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LACTIC ACID BACTERIA: PROBIOTIC APPLICATIONS

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ABSTRACT

Lactic acid bacteria (LAB) is a heterotrophic Gram-positive bacteria which under goes lactic acid fermentations and leads to production of lactic acid as an end product. LAB includes *Lactobacillus*, *Leuconostoc*, *Pediococcus*, *Lactococcus* and *Streptococcus* which are grouped together in the family *lactobacillaceae*. LAB shows numerous antimicrobial activities due to production of antibacterial and antifungal compounds such as organic acids, bacteriocins, diacetyl, hydrogen peroxide and reutrin. LAB are used as starter culture, consortium members and bioprotective agents in food industry that improve food quality, safety and shelf life. A variety of probiotic LAB species are available including *Lactobacillus acidophilus, L. bulgaricus, L. lactis, L. plantarum, L. rhamnosus, L. reuteri, L. fermentum, Bifidobacterium longum, B. breve, B. bifidum, B. esselnsis, B. lactis, B. infantis* that are currently recommended for development of functional food products with health-promoting capacities.

Keywords: Lactic acid bacteria; Probiotic; Bacteriocin.

INTRODUCTION

Lactic acid fermentations are deliberately exploited to produce various products such as pickled vegetables, bakery items, wine making, fermented meat, sausages and cultured milk products such as yogurts, cheeses, butter, buttermilk, kefir, koumiss etc. Natural lactic acid fermentations are brought about by lactic acid bacteria (LAB) which includes a large group of relatively fastidious, heterotrophic Gram-positive bacteria that produce lactic acid as an end product of carbohydrate fermentation. Core microbial genera of LAB include *Lactobacillus, Leuconostoc, Pediococcus, Lactococcus* and *Streptococcus* which are grouped together in the family *lactobacillaceae* [1]. Their industrial importance is evidenced by their ubiquitous occurrence in natural food products, Genarally Recognized as Safe (GRAS) status, and ability to exert health benefits beyond basic nutrition. LAB displays numerous antimicrobial activities which are mainly exhibited due to production of antibacterial and antifungal compounds such as organic acids, bacteriocins, diacetyl, hydrogen peroxide and reutrin [2]. Gratia was first to discover that the antimicrobial property of bacterial cells is exhibited by synthesizing proteinaceous toxins or bacteriocins that inhibit the growth of similar or closely related bacterial strain(s) [3]. Later on, series of bacteriocin producers have been identified and their importance in food fermentations was tested. Isolated pediocins and their producer strains such as *Pediococcus acidilactici, P. pentosaceous, P. damnosus* are also potential candidate for the development of novel antimicrobial and therapeutic agents [4-7]**.**

Highly promising results have been obtained in the studies underlying the functional importance of bacteriocinogenic LAB as starter culture, consortium members and bioprotective agents in food industry that improve food quality, safety and shelf life [8]. Applications of bacteriocin starter cultures and bacteriocin thereof in various food systems are addressed in a number of review articles [9]. LAB are commonly exploited in the dairy industry as producers of flavoring enzymes and metabolites that contribute to naturally rich flavor and texture of foods. A variety of probiotic LAB species including *Lactobacillus acidophilus*, *L. bulgaricus*, *L. lactis*, *L. plantarum*, *L. rhamnosus*, *L. reuteri*, *L. fermentum*, *Bifidobacterium longum*, *B. breve*, *B. bifidum*, *B. esselnsis*, *B. lactis*, *B. infantis* are currently recommended for development of functional food products with health-promoting capacities [10].

WHAT PROBIOTIC MEANS?

Scientific evidence has proven that we can treat and even prevent some illnesses with foods and supplements containing certain types of live bacteria. The concept of probiotics has been around for nearly a hundred years, beginning with the work of Prof. Elie Metchnikoff, the Nobel laureate of 1908, who wrote the first classic on probiotics called **"The Prolongation of Life"**. In his 'magnum opus' this brilliant Russian Biologist argued that friendly living bacteria, now called probiotics, normalize bowel habits, fight disease-carrying bacteria and extend normal life span.

