IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Www.Iosrphr.Org Volume 3, Issue 4 (May 2013), Pp 44-50

Lactic Acid Bacteria:Bacteriocin Producer: A Mini Review

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Summary: *LAB is a diverse bacterial group consisting of 11 genuses. These bacteria are Gram-positive, non-spore-forming, coccus or rods but aerotolerant, able to ferment carbohydrates into energy and lactic acid. Lactic acid bacteria produce various compounds such as organic acids, diacetyl, hydrogen peroxide, and bacteriocins or bactericidal proteins during lactic acid fermentations. Bacteriocins are peptides produced by a variety of microbes and have antimicrobial activity against closely related species. These antimicrobial agents are gaining more and more attention as an alternative therapeutics not only in pharmaceutical but also as a preservative in food industries. The main aim of this review is to highlight lactic acid bacteria and its bacteriocins.*
Keywords: *bacteriocins, lactic acid bacteria, alternative therapeutics, pharmaceutical. Bacteriocidal proteins*

I. LACTIC ACID BACTERIA (LAB)

Lactic acid bacteria (LAB) are known to be Gram-positive, non-spore-forming rods, cocci and cocco-bacilli non-aerobic but aerotolerant, able to ferment carbohydrates into energy and lactic acid1. Lactic acid bacteria (LAB) belong to the phylum Firmicutes. The different major genera of LAB include: *Lactobacillus, Weissella Lactococcus, Melissococcus, Enterococcus, Lactosphaera, Leuconostoc, Oenococcus, Pediococcus, Streptococcus, Vagococcus, Carnobacterium and Tetragenococcus*. Other genera include: *Aerococcus, Propionibacterium, Microbacterium, and Bifidobacterium*[2].LAB constitutes a highest percentage of bacteria that produce probiotic properties[3,4,5]Among compounds produce by Lactic acid bacteria during lactic acid fermentations are: organic acids, diacetyl, hydrogen peroxide, and bacteriocins or bactericidal proteins [6,7,8,9].

The vast majority of bacteriocins from gram-positive bacteriacome from lactic acid bacteria [10, 11].

II. BACTERIOCINS

Bacteriocinsare synthesizedribosomally and may be bacteriostatic or bactericidal proteins and peptides [12]. Different bacterial species are known to produce them including numerous members of the lactic acid bacteria [13].

Bacteriocins have been described as an inhibitory agent against a number of other bacteria [14, 15,16,17,18]. According to the findings of Todorov and Dicks [19],bacteriocins production is influenced mainly by the temperature, source of nutrients andpH.

Many physicochemical factors seemed to affect bacteriocin production as well as its activity. Despite the fact that antimicrobial peptides have an inhibition spectrum narrower than that of antibiotics [20,21], the bacteriocins produced by LAB have been reported to infiltrate the outer membrane of Gram-negative bacteria and to encourage the inactivation of Gram-negative bacteria in combination with other enhancing antimicrobial environmental factors, such as organic acid, low temperature and detergents materials [22,,23].

Bacteriocins are generally named based on the genus or species of the strain producing it. For example, *L. plantarum* produce plantaricin, Lactococcus spp. (lacticin, nisin), and Carnobacterium spp. (carnocin), Enterococcus spp (enterocin). Leuconostoc spp. (leucocin) Pediococcus spp. Pediocin.

2.1 Habitat of LAB

These microorganismsareubiquitous in nature found in milk, meat, fermented products, fermented vegetables and beveragessometimes as dominating microflora[24].Lactic acid bacteria isolate was first discovered in milk[2], soil, water, manure and sewage are other environments were LAB were isolated[8]. Human also harbor LAB [25,26,5]and in animal [27, 5]. .

