

Emerging Applications of Bacteriocins as Antimicrobials, Anticancer Drugs, and Modulators of The Gastrointestinal Microbiota

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Abstract

The use of bacteriocins holds great promise in different areas such as health, food, nutrition, veterinary, nanotechnology, among others. Many research groups worldwide continue to advance the knowledge to unravel a novel range of therapeutic agents and food preservatives. This review addresses the advances of bacteriocins and their producer organisms as biocontrol agents for applications in the medical industry and agriculture. Furthermore, the bacteriocin mechanism of action and structural characteristics will be reviewed. Finally, the potential role of bacteriocins to modulate the signaling in host-associated microbial communities will be discussed.

Key words: bacteriocin, bio-preservatives, agriculture, biomedical, microbial communities

Introduction

Bacteria living in microbial communities use several functions and strategies to survive or coexist with other microorganisms, competing to obtain nutrients and colonize space in their habitat (Hibbing et al. 2010). One of the strategies used by bacteria to guarantee their growth in communities is antagonism, which effectively limits the growth of other microorganisms (Russel et al. 2017). To accomplish antagonism, bacteria must produce inhibitory substances such as antibiotics, organic acids, siderophores, volatile organic compounds, antifungals, and bacteriocins (Riley 2009). In addition to inhibiting the growth of other microorganisms, bacteriocins have different traits that make them attractive for biotechnological applications. For example, while resistance against nisin exists, in general, the bacteriocin mechanism of action less often induces resistance as it happens with conventional antibiotics (Behrens et al. 2017). Furthermore, some bacteriocins are compounds produced by the natural host-associated microbiome;

therefore, they are harmless to the host. Bacteriocins also show selective cytotoxicity toward cancer cells compared to normal cells (Kaur and Kaur 2015).

Classification, mechanism of action, and structural characteristics

Bacteriocins are antimicrobial peptides synthesized by the ribosome representing the most abundant and diverse group of bacterial defense systems (Silva et al. 2018). Bacteriocins were considered to have a narrow antimicrobial spectrum that could only inhibit bacterial strains closely related to produced bacteria; however, several studies have shown that there are bacteriocins able to kill different genera of bacteria and even certain yeasts, parasites, and cancer cells (Kaur and Kaur 2015; Baidara et al. 2018).

The success of bacteriocins in eliminating multi-drug resistant pathogens (MDR) has led to medical applications to treat bacterial infections. *In vivo* tests

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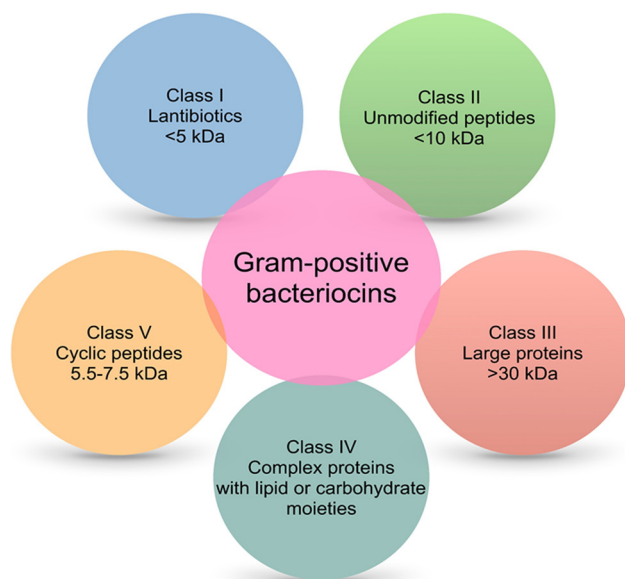


Fig. 1. Structure-based classification of Gram-positive bacteriocins.

have demonstrated the effectiveness of bacteriocins to treat infections in animal models, too (McCaughey et al. 2016; Van Staden et al. 2016). Lactic acid bacteria (LAB) produce bacteriocins, being nisin from *Lactococcus lactis*, the most well-known example (Silva et al. 2018). Nisin was approved for use as a food preservative for preventing the growth of *Listeria monocytogenes* and other Gram-positive pathogens (Price et al. 2018). The *Bacillus* genus also produces bacteriocins with attractive characteristics (Salazar-Marroquín et al. 2016), including subtilin (produced by *Bacillus subtilis*) and coagulins (produced by *Bacillus coagulans*). *Bacillus thuringiensis* produces bacteriocins with broad-spectrum activity, inhibiting various pathogens such as *L. monocytogenes*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Vibrio cholerae*, in addition to the *Aspergillus* fungus (Salazar-Marroquín et al. 2016).

Bacteriocins of Gram-positive bacteria are cationic and amphiphilic molecules whose mass varies from < 5 to more than 30 kDa (Balciunas et al. 2013) (Fig. 1). Many classifications of bacteriocins are available, but their diverse chemical structures and inhibitory activities make their classification into a specific group quite difficult. Class I bacteriocins, also known as lantibiotics, contain in their primary structure uncommon amino acids like lanthionine, β -methyl lanthionine, and dehydroalanine. These unique amino acids formed by post-translational modifications can provide antimicrobial activity and peptide stability. For example, they can create covalent bridges that result in internal rings that give stability to the peptide structure. In addition, internal rings contribute to the formation of a secondary structure in water that favors antimicrobial activity (Almeida and Pokorni 2012). Around 30%

of lantibiotics already identified have been purified from lactic acid bacteria, including the well-known nisin, mersacidin, and lactacin 3147 (Stoyanova et al. 2012). The class II bacteriocins are membrane-active and heat-stable peptides known as non-lantibiotics or pediocin-like antibiotics (Balandin et al. 2019). They do not harbor modified amino acids, and their molecular weights are lower than 10 kDa. Prototype bacteriocins of this group are pediocin PA-1, pentocin 31-1, enterocin P, sakacin G, enterocin A, two-peptide components (enterocin DD14, plantaricin E/F), sec-dependent secreted (acidocin B), and other not yet subclassified (bactofencin A peptides) (Liu et al. 2008; Balandin et al. 2019; Ladjouzi et al. 2020). The class III bacteriocins are large (> 30 kDa) heat-labile peptides composed of an N-terminal endopeptidase domain and a C-terminal substrate recognition domain. Bacteriocins of this group can lyse the cell wall of sensitive bacteria, although there are non-lytic bacteriocins in this group too, like helveticin J. Some examples of Class III bacteriocins are helveticin M, zoocin A and enterolysin A (bacteriolysins), and millericin B (murein hydrolase) (Alvarez-Sieiro et al. 2016; Sun et al. 2018). Class IV are complex peptide structures associated with lipid and carbohydrate moiety forming glycoproteins and lipoproteins. These structural characteristics make them sensitive to the action of glycolytic or lipolytic enzymes. Lactocin 27 and leuconocin S are prototype bacteriocins of this group and are recognized to disrupt bacterial cell membranes (Simons et al. 2020). Class V includes cyclic peptide structures like enterocin AS-48, pumilarin, lactocyclin Q, and plantaricyclin A (Perez et al. 2018; Sánchez-Hidalgo et al. 2011). The circular nature of their structures provides Class V with superior stability against several stresses compared to most linear bacteriocins. Biosynthesis of circular bacteriocins involves cleavage of the leader peptide, circularization, and export to the extracellular space.

