



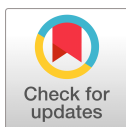
## Review Article

# Application of Bacteriocins Produced from Lactic Acid Bacteria for Microbiological Food Safety

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## Abstract

Foodborne disease caused by pathogenic bacteria is one of main concerns in food industry. To supply safe food products, chemical and thermal intervention technologies have been widely applied in food industry, however these treatments have their own limitations. The concept of biopreservation has recently received increased attention in response to industrial and consumer demands. The biopreservation technologies mainly include bacteriocin, bacteriophage, bacteriophage-encoded enzymes, and endolysins. Among them, bacteriocins have been widely recognized as a main biopreservative and have also been most studied. Bacteriocins, mainly consisting of antibacterial peptides, may have bactericidal or bacteriostatic effect which could prolong the shelf-life as well as maintain safety of foods. This review article offers a brief research trend about bacteriocins, focusing on microbial food safety. The antimicrobial mechanism of bacteriocins has been discussed and some efforts to inactivate foodborne pathogens have been analyzed in this review article. The challenges facing the application of bacteriocins have also been evaluated. Thus, this review will provide insights for researchers working in bacteriocin as well as industry personnel looking for a new method for fighting foodborne pathogens.

## Keywords

bacteriocins, biopreservation, lactic acid bacteria, food safety

## Introduction

Foodborne diseases are one of the serious public health concerns throughout the world. For this reason, the most important objective of food industry is to supply safe and nutritional food products without any contaminants and toxic elements which can cause diseases (Ghanbari *et al.*, 2013). For several decades, health hazards related to foodborne pathogens have been recognized. Hitherto, main control measures to reduce the risk of foodborne pathogens have relied on chemical preservatives or physical processing

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methods such as heating, high pressure processing, irradiation, etc. In spite of some potential advantages, such processing methods also possess several inevitable drawbacks and limitations. For example, the toxicity of some commonly applied chemical additive (e.g., nitrite, salt, sulfites, and acetic acid) (Aasen *et al.*, 2003) and the alteration of sensory, color, antioxidant and organoleptic properties of food items were exemplarily reported (Hisar *et al.*, 2005). Due to delicate nature of food, food industry and consumers demand more gentle and effective preservation methods which could keep foods safe without deterioration. As for alternative food preservation processing methods, growing attention has been paid to the treatment of biopreservatives, which prolongs the shelf-life and improves the safety of foods, therefore minimizing the negative effect on the nutritional and flavor properties. Biopreservation is a natural method to extend shelf life and ensure the safety of foods. The biopreservation methods mainly include bacteriocin, bacteriophage, bacteriophage-encoded enzymes, and endolysins. Among them, bacteriocins have been widely recognized as a main biopreservative and have also been most studied (Beaufort *et al.*, 2007). Bacteriocins, mainly consisting of antibacterial peptides, may have bactericidal or bacteriostatic effect which could prolong the shelf-life of foods. A wide range of bacteriocins from Gram-positive bacteria possess broad spectrum bactericidal properties. Bacteriocins have unique advantage especially for foodstuff that cannot be sterilized via thermal processing method. Some common bacteriocin have been mainly produced from lactic acid bacteria (LAB) such as *Lactococcus* sp., *Streptococcus* sp., *Pediococcus* sp., and *Lactobacillus* sp. These bacteriocins are of special focus as they play a role in inactivating foodborne pathogens and are considered as GRAS (generally recognized as safe) (Brillet *et al.*, 2005). Therefore, this review will highlight the structure of bacteriocins and their mode of actions on the inactivation of bacteria. Furthermore, current applications of bacteriocins will be examined as well as challenges and future research trends will be discussed.

## Structure and Mode of Action

Bacteriocins, bacterial ribosomally synthesizing peptides, conclude a heterogeneous group with respect to primary structure and physicochemical attributes. Most of the bacteriocins mainly comprise relatively large weight molecular proteins (up to 80 kDa) that may kill closely related bacteria on binding to cell membrane. Bacteriocins are mainly synthesized by Gram-positive LAB, which possess a wider spectrum of inhibitory activity (Campos *et al.*, 2006). As LAB have been considered as safe, bacteriocins produced from these LAB can be recognized as safe as well. Bacteriocins are categorized into four major classes. Class I comprises post-translationally modified peptides which possess the intramolecular rings of lanthionine and  $\beta$ -methyl-lanthionine. Class II comprises heat stable non-modified proteins and is also the largest type among all bacteriocins derived from Gram-positive LAB. In general, they are mainly short cationic peptides with relatively high isoelectric points. Class I and II bacteriocins are of particular interests because they possess the potential of anti-*Listeria* property. Class III encompasses large heat stable peptides with modest potential as biopreservatives. Class IV concludes circular peptides bonded between the C- and N-terminus (Fujinami *et al.*, 2007). Most LAB bacteriocins used as biopreservatives are included into Class I and II.