2.2 Benefits of LABand Its Bacteriocins

Probiotics can be defined as mono or mixed culture of living microorganisms, which beneficially affect the host (human and animal) by improving the balance of the indigenous microflora, when consumed in an adequate amount as part of the food [28]. In foods, LAB has founddifferentusage which includes the inhibition of the growth of pathogen, enhancing food nutritive quality and extending the shelf life of foods. They have also been used as flavor and texture enhancers. Certain LAB, for examplelactobacilli, *L. lactis*, and *Streptococcus thermophiles*, have the ability to inhibit food spoilage and pathogenic bacteria with the advantage of preserving the nutritive qualities of raw food material given it an extended shelf [13]. Health promoting LAB is found among lactobacillusLactococcus and Bifidobacterium [29,30]. LAB have been known to regulate intestinal ailments, somewhat due to the presence of IgM enhancing immune response, serum antibodies Iggyand secretory IgA [31,32].*Bifidobacterium sp. and Lactobacillus sp.*especially produce a positive effect on human health [33,34, and 35]Of recent LAB have found other uses which include the production of both chemicals used by industries and biological products likebiopolymers from *Leuconostoc* spp.,high quality enzymesfrom *Lactobacillus brevis*, ethanol, and lactic acid produced from*Lactobacillus casei, lactis, Delbrueckii, brevis.* Steidler et al. [36]discovered the importance of LAB as digestive enzymes and vaccine antigens when delivered orally.

The digestive tract of poultry could be a source where probiotic lactic acid can be isolated[37].The observation that many intestinal bacteria such as *Fusobacterium mortiferum* isolated from chicken ceca [38] are able to synthesize bacteriocins in vitro supports the notion that bacteriocins might be useful for survival in the intestinal tract. Some data from experiments with bacteriocin-producing bacteria also suggest an influence of bacteriocins on the ecology of the intestinal microbiota. For example, an avian *Escherichia coli* strain genetically engineered to produce the bacteriocin microcin-24 lowered intestinal *Salmonella typhimurium* counts in chickens when administered continuously in the water supply [39]. Similarly, the bacteriocin-producing *Enterococcus faecium* strain J96 isolated from the crop of a chicken exhibited some protective effect on chicks infected with *S. pullorum*[40].

Applications of a bacteriocin in poultry processing have been explored by Mahadeo, et al. [41]who demonstrated that niacin reduced the number of Listeria added to scald water from a poultry processing plant by two orders of magnitude, followed by further reductions upon refrigeration. Addition of probiotic such as Lactobacillus species to the micofloral of poultry intestine has impacted considerable effects on the resistance to infectious agents such as *Escherichia coli*[42], Salmonella sp, Campylobacter sp.[43]and lately, Eimeria acervulina [44].

Bacteriocin Producing Bacteria (BPB) has provided many benefits in livestock usage, of importance are the stimulation of animal productivity. The stimulation of productivity in animal is as a result of the inhibition of specific groups of organisms [45]. Reduction in the amount of carbon lost in the form of methane resulting from BPB that have the ability to synthesis bacteriocins against methhanogenic bacteria is known to improve feed efficiency [46].

Bacteriocins could help cellulolytic bacteria to become predominant in the rumen and increase cellulose degradation [47]. *Streptococcusbovis* is one of the bacteria responsible for acidosis when cattle consume grain-based diets and BPB capable of inhibiting that organism may promote rumen homeostasis [48].

Another rumen metabolic activity that could be inhibited to improve productivity is the reduction in amino acid degradation [49]. The utilization of BPB as a pre-harvest food safety strategy is considered as one of the most viable interventions for reducing the gastrointestinal colonization of livestock by foodborne pathogens [50]; in the processing of animal feeds like silage, lab is known to contribute immensely to this process [51, 52, and 55].