Gram-negative bacteria produce both high molecular weight (> 30 kDa) and low molecular weight (< 10 kDa) bacteriocins (Rebuffat 2016). The first bacteriocin identified from a Gram-negative bacterium was colicin, produced by *Escherichia coli* (Riley 2009). Bacteriocins of Gram-negative bacteria are classified into two main groups, colicins, and microcins (Fig. 2). Genes encoding colicins are found on plasmids whose products vary between 20 and 80 kDa. Colicins from *E. coli* inhibits closely related strains of the genus *Salmonella* and other *E. coli* strains. Colicins are organized in three different domains: the translocation domain (T) N-terminally located, the receptor binding (R) located in the central region, and the cytotoxic domain (C) located at C-terminus (Helbig and Braun 2011). Microcins are pH and heat-stable antimicrobial peptides ribosomally synthesized, hydrophobic, and low

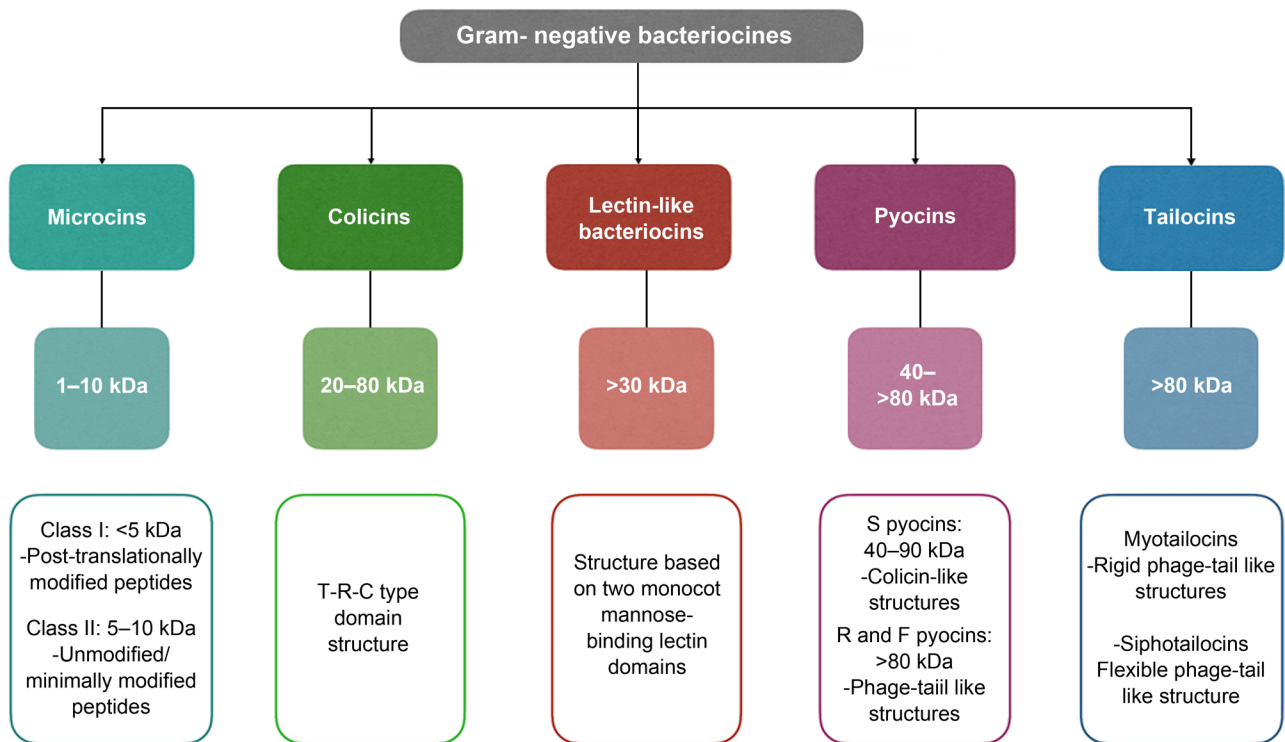


Fig. 2. Structural-based classification of Gram-negative bacteriocins.

molecular weight. In some cases, microcins require post-translational modifications to be active, and they do not require a lysis process to be secreted (Baquero et al. 2019). Microcin production has been reported in several Enterobacteriaceae and some cyanobacteria (Rebuffat 2016; Parnasa et al. 2019).

Microcin mJ25 produced by *E. coli* was initially described as a circular peptide; now it is known that there is no union between the terminal residues, but a union through the lactamic link between the amino group (Gly1) and the carboxyl group (Glu8). These structures are known as “lasso-peptides” and are also described in organisms of the genus *Streptomyces* (Hege-mann et al. 2015). Other types of high molecular weight bacteriocins of Gram-negative bacteria are pyocins (type R, F, and S), tailocins, and lectin-like bacteriocins. Genes encoding for pyocins are located on the bacterial chromosome, and their expression is induced by agents that damage DNA by activating the SOS response. R-type and F-type pyocins are non-flexible and flexible phage tail-like bacteriocins, respectively. The S-type pyocin is like the colicins and is formed by two proteins (a big one and a small one) that remain associated even during its purification process. The large protein is responsible for the antimicrobial activity, and the small one has an immune function for the producing bacteria (Michel-Briand and Baysse 2002; Atanaskovic and Kleanthous 2019; Oluyombo et al. 2019).

Tailocins are bacteriocins like phage tails and display a rigid or flexible structure, similar to R-type and

F-type pyocins. Tailocins with contractile and flexible tail morphologies are designated as myotailocins and siphotailocins, respectively (Yao et al. 2017). These bacteriocins have been described in plant-associated *Pseudomonas* and *Burkholderia* strains, although similar bacteriocins are also produced by *Clostridium difficile*, *Serratia plymthicum*, and *Serratia proteamaculans* (Gebhart et al. 2015; Ghequire and De Mot 2015; Hurst et al. 2018).

Lectin-like bacteriocins (LlpAs) represent another type of antimicrobial protein secreted by members of the genus *Pseudomonas*. LlpAs are ~30 kDa proteins that resemble monoco mannose-binding lectins (MMBL) consisting of two B-lectin domains followed by a short carboxy-terminal extension and do not contain an immunity protein. They also include a preserved consensus sequence QxDxNxVx necessary for the activity of the bacteriocin. The best examples of LlpAs include LlpABW11M1 of *Pseudomonas mosselii*, LlpA1Pf-5 of *Pseudomonas protegens* Pf-5, and pyocin L1 of *P. aeruginosa* (Ghequire et al. 2018a). The production of LlpAs has also been reported in *Burkholderia cepacia* strains.

Bacteriocins exert several mechanisms of action towards Gram-positive and Gram-negative bacteria (Fig. 3). Class I bacteriocins produced by Gram-positive bacteria permeabilize bacterial membranes through pore-formation, leading to ion leakage and cell death. These include bacteriocins produced by *Bacillus*, *Lactococcus*, and *Pediococcus* genera. They cause