The mechanism of bacteriocins has been extensively studied although most pioneering studies were basically focused on nisin that is the first reported as bacteriocin produced from Gram-positive LAB. Because of its cationic and their hydrophobic properties, most of such peptides function as cell membrane permeabilizers (Martinez-Cuesta *et al.*, 2006). Consequently, pore formation generated by such permeabilizers may cause dissipation of the proton motive force, finally leading to cell death. In this process, lipid II proteins in bacterial membrane act as the docking molecule. Hence, both pore formation and inhibition of peptidoglycan biosynthesis are combined for effective antimicrobial activity (Modi *et al.*, 2001). This mode is

also applied by other non-pore forming bacteriocins like the non-lantibiotic Lcn972 (Martinez *et al.*, 2008). Besides, several class II bacteriocins were reported to apply the cell wall-associated component of the mannose-phosphotransferase system as certain receptor (Manoharadas *et al.*, 2009). Some LAB bacteriocins are potent against many Gram-positive pathogens including some antibiotic resistant bacteria. On the other hand, Gram-negative pathogens are intrinsically resistant to these bacteriocins, owing to the protective role of the outer membrane of cells. Nisin and lactacin 3147 have been applied as commercial prophylactic methods against many spoilage and foodborne pathogens in a wide range of foodstuffs such as dairy, meat and vegetable products. Meanwhile, bacteriocins have also been considered as a promising alternative for feeding, effectively decreasing the carriage of zoonotic pathogens (Line *et al.*, 2008). Bacteriocins are used basically in three various types: i) *in situ* production method by starter and protective cultures, ii) as components, or iii) as additives. Some nisin-producing starters have been used to certainly inhibit *Staphylococcus aureus* and *Clostridium tyrobutyricum* in acid-coagulated and semi-hard cheeses, respectively (Martinez-Cuesta *et al.*, 2006). Due to the fact that protective cultures do not alter flavor attributes of food, they have been used to maintain the hygienic quality of ready-to-eat meat and seafood products (Rilla *et al.*, 2004). The application of bacteriocins as additives needs new methods for large scale production in economically food-grade media. For instance, lactacin 3147 and the enterocin AS-48 were generated in whey-based media (Fallico *et al.*, 2011). The application of whey as ingredient is a potential option because it can be recycled in the dairy industry. Bacteriocins have been also shown to help cheese ripening via enhancing the release of intracellular enzymes and a corresponding increase of volatile compounds in matured cheese (Abdollahzadeh *et al.*, 2014). Besides, bacteriocins producers were also reported to hold back the pathogen microbiota and ensure the quality of homogenous fermented products (Simoncini *et al.*, 2014).

## Bacteriocin-based Intervention Strategies for Food Preservation

Bacteriocins are GRAS substances as the compounds are inactive, non-toxic on eukaryotic cells. In addition, they can be easily inactivated by digestive proteases and thus have minimal effect on gut microbiota. Bacteriocins are generally pH and heat tolerant with a wide range of antimicrobial effect against foodborne pathogenic and spoilage bacteria with the main mode of bactericidal effect acting on the bacterial cytoplasmic membrane as described previously. Bacteriocins can be genetically manipulated as their genetic determinants are encoded in the plasmid (Gálvez *et al.*, 2007). One of the common type of bacteriocins utilized in the food industry are produced by Gram-positive LAB which consists of four main classes of bacteriocins, grouped according to structure and mode of action (Bogovic-Matijasic and Rogelj, 2011).

