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Bacteriocin as a new generation of antimicrobials and its potential applications in food preservation and human health: A review

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ABSTRACT

Bacteriocins are a heterogeneous group of bioactive bacterial peptides or proteins that are synthesized ribosomally that prevent or kill other related or unrelated microorganisms. They are industrially grand molecules due to their great potential as natural preservatives in food, feed and cosmetic industries and other sectors such as organic fertilizers, environmental protection and personal care yields. In recent decades, there has been a lot of attention in the form of antimicrobial compounds. Although bacteria have been mainly exploited as food protectors, they are now receiving more attention as potential clinical antimicrobial and potential immune modulation mediators. Infections caused by antibiotic resistant bacteria have been declared a global threat to public health. Bacteriocins represent a potential solution to this worldwide hazard due to their broad or narrow spectrum activity against antibiotic-resistant bacteria. Especially, their role in food safety as natural alternatives as compared to chemical preservatives. Various features like rapidly degradation by gastric enzymes, heat stability, potently inhibition of numerous food spoilage as well as pathogenic bacteria have attracted the attention of researchers to study bacteriocins for their necessary properties and probable applications as next-generation antimicrobial agents. Here we focus on the most recent trends relating to the application of bacteriocins in food preservation, their classification, mode of action, antimicrobial nature and future prospects.

1. Introduction

The discovery of antibiotics by Alexander Fleming in 1928 was a breakthrough in the field of treatment of diseases caused by bacterial pathogens. Role of antibiotics is either killing bacteria or they may inhibit bacterial growth. Although antibiotics have revolutionized medicine, their overuse has resulted in the appearance of antibiotic resistance, a major disadvantage to the control of bacterial infections worldwide. The widespread emergence of antibiotic-resistant bacteria and slow-down in the discovery of new classes of antibiotics are considered as serious public health issues (Baquero and Moreno 1984, Klaenhammer, 1988, O'Neill, 2016). Moreover, the subsequent spread of resistant bacterial strains from person to person or humans from non-human sources in the environment, such as from livestock or food animal treated with antibiotic similar to those employed to treat human infection, has been a major factor in the expansion of antibiotic resistance (Ansari, 2015 and CDC 2018). So, this has necessitated the need for newer alternatives to conventional antibiotics. Bacteriocins are a heterogeneous group of ribosomally synthesised antimicrobial peptides with the ability to kill closely related (narrow spectrum), or a diverse range of (broad spectrum), microorganisms (Ga´lvez, *et al.* 2007). Gram-positive and Gram-negative bacteria secrete these antimicrobial peptides or proteins (Duquesne, *et al.* 2007, Drider and Rebuffat 2011, Hammami, *et al.* 2013). Moreover, it has been decribed that many bacteriocins are effective in treating human and animal infections. (Kim, *et al.* 2010, Van Staden, *et al.* 2012, Campion, *et al.* 2013). Due to a narrow range of bacteriocin, specific pathogens can be targeted without any effect on normal commensal microflora, unlike antibiotics, *i.e.*,

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bacteriocins are completely safe to use as therapeutic agents for humans. However, recent years studies clearly indicate that the bacteriocins application in food preservation can offer several benefits (Thomas, *et al.* 2000): (i) an extended shelf life of foods (ii) provide extra protection during temperature abuse conditions (iii) decrease the risk for transmission of foodborne pathogens through the food chain (iv) ameliorate the economic losses due to food spoilage (v) reduce the application of chemical preservatives (vi) permit the application of less heat treatments for better preservation of organoleptic properties of foods, food nutrients and vitamins (vii) permit the comercialization of "novel" foods (less acidic, with a higher water content and with a lower salt content,), and (viii) they may serve to satisfy consumers and industrial demands. For thousands of years, fermented foods have been essential part of the human diet and and improve food safety by inhibiting food spoilage/pathogen (Ross, *et al.* 2002). Lactic acid bacteria (LAB) are naturally present in many fermented foods and have great contribution in food bio preservation. They exert their preservative effects through the production of antimicrobial metabolites including dactyl, ethanol, organic acids hydrogen peroxide and bacteriocins. So, in the present time, Bacteriocins are the focus of increased attention due to i) consumer requirements for minimally processed foods free from chemical additives (Silva, *et al.* 2018) ii) their potential as natural alternatives to antibiotics due to increasing concerns about the emerging problem of antimicrobial resistance (Cotter, *et al.* 2013, WHO, 2017) iii) as modulators of the human microbiome and, therefore, potential to address complex metabolic conditions such as diabetes and inflammatory bowel disease (Garcia-Gutierrez, *et al.* 2019) and iv) as bacteriocin-producing probiotic cultures for inclusion in animal feed to promote growth, improve animal health and/or reduce infection (Vieco-Saiz, *et al.* 2019).