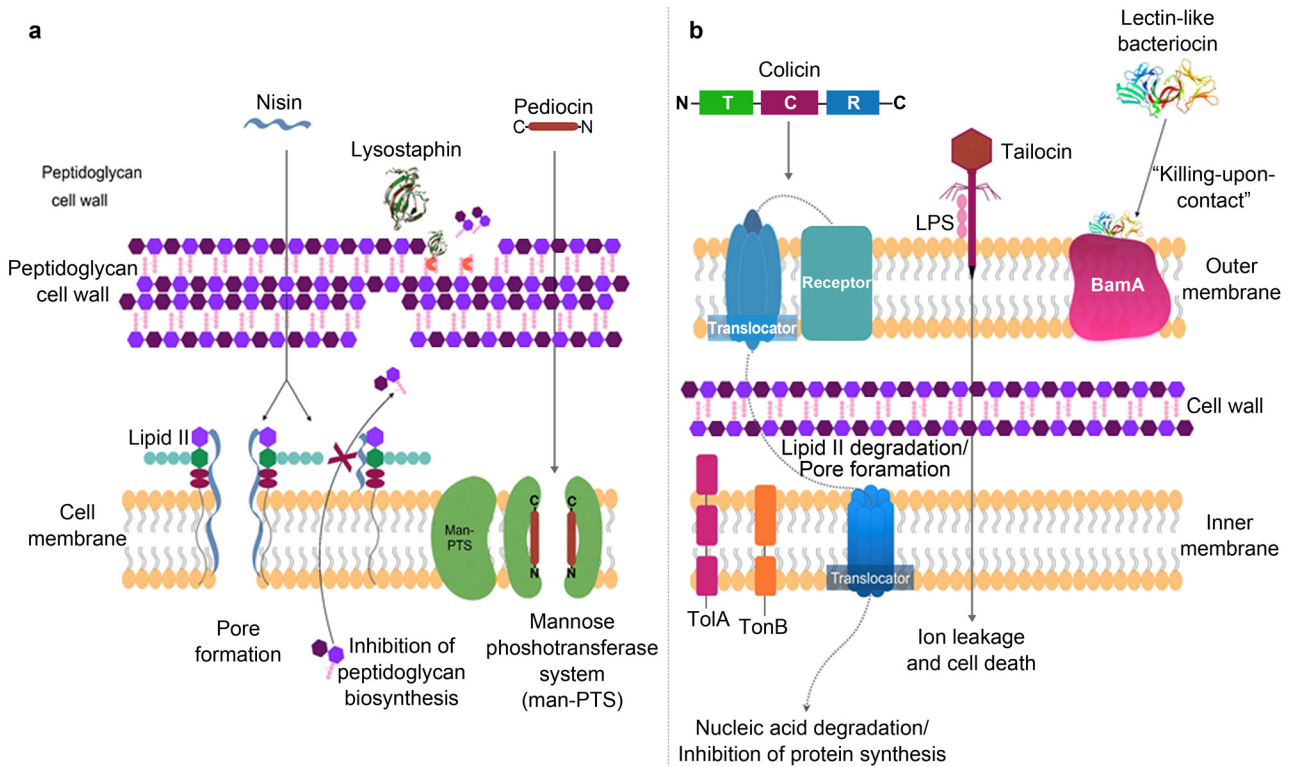


Fig. 3. Bacteriocin mechanism of action on a) Gram-positive and b) Gram-negative bacteria.

pore-formation by recognizing lipid II or the mannose phosphotransferase system (Paiva et al. 2011). Class I bacteriocins of Gram-positive bacteria also inhibit cell wall synthesis (Abriouel et al. 2011; Sun et al. 2018) (Fig. 3a). Class II bacteriocins make pores as described by the barrel stave or carpet model. Some class III bacteriocins produced by *Bacillus* inhibit the activity of the phospholipase A2, responsible for membrane repair (Abriouel et al. 2011). Class III bacteriocins, like lysostaphin, act directly on the cell wall inhibiting peptidoglycan synthesis without permeabilizing the membrane (Mitkowski et al. 2019). The mannose phosphotransferase system is involved in recognition of some Gram-positive bacteriocins, such as lactococin A and pediocin, leading to pore-formation and membrane permeabilization (Zhou et al. 2016).

The mechanism of action of Gram-negative bacteriocins, such as colicins, is through recognizing cell surface receptors of a target cell, through the Tol or TonB machinery, as shown in Fig. 3b. Colicins C domain (cytotoxicity domain) is responsible for eliminating other microorganisms through various mechanisms such as membrane permeabilization, nuclease activity, and inhibition of peptidoglycan or lipopolysaccharide O-antigen synthesis (Budič et al. 2011). *Salmonella* colicins (salmocins) display three mechanisms of action: SalE1a and SalE1b cause pore-formation in the membrane, SalE2 and SalE7 have DNase activity, and SalE3 have RNase activity (Schneider et al.

2018). Microcins are also membrane-pore formers, have DNase or RNase activity, and may inhibit protein synthesis (Yang et al. 2014).

The genus *Pseudomonas* produces high molecular weight bacteriocins such as R, F, and S type pyocins (Oluyombo et al. 2018). Besides the type B microcins (Ghequire et al. 2018a), tailocins (Ghequire and De Mot 2015), and LlpAs (Ghequire et al. 2018b). Pyocins and tailocins are characterized by having a complex structure that resembles phage tails (Ghequire and De Mot 2015; Patz et al. 2019), and the mechanism of action is based on the recognition of specific receptors on the cell surface causing pore formation, nonspecific degradation of nucleic acids or lipid II-degradation (Ghequire and De Mot 2018; Patz et al. 2019) (Fig. 3b).

Pyocins have a limited antimicrobial spectrum, mainly inhibiting competitors highly related to the producer strain (Redero et al. 2018). However, some R-type pyocins can inhibit other species such as *Campylobacter* sp., *Neisseria gonorrhoea*, *Neisseria meningitidis*, and *Haemophilus ducreyi* (Naz et al. 2015). Since the mechanism of action of pyocins depends on a cellular receptor, its use has been proposed to replace broad-spectrum antibiotics, to reduce the damage that antibiotics usually cause to the human microbiome (McCaughey et al. 2014).

LlpAs have a selective mechanism of action, different from other bacteriocins produced by *Pseudomonas* species. Probably because their structure does not

consist of the classic three-domain model present in bacteriocins of similar size (T, R, and C). Instead, they contain two monocotyledonous mannose-binding lectin (MMBL) domains associate with the recognition of BamA (Ghequire et al. 2018a). This protein of the outer membrane of Gram-negative bacteria facilitates the insertion of other proteins into the cell membrane (Noinaj et al. 2014). Although the mechanism of action of LlpAs remains unknown, a “killing upon contact” mechanism has been suggested (Ghequire et al. 2018a).

Bacteriocins and natural DNA transformation

Bacteria can take up exogenous DNA and incorporate it into their genome through a process termed competence. Competent bacteria can use absorbed DNA as a source of nutrients, DNA repair, or recombination with the genome. Natural DNA transformation happens when absorbed DNA is integrated into the genome (Veening and Blokesch 2017). This process is considered the primary mode of horizontal gene transfer (HGT) in bacteria, along with conjugation (direct cell to cell transfer of DNA via a specialized conjugal pilus) and phage transduction (DNA transfer mediated by viruses). Naturally competent bacteria couple the DNA-uptake process with other physiological responses, such as growth arrest and synthesis of antimicrobial polypeptides (bacteriocins) (Mignolet et al. 2018). Bacteria secrete bacteriocins upon entry into the competence state to kill surrounding competitors.

The competence pathway in *Streptococcus pneumoniae* is regulated by a secreted peptide pheromone, the competence-stimulating peptide (CSP). The precursor peptide of CSP, ComC, is processed by an ABC transporter/protease, ComAB, immediately after the double-glycine motif to yield the active CSP (Shanker and Federle 2017). Extracellular CSP activates the ComCDE two-component signal-transduction pathway, which turns on the sigma factor gene *sigX/comX*, to activate the expression of over 100 genes upon entering the competent state (reviewed by Shanker and Federle 2017). At least six CSP-responsive genes are involved in fratricide (killing/lytic factors directed against non-competent siblings). Among them, *cibABC* encodes a two-peptide bacteriocin responsible for lysis of cells lacking the corresponding immunity factor, CibC. The *cbpD* gene encodes a murein hydrolase containing a cytosine, histidine-dependent amidohydrolase peptidase. *lytA* encodes an effector of autolysis in *S. pneumoniae*. Interestingly, this predation mechanism appears to be restricted to isogenic or closely related strains, suggesting that competent cells target corresponding cells to acquire homologous DNA sequences to maintain genome integrity or acquire new

gene alleles from siblings. This ability to tackle closely related strains would be discussed in the section “Bacteriocins as modulators of gastrointestinal microbiota and population diversity”. *Streptococcus salivarius*, on the other hand, modules competence and bacteriocin production through the ComRS complex, which serves as the connector that directly regulates both *comX* and bacteriocin genes (Mignolet et al. 2018). *S. salivarius* bacteriocins have a broad spectrum of bacterial prey including the closely related *Streptococcus vestibularis*, more distant streptococci (*Streptococcus mutans* and *Streptococcus pyogenes*), and opportunistic pathogens such as *Enterococcus faecalis*, *L. monocytogenes*, and *S. aureus* (Mignolet et al. 2018).

