Bacteriocins from Lactic Acid Bacteria and their emerging applications

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In the last few decades, there has been a growing interest in natural preservatives owing to the consumers demand for healthy, safe, fresh-tasting, ready-to-eat, minimally processed foods and also novel food products. The use of bacteriocins is a promising alternative for chemical preservatives. Bacteriocins are ribosomally synthesised, extracellularly released, antibacterial peptides of bacterial origin. Large numbers of bacteriocins are produced by all genera of the lactic acid bacteria (LAB). The bacteriocins from LAB are commonly categorized into three groups: class I – the lantibiotics, class II – the heat stable unmodified bacteriocins, class III – the larger heat labile bacteriocins.

Bacteriocins find increasing interest in food processing technologies in that their use can reduce the addition of chemical preservatives and heat treatments so that the organoleptic and nutritional properties of food can be preserved naturally. Bacteriocins from lactic acid bacteria have been largely studied with the perspective of food protection against pathogenic and spoilage bacteria. Narrow spectrum bacteriocins have the advantage of selectively inhibiting the growth of food spoilage bacteria such as *Listeria monocytogenes* so that the beneficial microflora remains unaffected. There are bacteriocins with a broad spectrum of antibacterial activity which can find wider applications. Enterococcal bacteriocins active against food-borne pathogens such as *Listeria* spp. and *Clostridium* spp. are reported. The efficacy of bacteriocins is influenced by several environmental factors like pH, temperature, food composition and structure, as well as the food microbiota. Bacteriocins produced by strains such as *Enterococcus faecium* and *Enterococcus faecalis* reveal thermostable properties which can recruit them for interesting technological applications.

Bacteriocins can be added to foods in the form of purified or partially purified preparations as food preservatives, shelf-life extenders, additives or ingredients. They can also be produced *in situ* by bacteriocinogenic starters, adjunct or protective cultures. Immobilized bacteriocins can also find application for development of bioactive food packaging. In recent years, application of bacteriocins as part of hurdle technology has gained great attention. Several bacteriocins can either enhance the action of other antimicrobial agents or act synergistically when used in combination with other antimicrobial agents, including chemical preservatives, natural phenolic compounds, as well as other antimicrobial proteins. Different bacteriocins may also be used in blend which helps to evade the development of resistant strains. The combination of bacteriocins and other treatment methods provides an additional barrier to more resistant forms like bacterial endospores which offer a better method for more effective preservation of foods.

Recent research has witnessed extending the applications of bacteriocins from food to human health. The rapid developments in genetics and nanotechnology have demonstrated possibilities for upgrading bacteriocins into next generation antibiotics with novel applications as carrier molecules and also in the treatment of cancer.

Keywords: bacteriocin; lactic acid bacteria; food preservation; food spoilage; health

1. Introduction

Last few decades have witnessed a growing interest in natural preservatives owing to the consumers demand for healthy, safe, fresh-tasting, ready-to-eat, minimally processed foods and also novel food products. In this milieu, bacteriocins find a wide application in food industry with respect to food safety and preservation. Bacteriocins find increasing application in food preservation because they can render an extended shelf life for preserved foods and also provide extra protection in adverse temperature conditions which in turn reduce the economic loss due to food spoilage. Since bacteriocins prevent the growth of food borne pathogens, they reduce the risk of transmission of these pathogens. Bacteriocin application offers a natural mechanism for food preservation permitting chemical preservatives to be ruled out either completely or partially. Furthermore, bacteriocin application allows that food be processed at less severe temperatures at which the heat labile nutrients such as vitamins as well as the organoleptic properties of the food can be preserved without negotiating food safety [1, 2].

Like all other living organisms, bacteria also produce antimicrobial peptides. Generally bacteria produce two types of antimicrobial peptides – ribosomally synthesized antimicrobial peptides and non-ribosomally synthesized antimicrobial peptides. Of these, ribosomally synthesized antimicrobial peptides are called bacteriocins [3]. In general, bacteriocins are defined as ribosomally-synthesized multifunctional proteinaceous antibacterial substances, which have been examined for applications in microbial food safety. They differ from antibiotics which are secondary metabolites that are not ribosomally synthesized. They also differ from antibiotics in their mode of action, antimicrobial spectrum, toxicity and resistance mechanisms [4, 5]. The first characterized and most studied of the bacteriocins are the colicins of *E. coli*, a Gram negative bacteria [6]. Among the Gram-positive bacteria, the Lactic Acid Bacteria (LAB) has been demonstrated as a source of antimicrobial peptides with food safety applications.