Bacteriocin: Classification

Bacteriocins according to their size, molecular composition, structure, or modification process can be divided into several classes. In Gram-positive bacteria, they can be classified as Class 1, 2, 3 & 4.

Classification	**Major Characterstics**	**Examples**
Class I		
Lantibiotics/lanthionine-containing bacteriocins subdivided into: **Type A** lantibiotics **Type B** lantibiotics	Small (<5k Da) membrane-active unusual amino acids -elongated peptides with a net positive charge -small globular peptide with negative or no net charge	Type A Nisin, lactocin S, lacticin 481 Type B Mersacidin
Class II		
Non-lanthionine contains Bacteriocin subdivided into; Subclass II Subclass Ib Subclass llc	Heterogeneous class-(<10 kDa) Post-translation unmodified lantibiotics II a: pediocin-like II b: two peptide II c: with a wide range of effects on membrane permeability and cell wall formation	Ila*:* pediocin PA1, sakacin A, sakacin P, leucocin A. curvacin A Ilb: lactococcin G, lactococcin M. lactacin F.plantaricin A Ilc: acidocin B. enterocin P. enterocin B reuterin 6
Class III		
Bacteriolysins	Large- i.e greater than 30 KDa ,heat-labile antimicobial complex proteins with domain type structure that function through the lyses of sensitive and cell by Catalyzing cell wall hydrolysis	Lysostaphin,enterolysin A.helveticin J. helveticin V-1829
Class IV		
	Complex bacterive in varying lipid or carbohydrate mogelies	Plantariem S, leuconsin Slachoci Kumaria *et al.* (2019)

Class 1: Lantibiotics

These are antibiotics that confer the thermomostable properties and are of very low molecular weight. As the name suggests, they contain lanthionine and β-methyl lanthionine amino acids. The thermomostable properties are caused by dehydrated amino acids. Since amino acids are the result of post-translational modification which includes dehydration and cyclization of amino acid residues, it is linked to the blockage of many food-borne pathogens. Class 1 Lantibiotics are further divided as Class 1a and 1b on the basis of their particular synthesis, structural and biosynthetic activity. Nisin is a Class 1 bacteriocin. Class 1a consists of positively charged elongated peptides which usually form pores in the bacterial membrane and the Class 1b consists of negatively charged globular peptides which are related to the inhibition of those particular enzymes which are required by the bacteria. Mersacidin is a Class 2 bacteriocin

Class 2: Non-lanthionine containing Bacteriocins

These are Non-Lantibiotics i.e., they do not have post-translational modifications in the peptide chain such as lanthionine or β-lanthionine. They are small thermostable peptides (30-60 amino acids) and are further classified as Subclass 2a, 2b, 2c and 2d Bacteriocins. The members of the subclass II-A have high antibacterial activity against food borne pathogens *i.e.* Pediocin PA-1/AcH etc. Subclass II-B includes heterodimeric bacteriocins which consist of two peptides, it shows the antibiotic activity as they form cation or anion-specific pores. Subclass II-C has a circular structure that is associated with a covalent bond between C and N terminals due to which peptides are of cyclic shape from head to tail. They have a leader peptide sequence with one or two cysteine residues and their mode of action is due to disruption in PMF (proton motive force) pump. Subclass II-D is another subclass under Class 2 bacteriocin and they require carbohydrate or lipid moiety for their activity.