Bacteriocins as food antimicrobial and anticancer agents

Bacteriocin applications have been focused primarily on food preservation, either alone or in combination with other compounds. The long shelf life of food products relies on adding chemicals, sugars, salts, and other preservatives allowed by the regulation. The addition of these substances reduces water activity, inhibiting the growth of undesirable pathogenic microorganisms that can spoil food. However, the addition of these chemicals benefits the industry but not the consumer since the continuous consumption of chemical preservatives through packaged foods can affect consumers' health. There is an association of these additives with chronic degenerative diseases, and the intake of these additives can prompt the development of some types of cancer (Monteiro et al. 2010; Moubarac et al. 2013). A more friendly strategy to preserve food products is the use of bacteriocins beneficial for both the food industry and consumers, helping to reduce the use of chemical preservatives in food (Sarika et al. 2019). The growth of pathogens in food can be controlled by the inoculation of bacteriocin-producing lactic acid bacteria or by the addition of purified bacteriocins (Silva et al. 2018). Bacteriocins have also been added to the coating of food packaging to reduce food spoilage (Salgado et al. 2015; Castellano et al. 2017).

The use of bacteriocins as food preservatives does not affect the organoleptic properties of foods. There are safe bacteriocins for human consumption, such as Enterocin AS-48 (Sánchez-Hidalgo et al. 2011), lactacin 3147 (Mills et al. 2017), and salmocins (Schneider et al. 2018) but only nisin (Nisaplin™, Biosafe™), pediocin PA-1 (Microgard™, Alta 2431), sakacin (Bactoferm™ B-2, Bactoferm™ B-FM) and leucocin A (Bactoferm™ B-SF-43) are commercially used to improve shelf-life of food (Vijay Simha et al. 2012; Daba and Elkhateeb 2020).

The Food and Agriculture Organization (FAO) support the use of probiotics in food systems, since probiotics offer health benefits, especially for the gastrointestinal tract. Probiotics play an important role in modifying some metabolic pathways that, in turn, regulate cell proliferation, apoptosis, differentiation, angiogenesis, inflammation, and metastasis, which are relevant aspects to prevent the development of cancer (Bermudez-Brito et al. 2012).

Bacteriocins have shown cytotoxic activity against cancer cells, and therefore they could be considered tools to develop new anticancer drugs (Baindara et al. 2018). The charge of normal cell membranes is neutral, while cancer cells have a negative charge due to the high content of anionic phosphatidylserine, o-glycosylated mucins, sialylated gangliosides, and heparin sulfates. Bacteriocins, being cationic peptides, can preferentially bind to the negatively charged membrane of cancer cells compared to normal cells. Some bacteriocins with anticancer activities are colicins, which

have shown cytotoxic activity against various human tumor cell lines such as breast cancer, colon cancer, and bone cancer (Kaur and Kaur 2015). Some examples of the potential applications of bacteriocins are shown in Table I.

The potential therapeutic uses of bacteriocins produced by lactic acid bacteria have increased over time. López-Cuellar et al. (2016) found that 37% of the investigations on bacteriocins were focused on medical applications including cancer, systemic infections, stomatology, skincare, and contraceptives. 29% of studies focused on food preservation, 25% on bio-nanomaterials, and 9% within veterinary. The number of patents on bacteriocins has also increased. From 2004 to 2015, 245 bacteriocin patents were issued, 31% related to the biomedical field, 29% to food preservation, 5% to veterinary medicine, 13% to production and purification process, and 16% to molecular modifications in producer strains. The smallest proportion concerns bio-nanomaterials and industrial applications.

Table II
Biocontrol potential of bacteriocin-producing microorganisms in agriculture.

Bacteriocin	Producer bacterium	Phytopathogen	Reference
Amylocyclin	<i>B. amyloliquefaciens</i>	<i>Ralstonia solanacearum</i> and <i>X. campestris</i>	(Scholz et al. 2014)
Bacteriocin 32Y	<i>P. aeruginosa</i> RsB29	<i>Fusarium</i> sp.	(Sindhu et al. 2016)
Carocin D	<i>P. carotovorum</i> subsp. <i>carotovorum</i>	<i>P. carotovorum</i> subsp. <i>Carotovorum</i>	(Grinter et al. 2012; Roh et al. 2010)
Enterocin UNAD 046	<i>E. faecalis</i>	<i>B. theobromae</i> , <i>A. niger</i> , <i>P. expansum</i> , <i>P. ultimum</i> .	(David and Onifade, 2018)
Fluoricin BC8	<i>P. fluorescens</i> BC8	<i>P. solanacearum</i>	(Sindhu et al. 2016)
Gluconacin	<i>G. diazotrophicus</i> PAL5	<i>X. albilineans</i> and <i>X. vasicola</i> pv. <i>vascolorum</i> .	(Oliveira et al. 2018)
LlpA	<i>P. putida</i> BW11M1	<i>P. syringae</i>	(Parret et al. 2005)
Morricin 269, Kurstacin 287, Kenyacin 404, Entomocin 420, Tolworthcin 524	<i>B. thuringiensis</i>	<i>Trichoderma</i> spp., <i>A. nodulans</i> , <i>F. graminis</i> , <i>F. oxysporum</i> , <i>Rhizopus</i> sp., <i>Mucor rouxii</i>	(De La Fuente-Salcido et al. 2008; Salazar-Marroquín et al. 2016)
NE	<i>P. syringae</i> pv. <i>ciccaronei</i>	<i>P. syringae</i> subsp. <i>savastanoi</i>	(Lavermicocca et al. 2002)
BLIS RC-2	<i>B. amyloliquefaciens</i> RC-2	<i>R. necatrix</i> , <i>P. oryzae</i> , <i>A. tumefaciens</i> , <i>Xanthomonas campestris</i> pv. <i>campestris</i> , <i>C. dematium</i>	(Abriouel et al. 2011)
NE	<i>B. gladioli</i>	<i>Tatumella ptyseos</i>	(Marín-Cevada et al. 2012)
BL8	<i>B. thuringiensis</i> subsp. <i>tochigiensis</i> HD868	<i>A. niger</i> , <i>A. fumigatus</i> , <i>A. flavus</i> , <i>Cryphonectria parasitica</i> , <i>F. oxysporum</i> , <i>Penicillium digitatum</i> .	(Subramanian and Smith 2015)
Plantazolicin	<i>B. velezensis</i> FZB42 (<i>B. amyloliquefaciens</i> subsp. <i>plantarum</i>)	<i>B. anthracis</i> and nematodes.	(Chowdhury et al. 2015)
Putidacin L1	<i>P. protegens</i> , <i>P. putida</i>	<i>P. syringae</i>	(Rooney et al. 2020)
Rhizobiocin	<i>Rhizobium</i> spp.	<i>P. savastanoi</i>	(Kaur Maan and Garcha 2018)
SF4c tailocins	<i>P. fluorescens</i> SF4c	<i>X. vesicatoria</i>	(Príncipe et al. 2018)
Syringacin M	<i>P. syringae</i> pv. <i>tomato</i> DC3000	<i>P. syringae</i>	(Li et al. 2020)

