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Review

Bacteriocins and lactic acid bacteria - a minireview

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Fermentation of various foods by lactic acid bacteria (LAB) is one of the oldest forms of biopreservation practised by mankind. Bacterial antagonism has been recognized for over a century but in recent years this phenomenon has received more scientific attention, particulary in the use of various strains of lactic acid bacteria. One important attribute of LAB is their ability to produce antimicrobicrobial compounds called bacteriocin. In recent years, interest in the compounds has grown substantially due to their potential usefulness as natural substitute for chemical food preservatives in the production of foods with enhanced shelf life and/or safety. This balance is achived by its inhibitory effect upon the harmful pathogenic microorganisms. This paper presents some background on the scientific research about lactic acid bacteria as probiotics and their bacteriocins for healthy nutrition of fermented food. Probiotics had been of interest in the promotion of good health in animals and man. Some of the positive effects of probiotics are: growth promotion of farm animals, protection of host from intestinal infections, alleviation of lactose intolerance, relief of constipation, anticarcinogenic effect, anticholesterolaemic effects, nutrient synthesis and bioavailability, prevention of genital and urinary tract infections and imunostimulatory effects.

Key words: Bacteriocins, lactic acid bacteria, fermented food, probiotics

INTRODUCTION

Lactic acid bacteria (LAB) occur naturally in several raw materials like milk, meat and flour used to produce foods (Rodriguez et al., 2000). LAB are used as natural or selected starters in food fermentations in which they perform acidification due to production of lactic and acetic acids flavour. Protection of food from spoilage and pathogenic microorganisms by LAB is through producing organic acids, hydrogen peroxide, diacethyl (Messens and De Vugst, 2002), antifungial compounds such as fatty acids (Corsetti et al., 1998) or phenullactic acid (Lavermicocca et al., 2000) and/or bacteriocins (De Vugst and Vandamme, 1994). LAB play an important role in food fermentation as the products obtains with their aid are characterized by hygienic safety, storage stability and attractive sensory properties.

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Many bacteria of different taxonomic branches and residing in various habitats produce antimicrobial substances that are active against other bacteria. Both Gram negative and Gram positive bacteria produce bacteriocins. Bacteriocins are proteinaceous antibacterial compounds, which constitute a heterologous subgroup of ribosomally synthesized antimicrobial peptides (De Vugst and Vandamme, 1994). In general these substances are cationic peptides that display hydrophobic or amphiphilic properties and the bacterial membrane is in most cases the target for their activity. Depending on the producer organism and classification criteria, bacteriocins can be classified into several groups (Ennahar et al., 2000; Jack and Jung, 2000; Cleveland et al., 2001; McAuliffe et al., 2001) in which classes I and II are the most thoroughtly studied. Class I, termed lantibiotics, constitue a group of small peptides that are characterized by their content of several unusual amino acids (Gruder et al., 2000). The class II bacteriocins are

Table 1. Orla-Jensen (1919) key to differentiation of the lactic acid bacteria and current taxonomic classification.

Genus[a]	Shape	Catalase	Nitrite reduction	Fermentation	Current genera
Betabacterium	Rod	-	-	Hetero	*Lactobacillus Weissella*
Thermobacterium	Rod	-	-	Homo	*Lactobacillus*
Streptobacterium	Rod	-	-	Homo	*Lactobacillus Carnobacterim*
Streptococcus	Coccus	-	-	Homo	*Streptococcus Enterococcus* *Lactococcus Vagococcus*
Betacoccus	Coccus	-	-	Hetero	*Leuconostoc Oenococcus Weissella*
Microbacterium	Rod	+	+	Homo	*Brochothrix*
Tetracoccus	Coccus	+ [b]	+	Homo	*Pediococcus Tetragenococus*

[a]Accoring to Orla Jensen (1919).
[b]In genera Pediococci are catalase negative but some strains produce a pseudocatalase that results in false positive reactions.

small, nonmodified, heat stable peptides (Nes and Holo, 2000). Many bacteriocins are active against food borne pathogens (Vignolo et al., 1996; De Martins and Franco, 1998; Bredhott et al., 1999).

A large number of bacteriocins have been isolated and characterized from lactic acid bacteria and some have acquired a status as potential antimicrobial agents because of their potential as food preservatives and antagonistic affect against important pathogens. The important ones are nisin, diplococcin, acidophilin, bulgarican, helveticins, lactacins and plantaricins (Nettles and Barefoot, 1993). The lantibiotic nisin which is produced by different *Lactococcus lactis* spp. is the most thoroughtly studied bacteriocin to date and the only bacteriocin that is applied as an additive in food worldwide (Delves Broughton et al., 1996). One of the reason for increased consumption of fermented milk products is that fermented dairy products containing probiotics which have many proposed health benefits are available on the market. In this paper the diversity of bacteriocins their appliction and lactic acid bacteria used are probiotics are reviewed.