Class 3: Bacteriocins have a high molecular weight (30 KDa) which is thermolabile. These bacteriocins have antibiotic activity linked to the enzymatic activity which induces lysis of the cell wall of the target organism. Most of this class bacteriocins are produced by genus *Lactobacillus*. For example, Lactacin B, which is produced by *Lactobacillus acidophilus.*

Class 4: Bacteriocins are large peptides combined with carbohydrates or lipids. These are complex and cyclic in nature. These too disrupt the cell membrane of the target microorganism *i.e.* Lactocin 27, Leuconocin S etc.

Besides above four classes, in Gram-negative bacteria, colicins with a molecular weight of more than 10 kDa are important bacteriocins produced by Escherichia coli. These have two subclasses- subclass 1 forms pore in the bacterial cell wall and subclass 2 degrades nucleic acid structures. In another class, there is colicin-like bacteriocins which are similar to Escherichia coli but are produced by *Klebsiella sp.* and *Pseudomonas aeruginosa*. These have two subclasses having similar functions like colicin subclasses.

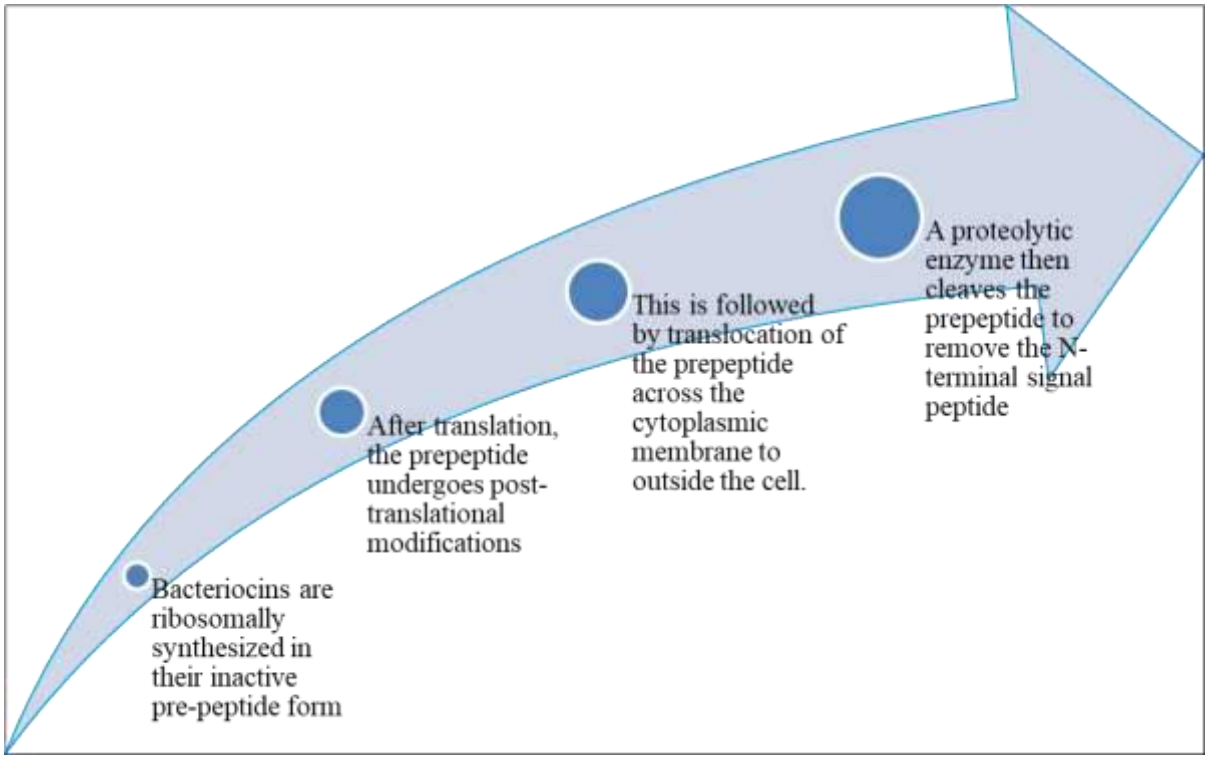
Microcins are another type of bacteriocins produced by gram-negative bacteria with a molecular weight lower than 10 kDa and this too can be divided into two subclasses. Subclass 1 is post-translationally modified with extremely low molecular weight, less than 5 kDa, and Subclass 2 are unmodified with a molecular weight ranging between 5 to 10 kDa. Subclass 1 microcins target cells in such a way that they inhibit vital bacterial enzymes ultimately leading to cell death. One such microcin, Subclass 2 microcins target the inner membrane or their components such as Microcin H47 targets the F0 proton channel of ATP synthase.