NE – non specified

Bacteriocins in agriculture

The indiscriminate use of agrochemicals has caused severe damage to human health and the environment. This problem aims to find alternatives to fight pests and diseases in a more environmentally friendly way. Bacteria that produce inhibitory substances have been used as inoculants to indirectly stimulate the growth of crops, fighting the phytopathogens. Plant growth-promoting rhizobacteria (PGPR) are generally marketed in the form of mono or multi-inoculants that include bacteria such as *Streptomyces venezuelae*, *Gluconacetobacter diazotrophicus*, *Burkholderia* sp., *Azospirillum brasilense*, *P. protegens*, *Pseudomonas putida*, among others. Most of these formulations have been traded to promote plant growth and not fight plant pathogens (Cesa-Luna et al. 2020). Therefore, little efforts have been focused on applying of bacteriocins for plant disease biocontrol, and hence their production by PGPR is poorly understood.

Some examples of bacteriocins applied to agriculture are agrocin 84 and thuricin 17. Agrocin 84 is produced by *Agrobacterium radiobacter* K84 and is useful to kill *Agrobacterium tumefaciens*, the causal agent of crown gall disease in plants (Kim et al. 2006). Thuricin 17 is produced by *B. thuringiensis* NEB17, this bacteriocin is a plant biostimulant with no harmful effects on nodulating rhizobia or other PGPR (Nazari and Smith 2020). *Pseudomonas syringae* pv. *ciccaronei* strain NCPPB2355 produces an inhibitory bacteriocin against *P. syringae* subsp. *savastanoi*, the causal agent of olive knot disease. Other important bacteriocins are those produced by the genus of *Pseudomonas* and *Bacillus* (Table II). These bacteriocins inhibit one of the primary phytopathogenic fungi, *Fusarium*, which can infect different types of plants, including celery, onion, cabbage, banana, cucumber, tomato, eggplant, cantaloupe, watermelon, spinach, among others. Direct application of bacteriocin induces a resistance mechanism in plants against pathogens and abiotic stresses. Application of thuricin 17 on plants enhanced production of phenolics, phenylalanine ammonia-lyase activity, and antioxidant defense (Nazari and Smith 2020).

Bacteriocins as modulators of gastrointestinal microbiota and population diversity

The autochthonous bacteria that colonize the entire human gastrointestinal tract, from the mouth to the colon, confer various physiologic benefits to the host. The prokaryotic symbiont population in humans ranges from 10^3 – 10^5 CFU/ml in the jejunal lumen) of healthy individuals to 10^{11} – 10^{12} CFU/ml in the colon, gut microbiota, prevents pathogen growth in the gas-

trointestinal tract (Sundin et al. 2017). This regulation is given through various microbial mechanisms, one of them is the release of bacteriocins, which prevent dysbiosis and consolidate the homeostasis of the gastrointestinal microbiota. The homeostatic balance in the human gut microbiota has become a significant public health problem due to changes in eating habits, type of diet, and administration of broad-spectrum antibiotics (Cotter et al. 2013). Ultra-processed food intake has increased saturated fats, omega-6 fatty acids, trans-fatty acids, and simple carbohydrates in the human diet while it has decreased the intake of omega-3 fatty acids, fiber, and complex carbohydrates. This diet high in fat and carbohydrates and low in micronutrients can disturb the human microbiota with concomitant metabolic disorders (Miclote and Van de Wiele 2020).

Probiotics can colonize, at least temporally, the human gastrointestinal tract due to the efficient competition mediate by bacteriocin production. Thus, the intake of *Lactobacillus* species in probiotherapy has shown health-promoting effects on treating inflammatory gastrointestinal diseases like constipation, diarrhea, irritable bowel syndrome, gastritis, gastroesophageal reflux, ulcerative colitis syndrome, Crohn's disease, among others (Kumar et al. 2016). Bacteriocins can play an essential role in the homeostasis of different subpopulations of microbial communities. For example, in the relationship of certain bacteriocin-producing, sensitive, and resistant bacterial populations bacteria can interact with each other in a set of incessant battles without a clear winner (Kerr et al. 2002).

In some cases, the growth rate of a resistant population can be higher than that of the bacteriocin-producing population (P), which generally possess a plasmid with genes encoding the bacteriocin and bacteriocin-specific immunity protein that make the bacteriocin-producing population immune to its bacteriocin. Still, at the same time, the resistant population (R) has a slower growth rate than that of the sensitive population (S). The susceptible population has an advantage over the resistant population because sensitive bacteria have a higher growth rate. The resistant population has an advantage over the bacteriocin-producing population because of its higher growth rate. And the bacteriocin-producing population can displace susceptible populations because bacteriocin-producing bacteria can kill sensitive bacteria making the three types of bacterial populations coexist in a balance of subpopulations preserving the diversity of the community (Kerr et al. 2002).

The bioinformatic analysis of bacteriocins encoded within 317 microbial genomes found in the human intestine revealed 175 bacteriocins in Firmicutes (which includes LAB), 79 in Proteobacteria, 34 in Bacteroidetes, and 25 in Actinobacteria (Drissi et al. 2015).

Table I
Bacteriocins with potential application as therapeutic and food preservatives.

