin is non-toxic, rapidly hydrolyzed by gastric enzymes, and is not immunogenic. It has a broader bactericidal activity when compared to other pediococcal bacteriocins (Parente et al., 1998). It is used to ensure food safety in many heat-treated products, particularly meat and dairy products. Food preservation methods include the addition of LAB bacteriocins to meat products before fermentation, a small amount of nitrite in combination with substances such as ascorbate and alpha-tocopherol, and the addition of sorbate and bacteriocins. Bacteriocin-producing strains are also used as starter culture or by incorporating techniques in which a starter culture is mixed into the packaging material in which the food is packaged (Ahmad et al., 2017).

6. The main pediocin producer genus: Pediococci

Members of the genus *Pediococcus*, including *P. acidilactici*, *P. pentosaceus* and *P. damnosus*, have been isolated from many food sources and can produce bacteriocins similar to pediocin. For example, *P. acidilactici* PAC1.0 strain produces Pediocin AcH/PA-1 which is one of the most well-known bacteriocins. Pediocin L50, AcM, and F are known to have been originally produced from *P. acidilactici* L50, *P. acidilactici* M, and *P. acidilactici* F spp., respectively, which were isolated from sausage. Pediocins are also produced from *P. pentosaceus* ST18 and *P. pentosaceus* K23-2 strains isolated from kimchi, a traditional fermented dish in Korea. Furthermore, pediocin PD-1 can also be produced by *P. damnosus* (Schved et al., 1993; Cintas et al., 1995; de Nadra and de Saad, 1995; Elegado et al., 1997; Miller et al., 1998; Wu et al., 2004; Bauer et al., 2005; Anastasiadou et al., 2008; Xie et al., 2011).

Pediococci can easily grow in salt concentrations ranging from 4.0 - 6.5 % and at an optimum temperature range from 25-40 °C. The optimal pH range for growth of pediococcal colonies is between 6.0-6.5. They are also known as facultative anaerobic or microaerophilic bacteria (Raccach, 2014).

Altuntaş et al. (2014) investigated growth parameters and bacteriocin production by the strain *Pediococcus acidilactici* 13 isolated form a sausage sample in a previous study by Cosansu et al. (2007). The inhibitor substance produced by this strain was highly effective against *L. monocytogenes* with 204,800 AU/mL (Activity Units/mL). The strain was able to grow in a wide temperature range (25–50 °C) and upto 10 % NaCl concentrations. Purification methods were allowed to reach 819,200 AU/mL anti-listerial activity in this study. The identification of the current bacteriocin and related proteins was done using two-dimensional gel electrophoresis and a matrix-assisted laser desorption ionization/time of flight mass spectrometry (MALDI-TOF MS) analysis. The peptide produced by *P. acidilactici* 13 was found to be similar to pediocin PA-1 from the UniProtKB/Swiss-Prot databank (Altuntaş et al., 2014).

6.1 *P. acidilactici*

Generally, *P. acidilactici* is isolated from plants and milk. Its optimal growth temperature and the pH value are 40 °C and 6.0, respectively. The pH value may be reduced to 3.6 during growth (Papagianni and Anastasiadou, 2009; Anastasiadou et al., 2008) . Most *P. acidilactici* strains ferment glucose, ribose, xylose, fructose and galactose into D, L-lactate. Several other strains can ferment lactose, sucrose and maltose (Abbasiliasi et al., 2012). Some strains have heme-requiring catalase while all strains hydrolyze arginine. However, the optimum production and the optimum growth conditions may differ in the strains; some species have been found to produce pediocins (Anastasiadou et al., 2008). *P. acidilactici* is used for the fermentation of vegetables and meat-based products like dry sausages. Like other LAB, pediococci are considered safe, but rarely clinical problems are encountered. Some vancomycin-resistant *P. acidilactici* strains have been identified as the bacteria responsible for recurrent septicemia (Lozano et al., 1992).