Bacteriocins vs. Antibiotics

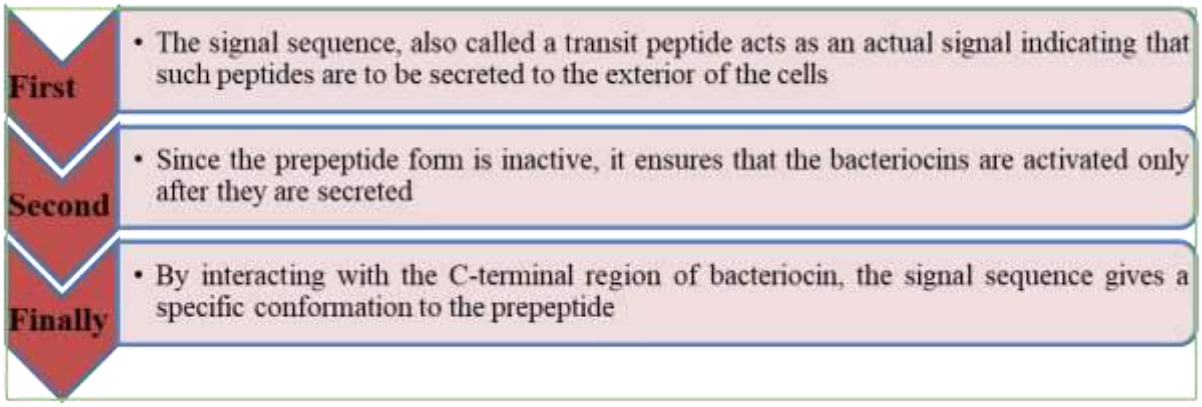
Characteristic	Bacteriocins	Antibiotics
Application	Food	Clinical
Synthesis	Ribosomal	Secondary metabolite
Activity	Narrow spectrum varying	Varying/Wide spectrum
Host cell immunity	Yes	No
Mode of action	Cell wall biosynthesis in few cases but mostly pore formation,	Cell membrane or intracellular targets
Interaction requirements	Sometimes docking molecules	Specific target
Mechanism of target cell resistance or tolerance	Tolerance membrane composition or adaptation affecting cell resistance	Usually, a genetically transferable determinant affecting different sites depending on the mode of action
Interaction requirements	Sometimes docking molecules	Specific target

Toxicity/side effects	None known	Yes
Stability	High for Class 1 and 2	Low
Bio flexibility	High	Low

Biosynthesis of Bacteriocins-



- The N-terminal signal sequence plays three important roles



Bacteriocins: Mode of action

Class		Features	Example	Mechanism of action	Receptors	Producers	Bacterial spectrum
1	1a	Lantibiotics (< 5 kDa peptides containing lanthionine and β-methyl lanthionine)	Nisin	Membrane permeabilization by pore formation	Lipid II	*L. lactis*	Gram-positive bacteria
	Ib	Carbacyclic lantibiotics containing labyrinthin and labionine	Labyrinthopeptin A1	Not known	Not known	*Actinomadura namibiensis*	HIV, HSV