Bacteriocin	Producer bacteria	Target microorganism	Use	Reference
1. Food preservation				
AMA-K, Leucocin K7	<i>L. plantarum</i> AMA-K	<i>Enterococcus</i> spp., <i>E. coli</i> , <i>K. pneumoniae</i> , <i>Listeria</i> spp.	Amasi, fermented milk product	(Todorov 2008)
Aureocin A70	<i>S. aureus</i> A70	<i>L. monocytogenes</i>	Dairy product	(Carlin Fagundes et al. 2016)
Bacteriocin 32Y	<i>L. curvatus</i>	<i>L. monocytogenes</i>	Pork and beef	(Gálvez et al. 2007)
Bacteriocin GP1	<i>L. rhamnosus</i> GP1	<i>Staphylococcus</i> sp., <i>Aeromonas</i> sp., <i>Lactobacillus</i> sp., <i>Pseudomonas</i> sp., <i>Vibrio</i> sp.	Fish	(Sarika et al. 2019)
Bovicin HC5 + Nisin	<i>Streptococcus bovis</i> HC5	<i>L. monocytogenes</i> , <i>S. aureus</i>	Fresh cheese	(Pimentel-Filho et al. 2014)
Divergin M35	<i>Carnobacterium divergens</i> M35	<i>L. monocytogenes</i>	Smoked fish	(Benabbou et al. 2020)
Enterocin	<i>E. faecium</i> FAIR-E 198	<i>Listeria</i> spp.	Feta cheese	(Sarantinopoulos et al. 2002)
Enterocin 416K1	<i>E. casseliflavus</i> IM 416K1	<i>L. monocytogenes</i> NCTC 10888	Cottage cheese	(Iseppi et al. 2008)
Enterocin AS-48	<i>Enterococcus</i> sp.	<i>L. monocytogenes</i> , <i>B. cereus</i>	Cheese, vegetable, purees, and soups	(Gálvez et al. 2007)
H1, H2, H3, H4	<i>Bacillus</i> sp.	<i>V. alginolyticus</i> , <i>Aeromonas hydrophilla</i> , <i>P. stutzeri</i>	Antimicrobial used in fish	(Feliatra et al. 2018)
Lacticin 3147	<i>L. lactis</i>	<i>L. monocytogenes</i>	Matured and cottage cheese	(Mills et al. 2017)
Lacticin NK24	<i>L. lactis</i>	<i>Leuconostoc mesenteroides</i> KCCM 11324	Seafood	(Lee and Paik 2001)
Leucocin K7	<i>L. mesenteroides</i> K7	<i>L. monocytogenes</i>	Dairy product	(Shi et al. 2016)
Mecedocin	<i>S. macedonicus</i> ACA-DC 198	<i>C. tyrobutyricum</i> LMG 1285T	Kasseri cheese	(Anastasiou et al. 2009)
NE	<i>L. gasseri</i> K7 (Rifr), <i>L. gasseri</i> LF221(Rifr)	<i>C. tyrobutyricum</i>	Semi-mature cheese	(Bogovič Matijašić et al. 2007)
Nisin	<i>Lactococcus</i> spp., <i>Streptococcus</i> spp.	<i>L. monocytogenes</i> , <i>Clostridium botulinum</i> , <i>S. mutans</i> , <i>L. innocua</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>B. cereus</i>	Dairy products, meat, seafood	(Juturu and Wu 2018)
Pediocin PA1	<i>P. acidilactici</i>	<i>L. monocytogenes</i>	Dairy products, meat	(Liu et al. 2008)
Plant-made salmocins	<i>Salmonella</i> spp.	<i>S. enterica</i>	Red meat	(Schneider et al. 2018)
Plant-made colicins (GRN 676, GRN 593)	<i>E. coli</i>	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>Salmonella</i> spp.	Meat, fruits, or vegetables	(Hahn-Löbmann et al. 2019)
Psicolin 126, carnocyclin A	<i>C. maltoaromaticum</i>	<i>L. monocytogenes</i>	Ready-to-eat meat products	(Liu et al. 2014)
Reuterin	<i>L. reuteri</i>	<i>E. coli</i> , <i>S. aureus</i> , <i>Candida albicans</i>	Food preservation	(Helal et al. 2016)
Sakacin P	<i>L. sakei</i>	<i>L. monocytogenes</i>	Beef and Salmon	(Teneva-Angelova et al. 2018)
Thuricin BtCspB	<i>B. thuringiensis</i>	<i>B. cereus</i>	Food preservation and disease associate to <i>B. cereus</i>	(Huang et al. 2016)
2. Bacterial infections				
ABP118	<i>L. salivarius</i> subsp. <i>salivarius</i> UCC118	<i>Bacteroides</i>	Antimicrobial agent	(Riboulet-Bisson et al. 2012)
Colicins Js and Z	<i>E. coli</i>	<i>Enteroinvasive</i> , <i>E. coli</i> (EIEC) and <i>Shigella</i>	Gastrointestinal infections	Bosák et al. 2021
Divercin V41	<i>C. divergens</i>	<i>L. monocytogenes</i>	Antimicrobial agent	(Rihakova et al. 2010)
Duramycin	<i>Streptomyces cinnamomeus</i>	<i>B. subtilis</i>	Antimicrobial, antiviral, immunomodulation, ion channel modulation, treatment of atherosclerosis and cystic fibrosis	(Huo et al. 2017)

Table I. Continued

Bacteriocin	Producer bacteria	Target microorganism	Use	Reference
Enterocin CRL35	<i>E. mundtii</i>	<i>L. monocytogenes</i>	Gastrointestinal infections	(Salvucci et al. 2012)
Epidermin and mersacidin-like peptides	<i>S. epidermidis</i>	<i>P. acnes</i>	Acne, folliculitis.	(Gillor et al. 2008)
Gallidermin/epidermin	<i>S. gallinarum</i>	<i>S. epidermidis</i> , <i>S. aureus</i>	Skin infections or associated with implants and prostheses	(Bengtsson et al. 2018; Bonelli et al. 2006)
Gassericin E	<i>L. gasseri</i> EV1461	Pathogens associated with vaginosis	Vaginal infections	(Maldonado-Barragán et al. 2016)
Haemocin type B	<i>Haemophilus haemolyticus</i>	<i>H. influenza</i>	Respiratory infections	(Latham et al. 2017)
Lactocin 160	<i>L. rhamnosus</i>	<i>G. vaginalis</i>	Urogenital tract infections, bacterial vaginosis	(Turovskiy et al. 2009)
Laterosporulin10	<i>Brevibacillus</i> sp. strain SKDU10	<i>S. aureus</i> , <i>Mycobacterium tuberculosis</i> (Mtb H37Rv), <i>M. smegmatis</i> MC2 155	Human microbial pathogens	(Baindara et al. 2016)
Mersacidin	<i>B. amyloliquefaciens</i>	Methicillin-resistant <i>S. aureus</i> (MRSA)	Skin infection	(Kruszewska et al. 2004)
Microcin J25 (lasso-peptide)	<i>E. coli</i>	<i>S. enterica</i> , <i>E. coli</i> , <i>S. flexnerii</i>	Gastrointestinal infections	(Dobson et al. 2012)
Nisin A, Nisin Z, Nisaplin	<i>L. lactis</i>	<i>S. mutans</i> , <i>S. aureus</i> , <i>E. faecalis</i> , <i>S. mastitis</i> , <i>C. albicans</i>	Gastrointestinal, respiratory, and skin infections, oral health	(Shin et al. 2016)
Oralpeace TM (encapsulated nisin)	<i>L. lactis</i>	<i>S. mutans</i> , <i>P. gingivalis</i>	Dental caries, gingivitis	(Perez et al. 2014)
Piscicolin 126	<i>Carnobacterium</i> spp.	<i>Listeria</i> spp.	Antimicrobial agent	(Miller and McMullen 2014)
Plantaricin 423	<i>L. plantarum</i>	<i>Listeria</i> spp.	Antimicrobial agent	(Guralp et al. 2013)
PLNC8 $\alpha\beta$	<i>L. plantarum</i>	<i>Staphylococcus</i> sp., <i>Porphyromonas gingivalis</i>	Antimicrobial agent	(Bengtsson et al. 2020)
R-pyocins	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	Antimicrobial agent	(Redero et al. 2018)
TOMM Streptolysin S (SLS)	<i>S. pyogenes</i>	<i>Clostridium</i> sp., <i>Listeria</i> sp.	Hemolytic and cytotoxic activity against macrophages and neutrophils	(Molloy et al. 2015)
3. Anticancer drugs				
Cancer cell lines				
Azurin	<i>P. aeruginosa</i>	MCF-7, UIISO-Mel-2, osteosarcoma (U2OS)		(Nguyen and Nguyen 2016)
Bovicin HC5	<i>S. bovis</i> HC5	MCF-7, HepG2		(Rodrigues et al. 2019)
Colicin E3	<i>E. coli</i>	P388, HeLa, HS913T		(Kohoutova et al. 2014)
Duramycin	<i>S. cinnamoneus</i>	AsPC-1, Caco-2, Colo320, CT116, JLN3, Lovo, MCF-7, MDA-B-231, MIA PaCa-2		(Rodrigues et al. 2019)
Enterocin LNS18	<i>E. thailandicus</i>	HepG2		(Al-Madboly et al. 2020)
Laterosporulin LS10	<i>Brevibacillus laterosporus</i> SKDU10	HeLa, MCF-7, H1299, HEK293T, HT1080		(Baindara et al. 2016)
M2163, M2386	<i>L. casei</i> ATCC 334	SW480		(Rodrigues et al. 2019)
Microcin E492	<i>K. pneumoniae</i>	HeLa, Burkitt lymphoma variant (RJ2.25)		(Kaur and Kaur 2015)
Nisin A	<i>L. lactis</i>	Head and neck squamous cell carcinoma (HNSCC)		(Shin et al. 2016)
Pediocin K2a2-3	<i>P. acidilactici</i> K2a2-3	HT2a, HeLa		(Villarante et al. 2011)
Pediocin CP2	<i>P. acidilactici</i> CP2 MTCC501	HeLa, MCF-7, HepG2, murine myeloma (Sp2/0-Ag 14)		(Kumar et al. 2012)