6.2 *P. pentosaceus*

P. pentosaceus and *P. acidilactici* share many characteristics. The strains grow best at temperatures between 28-35 °C. Most strains ferment glucose, ribose, galactose, arabinose, and fructose into D, L-lactate while a few strains ferment lactose and xylose (Abbasiliasi et al., 2012), and some strains of *P. pentosaceus* have catalase activity (Kuhl and De Dea Lindner, 2016; Dobrogosz and

Table 1: Types, producer organisms, and properties of some pediocins and pediocin-like bacteriocins (PLBs).

Pediocin/PLB	Producer Organism	Properties of the Pediocin/PLB	References
Pediocin PA-1	*P. acidilactici*	Antibacterial effect against *Listeria monocytogenes*, *Clostridium perfringens*, and *Oenococcus oeni*.	(Díez et al., 2012; Nieto-Lozano et al., 2010; Ray and Hoover, 1993)
Pediocin PA-1 (similar)	*P. acidilactici* 13	Strong anti-listerial activity with 819,200 AU/mL	(Altuntaş et al., 2014)
Pediocin SJ-1	*P. acidilactici* SJ-1	Bactericidal effect against *L. monocytogenes*, *C. perfringens*, and *Lactobacillus plantarum*.	(Schved et al., 1993, 1994)
Pediocin L50	*P. acidilactici*	Highly resistant against pepsin, bile, and low pH. Antibacterial effect against *L. monocytogenes* and *S. aureus*	(Chelliah et al., 2020; Cintas et al., 1995)
Pediocin AcM	*P. acidilactici* M	Resistant to extreme pH (1-12) and 121 °C temperature. Antibacterial effect against *S. aureus*, *L. monocytogenes*, *C. perfringens*, *Weizmannia coagulans*, *Bacillus cereus*, and *Aeromonas hydrophila*.	(Elegado et al., 1997)
Pediocin SA-1	*P. acidilactici* NRRL B5627	Can resist up to 121 °C for 60 minutes. Bactericidal effect against *L. monocytogenes*	(Anastasiadou et al., 2008)
Pediocin NV5	*P. acidilactici* LAB 5	Antibacterial effect at high doses (20,000 AU/mL) against *L. monocytogenes*.	(Mandal et al., 2010)

Stone, 1962).

P. pentosaceus plays a role in a variety of fermentation processes including starter cultures in beer production and sausage fermentations (Raccach, 1987). They are also involved in silage fermentation and found in dairy, vegetables, and plant-based products (Kimura et al., 1997). Specific *P. pentosaceus* strains produce pediocin and, therefore, have been used in many studies on food preservation. While *P. pentosaceus* has been identified as an opportunistic pathogen (Corcoran et al., 1991), it is considered as a probiotic bacterium with a higher number of probiotic products than other LAB (Raccach, 1987).

P. acidilactici and *P. pentosaceus* are genetically related species. In terms of physiology and genetics, the com-plete genome sequence of *P. pentosaceus* ATCC 25745 consists of 1,832,387 nucleotides organized in a circular pattern. The genome contains 1,755 protein-coding genes and 72 RNA genes, with a GC content of 37.4 % (Makarova et al., 2006).

6.3 *P. damnosus*

P. damnosus is phylogenetically distinct from *P. acidilactici* and *P. pentosaceus* (Collins et al., 1991), and thus has distinct characteristics. It grows at 35 °C rather than 22 °C. The optimal pH value for growth of the strains is 5.5. The growth of the strains is completely inhibited at 4 % NaCl and does not hydrolyze arginine, arabinose, xylose or lactose. Only a few strains metabolize maltose and sucrose, while most strains ferment glucose, sucrose, and galactose homofermentatively. *P. damnosus* is also known as a beer and wine spoilage bacterium (Calmin et al., 2008; Collins et al., 1991), and is able to produce exopolysaccharide and bacteriocin (Bauer et al., 2005; Skyttä et al., 1993).

7. The general properties of pediocins

Pediocins isolated from *P. acidilactici*, *P. pentosaceus* and *P. damnosus* strains are mostly small, hydrophobic proteins. The most important known property of pediocins is their resistance to heat. As a result, the bactericidal effects are sometimes resistant to heat, even at sterilization temperatures, and in a cooled-down working environment – even at -80 °C. Their activities are maintained across a wide range of pH values. They are sensitive to most proteases. These properties are attributed to pediocin AcH/PA-1, pediocin ST18 (Todorov and Dicks, 2005), pediocin AcM (Ray and Hoover, 1993), and pediocin PD-1 (Green et al., 1997). Pediocins that are produced by *P. pentosaceus* are common in a variety of pediocins, such as Pep1 (Osmanagaoglu and Lu, 2001) and *P. pentosaceus* K23-2 (Osmanagaoglu, 1998; Shin et al., 2008).