Taxonomy of lactic acid bacteria

The classification of LAB was initiated in 1919 by Orla-Jensen (Table 1) and was until recently primary based on morphological, metabolic and physiological criteria. Lactic acid bacteria comprise a diverse group of Gram-positive, non spore forming, non motile rod and coccus shaped, catalase-lacking organisms. They are chemo-organotrophic and only grow in complex media. Fermentable carbohydrates and higher alcohols are used as the energy source to form chiefly lactic acid. LAB degrades hexoses to lactate (homofermentatives) or lactate and additionnal products such as acetate, ethanol, CO_2, formate or succinate (heterofermentatives). They are widely distributed in different ecosytems and are commonly found in foods (dairy products, fermented meats and vegetables, sourdough, silage, beverages), sewage, on plants but also in the genital, intestinal and respiratory tracts of man and animals.

Current methodolgies used for classification of LAB mainly rely on 16S ribosomal ribonucleic acid (rRNA) analysis and sequencing (Olsen et al., 1994). Based on these techniques, Gram-positive bacteria are divided into two groups depending on their G + C content. The Actinomycetes have a G + C content above 50 mol% and contain genera such as *Atopobium*, *Bifidobacterium*, *Corynobacterium* and *Propionibac-terium*. In contrast, the Clostridium branch has a G + C content below 50 mol% and include the typical LAB genera *Carnobacterium, Lactobacillus, Lactococcus, Leuconostoc, Pediococcus* and *Streptococcus.*

Lactic acid bacteria as probiotics

Lactic acid bacteria were referred to as probiotics in scientific literature by Lilley and Stillwell (1965). However probiotic took on a different terminology when Sperti (1971) used the term « probiotic » to describe tissue extracts that stimulated microbial growth. Parker (1974) redefined it as organisms and substances that contribute to the intestinal microbial balance. The most recent and accurate description of probiotics was undertaken by Fuller (1989) who redefined it as « a live microbial feed supplement beneficial to the host (man or animal) by improving the microbial balance within its body ». Another recent definition was by Schrezenmeir and De Vrese (2001) who defined probiotics as viable microbial food supplements which beneficially influence the health of the host.

The gastrointestinal tract contains food in different stages of digestion, digestive ferments, liquids and solid waste. Within the gut are also wide ranges of microbes that may be either harmful or beneficial. The beneficial ones assist in the breakdown of food while they also manufacters vitamins essential to the body, breaking down and destroying some toxic chemicals that may

have been ingested with the food. Under both healthy and sick conditions, several differnt types of bacteria compete or fight with each other to establish dominance in the warm and moist environment of the alimentary canal that serves as an ecosystem for their survival and propagation. The average human large intestine harbors over 400 different special of bacteria with a total population far outnumbering even the number of human cells in the body. Under ideal conditions of health and diet, the different strains of bacteria on microflora compete and check the excessive number of any one strain. Healthy condition can be achieved if a balance is maintened between the « good » and « bad » bacteria in the ratio of 85 percent to 15 percent. Oral supplement of diet with viable *Lactbacillus acidophilus* of human origin, which is bile resistant, led to a significant decline of three different fecal bacterial enzymes (Goldin and Gorbach, 1977). This decrease in the fecal bacterial enzyme activity observed in both humans and rats included beta glucuronidase, azoreductase and nitroreductase. All these enzymescatalyse the conversion of procarcinogens to proximal carcinogens in the large bowel leading to colon cancer.

Lactic acid bacteria including *Lactobacillus, leuconostoc, lactococcus, pediococcus* and *Bifidobacterium* are found throughout the gastrointestinal tract. The predominant population of lactic acid bacteria in the upper gastrointestinal tract is the *Lactobacillus* species which may colonize the mucosal surface of the duodenum as well as the stomach. *Lactobacillus* and *Bifidobacterium spp.* are prominent members of the commensal intestinal flora and are the commoly studied probiotics bacteria. They cause reduced lactose intolerance alleviation of some diarrhoeas, lowered blood cholesterol, increased immune response and prevention of cancer (Marteau and Ramband, 1993, 1996; Gilliland, 1996; Salminen et al., 1998a). The selection criteria for probiotic LAB include: human origin, safety, viability/activity in delivery vehicles, resistance to acid and bile, adherence to gut epithelial tissue ability to colonise the gastro intestinal tract, production of antimicrobial substances, ability to stimulate a host immune response and the ability to influence metabolic activities such as vitamin production, cholesterol assimulation and lactose activity (Salminen et al., 1996).