Table I. Continued

Bacteriocin	Producer bacteria	Cancer cell lines	Reference
Pep27anal2	<i>S. pneumoniae</i>	Jurkat, HL-60, AML-2, MCF-7, SNU-601	(Rodrigues et al. 2019)
Plantaricin A	<i>L. plantarum</i> C11	GH4, Reh, Jurkat, PC12, N2A	(Sand et al. 2013)
Plantaricin P1053	<i>L. plantarum</i> PBS067	E705	(De Giani et al. 2019)
Pyocin S2	<i>P. aeruginosa</i> 42A	HepG2, Im9, murine tumor (mKS-A TU-7), human fetal foreskin fibroblast (HFFF)	(Abdi-Ali et al. 2004)
Sungsanpin	<i>Streptomyces</i> spp.	A549	(Um et al. 2013)
Smegmatocin	<i>M. smegmatis</i> 14468	HeLa, AS-II, HGC-27, mKS-A TU-7	(Kaur and Kaur 2015)

NE – non specified

The analysis showed that bacteriocins produced by the intestinal bacteria display wide differences, in the size and amino acid composition, compared to other bacteriocins. These bacteriocins contain less aspartic acid, leucine, arginine, and glutamic acid but more lysine and methionine. Depending on their α -helical structure, charge, and hydrophobicity, they may have a broader spectrum of activity (Zelezetsky and Tossi 2006) but, in turn, lower antimicrobial activity and, therefore, they can better modulate microbial populations (Drissi et al. 2015). The microbial community that inhabits the human gut appears to impart specific functions to human metabolism and health by interconnecting signals from the brain, the immune system, the endocrine system, and the gut microbiota itself (Vivarelli et al. 2019). So, depending on the type of bacteria colonizing the gastrointestinal tract will determine the type of signaling molecules released and, therefore, the impact on host health and disease. That is why the microbial diversity of microbiota is tightly regulated. An example of this type of regulation exerted by bacteriocins is the effect of plantaricin P1053 produced by *Lactobacillus plantarum* strain PBS067; which exhibited a broad-spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria. Furthermore, plantaricin P1053 showed an improvement in the viability of healthy cells and a proliferation reduction of cancerogenic human intestinal cells. The mechanism involved in this case was through the epidermal growth factor receptor (EGFR) pathways (De Giani et al. 2019). *Bifidobacterium longum* subsp. *longum* NCC2705 produces the bacteriocin serpin, which is a protease inhibitor that interacts directly with the host factors. Serpin inhibits pancreatic and neutrophil elastases by mediating some gastrointestinal anti-inflammatory effects (Ivanov et al. 2006). The production of bacteriocins by the microbiota that inhabits the human gut affects the individual's metabolic processes, whether it improves health or causes dysbiosis and disease. Therefore, bacteriocins production by the microbiota is tightly regulated. One way of exploiting the bacteriocin potential of prevailing bacterial commensals to cure multiresistant

infections is to stimulate the endogenous bacteriocin producers at specific times and locations. *S. salivarius* population, for example, produces bacteriocins of high potency against infectious pathogens and is dominant and genetically diverse in the human digestive tract (Hols et al. 2019). Bacteriocin-related genes of *S. salivarius* can be activated upon addition of short ComS pheromone into the culture medium (Mignolet et al. 2018). Thus pheromone-based mobilization of bacteriocins in the commensal microbiota could be achieved *in vivo* by the addition of ComS pheromone which complexes with the ComR sensor activating the master regulator of competence (ComX), and coupling competence and predation response in *S. salivarius* (Hols et al. 2019). Nevertheless, oral administration of signaling pheromones remains elusive. To minimize environmental influences (i.e. resist most digestive proteases, the stomach barrier, and low solubility of signaling pheromones) and ensure the activating pheromone efficiency *in vivo*, more advanced enabling formulations to improve oral bioavailability is required.

A multidrug-resistant *E. faecalis* strain was actively killed by commensal enterococci. A heptapeptide pheromone, cOB1, produced by native *E. faecalis*; was involved in the killing of multidrug-resistant *E. faecalis* strain V583, the killing of V583, resulted from lethal cross-talk between accumulated mobile elements (Gilmore et al. 2015). Since multidrug-resistant *Enterococcus* possessed the limited ability to grow in the presence of commensal *Enterococcus* strains due to the production of peptide pheromones. We could hypothesize that infections caused by MDR strains can be fought by the same genera commensal strains using the suitable pheromone to activate the killing response. MDR enterococci colonize the patient after perturbing the native flora by antibiotic treatment when commensal enterococci strains are excluded. Therefore, a potential therapy could be the formulation of enterococci native strain along with the signaling pheromone. Currently, there is controversy over the adequate use of probiotherapy, more research must be done about whether probiotics are helpful and safe for various health condi-

tions. We still do not know the concentrations necessary to benefit healthy and sick individuals and the time of probiotics intake to improve individual health.

Bacteriocins commercially available: a patent perspective

According to the World Intellectual Property Organization (WIPO), over the last 30 years, more than 800 patent applications with the term “bacteriocin” in title or abstract were published, while Espacenet website reports more than 8900. Fig. 4 shows the patents published between January 1, 2000, and August 7, 2020, using the Patent Inspiration search engine with the term “bacteriocin”. Over the last 20 years, China has published 234 patents, followed by the United States with 132, while Mexico only published 17 patents (Fig. 4). Among these patents, 312 (36.4%) are associated with nisin and lactic acid bacteria.

Bacteriocins have fascinating properties concerning their size, structure, mechanism of action, inhibitory spectrum, and immunity mechanisms that endorse them with market potential. However, just four bacteriocin formulations are commercially available: nisin (Nisaplin™, Biosafe™, Oralpeace™), pediocin PA-1 (Microgard™, Alta 2341), sakacin (Bactoferm™ B-2, Bactoferm™ B-FM) and leucocin A (Bactoferm™ B-SF-43) are mainly used as food preservatives in the United States and Canada (Daba and Elkhateeb 2020; Radaic

et al. 2020). Other FDA-approved bacteriocins, with the intended use as an antibacterial for food, are colicins, salmocins, and *Clostridium* phage lysins, but they are not in the market yet (Hahn-Löbmann et al. 2019). One limitation of using purified bacteriocins in the food industry could be the high cost of production and purification compared to the price of food additives. It is more feasible to produce formulations of whole bacteria with their metabolites and use them as “protective cultures” on foods. Thus, several bacteria that produce bacteriocin have obtained the GRAS status and are used commercially as a preservative in a wide range of food products or as probiotics. In the list is *Carnobacterium divergens* M35, *Bacillus coagulans* GBI-30, *Bacillus subtilis* strain SG 188, *Lactobacillus plantarum* Lp-115, *Lactobacillus fermentum* CECT5716, *Lactobacillus paracasei* strain F19, *Lactobacillus plantarum* strain 299v, *Bacillus coagulans* SNZ1969, *Lactobacillus acidophilus* DDS-1, *Bifidobacterium animalis* subsp. lactic UABla-12, *Bifidobacterium longum* BB536, *Bifidobacterium bifidum* Rosell®-71, *Bifidobacterium longum* ssp. infantis Rosell®-33, *Lactobacillus helveticus* Rosell®-52, *Lactobacillus rhamnosus* LGG®, *Lactobacillus curvatus* DSM 18775, and *Streptococcus salivarius* K12. An alternative to the costly fermentation production and purification of bacteriocins from a natural producer strain is chemical synthesis. Advances in solid-phase peptide chemical synthesis, lower price for reagents and building blocks, has made the chemical synthesis of bacteriocins more attractive and competitive. Furthermore, through