Temperature has a significant effect on the antimicrobial and the receptor-binding activity of amphipathic α-helix of the C-terminal of class II bacteriocins (Kaur et al., 2004). While pediocin PA-1 preserves its main structure at high temperatures, pediocins lacking a secondary C-terminal disulfide bond, such as sakacin P, curvasin A, and enterocin P, partially lose their stability and are 30-50 times more active at 37 °C than 25 °C. Interestingly, a chemically synthesized mutant of pediocin PA-1 with norleucin instead of methionine to achieve stability against aerobic oxidation, is equally active at all temperatures (Papagianni and Anastasiadou, 2009).

As previously stated, pediocins are peptides that typically retain their main structure over a wide pH range. Pediocins like pediocin PA-1/AcH, pediocin A, pediocin F, pediocin SA-1, and pediocin L50 remain stable at pH values ranging from 2 to 10 and retain their activity against protease enzymes like pepsin, papain and trypsin (Cintas

et al., 1995; Niamah, 2018). Pediocin AcM can even remain stable at extreme pH values of 1 to 12 (Elegado et al., 1997). Another pediocin member, pediocin SJ-1, is only stable between pH values of 4-5 (Papagianni and Anastasiadou, 2009). Even though it has a strong heat resistance at high temperatures such as 121 °C (Amado et al., 2016), pediocin SA-1 does not retain its activity when incubated at pH values other than 2-10 for 30 minutes (Anastasiadou et al., 2008).

When the heat resistance of pediocins is examined, it can be concluded that it correlates with disulfide bond formations, particularly at the C-terminal. Multiple studies have already reported the importance of disulfide bonds in peptides at heat resistant temperatures (Liu et al., 2016; Balgir et al., 2010; Henderson et al., 1992; Luckey et al., 1991). When considering pediocin acid resistance, the wide range of active pH values may be related to disulfide bond formations within their structure.

8. Pediocin biosynthesis

Class IIa bacteriocins are first ribosomally synthesized as precursors or pre-peptides (Ennahar et al., 2000). These pre-peptides and precursors are inactive and contain an N-terminal extension or leader sequence (Nes et al., 1996; Ennahar et al., 2000). In contrast, lantibiotics such as nisin, on the other hand, lack the N-terminal extension (Nes et al., 1996).

The leader sequence in class IIa bacteriocins can be as long as 18-27 residues. The leaders are signaling peptides which play role in processing and secretion of class IIa bacteriocins. Generally, there are 2 glycine residues in the C-terminal of the leader sequence. These residues are positioned at Q1 and Q2 (Ennahar et al., 2000). The transport system which carries bacteriocins outside of the cell includes an ATP-binding cassette (ABC)-type translocator and an accessory protein (Nes et al., 1996; Ennahar et al., 2000). The N-terminal extension of the bacteriocin transporters has cysteine (QX4D/ECX2AXa MX4Y/FGX4I/L) and histidine (HY/FY/VVXIoFL XDP) motifs that are conserved across subtypes (Nes et al., 1996).

ABC-transporters contain a hydrophobic integral membrane domain and a cytoplasmatic ATP-binding domain (Nes et al., 1996). The hydrophobic residues of the leader sequence are found at positions Q4, Q7, Q12 and Q15, while hydrophilic residues are found at positions Q5, Q6 and Q11 (Ennahar et al., 2000). The net charges of these leaders at neutral pH range from Q3 for leucocin A to +1 for enterocin A, pediocin AcH, and mesentericin Y105 (Ennahar et al., 2000). The proteolytic domain of the ABC-transporter binds a bacteriocin precursor (Havarstein et al., 1995). The hydrolysis of ATP induces conformational changes in the transporter leading to an integrated process of removing the leader sequence and transport of the bacteriocin molecule across the cytoplasmatic membrane (Ray and Hoover, 1993; Gilson et al., 1990). The N-terminal of the pediocin PA-1 ABC-transporter takes part in the proteolytic removal of the bacteriocin leader (Venema et al., 1995).