	Ic	Sactibiotics (sulphur to alpha carbon-containing antibiotics)	Thuricin CD	Not known	Not known	*B. thuringiensis*	Gram-positive bacteria
II	IIa	Small heat-stable peptides, synthesized in a form of precursor which is processed after two glycine residues, active against Listeria, have a consensus sequence of YGNGV-C in the Nterminal	Pediocin PA-1, sakacins A and P, leucocin A	Membrane permeabilization by pore formation	Mannose permease	*P. pentosaceus, P. acidilactici, Lactobacillus sakei*	Gram-positive and Gram-negative bacteria
	IIb	Two component systems: an active poration complex formation requires two different peptides	Lactococcins G, plantaricin EF and plantaricin JK	Membrane permeabilization by pore formation	UppP (undecaprenyl pyrophosphate phosphatise)	*L. lactis subsp. cremoris, Lb. plantarum*	Gram-positive bacteria
	IIc	Circular bacteriocins	Gassericin A, enterocin AS-48, garvicin ML	Membrane permeabilization by pore formation	ABC transporter	*L. gasseri, E. faecalis, L. garvieae*	Gram-positive bacteria
	IId	Unmodified, linear, leaderless, non pediocin-like bacteriocins	Bactofencin A, LsbB	Membrane permeabilization by pore formation	Metallope-ptidase	*L. salivarius, L. lactis subsp. Lactis*	Gram-positive bacteria
III		Large molecules sensitive to heat	Helveticin M, helveticin J and enterolysin A	Membrane permeabilization by pore formation	Not known	*Lb. crispatus, L. helveticus, E. faecalis*	Gram-positive and Gram-negative bacteria

Kumaria *et al.* (2019)

Bacteriocins inhibit the growth of target organisms in various ways which entirely depends upon their class. They generally act mainly by pore formation, nuclease activity, peptidoglycanase activity. Bacteriocins concerning Gram positive bacteria works by disrupting their cell membranes or by pore formation. Some use lipid 2 component as a docking material leading to pore formation or some inhibit lipid 2 eliminating synthesis of peptidoglycan. Enzymatic inhibition of peptidoglycan synthesis can also occur, due to which cytoplasmic accumulation of peptidoglycan precursor happens and ultimately bacterial membrane gets disrupted. Some bacteriocins bind to Mannose phosphotransferase system (Mannose-PTS). Nisin uses Lipid 2 as a docking material due to which membrane permeability gets increased and ultimately target cell is destroyed. Class 2 bacteriocin, Lactococcin A targets Mannose-PTS receptor, which is used to couple import and phosphorylation of sugars. A protein specific complex, Enzyme E2 is present in the system is the target site of bacteriocin. The bacteriocin interacts with Mannose PTS receptor, which results in permanent opening of the receptor and uncontrolled and continuous efflux of intracellular molecules occurs. Lactococcin G, another Class 2 bacteriocin also acts by pore formation. Bacteriocins concerning gram negative bacteria, acts either by pore formation or by targeting vital enzymes. Microcins, in order to work must enter the targeted cell, which they do so by employing specific inner membrane receptors. They use the specific receptors at the outer membrane of sensitive strain, including the receptors which are involved in iron uptake after entering the targeted cell. Microcin B 17, using inner membrane receptors including Sda C and Sbm A proteins enter the cell and once inside the cell, they inhibit DNA gyrase, inhibiting supercoiling of DNA and relaxation reactions of DNA gyrase. Ultimately, due to accumulation of

covalent complexes of DNA gyrase with cleaved DNA, double stranded DNA breaks and DNA replication is inhibited. Microcin C inhibits aspartyl tRNA synthase, blocking protein synthesis in target cell.