2. Lactic acid bacteria as sources of bacteriocins

Lactic acid bacteria (LAB) are Gram-positive, non-sporulating microaerophilic bacteria whose main fermentation product from carbohydrates is lactate [7] and they form the natural microflora in raw milk [5, 8]. LAB-derived bacteriocins are heterogeneous since they vary greatly in their spectrum of activity, mode of action, molecular mass, genetic origin and biochemical properties [5, 9]. LAB produce bacteriocins as a first line of defense since these peptides can kill or inhibit bacterial counterparts which compete for the same nutrients [10]. Bacteriocin-producing strains also produce specific immunity proteins which protect them from the inimical action of their own bacteriocin [11].

Bacteriocins of LAB origin are ideal candidates for food industry to check undesirable bacteria because of their desirable properties which are as follows:

(i) Majority of the LAB sources of bacteriocins are natural food isolates and are of GRAS status (generally regarded as safe).
(ii) They are active only on bacterial cells and not toxic to eukaryotic cells.
(iii) They have little influence on intestinal microbiota since they are readily inactivated and digested by proteases of the alimentary canal.
(iv) Generally they have high pH and temperature tolerance
(v) Their action could be against a specific group or a broad spectrum of microbes which are food-borne pathogens or spoilage bacteria.
(vi) They do not show any cross resistance with antibiotics since they act usually on the bacterial cytoplasmic membrane.
(vii) They are suitable for genetic manipulation since the genes encoding bacteriocins are located in plasmids rather than in chromosome [2].

LAB species belonging to the genera *Lactobacillus, Lactococcus, Streptococcus, Pediococcus, Oenococcus, Enterococcus, Leuconostoc* and *Carnobacterium* produce a variety of bacteriocins [12]. These bacteriocin producing bacteria are probably amongst the most promising natural food biopreservatives.

3. Classification of bacteriocins

In general, bacteriocins are categorized into three groups: class I – the lantibiotics, class II – the heat stable unmodified bacteriocins, class III – the larger heat labile bacteriocins.

3.1 Class I Bacteriocins – Lantibiotics

Lantibiotics are small (<5 kDa) heat stable peptides characterized by their unusual polycyclic thioether amino acids, such as lanthionine (Lan) or methyl-lanthionine (MeLan), as well as the unsaturated amino acids dehydrobutyrine and 2-aminoisobutyric acid [10, 13]. Lantibiotics typically have from 19 to 50 amino acids. They are further subdivided into two types – Class Ia and Ib – based on structural similarities. Zacharof and Lovitt [13] have stated that class Ia lantibiotics with a molecular mass between 2 to 4 kDa comprises of relatively elongated, positively charged, amphipatic molecules. They have a flexible structure and consist of cationic and hydrophobic peptides that form pores in target membranes through depolarization of the cytoplasmic membrane of the sensitive target species. Class Ib lantibiotics are neutral or negatively charged peptides with a rigid globular structure and they interfere with cellular enzymatic reactions. Their molecular mass, lies between 2 to 3 kDa and either they have no net charge or a net negative charge. However, recently Chikindas et al. [3] pointed out that there is no need to define bacteriocins as having a net positive charge and amphipathic nature, since there are anionic bacteriocins such as subtilosin A reported in the literature [14]. The sactibiotics are a recently designated subclass of bacteriocins that contain characteristic cysteine sulphur to α -carbon linkages mediated through post-translational modifications [14]. Recently Coelho et al. [15] has reported another class of lantibiotics, class Ic, which comprises labionin-containing lantibiotics. Sactibiotics and labionin-containing lantibiotics are posttranslationally modified bacteriocins. Labionine-containing lantibiotics have carbacyclic triamino triacid labionin, a structural variant of lanthionine, and a methyl-substitute labionin derivative, which gives the molecule a labyrinthine structure. Sactibiotics are circular or linear peptides and are characterized by the presence of cross-linkages formed by the thiol group of cysteine residues and the α-carbon of acceptor amino acids [15].