9. The molecular structure of pediocins

Class IIa bacteriocins are cationic peptides with similar primary structures. PLBs are especially characterized by a specific amino acid sequence called the "–YGNGV- box", which is located on their N-terminal while their C-terminal is poorly preserved (Fig. 1, Cotter et al. (2013)). While N-terminal of class IIa bacteriocins is positively charged, the C-terminal is critical for target specifity (Drider et al., 2006).

Pediocin AcH was identified in 1988 from the *P. acidilactici* H strain (Bhunia et al., 1988). Pediocin PA-1/AcH is widely distributed and used for a variety of purposes, including food safety (Devi and Halami, 2011). A complete set of genes encoding PLBs has been identified in the nucleotide sequences determined by the microbial genome sequencing of the human microbiome (Zheng et al., 2015).

9.1 Mode of action of pediocins

As previously stated in this review, pediocins and PLBs are primarily used in the food industry due to their antibacterial and bacteriostatic properties. Pediocins and PLBs are particularly effective against serious pathogenic bacteria such as *L. monocytogenes* and *C. perfringens* (Nieto-Lozano et al., 2010; Ramos et al., 2020). Two models have been developed to describe the mechanism of action of pediocin and PLBs: (i) Pore formation as a result of interactions between the N- and C- terminal and bilayer membrane phospholipids of bacteriocins; and (ii) destabilization of the bacterial membrane as a result of the specific receptor-ligand reactions.

As mentioned previously, the hydrophilic N-terminal (Fimland et al., 2000) gives the peptide a positive charge allowing pediocins to interact with the negatively charged bacterial membrane via the attraction between opposite charges. The C-terminal of pediocins has a high potential to interact with phospholipids on the bacterial membrane due to its hydrophobic properties (Ríos Colombo et al., 2018). While the N-terminal is likely conserved between pediocins and PLBs (e.g., YGNG box), the C-terminal differentiates between types of PLBs. When channels are formed or activated, the bacterial membrane loses its optimum fluidity, allowing influx (like Na^+ and Ca^{2+}) or efflux (like K^+ and Mg^{2+}). Changes in the phospholipid membrane and intracellular ion concentrations lead to bacterial cell death (Conrard and Tyteca, 2019) (Fig. 2).

Lysine residues on the α-helix of the C-terminal of class IIa bacteriocins plays a critical role in interacting with bacterial membranes. The interaction of lysine residues with bacterial membranes has been reported as a property of nisin, the most well-known bacteriocin (Oscáriz and Pisabarro, 2001). Disulfide bonds on the peptide structure also play a critical role in antibacterial activity. When a pediocin PA-1 analog lacking a disulfide bond is tested against *Listeria ivanovii*, *L. monocytogenes*, and *P. acidilactici*, the pediocin PA-1 analog does not exhibit any antibacterial activity up to 100 µM concentrations, whereas pediocin PA-1 has a 6.8 nM minimum inhibitory concentration (MIC) (Bédard et al., 2018). According to Oppegård et al. (2015), the disulfide bond formation

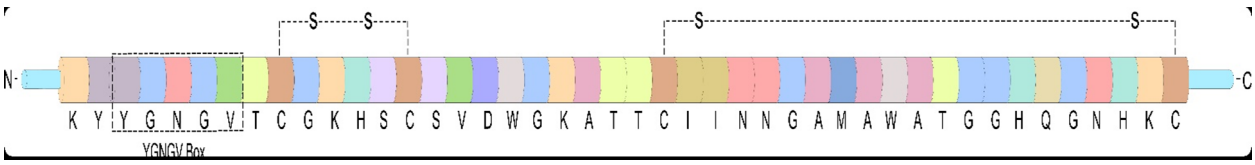

Figure 1: Structural representation of the pediocin molecule. There are 2 main structural domains in pediocins and PLBs: i) the N terminal domain and ii) the C terminal domain. Even though there is a lot of structural diversity among different pediocin molecules, the N terminal domain is highly conserved among the pediocin variations. Unlike the N terminal domains, the C terminal domains vary between organisms. The pediocin molecule has two disulfide bonds which make it more active and resistant.