Bacteriocin: Antimicrobials nature

Bacteriocin VJ13, Bacteriocin PJ4 and Paracaseicin A have shown antimicrobial activity against several pathogenic bacteria. Bacteriocin VJ13, isolated from *Pediococcus pentosaceus* shows antibacterial activity against *Clostridium sp.*, *S. aureus* and *Klebsiella pneumoniae*. Bacteriocin PJ4, produced by *Lactobacillus helveticus* is found to be active against *Enterococcus faecalis*, S. *aureus, E. coli, P. aeruginosa*. Moreover, Bacteriocin PJ4 is heat stable and also pH stable. Paracaseicin A, from *Lactobacillus paracasei* is active against several MDR gram positive and gram negative bacteria. Even at higher temperatures 60° to 120° C and at pH 2 to 5, it showed active antimicrobial activity. Bacteriocin NVB302, isolated from *Actinoplanes liguriae* is effective against *Clostridium difficile*. Bacteriocins are also important in treating Cystic fibrosis patients which is due to bacterial biofilms. Gallidermin, produced by *Staphylococcus gallinarum* is active against even MDR Gram positive bacteria. Gallidermin inhibits Atl and Ica genes necessary for biofilm production which is helpful in tackling diseases caused by bacterial biofilms. Microcin E 492 work against E. coli, *Klebsiella pneumoniae* and *Salmonella enteritidis.* Microcin J25 is active against even pathogenic strains of *E. coli. Helicobacter pylori* is a pathogenic gram-negative bacterium that causes gastroduodenal ulceration and gastric cancer. Studies have found that LAB bacteriocins have excellent antimicrobial activity against *H. pylori*. *H. pylori* cells attachment to the gastric epithelium followed by invasion, are the preliminary processes that are responsible for chronic infection. Therefore, assays to test anti- *H. pylori* activity of LAB bacteriocins in addition to in-vitro experiments, have been conducted when the bacteria are attached to epithelial cells. Furthermore, administration of bacteriocin producing LAB has also been found to prevent Helicobacter infection in mice. The bacteriocins produced by some LAB such as *L. acidophilus, L. pentosus, L. jensenii, L. salivarius,* and *L. fermentum* were found to possess antibacterial activity against BV associated pathogenic bacteria such as *G. vaginalis*, other vaginal fungal pathogens such as *Candida albicans*, and the pathogens associated with sexually transmitted diseases, such as *Neisseria gonorrhoea*. A wide variety of gram-positive bacteria such as *Streptococcus mutans* and other species are involved in the formation of plaques as well as the generation of malodour in the oral cavity. Bacteriocins produced by LAB such as *L. salivarius* have been found to have excellent properties against such oral pathogens and against *S. pyogenes* and *S. pneumoniae*. Furthermore, nisin has also been found effective in inhibiting biofilm formation by *S. mutans.* All these examples prove the antimicrobial nature of bacteriocin.

Bacteriocins: Applications in food preservation and human health

Bacteriocins with optimal potential as bio preservatives are safe for human consumption, have minimal effects on the human microbiota, are effective against food pathogens/spoilage micro-organisms and stable in the food matrix, in which they are employed, which may require resistance to heat, pH and food associated enzymes (Johnson, *et al.* 2018). Because of their antimicrobial activity, bacteriocins have obvious application in preventing the growth of spoilage-causing and pathogenic bacteria in foods (Vuyst and Leroy 2020, Yang, *et al.* 2014).

Bacteriocins can be added to foods in three ways; i) as a pure bacteriocin preparation ii) as bacteriocin containing fermentates iii) as bacteriocin-producing cultures. As natural antimicrobial agents, bacteriocins are an attractive alternative to chemical preservatives when it comes to satisfying the increasing consumer demands for safe and ready to-eat foods (Gálvez, *et al.* 2007) with minimum processing (Abbasiliasi, *et al.* 2017). Since bacteriocins are odourless, colourless, and tasteless (Perez, *et al.* 2014), food products may be incorporated with bacteriocins without changing their organoleptic properties. Nisin A is a broad spectrum Class I lantibiotic, produced by *Lactococcus lactis*, characterised by five intermolecular lanthionine rings that deliberate inherent heat and protease constancy. It is the most studied bacteriocin and it is the only commercially produced bacteriocin approved as a food additive by regulatory agencies including the World Health Organisation (WHO)/Food Development Authority (FDA) in the USA and the European Food Safety Authority (ESFA) in Europe (Chikindas, *et al.* 2011). It is exploited in different commercial preparations, such as Nisaplin (Danisco), Chrisin (Chris Hansen) and DelvoNis (DSM). It is widely used in dairy industries to control *Clostridia* (Krivorotova, *et al.* 2016) and post-processing contamination from strains of *Listeria* (Thomas and Delves-Broughton 2001).