3.2 Class II Bacteriocins – Non-lantibiotics

Class II contains small (<10 kDa) heat-stable, non-lanthionine containing membrane active peptides. They can be further subdivided into Class IIa and IIb [13]. According to conventional classification, Class IIa includes Pediocin-like *Listeria* active peptides with a conserved N-terminal sequence Tyr–Gly–Asn–Gly–Val and two cysteines forming a S–S bridge in the N-terminal half of the peptide. They show a high degree of homology (40%-60%) when the corresponding amino acid sequences are aligned and they are synthesized with a leader peptide which is removed by proteolytic processing, usually after a double glycine residue for example like pediocin PA-1, sakacin A [16]. Class IIb comprises bacteriocins composed of two different peptides which differ in their primary amino acid sequences. To facilitate an antimicrobial activity, it is

pertinent to have a synergistic action of the two peptides of these bacteriocins. Lactacin F and lactococcin G are members of this group [17].

3.3 Class III Bacteriocins – Heat labile bacteriocins

The Class III bacteriocins consists of heat labile proteins which are in general of large molecular weight (>30 kDa). Only less information is available regarding this class since it has been poorly investigated. Bacteriocins representing this group are helveticin I by *Lactobacillus helveticus and* enterolysin produced by *Enterococcus faecium* [13, 18, 19].

4. Common bacteriocins produced by LAB

Many different types of LAB bacteriocins have been studied and characterized, but the most widely known are: nisin, lacticin, enterocin, pediocin, and plantaricin [20]. The common LAB sources of bacteriocins are summarized in Table 1.

4.1 Nisin

Nisin, discovered in England by Rogers and Whittier in 1928, is a bacteriocin belonging to the family of lantibiotics with unusual amino acids, lanthionine and methyllanthionine, which bequeath it with functional properties such as acid tolerance, stability at high temperature and low pH and a specific bactericidal mode of action. It has cationic and hydrophobic properties. It is comprised of 34 amino acids and a molecular weight of 3500 Da. Nisin occurs as two variants, A and Z, which differ in a single amino acid at the 27th position. Nisin A has histidine amino acid at 27th position, where as in nisin Z, it is replaced by asparagine. Despite this variation in amino acid composition, the antimicrobial activity of both remains equal. On the other hand, in comparison to nisin A, the Z variant has a better solubility and diffusion characteristics which are desirable properties for food applications [5]. It is produced by certain species of *Lactococcus lactis* subsp. *lactis* [18] during the exponential growth phase and the biosynthesis is completely obliterated as the cells enter the stationary phase of their growth cycle [21].

Nisin is effective against Gram-positive bacteria such as *Lactococcus, Streptococcus, Staphylococcus, Micrococcus, Pediococcus, Lactobacillus, Listeria* and *Mycobacterium.* It is active against both bacterial spores as well as vegetative cells. The bactericidal action of nisin is through the formation of pores in the cytoplasmic membrane which causes the leakage of ions thereby disrupting the proton motive force and the pH equilibrium that ultimately results in the hydrolysis of ATP and cell death [10, 22]. The spores of bacterial strains such as *Clostridium anaerobe* PA3679, which have survived heat treatment, are more sensitive to nisin and this makes nisin attractive as a food preservative in heat processed foods [23].

4.2 Pediosin

Pediocins is an antilisterial bacteriocin belonging to the Class II of unmodified bacteriocins. The pediocin-like bacteriocins are produced by many LAB. They show nearly 40-60% similarity in the amino acid sequence and are characterized by a consensus sequence in the N terminus (Tyr-Gly-Asn-Gly-Val-Xaa-Cys), a small hydrophobic region, and disulfide bridges, all of which have been shown to be essential for bacteriocin activity [13, 24]. Generally they have a narrow spectrum of activity and are active against *Listeria* and hence categorized as antilisterial bacteriocins. The pediocins produced by strains of *Pediococcus acidilactici* and *Pediococcus pentosaceus* are active against phylogenetically related bacterial species [25, 26], whereas Pediocin PD-1 produced by *Pediococcus damnosus* is not active on other pediococci [27].