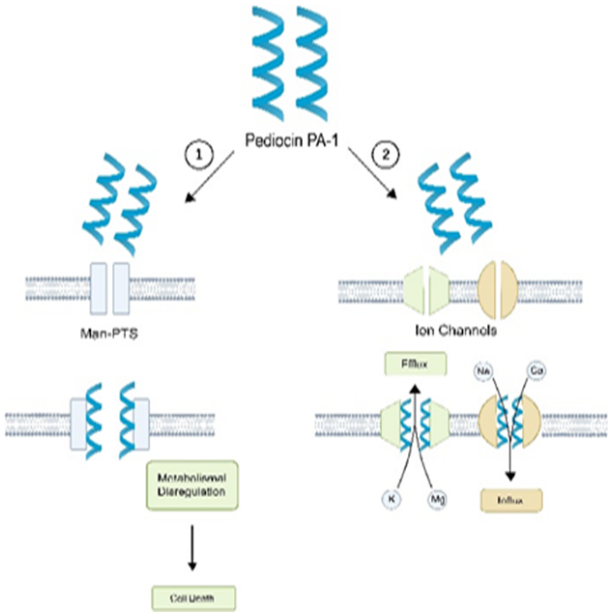

Figure 2: Class IIa bacteriocins and their mechanism of action. 1) Class IIa bacteriocins allow pore formation by binding to the man-PTS receptor which is embedded in the cell membrane. Following this pore formation, the permeability of the cell membrane increases and causes cell death. 2) Formed or activated channels cause the bacterial membrane to lose its optimum fluidity and allow influx (like Na^+ and Ca^{2+}) or efflux (like K^+ and Mg^{2+}). Changes in the phospholipid membrane and intracellular ion concentrations lead to bacterial cell death.

is corrected by the pediocin PA-1 ATP-binding cassette (ABC) transporter and accessory protein regions, which are located on the same operon of pediocin PA-1 coding gene (Oppegård et al., 2015).

The mannose phosphotransferase system complex (man-PTS) is a specific receptor for class IIa bacteriocins that functions primarily as a transmembrane carrier in bacterial carbohydrate metabolisms. The structure-activity relationships between the groups of the man-PTS receptors and pediocins and PLBs are not fully understood. However, these interactions are thought to be largely related to the interactions between the IIC and IID subunits of the man-PTS and the N-terminal of pediocins (Diep et al., 2007; Zhou et al., 2016).

So far, four types of man-PTS groups have been discovered: (i) glucose-fructose-lactose transporters; (ii) ascorbate and galactitol carriers; (iii) mannose carriers; and (iv) dihydroxyacetone carriers (Nguyen et al., 2006; Saier et al., 2005). Among these groups, class IIa bacteriocins interact with the group 1 man-PTS receptors (Kjos et al., 2009). The N-terminal, which is largely conserved between pediocin and PLBs, interacts with the IIC subunit of man-PTS. Presumably, the C-terminal then interacts with the hydrophobic regions of the man-PTS, stabilizing the complex (Ríos Colombo et al., 2018). The disruption of the bacterial cell membrane as a result of these events leads to the death of the bacteria. Furthermore, it is possible that man-PTS complex blockage, which is one of the regulators of carbohydrate metabolism for bacteria, may cause bacterial death as a result of carbohydrate metabolism disregulation (Jeckelmann and Erni, 2020).

When bacterial strains are exposed to bacteriocins that target specific man-PTS for an extended period of time, they may develop resistance to these peptides. One of these resistance mechanisms is the reduction of the man-PTS expression. On the other hand, interestingly, the expression of man-PTS is increased. However, the bacterium's metabolism shifts from glucose to galactose. Therefore, structural changes such as receptor amino acid sequence are thought to be effective in the development of resistance. Bacteriocins remain ineffective against bacteria as a result of these two pathways (Kjos et al., 2011).