The term probiotic was first introduced in 1953 by Kollath [11]. In 1989, Roy Fuller in his book on **"Probiotics: The Scientific Basis"** suggested a definition of probiotics which has been widely used: "*A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance*" [12]. Probiotic gut-dwelling LAB help to keep harmful bacteria in check, aid digestion and nutrient absorption, and contribute to immune function. To remain healthy, our biological systems must be in balance, with enough beneficial bacteria to keep the opportunistic pathogens in check. What can we do to achieve the balance? Probiotics could be the answer.

According to Natasha Trenev, who authored the book **"Probiotics: Nature's Internal Healers",** "Probiotics are a category of dietary supplements consisting of beneficial microorganisms. They limit the proliferation of disease-causing microorganisms by competitive exclusion in the gastrointestinal tract of man and animals." Most probiotics are bacteria similar to those naturally found in people's guts, especially in those of breastfed infants (who have natural protection against many diseases).

HOW DOES A PROBIOTIC WORK?

Most live bacteria that are ingested, die when they reach the acid conditions of the stomach. For a beneficial bacterium to be classified as a probiotic it must be resistant to gastric, bile and pancreatic juices to reach the colon alive. The probiotics attach to the wall of the intestine where they increase the number of beneficial bacteria and fight against harmful bacteria thus maintaining a balance between the beneficial and harmful bacteria. For organisms to be considered as probiotics, the following criteria need to be fulfilled:

- It should be isolated from the same species as its intended host
- It should have a demonstrable beneficial effect on the host
- It should be non-pathogenic
- It should be able to survive transit through the gastrointestinal tract
- On storage, large number of viable bacteria must be able to survive prolonged periods.

Probiotics can be bacteria, moulds, yeast. Among bacteria, strains of *Bacillus clausii, B. subtilis, Bifidobacterium breve* (Yakult), *B. bifidum* (Bb-12), *B. esselensis* (Danone {Bio Activia}), *B. infantis*

(Shirota, Immunitass, 744, 01), *B. lactis* (Bb-02), *B. longum* (BB536, SBT-2928), *Enterococcus faecium*, *E. faecalis*, *Lactobacillus acidophilus* (La2, La5, Johnsonii, CRL 639, NCFM, DDS-1, SBT-2062), *L. bulgaricus* (Lb12), *L. casei* (Shirota), *L. delbrueckii*, *L. fermentum* (RC-14), *L. gasseri* (OLL2716), *L. helviticus*, *L. johnsonii*, *L. lactis* (La1, A164, BH5), *L. plantarum* (299v, Lp01), *L. rhamnosus* (GG, GR-1, 271, LB21, R0011), *L. reuteri* (SD2112), *L. salivarius* (WB1004), *Saccharomyces boulardii* and *Streptococcus thermophilus, Weissella confusa* are commonly used bacterial probiotics [13-16]**.** A probiotic may be made out of a single bacterial strain or it may be a consortium as well. Probiotics can be in powder form, liquid form, gel, paste, granules or available in the form of capsules, sachets, etc.

PROBIOTIC ATTRIBUTES OF LACTIC ACID BACTERIA

The mammalian gastro-intestinal tract contains a complex and diverse society of both pathogenic and nonpathogenic (probiotic) bacteria. Probiotics are thought to supplement the microbial gut community, maintain epithelial barrier function and promote general immune homeostasis [17]**.** More recent commercial efforts focus on food supplementation with live probiotic cultures in the form of fermented milk products. Interestingly, the stimulatory capacity of probiotics have been tested in farm animals where their contribution to improve overall health status, immune system functions, reducing risk of infection and improvement in the yield of poultry and meat products is highly appreciated [18]**.** Evidences support the stimulatory capacity of the probiotic microorganisms, but the final verdict is not out, yet. Questions as to which species, strains or mixtures thereof are most beneficial, and the molecular basis for these effects, require more detailed studies [19-20]**.** A series of review articles have been published in the past year outlining the efficacy of probiotics in human health [21-24]**.** Some of which are enlisted below;