4.3 Enterocin

Enterocins are the bacteriocins produced by the LAB belonging to the genus *Enterococcus* which are found in many food products. According to the scheme of classification proposed by Franz et al [28], enterocins have been divided into four major classes: Class I consisting of post-translationally modified lantibiotic enterocins, Class II consisting of linear, unmodified peptides having molecular mass less than 10 kDa, Class III consisting of cyclic peptides and Class IV encompassing the large, heat labile proteins [29]. The enterocins of Class II and III (particularly enterocin AS-48) are active against not only closely related species but also Gram positive spoilage and pathogenic bacteria [30]. In particular, enterocins with high anti-listerial activity are promising candidates as useful antimicrobial agents in food preservation [29]. Enterocin CCM 4231, produced by *Enterococcus faecium* CCM 4231, finds applications in dairy products owing to their ability to inhibit *Staphylococcus aureus* in skim milk and yoghurt and also *Listeria monocytogenes* in yoghurt [31].

Table 1 Bacteriocins produced by different lactic acid bacteria and their target organisms

Bacteriocin	Lactobacillus strain	Target organism	Reference
Amylovorin L	*Lactobacillus amylovorus* DCE 471	Other *Lactobacillus* spp.	[32]
Fermenticin HV6b	*Lactobacillus fermentum* HV6b MTCC10770	*Gardnerella vaginalis*	[33]
Lactocin 160	*Lactobacillus rhamnosus*	*Gardnerella vaginalis* *Prevotella bivia* *Bacteroides* *Peptostreptococcus* *Mobiluncus* spp.	[34]
Plantaricin	*Lactobacillus plantarum* MBSa4	*Listeria monocytogenes*	[35]
Sakacin	*Lactobacillus sakei*	*Enterococcus* spp. *Listeria* spp. *Escherichia coli* *Klebsiella* spp. *Pseudomonas* spp. *Staphylococcus* spp. *Streptococcus* spp	[36]
Curvacin A	*Lactobacillus curvatus*	*Listeria monocytogenes* *Enterococcus faecalis*	[37]
Lactobin A	*Lactobacillus amylovorus*	*Lactobacillus acidophilus* *Lactobacillus delbrueckii*	[37]
Lactocin 705	*Lactobacillus casei*	*Listeria monocytogenes* *Lactobacillus plantarum*	[37]
Enterocin A	*Lactococcus lactis* MG1614	*Listeria monocytogenes*	[38]
Enterocins L50A and B	*Enterococcus faecium* F58	*Listeria monocytogenes*	[39]
Enterocin CCM 4231 Enterocin 13	*Enterococcus faecium* CCM 4231 *Enterococcus faecium* RZS C13	*Listeria* spp.	[40]
sakacin K	*Lactobacillus sakei* CTC494	*Listeria* spp.	[40]
Nisin	*Lactococcus lactis* subsp. *lactis*	*Lactococcus Streptococcus* *Staphylococcus Micrococcus Pediococcus* *Lactobacillus* *Listeria Mycobacterium*	[18]
Pediocin	*Pediococcus acidilactici* *Pediococcus pentosaceus*	*Listeria*	[26]
Divergicin	*Carnobacterium divergens*	*Listeria*	[41]
Macedocin	*Streptococcus macedonicus* ACA-DC 198	*Clostridium tyrobutyricum*	[42]
Gassericin	*Lactobacillus gasseri* LA158	*Bacillus cereus Listeria monocytogenes* *Staphylococcus aureus*	[43]

4.4 Plantaricin

Plantaricin is a two-peptide lantibiotic produced by *Lactobacillus plantarum* with remarkable anti-listerial activity. It is heat-stable with activity after treatment at even 121°C for 15 min, unaffected by pH 2.0 to 6.0 and active against all *Listeria monocytogenes* strains and several fungal strains which include *Penicillium roqueforti, Penicillium expansum, Fusarium sp., Mucor plumbeus, Cladosporium sp.* and *Debaromyces hansenii* that can produce health-damaging mycotoxins [35]. *Lactobacillus plantarum* is considered to produce six different plantaricins- plantaricin A, plantaricin JK, plantaricin EF, plantaricin S, plantaricin W and plantaricin T- all of which are primarily produced as precursors containing a double glycine moiety and post-translationally modified to form distinct forms of bacteriocins. Plantaricins exhibit inhibitory action against a broad range of LAB which includes *Pediococcus, Carnobacteria, Clostiridia* and *Propionibacteria* [10].