Recently a study performed to investigate the pore formation in the man-PTS of *L. monocytogenes* by pediocin PA-1 (Zhu et al., 2022a). The cryo-electron microscopy structures of man-PTS from *L. monocytogenes* were evaluated in the presence of pediocin PA-1 at resolution of 2.45 Å. The researchers reported that pediocin PA-1 opens the core domain of man-PTS following the binding and creates a pore through the cytoplasmic membranes of pathogen cells. The role of the N-terminal β-sheet part of pediocin PA-1 is determined as attaching to the extracellular surface of the man-PTS core domain, while the C-terminal region of the peptide half-penetrates to the membrane like a wedge which causes to crack the man-PTS. During bacteriocin biosynthesis, the producing organism simultaneously produces immunity proteins to protect them against their own bacteriocins. Zhu et al. (2022b) explained the cryo-electron microscopy structure of the bacteriocin-receptor-immunity system of *Lactobacillus sakei*. During bacteriocin attack, man-PTS displays its cytosolic side for recognition of the N-terminal four-helix bundle of the immunity protein, then C-terminal loop of

the immunity protein inserts and blocks leakage from the pore.

Pediocins and PLBs can form fusion proteins by combining with each other to expand their spectrum of action, increase their antibacterial properties, develop a structure that can serve for multiple purposes, and improve their structural properties. In addition, changes in the amino acids of a pediocin or a PLB will improve its antimicrobial spectrum and structural properties. Pediocin PA-1/enterocin E50-52 (PE) is one of the fusion proteins formed by combining pediocin and PLBs. The PE protein contains pediocin PA-1 at its N-terminal while the C-terminal is originated from enterocin E50-52. PE protein is also effective against Gram-negative bacteria (*S. enteritidis* and *E. coli*). The MIC value of the PE protein was determined to be 1.56 µM. The MIC value of enterocin E50-52 is approximately 8-fold of that of PE (enterocin E50-52 = 12.5 µM, pediocin PA-1 = 100 µM, PE = 1.56 µM), whereas the MIC value of pediocin PA-1 is approximately 64-fold that of PE (Tiwari et al., 2015). Furthermore, changing to the leucine A analog of the N-terminal of class IIa bacteriocins (amino acid region 37) resulted in a structural shortening of the β-tail. A bacteriocin with the leucine A analog has been shown to have a stronger antibacterial effect against *Carnobacterium divergens* and *L. monocytogenes* (Bodapati et al., 2013). Moreover, it has been reported that changing methionine in the 31st position to leucine increased the stability of the molecule during storage (Bédard et al., 2018). The new protein formed by the conversion of the amino acid glycine at the 29th position of pediocin PA-1 to alanine has been shown to be more powerful in interacting with membrane receptors. According to the same study, changing the alanine change at the 32nd position makes the protein more hydrophobic by making the hairpin structure of the α-helix region of the protein smaller, thereby increasing the binding affinity to the hydrophobic regions of the man-PTS complex receptors (Sun et al., 2015). It has been reported that combining the hydrophobin protein with pediocin PA-1 has a greater antibacterial effect against *S. aureus* than standard pediocin PA-1 (Wang et al., 2017). Furthermore, an increase in antibacterial activity of pediocin AcH has been reported when hybridized with nisin (Hanlin et al., 1993), leucosin F10 (Parente et al., 1998), lactacin B or F, and lactacin 481 (Mulet-Powell et al., 1998).

9.2 Comparison of structural differences between pediocins and PLBs at molecular level

PLBs form a group of LAB that produced 37 to 48 residual cationic membrane permeable peptides. After exposure to membrane mimicking entities, the hydrophilic, cationic, and highly conserved N-terminal region forms a three-strand antiparallel β-layer supported by a shielded disulfide bridge. This N-terminal β-leaf region is followed by a central amphiphilic α-helix, followed by a rather long C-terminal tail that folds back into the central α-helix in most – if not all – of these peptides. In light of all these characteristics, new pediocin analogs are produced either by preserving the peptide structure or by obtaining them recombinantly (Ennahar et al., 2000).