III. FACTORS EFFECTING INHIBITION MICROBIAL PATHOGENS BY PROBIOTIC LAB

Several factors that areresponsible for the inhibition of harmful bacteria from multiplying on and attaching to the intestinal epithelium includebacteriocins and organic acids (antimicrobial agents) production and secretion [54,25], adherence via competition for the binding sites and steric hindrance [29,55,5]. pH reduction as a result of lactic acid production from sugar fermentation process is one of the major factor for the prevention of the proliferation of this undesirable microorganisms [56,57]. Lactic Acid Bacteria (LAB) reduce the pH in food to such an extent that it becomeunfavourable for the growth of other microorganisms including pathogenic microbes common to humans which helps to lengthen the shelf-life of the food [58].The production of lactic acid from the fermentation processes of LAB lead to the resultantpH reduction resulting in the liposolubility of organic acids therebyenhancing the ease with which the LAB penetrate the cell membrane and gain entrance into the pathogen cytoplasm [58]. Other contributing factors include the LAB competingfor required nutrients.

3.1 Mode of action of bacteriocins

Most LAB bacteriocins are cationic peptides (confide by the presence of lysine, arginine and histidine) at a neutral pH, hydrophobic in nature (supplied by the following amino acids alanine, valine, leucine, isoleucine, proline, methionine, phenylalanine and tryptophan) and amphiphilic, containing 20 to 60 amino acids [59].

The activity of bacteriocin is related to these properties when acting on the cytoplasmic membrane, where the positively charged proteins bind to negatively charged phospholipids that make up part of the membrane of sensitive cells. The distribution of the bacteriocins throughout the membrane is aided by its amphipathic nature of bacteriocins [60]. Generally, Class I and Class II bacteriocins are active at acidic and neutral phis, but they are inactivated by proteolytic enzymes, including those of pancreatic (trypsin and chymotrypsin) and gastric (pepsin) origin, despite the fact that these bacteriocins are known to withstand extremes pH values, temperature and salinity.

Most LAB bacteriocins inhibit bacteria by forming pores in the cell membrane and dissipating the proton motive force. Gram-negative bacteria are protected from the lethal effect of LAB bacteriocins by the outer membrane. Upon contact with target membranes, their cationic N-terminal half forms a sheet-like structure that binds to the target cell surface, while their more hydrophobic helical-containing C-terminal half penetrates into the hydrophobic core of the target-cell membranes and apparently binds to the mannose phosphotransferase permease in a manner that results in membrane leakage. Immunity proteins that protect cells from being The killed by pediocin-like bacteriocins bind to the bacteriocin-permease complex and prevent bacteriocin-induced membrane-leakage. Recent structural analyses of two-peptide bacteriocins indicate that they form a helix-helix structure that penetrates into cell membranes. Also these bacteriocins may act by binding to integrated membrane proteins.