4.5 Lacticin

Lacticin 3147 is a bacteriocin produced by *Lactococcus lactis* subsp. *lactis* DPC3147 isolated from an Irish kefir grain used for making buttermilk. It has gained interest owing to its activity against a broad range of organisms of importance in foods. Lacticin 481, another bacteriocin produced by *Lactococcus lactis* subsp. *lactis* strain DPC5552, was shown to cause membrane permeabilization of starter cultures in Cheddar cheese thus facilitating cheese ripening [44].

4.6 Divergicin

Divergicin is a class IIa bacteriocin, with potent anti-listerial activity and produced by *Carnobacterium divergens* strain isolated from frozen smoked mussels. Tahiri et al [41] studied the factors influencing the growth of *Carnobacterium divergens* strain M35 and its ability to produce divergicin M35 in various synthetic media and in medium supplemented with snow crab hepatopancreas, a natural-grade by-product of crustacean processing.

4.7 Macedocin

Streptococcus macedonicus ACA-DC 198, a strain isolated from Greek Kasseri cheese, produces the food-grade lantibiotic, macedocin, when grown in skim milk supplemented with nitrogen sources [42, 45]. Macedocin shows inhibitory activity towards several lactic acid bacteria and against *Clostridium tyrobutyricum*. It is active at pH values between 4.0 and 9.0 and withstands sterilization [45].

4.8 Gassericin

Takeda et al. [43] reported the production of a two-component bacteriocin, gassericin T, from *Lactobacillus gasseri* LA158 from human infant faeces. This gassericin T bacteriocin is homologous to lacatcin F from *Lactobacillus johnsonii* VPI11088 [46] and acidocin LF221B from *Lactobacillus gasseri* LF221 [47]. It is two-component bacteriocin and consists of hydrophobic Gat A and Gat X molecules that are encoded on the chromosomal *gat* operon [48]. Gassericin T exerts its antibacterial effect by the formation of pores on the cytoplasmic membranes of target cells. It is active against food spoilage and pathogenic bacteria such as *Bacillus cereus, Listeria monocytogenes* and *Staphylococcus aureus* [49]. Arakawa et al., [49] proposes gassericin T as a potential candidate for use in biopreservation of food and animal health maintenance.

5. Applications of LAB bacteriocins

5.1 Food industrial applications

The applications of bacteriocins in food industry include food preservation, enhancing food quality and safety, food packaging and storage. Figure 1 depicts the important applications of LAB bacteriocins.

5.1.1 Food preservation

Bacterial fermentation of raw food materials has been in use for centuries to extend their shelf life without compromising the nutritive value. Moreover, the consumers also demand for minimally processed food without any chemical preservatives, which entails that the food be preserved naturally. The bacteriocins of LAB origin are of particular interest in natural food preservation owing to their GRAS status. The bacteriocinogenic strains of LAB may be used in food as starter or protective cultures thereby improving food quality and safety [50]. These LAB starter cultures are able to produce their bacteriocins in food matrices consequently inhibiting the growth of undesirable spoilage or pathogenic bacteria. Only fermented foods such as fermented sausage and dairy products such as Cheddar cheese can resort to *in situ* application of bacteriocinogenic starter culture [51]. *In situ* production of nisin for the microbial control of a number of dairy products, especially cheese manufacturing has been demonstrated [52]. In non-fermented and minimally processed food to be kept under refrigeration, bacteriocins need to be added directly to the food as preservative, shelf-life extender or as an ingredient. In this case only those bacteriocin producer strains can be employed which can produce sufficiently high titres of bacteriocins with no other metabolic products at detrimental levels, as the food quality may be affected otherwise [20].