Fuller (1989) and Conway (1996) listed the following organisms as species used in probiotic preparation: *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus casei* subsp. *rhamnosus, Lactobacillus fermentum, Lactobacillus reuteri Lactococcus lactis* subsp. *lactis, Lactococcus lactis* subsp. *cremoris, Lactobacillus bulgaricus, Lactobacillus plantarum*, *Streptococcus thermophilus, Enterococcus faecium, Enterococcus faecalis, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium adolescentis, Bifidobacterium longum, Bifidobacterium breve.*

Probiotics benefit in the gastro intestinal tract and immune system

Certain LAB species are found not only as components of the human intestinal microflora but also of the man made ecosytem present in fermented food. That is why fermented milks containing viable LAB are known to be beneficial to healh acting as prophylaxis against intestinal infections. Thus many investigators have evaluated the effect of yoghurt on the immuno response of animals and humans.

Many studies have been conducted on their effect on the incidence and duration of various types of diarrhoea (Isolauri, 2001; Bhatnagar et al., 1998). LAB can be effective in preventing gastrointestinal disorders and in the recovery from diarrhoea of miscellaneous causes (Marteau et al., 2001). A decrease in the severty and duration of persistent diarrhoea has been reported with LAB (Bhatnagar et al., 1998). Guandalini et al. (2000) also reported that the administration of *Lactobacillus rhamnosus GG* to 287 children aged 1- 36 months with acute diarrhoea significantly reduced the duration in infected children by rotavirus compared with those receiving placebo. Administration of *Lb rhamnosus* GG also shortened the duration of the hospital stay.

CLASSIFICATION OF BACTERIOCINS

The bacteriocins produced by Gram-positive bacteria like LAB are small peptides, 3-6 kDa, in size (Nes et al., 1996), although there are exceptions (Jorger and Klaenhammer, 1990). On a sound scientific basis three defined classes of bacteriocins have been established: Class I, the lantibiotics; class II, the small heat stable non lantibiotics; and class III, large heat labile bacteriocins (Table 2). A fourth class of bacteriocins is composed of an undefined mixture proteins, lipids and carbohydrates. The existence of the fourth class was supported mainly by the observation that some bacteriocin activities obtained in cell free supernatant, exemplified by the activity of *Lb plantarum* LPCO 10 were abolished not only by protease treatements, but also by glycolytic and lipolytic enzymes (Jimenez-Diaz et al., 1993).

Most of the Gram positive bacteriocins are membrane active compounds that increase the permeability of the cytoplasmic membrane (Jack et al., 1995). They often show a much broader spectrum of bactericidal activity than the colicins (Gram negative bacteriocins which are produced by *Escherichia coli*). They fall with in two broad classes, viz the lantibiotics (Jack et al., 1995) and the non lantibiotic bacteriocins (Nes et al., 1996). Nisin (Table 3) prevents clostridal spoilage spoilage of processed and natural cheeses, inhibits the growth of some psychrotropic bacteria in cottage cheese, entends the shelf life of milk in warm countries, prevents the growth of spoilage *lactobacilli* in beer and wine fermentations and provides additional protection

Table 2. Antimicrobial peptides (peptide-bacteriocins) produced by lactic acid bacteria (Nissen-Meyer et al., 1997).

Group I: Modified bacteriocins (the lantibiotics)		Group II: Unmodified bacteriocins	
Type A	**Type B**	**One peptide bacteriocins**	**Two peptide bacteriocins**
Nisin	NK [a]	Pediocin-like bacteriocins [b]:	Lactococcin G
Lactocin S		Pediocin PA1, Leucocin A,	Lactacin F
Lacticin 481		Sakacin P, Curvacin A,	Plantaricin E/F
Carnocin UI 49		Mesentericin Y105,	Plantaricin J/K
Cytolysin		Carnobacteriocin BM1, Carnobacteriocin B2, Enterocin A, Piscicolin 126, Bavaricin MN, Piscicocin V1a	Lactobin A Plantaricin S[c] Pediocin L50[d] Thermophilin 13
		Nonpediocin- like bacteriocins: Lactococcin A and B, Crispacin A, Divergicin 750, Lactococcin 972, AS-48[e], Enterocin B, Carnobacteriocin A	

[a] Not known: lantibiotics of type B produced by lactic acid bacteria are presently not known
[b] References for the pediocin like bacteriocins are: Pediocin PA1 (Henderson et al.,1992 ; Marug et al., 1992), leucocin A (Hastings et al., 1991), sakacin P (Tichaczek et al., 1992), curvacin A (Tichaczek et al., 1992 ; Holck et al., 1992), mesentericin Y105 (Hechard et al., 1992), carnobacterioin BM1 and B2 (Quadri et al., 1994), enterocin A (Aymerich et al., 1996), piscicolin 126 (Jack et al. , 1996), bavaricin MN (Kaiser , Montville ,1996), piscicocin V1a (20).
[c] Reference for plantaricin S: (Tichaczek et al., 1993).
[d] originally published as a modified ine peptide bacteriocin (Cintas et al. , 1995), but recent results indicate that is an unmodified two-peptide bacteriocin (Cintas et al.unpublished results)
[e] As-48 is a cvclic antimicrobial peptide produced by *Enterococcus faecalis* (Martinez-Bueno et al. , 1994).