### Class I bacteriocins

An example of a type A lantibiotics is nisin which possesses bactericidal effect against a wide range of Gram-positive bacteria as well as prevention of spore outgrowth. Currently, nisin produced from *Lactococcus lactis* is one of the bacteriocin that have attained the GRAS status due to the extensive toxicity studies (Hansen and Sandine, 1994). In a study conducted for the antimicrobial effect of reuterin individually or in combination with nisin against different foodborne pathogens in milk, nisin alone showed great antimicrobial effect against *Listeria monocytogenes* and *S. aureus*, however there were still resistant cells which regrew after 24 hours. On the other hand, the combined treatment with reuterin showed synergistic effect, keeping *L. monocytogenes* below detection levels, while having a slight additive bactericidal effect against *S. aureus*. Unlike Gram-positive pathogens, nisin was ineffective against Gram-negative pathogens such as *Yersinia enterocolitica* and *Camphylobacter jejuni* (Arqués *et al.*, 2004). This is because the nature of antimicrobial mechanism of nisin is due to interaction with the membrane-bound lipid II



proteins, which causes pore formation in the cytoplasmic membrane of the target pathogens. The large size of nisin (1.8–4.6 kDa) is unable to permeate through the outer membrane of Gram-negative bacteria which consists of lipopolysaccharide (LPS) molecules in its outer leaflet and glycerophospholipids in the inner leaflet (Kuwano *et al.*, 2005).

The antimicrobial activity of nisin is dependent on its concentration, bacterial concentration, physiological state of the target microorganisms and the prevailing conditions. A more pronounced bactericidal effect is exerted on the vegetative cells when optimal conditions for bacteria growth are met in terms of temperature, pH, water activity, redox potential and nutrient availability. If optimal conditions were not met, nisin would be utilized as part of the hurdle technology, coupled with other bacterial inhibitory conditions. Due to the hydrophobicity of nisin, the presence of lipid components in foods can also affect distribution of nisin within the food matrix, thus may render it unavailable for reaction due to binding. Furthermore, it is known that food additives such as sodium meta-bisulphite and titanium dioxide have antagonistic effect to nisin (Delves-Broughton *et al.*, 1996).

## Class II bacteriocins

The most common class II bacteriocins utilized in the food industry belong to class IIa which are peptides with highly conserved hydrophilic and charged N-terminal region that has a disulphide bond linkage, generally having 'pediocin box' consensus amino acid sequence (Cotter *et al.*, 2005). These bacteriocins are produced from a bacterial species including *Lactobacillus* sp., *Enterococcus* sp., *Pediococcus* sp., *Carnobacterium* sp., *Leuconostoc* sp., *Streptococcus* sp., as well as *Weissella* sp. which are found in the gastrointestinal tract and various food products such as dairy products, fermented sausages and vegetables (Cui *et al.*, 2012). Similar to the mode of actions by lantibiotics, class IIa bacteriocins such as Pediocin-PA-1/AcH decreased intracellular ATP through induction of leakages of potassium ions, amino acids as well as low molecular weight molecules via formation of ion-selective

pores in pediocin-sensitive cells (Drider *et al.*, 2006). Pediocin PA-1/AcH can be applied to dairy products due to its anti-*Listeria* activity as well as stability in aqueous solutions at ambient temperature and during heating and freezing (Galvez *et al.*, 2014). Pediocin PA-1 is produced from *L. plantarum* or more commonly from *Pediococcus acidilactici* strains of meat origin and it is especially effective against *Listeria* species which is prevalent in dairy products at low temperatures and pH. Although pediocins PA-1 are produced from these LAB strains, processing of the prepediocin to active pediocin PA-1 differs between these two strains. The conversion of pediocin from prepediocin is effective at pH of equal or less than pH 5 for *P. acidilactici* strains, while the conversion is not affected by pH for *L. plantarum*. In addition, *P. acidilactici* have poor adaption for colonization on foods and thus they are less effective when utilized to control growth of *L. monocytogenes* in dairy products (Horn *et al.*, 1998). Generally, pediocin PA-1 effectively retained some activity after being exposed to a wide pH range between pH 2 to pH 10 for 24 hours at room temperature, while able to maintain stability at 15°C after 21 days at optimal pH of 4 to pH 6. Although unaffected when treated with other catalytic enzymes such as phospholipase or DNase, pediocin PA-1 is readily hydrolyzed by proteolytic enzymes such as protease like other bacteriocins. In addition, pediocin PA-1 can be converted to a less active pediocin PA-1-ox form when oxidized (Rodríguez *et al.*, 2002).