The bacteriocin most widely used in food industry is nisin. Thus far nisin is the only commercially produced food-grade bacteriocin utilized as a preservative in a variety of food products, having FDA approved GRAS status. However, there are studies reporting the control of food-borne pathogens through the use of multi-bacteriocin producing strains, wherein nisin is used in combination with other bacteriocins [3]. Mills et al., [53] has reported the use of a multi-bacteriocin cheese starter system comprising nisin and lacticin 3147 in *Lactococcus lactis*, in combination with plantaricin from *Lactobacillus plantarum*. Nisin is suitable for use in a wide range of foods which may be liquid or solid, canned or packaged, chilled or of warm ambient storage. Nisin can be used to prevent spoilage by Gram-positive endospore forming bacteria especially in heat processed food. It can be used for preventing spoilage by certain lactic acid bacteria and similar spoilage bacteria like *Brocothrix thermosphacta*. It can also be used to kill or inhibit Gram-positive pathogenic bacteria such as *Listeria monocytogenes* and *Clostridium botulinum*. Ariyapitipun et al [54] has reported the application of nisin for the control of *Listeria monocytogenes* in ready-to-eat meats. Nisin can be added either as an aqueous solution or as a powder, in either case uniform dispersal throughout the food is important in checking the growth of spoilage bacteria. In addition to this, nisin can also be used for surface decontamination wherein a high concentration of nisin is sprayed on to the surface of the food. Nisin is used in a variety of products including pasteurized, flavoured and long-life milks, aged

and processed cheeses, and canned vegetables and soups. It is also used to inhibit the growth of undesirable LAB in beer and wine [20].

Encapsulation may provide increased stability and antimicrobial efficiency to bacteriocins. In a recent work, de Mello et al [55] encapsulated the antilisterial peptide pediocin in nanovesicles prepared from partially purified soybean phosphatidylcholine. In comparison to the free pediocin, the encapsulated pediocin could maintain 50% of is initial antimicrobial activity against *Listeria monocytogenes, Listeria innocua* and *Listeria ivanovii*. Nanotechnology has also found application in bacteriocin-based food preservation methods. Zhang et al. [56] reported the use of nisin on antimicrobial activity of d-limonene and its nanoemulsion. A cocktail of several bacteriocins also is effective against spoilage bacteria.

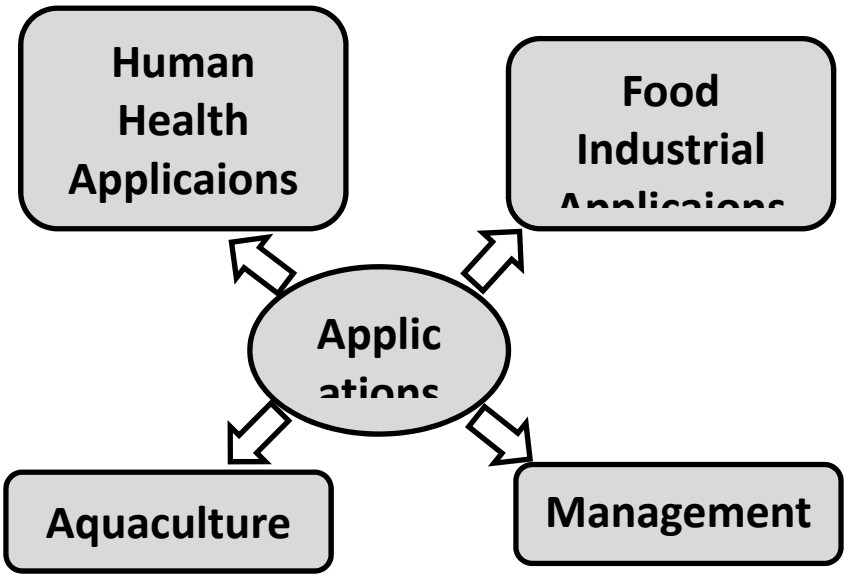

Fig. 1 Applications of LAB bacteriocins.