Table 3. Properties of some well characterized bacteriocins (Soomro et al., 2002).

Bacteriocin	Producer organism	Properties
Nisin	*Lactococcus lactis subsp.lactis ATCC 11454*	Lantibiotic, broad spectrum, chromosome / plasmid mediated, bactericidal, produced late in the growth cycle Broad spectrum, plasmid mediated
Pediocin A	*Pediococcus Pentosaceus FBB61 and L-7230*	
Pediocin AcH	*Pediococus Acidilactici H*	Broad spectrum, plasmid mediated
Leucocin	*Leuconostoc gelidum UAL 187*	Broad spectrum, plasmid Mediated, bacteriostatic, produced early in the growth cycle
Helveticin J Carnobacteriocn	*L.helveticus 481 Carnobacterium piscicola LV17*	Narrow spectrum, chromosomally mediated, bactericidal Narrow spectrum, plasmid mediated, produced early in the growth cycle.

against *Bacillus* and clostridial spores in canned foods. Nisin is a permitted food additive in more than 50 countries including the US and Europe under the trade name Nisaplin (Vandenberg, 1993; Delves-broughton et al., 1996). Nisin is active against many gram positive bacteria icluding *Listeria spp*.

BACTERIOCIN BIOSYNTHESIS

Bacteriocins are synthesized as pre-propeptide which are processed and externalised by dedicated transport machinery (Nes et al., 1996). Bacteriocin production in LAB is growth associated: it usually occurs throughout the growth phase and ceases at the end of the exponential phase (or sometimes before the end of growth (Parente et al., 1997; Lejeune et al., 1998). Bacteriocin production is affected by type and level of the carbon, nitrogen and phosphate sources, cations surfactants and inhibitors. Bacteriocins can be produced from media containing different carbohydrate sources. Nisin Z can be produced from glucose, sucrose and xylose by Lactococcus lactis IO-1 (Matsuaki et al., 1996; Chinachoti et al., 1997a,b) but better results were obtained with glucose compared to xylose. Glucose followed by sucrose, xylose and galactose were the best carbon sources for the production of Pediocin AcH in an unbuffered medium

(Biswas et al., 1991).

All bacteriocins are synthesized with an N terminal leader sequence and until recently only the double glycine type of leader was found in class II bacteriocins (Holo et al., 1991; Muriana and Klaenhammer, 1991; Klaenhammer, 1993; Havarstein et al., 1994). However, it has now been disclosed that some small, heat stable and non modified bacteriocins are translated with sec dependent leaders (Leer et al., 1995; Worobo et al., 1995). The structural bacteriocin gene encodes a preform of the bacteriocin containing an N-terminal leader sequence (termed double glycine leader) whose function seems to prevent the bacteriocin from being biologicalhy active while still inside the producer and provide the recognition signal for the transporter system.

A number of genes, often found in close proximity to each other are required for production of lantibiotics. These genes include:

(a) The structural gene, lan A,
(b) immunity genes (Lan I and in some cases Lan E, Lan F and Lan G) encoding proteins that protect the producer from the producer lantibiotic,
(c) a gene Lan T encoding what appears to be a membrane associated ABC transporter that transfers the lantibiotic across the membrane,
(d) a gene, lan P, encoding a serine proteinase which removes the leader sequence of the lantibiotic prepeptide,
(e) two genes, lan B and Lan C (or in some cases only one gene, Lan M), with no sequence similarity to other known gens thought to encode enzymes involved in the formation of lanthionine and methyl lanthionine, and
(f) two genes lan k and lan R encoding two component regulatory proteins that transmit an extracellular signal and therby inducing lantibiotic production.

CONCLUSION

The potential application of bacteriocins as consumer friendly biopreservatives either in the form of protective cultures are as additives is significant. LABS are typically involved in a large number of spontaneous food fermentations but they are also closely associated with the human environment. Food fermentations have a great economic value and it has been accepted that these products contribute in improving human health. LABS have contributed in the increased volume of fermented foods world wide especially in foods containing probiotics or health promoting bacteria. Bacteriocins produced by LAB are the subject of intense research because of their antibacterial activity against foodborne bacteria.

Further studies should be focused on the mechanisms of action of LAB within the gastro intestinal tract and in the immune system which stimulate the *in vivo* immunity effects. Furthermore, genetic engineering of already idenfied probiotics and those newly discovered to make them more efficacious should be pursued.

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