- Probiotic LAB strains help to restore a healthy microbial balance in the digestive tract [25].
- They reduce the chance of infection by opportunistic pathogens like *Bacillus cereus, Campylobacter jejuni, Clostridium botulinum, C. perfringens, C. sporogenes*, *Enterococcus faecalis*, *Escherichia coli, Leuconostoc mesenteroides, Listeria monocytogenes, Neisseria mucosa*, *Pseudomonas putida, P. aeruginosa*, *Salmonella, Staphylococcus aureus, Shigella*, *Streptococcus mutans* and *Salmonella typhimurium* are only a few to name them [26].
- They are used to treat ulcerative and gastrointestinal illness [27].
- They can be useful for development of personal health care products for treating vaginal and urinary infections [28-29]**.**
- They inhibit growth and translocation of peptic ulcer causing *Helicobacter pylori* [30].
- They promote recovery from antibiotic associated diarrhea, constipation, diarrhea and dysentery [31].
- Probiotic LAB can increase the bioavailability of protein and fats in the diet by breaking down these nutrients in the digestive tract. This is particularly important for infants, toddlers and patients who need building up during and after illness.
- They contribute to health by enhancing specific and nonspecific immunity [32].
- Probiotic bacteria produce interferon gamma (IFN-γ) that stimulates immune system of the host by improving phagocytic cell functioning (17, 32)**.** IFN-γ-activated macrophages inhibit growth of pathogenic bacteria like *Mycobacterium* as a result of TfR downregulation [17]**.**
- They improve immune functioning by increasing number of IgA-producing plasma cells, monocytes, macrophages, T lymphocytes and natural killer cells that collectively check pathogen growth [33].
- They stimulate gastrointestinal immunity by interacting with Payer's patches [34]**.**
- They have been proposed to optimize the effects of vaccines like rotavirus vaccine, typhoid fever vaccine [35].
- They are widely recommended to treat milk allergies caused primarily by lactose content [36].
- They are frequently used to treat allergies such as atopic eczema in pregnant women and newborns [37].
- They synthesize vital nutrients such as folic acid, niacin, riboflavin, vitamins B_6 and B_{12}.
- Due to synthesis of β-galactosidase, they increase lactose tolerance and are therefore prescribed to treat milk allergies [36].
- They also improve mineral absorption property of the gut [37].
- Probiotics may help to prevent liver damage caused by excessive alcohol intake.
- They reduce risk of certain cancers [38].
- They also detoxify carcinogens [39].
- They suppress growth of certain tumors [40].
- Oral doses of probiotic also help in controlling Halitosis (bad breath) caused by *Fusobacterium nucleatum* due to production of hydrogen peroxide [41].
- They significantly reduce serum cholesterol concentrations and normalize lipid profiles with more of the HDL component [42].
- They prevent tooth decay as LAB establishes a cariostatic effect by adhering to dental tissues where they fight against the cariogenic bacteria [43].
- They tend to reduce blood pressure in hypertensives [44].

Thus, probiotic microorganisms in the gut compete with pathogenic microorganisms, thereby preventing pathogenic colonization and invasion. Although most microorganisms are able to synthesize organic molecules required for their survival and maintenance, some molecules e.g. amino acids, fatty acids, nucleotides, enzyme cofactors etc. are used directly or metabolized from nutrients available in the host gut. Abundance of such nutrients within distinct host microenvironments led to loss of genes required for their biosynthesis in many microorganisms. This dependency on essential host nutrients represents a major force for pathogen selection of distinct host habitats. An instructive example for nutritive host-pathogen competition is represented by the mutual requirement for iron. Iron is an essential micronutrient for growth, basic metabolism and maintenance of most of the living organisms. Probiotic bacteria stimulates the immune system of the host by improving phagocytic cell functioning and inhibition of pathogenic bacterial growth as a result of TfR downregulation [10].