5.1.2 Bacteriocins in hurdle technology

When a single antimicrobial factor is used for food preservation, sometimes only a fraction of the bacterial population may receive a lethal dose, whereas the remaining fraction may survive and may develop mechanisms of resistance or adaptation that would render them immune to further treatment with that particular antimicrobial agent. As hurdle technology combines an array of antimicrobial factors, challenges posed to the spoilage and pathogenic bacteria are several times greater which make them energy exhausted in the effort to repair cell damages caused by antimicrobial agents and ultimately lead to cell death. Therefore there is only least probability for the survival and proliferation of spoilage and pathogenic bacteria after being exposed to multiple hurdles. Moreover, the several antimicrobial factors can act together in synergism, thus requiring only lower doses than that is required for individual application. The use of bacteriocins as part of hurdle technology has received wide acceptance since they can also act synergistically with other antimicrobial agents or enhance the action of other antimicrobial agents. Aznar et al [57] reported the use of bacteriocins in combination with curcumin, carvacrol and cymene against *Listeria monocytogenes, Salmonella typhimurium, Candida lusitaniae* and *Escherichia coli*. Similarly Nembe et al [58] tested the effect of a combination of essential oils and bacteriocins on the efficacy of gamma radiation against *Salmonella typhimurium* and *Listeria monocytogenes*. O'Sullivan et al [59] has reported the use of mixtures of LAB bacteriocins in combination with traditional methods of treatment for the enhancement of antibacterial effect. Other researchers has also reported an increase in microbial inactivation has been also reported by adding bacteriocins prior to a mild thermal or non-thermal treatment [52].

Hurdle technology is an alternative strategy for controlling spoilage and pathogenic microorganisms, whereby different preservation barriers or hurdles are combined to inhibit microbial growth and improve food safety. This method also ensures that the harmful microorganisms in the food are eliminated or controlled. Hurdle technology has been defined by Leistner [60] as an intelligent combination of hurdles which secures microbial safety and stability as well as organoleptic, nutritional quality and economic viability of food products. The preservation factors used in this technology are known as hurdles and the interaction between these hurdles is known as hurdle effect. The hurdles used in preservation can be modified in different ways and proportions to get better results. This approach was called intelligent hurdle technology. An intelligent approach of hurdle technology allows gentle and efficient preservation of food [60]. The hurdles can be preservation processes or food additives. The common hurdles used include temperature (high or low), water activity, acidity, redox potential, chemical preservatives such as sulphites, nitrites, sorbate, as well as competitive microbes that produce bacteriocins.

5.1.3 Food quality and flavour

In addition to preservation of food, bacteriocins can also improve the quality and flavour of certain foods. In the ripening of cheese, the non-starter LAB causes problems such as formation of calcium lactate crystals, slit formation and off-flavour development. Bacteriocinogenic LAB can be used to control non-starter LAB by inducing cell lysis thereby increasing the rate of proteolysis in cheese. Lacticin used in the production of low-fat cheddar cheese, proved to be effective in controlling non-starter LAB during cheese ripening [61].

5.1.4 Food packaging and storage

The need to extend shelf life of food products, together with the environmental concern to reduce solid wastes, necessitates the use of edible coatings for food packaging with integrated antimicrobial activities. The use of bacteriocin-films made by incorporating bacteriocins with biopolymers, such as nisin/chitosan combinations, for packaging of food prevents the growth of spoilage bacteria, *Listeria monocytogenes* during storage and distribution [62]. Immobilized bacteriocins can also find application for development of bioactive food packaging [34].

5.2 Management of livestock health

Bacteriocins find application in improving the productivity of cattle and poultry. There are several reports documenting the use of probiotic strains capable of producing bacteriocins to increase the growth rate of swine [20]. The bacteriocinogenic strains can be administered to livestock either sporadically or continuously, by mixing dried or wet cultures with feed or drinking water, for the control of *Salmonella* and other pathogenic bacteria [63]. These probiotic strains colonize the gastrointestinal tract where they produce bacteriocins and clear out all the pathogenic bacteria. The bacteriocinogenic LAB strains can be fed to the livestock as a preharvest food safety scheme [20]. De Kwaadsteniet et al [64] have reported the use of nisin in animal model for the control of respiratory tract infection by *Staphylococcus aureus*. *S. aureus* is also the causative organism for bovine mastitis in dairy cattle [20], and studies were conducted reporting the successful *in vivo* application of germicidal formulations containing nisin for combating mastitis [65].

5.3 Aquaculture

The disease prevention in aquaculture through vaccination or use of antibiotics is a tedious task since it is laborious, costly, and highly stressful to the animals. Moreover, the pathogenic bacteria may develop antibiotic resistance and also the residues of these drugs may continue to remain in the system long after use [20]. Bacteriocin-producing bacteria offer an alternative approach to disease prevention in aquaculture. Studies have been conducted to investigate the effect of probiotics and on growth performance and digestive enzyme activity of the shrimp, *Penaeus vannamei* and probiotic supplementation was recommended to improve productive performance [66]. Alchem Poseidon^{TM}, a commercial microbial formulation of *Bacillus subtilis*, *Lactobacillus acidophilus*, *Clostridium butyricum*, and *Saccharomyces cerevisiae*, is reported to significantly improve lysozyme activity and lower mucosal protein levels and also improve survival of Japanese flounder *Paralichthys olivaceusto* after infection with *Vibrio anguillarum* [67]. The probiotic bacteria can become established in the body of the host or in the aquatic system and this can be long term solution for the health issues of aquatic species.