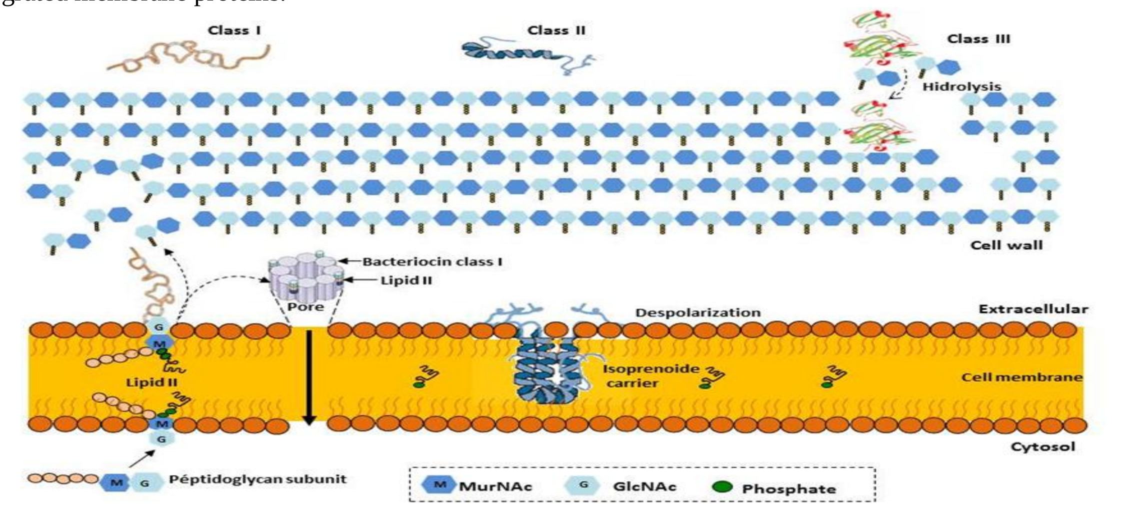

Fig. 1 Lactic acid bacteria bacteriocin mode of action. Adapted from [61, 62, 63, and 64].

Some Class I bacteriocins have been shown to have a dual mode of action and have the ability to bind to lipid II thereby causing cell death as a result of blockage of cell wall synthesis. Furthermore, they are able to cause rapid cell death when they utilize lipid II to form pores in the membrane. The amphiphilic nature of Class II bacteriocins makes easy insertion of the peptide into the membrane of the sensitive microorganism, causing depolarization and death[65].

Potency of bacteriocin on the target host will depend on different factors;

1. The microbial load of the contaminant, the higher the microbial load, the higher the concentration of bacteriocins needed to kill the target cells.
2. Non-actively growing cells may be more resistant to bacteriocins.
3. Changes of the target organisms in response to environmental stress factors may also result in decreased bacteriocin sensitivity. Inactive bacterial forms (endospores) may also be resistant to bacteriocins, although processing treatments may trigger the spore germination and outgrowth, increasing bacteriocin sensitivity.

Since bacteriocin production is linked to cell growth, it may also depend on factors affecting this parameter (such as inhibitory substances like salt or nitrite) or the lack of available nutrients (such as manganese in the case of many LABS). As an example, the production of enterocins A and B by *Enterococcus faecium* CTC492 was significantly inhibited by sausage ingredients and additives, with the exception of nitrate [65].

3.2 Advantages of LAB bacteriocin

Even though antimicrobial peptides possess a spectrum of activity narrower than conventional antibiotics [20,19], bacteriocins produced by LAB have the tendency to penetrate the outer membrane of Gram-negative bacteria and in combination with other augmenting antimicrobial environmental factors, such as low temperature, organic acid and detergents induce the inactivation of Gram-negative bacteria [21,22].

The bacteriocins produced by LAB offer several desirable properties that make them suitable for food preservation: (i) are generally recognized as safe substances, (ii) are not active and nontoxic on eukaryotic cells, (iii) are readily inactivated by the action of digestive proteases, with slight impact on the microorganism inhabiting the gut , (iv) they can tolerate a wide range of pH and temperature, (v) they have a fairly broad antimicrobial spectrum, against many food-borne pathogen of food origin and food spoiling bacteria, (vi) they exhibit bactericidal action on the target host, typically acting on the bacterial cytoplasmic membrane: no cross resistance with antibiotics, and (vii) their genetic determinants are usually plasmid-encoded, facilitating genetic manipulation.

Also the collection of studies carried out in recent years undoubtedly point out that the use of bacteriocins in food preservation can offer several advantages [67]: (a), an extended shelf life of foods, (b) offer extra protection during abnormal temperature conditions, (c) lessening the risk for spread of foodborne pathogens through the food chain, (d) lessen the economic losses due to food spoilage, (e) decrease the application of chemical additives, (f) the process allow the application of less severe heat treatments without compromising food safety: better preservation of food nutrients and vitamins, as well as organoleptic properties of foods, (g), permit the marketing of “novel” foods (less acidic, with a lower salt content, and with a higher water content), and (h) they may serve to satisfy industrial and consumers demands.

3.3 Disadvantages of Bacteriocins

The presence of bacteriocins in most of the food eating since ancient times makes them to be considered more natural as compared to the currently used antibiotics [68].