Depending on their primary structure, the peptide chains of PLBs are divided into two. The first is the cationic N-terminal beta layer domain, which mediates the binding of the bacteriocin to the target cell surface, and the second is the hydrophobic C-terminal, which is in contact with the hydrophobic part of the target cell (Bédard et al., 2018). Both terminals are linked to each other by hinge points, and the two areas move apart. A recombinant pediocin is also produced by changing the hinge points. Nuclear magnetic resonance (NMR) studies revealed that the N-terminal region forms a three-stranded anti-parallel layer supported by a shielded disulfide bridge. The N-terminal β-sheet region is followed by a central amphiphilic α-helix, followed by a rather long C-terminal tail that folds over the central α-helix, thus forming a hairpin-like structure at the C-terminal (Kim et al., 2007).

The C-terminal region of PLBs has been suggested to be important in determining target cell specificities, as pediocin-like variants modified in the C-terminal region by site-directed in vitro mutagenesis are frequently distinct from wild-type variants. The three-dimensional structure of PLBs suggests that more optimal hybrid bacteriocins can be formed if the hinge is used as the point of recombination and thus full domains are exchanged between bacteriocins. Immune proteins are well-structured, 4-helix bundled cytosolic proteins (Kim et al., 2007). Therefore, they only recognize and bind to their cognate adenosine monophosphates (AMPs), despite exhibiting a high degree of specificity to several AMPs that are closely related to their cognate AMPs (Johnsen et al., 2005).

10. Final remarks and future prospects

The biopreservative potential and antimicrobial properties of bacteriocins could explain their widespread use in the food industry. The demand for safe, high quality, and less processed foods is constantly increasing, as is interest in natural food preservatives. Bacteriocins produced by the *Pediococcus* genus are known as pediocins. Pediocins have an antibacterial effect on pathogenic bacteria, which are especially important in food spoilage. Pediocins are also relatively stable across a wide of pH and temperature. Pure or mixed cultures of the pediococci are being used today as protective cultures against common food spoilage bacteria and pathogens. Pediocins also improve the cost-effectiveness of the process as their production protocols are cost-friendly and clearly identified. When pediocins are considered for food additives, stability, especially in a complex food environment, seems to be the most important factor to consider.

Pediocins are thought to inhibit bacterial growth by either interacting with man-PTS receptors on bacterial membranes and disregulating cell metabolism, or by interacting with ion channels and disrupting proper ion transport. In addition, several PLBs contain methionine residues whose sulfur atoms may be oxidized, resulting in destabilization of the bacteriocin. Protecting food from foodborne pathogens requires a good solution. The stability of pediocins in the complex environment of food

is very important for their use as a food additive, and pediocins should be developed in hydrophobic residues.

Despite the high number of identified LAB bacteriocins over the years, only nisin, and pediocin PA-1 have been extensively studied as food additives in food systems. Pediocin PA-1, as a food biopreservative, could be of a special interest to the food industry as it has a strong antilisterial effect, which is one of the highest mortality rates. Establishing the relationship between its structure and its biological activity may be particularly important as it may facilitate the enhancement of pediocin PA-1 activity and may lead to a better understanding of the mechanisms of bacterial resistance to the peptide.

Molecular changes in pediocins are an open field for research. Pediocins with increased stability and enhanced features, as well as an extension of the antimicrobial spectrum to Gram-negative bacteria could be developed. When compared to commercial enzymes, the culture process could be performed in a milder and less expensive manner while still resulting in flavor and quality improvements due to the growth of the cultures themselves and the production of other metabolites at the same time.

Due to the expansive global problem of antibiotic resistance, pediocin applications can be more clinically focused. Furthermore, in recent years, in addition to its antimicrobial activity, the pediocin molecule is an alternative peptide in cancer therapy. Positively charged pediocin is notable in combating cancerous cells due to its affinity for negatively charged cancer cells due to anionic phosphatidylserine, O-glycosylated mucins, gangliosides and heparin sulfates compared to neutrally charged cells. More detailed studies on pediocin are expected to be conducted due to its promising properties in both the food and health fields.

Further in silico and in vitro studies for designing novel bioprocessing strategies and identifying the efficacy and toxicity limits of such strategies are still a necessity for discovering the safest, most affordable solutions in the industrial production of pediocins.

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