5.4 Human health applications

The emergence of human pathogens exhibiting multidrug resistance is one of the serious challenges faced by clinicians. Microbial pathogens, in particular Gram negative bacteria such as *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae* and *Acinetobacter baumannii* are resistance to multiple classes of antibiotics since they have an outer membrane that is highly impermeable to these antibiotics [68]. Most of them produce a spectrum of β-lactamases and carbapenemases which make them resistant to β-lactam antibiotics such as cephalosporins and carbapenems. The bacteria which cause infections by forming biofilms in the respiratory tract and urinary tract also show resistance to the conventional antibiotics [69, 70]. Another major issue with conventional antibiotics is that they cause dysbiosis which is induced by indiscriminate killing of bacteria [71]. Bacteriocins gain increasing interest in this scenario by offering an alternative therapeutic strategy for the treatment of both multi-drug resistant and chronic bacterial infections [72]. Moreover bacteriocinogenic strains produce highly specific bacteriocins to competitively exclude other closely related species of bacteria. This specificity offers a more targeted approach. Bacteriocins like labionin-containing peptides and sactibiotics exhibit potential biotechnological applications because of their remarkable antibacterial or antiviral activities, as well as their analgesic activity [15]. Recently there is a surge in the research on novel drug formulations combining conventional antimicrobials and novel naturally derived antimicrobials such as bacteriocins whereby the activity of the former can be enhanced by the latter [73]. Different bacteriocins can also act in synergism against different target microorganisms [3].

Bacteriocin-incorporated nanoparticles can also find applications in medicine. Recently in a review of research in bacteriocins, López-Cuellar et al [34] has documented that nanofibres with ethylene oxide and poly(D,L-lactic acid) including nisin or plantaricin could be used in deep wounds infected with *Staphylococcus aureus* although this technology has to be optimized. The health applications of LAB bacteriocins include oral and skin care, infectious diseases of the

respiratory tract, gastrointestinal tract, urogenital tract etc. [34]. In addition to anti-viral activity, bacteriocins could potentially be used in the post-surgical control of infectious bacteria [74].

Bacteriocins such as pediocin [75], lacticin, subtilosin and fermenticin HV6b [33], have the ability to affect sperm motility and hence find contraceptive applications for the preparation of spermicidal agents [34]. Kaur et al [33] has reported that high concentrations of fermenticin HV6b isolated from *Lactobacillus fermentum* HV6b MTCC10770 caused a significant reduction in the motility of human spermatozoa, not by simply restricting the movement, but by causing the sperm tails to become curved or coiled thereby damaging them. Fermenticin HV6b also has potential in feminine health care applications because of its ability to inhibit pathogenic vaginal bacteria such as *Gardnerella vaginalis* [33, 76].

Bacteriocins from LAB are also suitable for skin care applications such as to combat acne, bacterial and yeast infections, psoriasis and dermatitis [77] and also in the treatment of hospital infections of skin and mucosal wounds [78, 79]. Anti-cancer therapy also employs bacteriocins since they induce apoptosis or cytotoxicity in tumour cells [80]. Sand et al. [81] has reported that Plantaricin A, produced by *Lactobacillus plantarum*, permeabilizes the cell membrane of both normal and cancerous lymphocytes and neuronal cells. There are also studies reporting the potential of bacteriocins in the treatment of head and neck squamous cell carcinoma, oral cancer, breast cancer, lung cancer and colon cancer [82, 83].

6. Conclusion

The bacteriocin research in recent years shows a surge due to the potential applications of these antimicrobial peptides in poultry industry, aquaculture industry, food industry and human health care. LAB have been characterized as potential sources of bacteriocins for application in food and medicine. However, the concerns about the safety of certain LAB strains to be used as live cultures need to be further investigated.

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