Recently discovered novel bacteriocins with food preservatives potential include plantaricyclin A, a circular bacteriocin produced by the olive isolate *Lactobacillus plantarum NI326*, with antibacterial activity against the beverage spoilage bacterium. *Alicyclobacillus acidoterrestris*, which causes significant economic losses to the industry every year (Borrero, *et al.* 2018). Bacteriocin-producing cultures used as adjunct cultures or starter cultures serve a dual purpose as they can contribute to both food safety and flavour, providing and preservation and fermentation simultaneously. This is more cost effective than using pure

peptide and is subject to less regulatory control (Johnson, *et al.* 2018). LAB producing Bacteriocin are antibiotic alternatives that have the potential to improve gut health through their ability to survive in the gut environment, inhibit competitors and pathogens, modulate the immune system and prevent inflammation and oxidative stress (Dahiya, *et al.* 2017, Westfall, *et al.* 2017, Bauerl, *et al.* 2017, Dobson, *et al.* 2012). Bacteriocins are very specific and can destruct pathogens without causing harmful imbalances to the host microbiota. Another great development in recent years is the use of antimicrobial-containing edible films and coatings, composed of biopolymers layers that protect the food from the environment to improve food safety by inhibiting food pathogens during handling, transportation and storage of food products (Silva, *et al.* 2018, Chandrakasan, *et al.* 2019).

Bacteriocin: Future Prospects

Bacteriocin has proved its effectiveness as biotechnological means secreted by bacteria. Promotes their contribution to various industrial and medical applications to further study to examine various applications of bacteriocin in different fields. The important need for new drugs is that currently they can withstand the spread of deadly diseases with limited efficiencies of already discovered drugs, requires serious steps in the discovery of powerful compounds, as bacteriocin. Developing advanced techniques that facilitate the purification and characterization of novel bacteriocin is also of great importance. On the other hand, events in vivo studies are necessary to assess biologically active bacteriocin, which showed promising in vitro results. Thereafter, the safety of those bacteria should be evaluated to authorize their use in medical and drug applications. Studies should be more intensive to develop planned strategies and increase the antibacterial spectrum to overcome challenges such as low bacteriocin production. Studies using nanotechnology techniques and increasing stability of bacteriocin are also encouraged to widen amino acid replacements, anti-microbial spectra. Investigations focused on increasing bacterial yield, such as co-culture, and statistical adaptation techniques are also needed. Improved bacterial distribution to targeted cells requires advanced evaluation and further study. In addition, understanding the interaction between bacteriocin and nanomaterials can upgrade the use of bacteriocin in the future. A significant number of new discoveries, bacteria producing broad spectrum bacteriocin have been identified, although not much improvement has been achieved to get agreement from government agencies for their industrial applications. Considering the discovery of new bacteriocin with novel properties, it is worth examining food conservation and their applications in other areas such as animal feed, organic fertilizers and environmental protection as well as personal care products. Finally, it is very important to create new open-access data base engines designed to get information about identified bacteriocin, their properties and applications.

2. Conclusion

With increasing antimicrobial resistance and the development of multi-drug resistant strains, other potential therapeutic methods are required and, bacteriocins are a potential alternative to antibiotics that can be used to treat deadly human pathogens. In addition, excessive use of antibiotics, and especially of broad spectrum antibiotics, has been acquired impermanence as a cause of microbiome disruption in medical and food production and select for accumulation and transfer of resistance genes within the microbial population of the human intestine. Current research is strengthening the approach of bacteriocin as being multipurpose antimicrobial with key potential for bio preservatives, antibiotic options, health promotion group modulator and animal development promoter. Commercial-scale bacteriocins production is still hindering due to high cost and low peptide yield, but cost efficiency is being improved to throw away the adaptation of bioengineering strength to fermentation processes and maximum bacteriocins production. Overall, food conservation, intestinal modulation, decrease in antimicrobial resistance and expanding the potential role of bacteriocins in animal fodder shows if the obstacles mentioned are removed, then in the food and diet industries there are important opportunities for extensive bacterial applications.

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