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Research review paper

Pediococcus spp.: An important genus of lactic acid bacteria and pediocin producers

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ABSTRACT

Probiotics have gained increasing attention due to several health benefits related to the human digestive and immune systems. *Pediococcus* spp. are lactic acid bacteria (LAB) that are widely described as probiotics and characterized as coccus-shaped bacteria (arranged in tetrads), Gram-positive, non-motile, non-spore forming, catalase-negative, and facultative anaerobes. There are many *Pediococcus* strains that produce pediocin, an effective antilisterial bacteriocin. Pediocins are small, cationic molecules consisting of a conserved hydrophilic N-terminal portion containing the YGNGV motif and an amphiphilic or hydrophobic C-terminal variable portion. A number of studies have been developed with *Pediococcus* isolated from multiple biological niches to conduct fermentation processes for pediocin or *Pediococcus* cell production. This review gathers the most significant information about the cultivation, mode of action, and variability of bacteriocins produced by *Pediococcus* spp., emphasizing their applications in the areas of food and clinical practice. This updated panorama assists in delimiting the challenges that still need to be overcome for pediocin use to be approved for human consumption and the food industry.

Contents

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1. Introduction

Lactic acid bacteria (LAB) are commonly used in foods as preservatives and texture, flavor and scent enhancers. These properties result from the ability of these bacteria to produce different types of sugars and metabolites such as lactic acid, acetic acid, ethanol, diacetyl, acetone, exopolysaccharide, specific proteases and bacteriocin by fermentation (Barbosa et al., 2017; Cotter et al., 2013; Gaspar et al., 2013; Gudiña et al., 2015; Mazzoli et al., 2014; Papagianni, 2012; Saad et al., 2013). LAB from the genera *Lactobacillus*, *Bifidobacterium* and *Pediococcus* are commonly found in the mammalian gut microbiota, and some strains are classified as probiotic (WHO/WHO, 2002). The application of this bacterial group in the pharmaceutical and food industries has been increasing given that bacteriocin synthesis often occurs in several LAB strains, resulting in the protection of fermentation products against spoilage and/or pathogenic bacteria.

According to the bacteriocin classification proposed by Cotter et al. (2005), pediocins are biomolecules that can be synthesized by some LAB and present a broad spectrum of antimicrobial activity against Gram-positive bacteria (Papagianni and Anastasiadou, 2009), which highlights its efficient bactericidal effects against pathogenic bacteria, such as *Listeria monocytogenes*. The presence of this microorganism in dairy products, pâtés, sausages and vegetables can be harmful to immunocompromised patients and pregnant women.

Listeriosis is a serious disease that, in spite of its rarity, has a high mortality rate in infected patients (Schuppler and Loessner, 2010). Thus, extensive research on the biosynthesis and antimicrobial effects of pediocins, especially the ones produced from fermented milk cultures, is underway due to increasing industry concern for the control of food-borne pathogens.

Pediocins belong to the bacteriocin group class IIa, characterized as small unmodified peptides (<5 kDa) containing 36 to 48 amino acid residues, a conserved N-terminal portion containing the pediocin box $YGNGVX_1CX_2K/NX_3X_4C$ (X1-4: polar uncharged or charged residues) (Papagianni and Anastasiadou, 2009) and a variable hydrophobic or amphiphilic C-terminal region responsible for cell recognition. It is noteworthy that pediocin has antimicrobial effectiveness even at nanomolar quantities (Papagianni, 2003).

Pediococcus pentosaceus and *Pediococcus acidilactici* are the main species used in i) pediocin production, ii) fermentation processes as a starter (co-culture) for avoiding contamination, and iii) probiotic supplements for animals and humans. As several studies have been published about this topic, this review first focuses on aspects of pediocin covering its biosynthesis, autoimmunity, mode of action, resistance, structural properties and isoforms, with emphasis on molecular data from recent publications. Second, this review addresses biotechnological applications of pediocin and *Pediococcus* spp. in the areas of food and clinical practice. Despite the presence of various beneficial effects of this probiotic described in the literature, there are significant remaining barriers to overcome prior to the use of *Pediococcus* spp. for human consumption.

Nisin is the only bacteriocin approved as a food preservative (Gharsallaoui et al., 2016). The WHO/WHO established all parameters of nisin purity and activity as well as the specific methodology to analyze its antimicrobial activity (WHO/WHO, 1969). The commercial nisin applied in food industry should contain 2.5% w/w of its active form with 10^6 AU/g; the amount of nisin for each type of food (dairy products, meat, bakery wares) was also established by FAO/WHO (FAO/WHO, 2016). Undoubtedly, there is a large avenue for commercial approval of pediocin in the food and pharmaceutical manufacturing sectors: identification of pediocin variant sequences, methods for standardization of antimicrobial activity, and studies of pediocin toxicity or allergenicity. Hence, it is relevant to review pediocin studies and to analyze the state of the art and determine what is needed for its approval as a food preservative or biotherapeutic agent.

2. Pediocin

2.1. Biosynthesis

Bacteriocin production occurs *via* the quorum sensing response, which is related to population density or other environmental stress signaling (Cotter et al., 2005). Generally, these antimicrobial peptides are synthesized as biologically inactive molecules due to the presence of the leader peptide in the N-terminal region. These precursors are transported to the cytoplasmic side of the membrane, where the leader sequence is cleaved and the activated bacteriocin is secreted to the outside of the cell *via* bacteriocin transport or a general secretion system (*Sec*) (Aucher et al., 2005; Cotter et al., 2005; Nes et al., 1996; Xie and Van Der Donk, 2004). For pediocin, the 18- to 24-residue leader peptide is removed after reaching its glycine doublet motif and secreted by the ABC transporter and accessory proteins (Ray et al., 1999). In contrast to other prebacteriocins, the pediocin precursor displays significant biological activity; thus, in order to prevent antimicrobial effects on its own cell, it is suggested that as soon as the pediocin is synthesized, it is quickly transported out of the cell (Ray et al., 1999).

Genes encoding pediocin and proteins involved in pediocin processing, secretion, immunity and expression modulation are arranged in one or two clusters located in a plasmid or in the chromosome (Drider et al., 2006, Kotelkinova and Gelfand, 2002). Pediocin expression is regulated by a three-component system: i) the inducer factor (IF: pheromone or inducer factor), ii) the membrane histidine protein kinase MHK (pheromone receptor) and iii) the response regulator RR. The inducer factor is expressed constitutively at a basal level and exported to the outside of the cell through the ABC transporter system. When a high enough concentration accumulates outside the cell, the inducer factor interacts with the transmembrane histidine kinase, resulting in its autophosphorylation at the conserved histidine residue located in the cytoplasmic side. This phosphate group is transferred to the response regulator, resulting in its activated form (Fig. 1). Thus, this transcription factor binds to the pediocin promoter, triggering expression of bacteriocin-related genes, including the ones responsible for its regulation (IF, RR and MHK). The expression of the inducer factor acts as a positive feedback component in the pediocin circuit, promoting an autoregulated mechanism (Fig. 1). The current literature correlates IF with bacteriocin production and cell growth, although some studies revealed that other environmental signals might have an effect on class II bacteriocin regulation (Cotter et al., 2005). Diep et al. (2000) demonstrated that sakacin A production is temperature-sensitive as well as quorum-sensing-dependent. Under higher temperature conditions (33–35 °C instead of 30 °C) *Lactobacillus sakei* LB706 and *Lactobacillus curvatus* LTH1174 cells reduce IF and bacteriocin synthesis. Interestingly, when an exogenous pheromone is added, cells restore bacteriocin production, evidencing that higher temperature conditions exert an