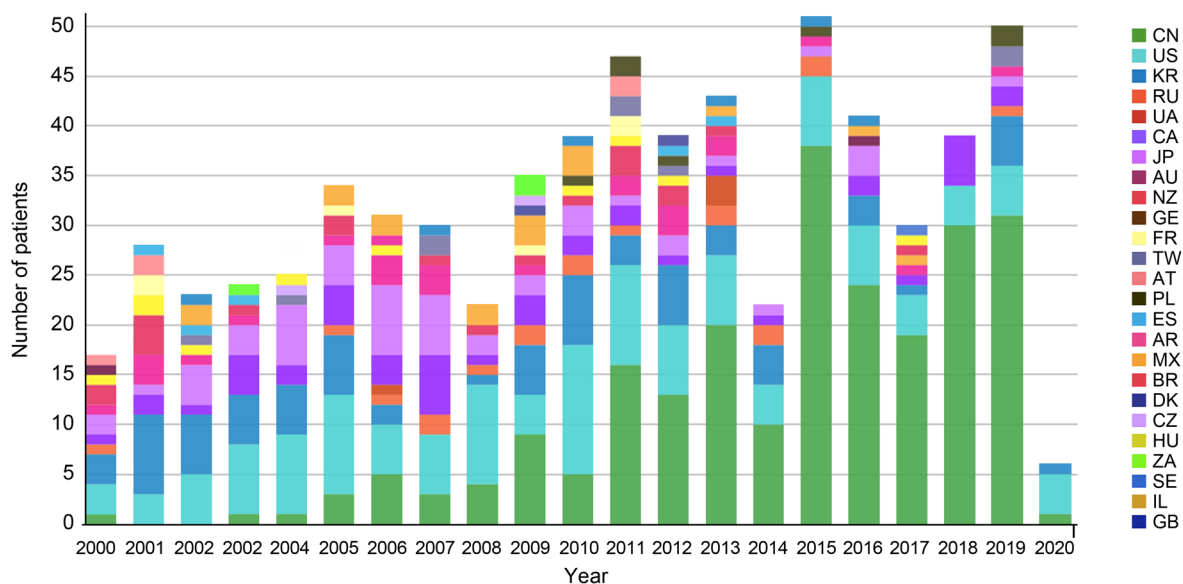


Fig. 4. Timeline of bacteriocin patents reported worldwide from January 1, 2000 to August 7, 2020. Countries with the highest number of reported patents per year are shown. The figure was generated with the Patent Inspiration search engine (<https://www.patentinspiration.com>).

CN – China, US – United States, KR – Korea, RU – Russian Federation, UA – Ukraine, CA – Canada, JP – Japan, AU – Australia, NZ – New Zealand, GE – Germany, FR – France, TW – Taiwan, AT – Austria, PL – Poland, ES – Spain, AR – Argentina, MX – Mexico, BR – Brazil, DK – Denmark, CZ – Czech Republic, HU – Hungary, ZA – South Africa, SE – Sweden, IL – Israel, GB – United Kingdom.

chemical approaches, it is possible to perform amino acid substitution, use non-natural or modified residues, and make backbone and side-chain modifications to improve potency or stability of bacteriocins (Bédard and Biron 2018). Those advanced chemical methods will surely enable the screening and identification of more potent or stable bacteriocins.

Bacteriocin formulations can be used as nutritional supplementation. Few *in vivo* experiments on bacteriocin dietary formulations have described the effects of bacteriocins on the gastrointestinal microbiota of mice, rats, rabbits, ruminants, fish, and poultry. A multispecies probiotic combination (*Lactobacillus reuteri*, *Enterococcus faecium*, *B. animalis*, *Pediococcus acidilactici*, and *Lactobacillus salivarius*) increased nutrient digestibility, digestive enzyme activities, and anti-inflammatory effect in broilers (Palamidi et al. 2016). The efficacy of *L. acidophilus*, *B. subtilis*, and *Clostridium butyricum* supplementation in broilers improved growth performance, ileal amino acids digestibility, and humoral immunity (Zhang and Kim 2014). The addition of nisin (alone or in combination with salinomycin or monensin) to broilers' diet was associated with an apparent nutrient digestibility (Kierończyk et al. 2017). Dietary supplementation with *Paenibacillus ehimensis* NPUST1 (bacteriocin-like activities against *Aeromonas hydrophila*) improved the growth performance, immunity, and disease resistance in Nile tilapia (Chen et al. 2019). Altogether, these reports indicate the potential of bacteriocins as nutritional supplementation.

Compared to the food industry, the medical field could represent a higher profit for the use of bacteriocins. However, to exploit the full potential of bacteriocins in the medical industry, they must overcome some drawbacks such as sensitivity to proteases, immunogenicity issues, and the development of bacteriocin resistance by pathogenic bacteria. In this regard, advanced chemical approaches can be used to make disulfide bridges, head-to-tail macrocyclization, N-terminus formylation, amino acid substitutions, and other modifications; to make bacteriocins more potent and stable, enabling them to surpass their current drawbacks (Bédard and Biron 2018). Another factor that prevents the commercial use of bacteriocins in medical applications might be attributed to the low approval of the regulatory process. Over the last decade, the number of *in vivo* trials has increased, but clinical application of bacteriocins requires more investigation to determine their efficacy, stability, and kinetic properties in/on the human body. For example, nisin ZP and nisin AP, significantly reduced the tumor volume in mouse-induced oral cancer. Lacticin 3147 reduced *S. aureus* Xen 29 growth and prevented dissemination of the pathogen in the spleen, liver, and kidney of a murine model. Salivaricin prevented *Candida albicans* coloni-

zation in the oral cavity of a mouse model. ESL5 has been applied as a lotion in a patient with inflammatory acne lesions caused by *Propionibacterium acnes* (López-Cuellar et al. 2016; Soltani et al. 2021). Lantibiotics such as nisin, clausin, and amyloliqueducin (AmyA) are effective in treating *S. aureus*-induced skin infection in mice (van Staden et al. 2016). AS-48 prevents and treats skin diseases, even with multi-drug resistant microorganisms, and has the potential as a leishmanicidal agent (Cebrian et al. 2019). Despite their therapeutic possibilities, bacteriocins have not yet entered into clinical use, and only a limited number have been selected for tests in clinical trials. NAI-107 (*Microbispora corallina*) and mutacin 1140 (*S. mutans* JH1000) are at the late preclinical phase; NVB302 and Moli1901 (*Actinoplanes liguriae* NCIMB41362) have completed phase I and phase II clinical trials (for clinical studies, see Ongey et al. 2017; Soltani et al. 2021). Finally, apart from those technical limitations mentioned, several factors not covered in this review preclude most patented products make it to market.

Conclusions

Bacteriocins have become an attractive tool to preserve food and improve human health. Bacteriocins can eliminate specific pathogen microorganisms while favoring the preservation of other populations. Since the impact of bacteriocins on each microbial community is not well understood yet, there are limitations to exploit all their potential. It is necessary to continue performing rigorous research focused on developing antimicrobials, anticancer agents, and microbiota modulators before bacteriocins can be available to consumers.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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