Despite the fact that bacteriocins producing strains e.g. colicins has been used successfully in live-stock but there is very little evidence that administering bacteriocins alone to livestock has ever been done. The absence of this analysis could be probably due to the rapid degradation of these proteinaceous compounds in the digestive tract of mammals. In most cases, bacteriocin production and activity has been demonstrated only in the laboratory. Evidence for a role played by bacteriocins in natural systems such as the intestinal tract is largely circumstantial. This setback may be due to the following reasons:

Cost-effective approach in the development of suitable producer strains and for the production of purified bacteriocins can become a significant barrier. Production of all but the smallest bacteriocins is currently only imaginable by culture of natural or genetically engineered producer organisms. Investments in research and development can be expected to be high, and the size of the market is difficult to predict.

The fate of bacteriocins in the intestinal tract, some data suggests that some of the low molecular weight bacteriocins can survive at least some of the intestinal environments and possibly could be administered with feed.The narrow range specificity of some bacteriocins such as nisin against other specie types require the additions of chelating agents such as EDTA and detergents such as Tween 80 in order to enhance the activity of nisin against gram-negative bacteria.

The issue of resistance also has to be considered for bacteriocins. The action of bacteriocin on the target organisms differ with the type of bacteriocins, while most bacteriocins target the membrane others attack the DNA. Resistance could usually be as a result of changes in the membrane of bacteria targeted by a bacteriocin[69, 70, 71], inactivation due to degradation has been observed for Nisin [70].

Production of resistance strain in normally susceptible bacteria to commercial antibiotics. Until recently, the development of resistance to bacteriocins was not considered as affecting resistance to currently used antibiotics. Carlson., Frana and Griffith [72] demonstrated that exposure of Salmonella to the bacteriocin microcin-24 can result in microcin-resistant cells exhibiting resistance to multiple common antibiotics. Could this be unique to this bacteriocins or this effect can also be produced by other bacteriocins? Mantovani, H.C and Russell, J.B [44] reported that nisin-resistant mutants of *Streptococcusbovis* exhibited a 1,000-fold higher resistance to ampicillin than the original nisin-sensitive isolates.

IV. Production stage

The bacteriocin production is highest at the end of the exponential and early stationary phase [72,65] and reduction is caused by proteolytic degradation of the bacteriocin [74,65].

V. Bacteriocin producing LAB

Among bacteriocinogenic lactic acid bacteria, some species of the genus Lactobacillus occupy an important place, such as Lb. sakei (bacteriocin sakacin), Lb. curvatus (curvacin), Lb. plantarum (plantaricin), Lb. acidophilus (lactacin, acidocin) and Lb. bavaricus (bavaricin). Moreover, production of bacteriocins is also noticed in other lactic acid bacteria e.g. Carnobacterium spp. (carnocin), Pediococcus spp. (bacteriocin pediocin), Leuconostoc spp. (leucocin), Enterococcus spp. (enterocin), and Lactococcus spp. (lacticin, nisin),[75].

VI. Extraction methods

Methods of extracting bacteriocins are based on their affinity to organic solvents [76], their variation in solubility in concentrated salt solutions [77] and at a given pH value [78]. The presence of hydrophobic regions inbacteriocin molecules is essential for their activity against sensitive bacteria. Inactivation of micro-organisms by bacteriocins depends on the hydrophobic interaction between cells and bacteriocin molecules [79]. The amphiphilic properties of bacteriocins have been used to separate these peptides at the interface of immiscible liquids [80].In conclusion lactic acid bacteria appear to be a major producer of bioactive peptides known to be inhibitory to other closely related microbes. Though, they are known to have some detrimental properties, the advantages over weight these disadvantages. Most of all they are known to impact little or no side effects on the hosts. Amongst all bacteria, LAB happens to be the highest producer of bacteriocins and enterococci spp leads them all despite its ambivalent nature.Lactic acid bacteria and its bacteriocins have also found diverse usage in human, livestock and poultry

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