## Class III bacteriocins

Class III bacteriocins or termed bacteriolysin comprised of two subgroups. Group A consists of bacteriolytic enzymes which kill sensitive strains by lysis of the cell wall and group B consists of non-lytic proteins. Enterolysin A and caseicins are examples of bacteriolysin classified under group A and group B, respectively (Yang *et al.*, 2014). Enterolysin A purified from *Enterococcus faecalis* could inhibit the growth of selected enterococci, pediococci, lactococci, and lactobacilli via bacteriolytic mode of action due to the fact that this bacteriocin possesses a N-terminus homologous to the catalytic domains of cell wall-degrading



proteins with modular structures. The homologous domain binds to specific target bacteria where bactericidal effect was exerted by the hydrolysis of peptide bonds in the peptidoglycan. Enterolysin A is effective to certain Gram-positive bacteria, whereas Gram-negative bacteria such as *Aeromonas salmonicida*, *Vibrio anguillarum*, *Pseudomonas* sp., *Yersinia ruckeri*, and *Escherichia coli* were insensitive to the inhibitory effects of enterolysin A, due to the lack of similar sequences. Similar to other bacteriocins, the production of enterolysin A is influenced by pH, temperature, inoculum size, and other environmental factors (Nilsen *et al.*, 2003). Caseicin obtained from *Lactobacillus casei* possesses a weak but definitive bactericidal effect due to the partial inhibition of thymidine formation, which affects DNA and protein biosynthesis (Muller and Radler, 1993).

#### Class IV bacteriocins

In general, class IV bacteriocins consist of complex bacteriocin with lipid or carbohydrate moieties that is crucial for activity. However, this classification is generally unaccepted due to possibility of inclusion of regular bacteriocin that are not properly purified (Saeed *et al.*, 2014).

### Applications and Challenges

Although certain bacteriocins such as nisin and pediocin PA-1 are currently available and sold as commercial products, bacteriocins may be a direct product produced from inoculation of the food product with starter cultures. The presence of these bacteriocins can inhibit the growth of food spoilage or pathogenic bacteria and these are commonly utilized in production of fermented products such as sausage, vegetables as well as in dairy products (Leroy and De Vuys, 2004). Starter cultures themselves can contribute to increased food safety and/or attributes to organoleptic, technological, nutritional, or health advantages. The production of bacteriocins leads to the increase of competitiveness of the producer strain within the food matrix thus minimizing food spoilage (Ross *et al.*, 2000). Other than direct addition to food products, antimicrobial

packaging and nanotechnology can be developed through the immobilization of bacteriocins via covalent links onto packaging materials which provide added stability against proteolytic enzymes. Creation of such bacteriocin-bio-polymer systems such as nisin and chitosan combination showed higher effect in inhibiting the growth of *Listeria* strains (López-Cuella *et al.*, 2016).

However, there are inherent challenges to the usage of bacteriocins and their starter cultures in the application of food. For example, the isolation of a specific bacteriocin requires massive screening from various sources (Parada *et al.*, 2007), and thus continual identification of novel bacteriocins, their antimicrobial spectrum and their mode of actions are required as a one-solution-for-all bacteriocin may not be possible (Gould, 1995). Another concern of bacteriocin is the development of resistances in the target microorganism. Currently, it had been reported that development of natural resistance to class IIa bacteriocins occurs in 1 to 8% of tested wild-type strains, while variations in natural sensitivity to nisin had also been observed (Ennahar *et al.*, 2000). A research article studying the frequency of bacteriocin resistance development in *L. monocytogenes* indicated the development of nisin resistance in target microorganism by sequential exposure also caused the cross-resistance to class IIa such as pediocin which is another common bacteriocin used in the food industry (Gravesen *et al.*, 2002).

Despite all these challenges, a knowledge-based approach to explore bacteriocin producing bacteria for food safety can be achieved by the advent of genomic sequencing technology, enabling metabolic or molecular engineering of microorganisms to produce stable bacteriocins that would be beneficial to the food safety (Ross *et al.*, 2002).

### Conclusion

Despite of the massive knowledge on bacteriocins produced from LAB, more fundamental and applied researches are needed to further exploit their antimicrobial potential for microbiological food safety. Besides, resistance property is a main concern when designing new kind of biopreser-



vatives as bacterial resistance to bacteriocins is confirmed under laboratory conditions. The high throughput technology can be used to elucidate how pathogenic cells respond to bacteriocin treatment for a better understanding of bacterial resistance to bacteriocins. Additionally, hurdle technology by combining bacteriocins with other thermal or non-thermal technologies will be paid more attentions to inactivate bacterial spores and Gram-negative pathogens. Since this hurdle technology uses less harsh conditions, physicochemical and nutritional quality of foods could be also improved compared with traditional preservation treatments. Therefore, specific needs in fundamental research on bacteriocins may be clustered into three main aspects: i) bacterial resistant mechanisms, ii) synergistic effect with other intervention technologies, and iii) screening of novel bacteriocins with wide antimicrobial spectrum.

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