MECHANISM OF ACTION

Probiotics may exert some of their protective functions through modulation of immune activity and epithelial functions in both the large and small intestine. Immune and epithelial cells can discriminate between healthy and pathogenic microbial species through activation of TLR's [45]**.** Epithelial cells release interleukin-8 in response to pathogenic bacteria but not to probiotic strains [46]. A study has demonstrated the role of probiotics to counteract stress-induced changes in intestinal barrier function, visceral sensitivity and gut motility in a strain specific manner. Probiotics may elicit these beneficial responses through various mechanisms viz. competition with pathogens for essential nutrients, induction of epithelial heat-shock proteins, restoration of tight junction protein structure, up-regulation of mucin genes, secretion of defensins, and regulation of the NF-κB signalling pathway. In addition, cannabinoid receptors reduce the perception of intestinal pain [10, 47].

HEALTH BENEFITS

Importance of probiotics is evidenced by their ubiquitous occurrence in natural food products, their GRAS (Generally Recognized as Safe) status and their ability to exert health benefits beyond basic nutrition. Their growth lowers pH which is inhibitory to the growth of most of other microorganisms. The biochemical conversions involved in growth enhance the flavor

and improve organoleptic and nutritional properties [48]. Probiotic organisms display numerous antagonistic effects which are exhibited through production of organic acids, H_2O_2 and diacetyl, but also of other compounds such as bacteriocins and antifungal compounds [49]. Applications of bacteriocin starter cultures and bacteriocin thereof in various food systems were already addressed in a number of review articles [9]. Health claims of various probiotic strains include normalization of gastro-intestinal [34] and vaginal ecosystem [29], improvement of specific and non-specific immune responses [32], detoxification of carcinogens and suppression of tumors and cancers [39-40], reduction of cholesterol [42] and blood pressure in hypertensive patients [44]. Importance of probiotic lactic acid bacteria in treatment of milk allergies [36] and improvement of mineral absorption capacity of the intestine are also well documented [38].

Probiotic microorganisms in the intestine compete with pathogenic microorganisms, thereby preventing pathogenic colonization and invasion. Although most microorganisms are able to synthesize organic molecules required for their survival and maintenance, some molecules e.g. amino acids, fatty acids, nucleotides, enzyme cofactors etc. are used directly or metabolized from nutrients available in the host gut. Abundance of such nutrients within distinct host microenvironments led to loss of genes required for their biosynthesis in many microorganisms [17]. This dependency on essential host nutrients represents a major force for pathogen selection of distinct host habitats. An instructive example for nutritive host-pathogen competition is represented by the mutual requirement for iron. Iron is an essential micronutrient for growth, basic metabolism and maintenance of most of the living organisms. Thus, deprivation from essential growth factors represents an integral part of host defense functions.

BACTERIOCINS AS MICROBIAL WARFARE AGENTS

Many probiotic strains exhibit their antimicrobial property by synthesizing proteinaceous toxins that inhibit the growth of similar or closely related bacterial strain(s). Gratia in 1925 first discovered a colicine ‘colicines’. Pediocins are produced by several strains of *Pediococci* including *P. acidilactici, P. pentosaceous, P. damnosus* (6). Carnocin is produced by a strain of *Carnobacterium* and nisin by *Lactococcus lactis* [50].

LABs commonly harbour plasmid-borne genetic determinants for bacteriocin production and for maintaining immunity of the producer cells to their bacteriocins [51]. Yet, there have been reports suggesting that chromosomal determinants may be involved as well in the bacteriocin production [52]. Most commonly the structural and immunity genes are in a cluster with two other genes that produce dedicated proteins for export of bacteriocin from the cell. Lactococcins A, B and M are all encoded on one plasmid with separate secretion protein [53]. *Carnobacterium piscicola* LV17 produces at least three class II bacteriocins: carnobacteriocins A and B2, which are encoded on separate plasmids with separate secretion proteins, and carnobacteriocin BM1, with its structural and immunity genes located on the chromosome [54].

Bacteriocin activity is usually lethal to the bacteria. Mode of action of bacteriocin was extensively reviewed by Jack *et al.* [55] and Moll *et al.* [56]. Various mechanisms have been proposed to describe the bactericidal action of bacteriocins. Bactericidal activities include formation of selective or nonselective anion carrier pores, inhibition of outgrowth of spores and modulation of enzyme activity [57]. Pore formation is the best described mechanism. The relatively small action spectrum of some bacteriocins suggests the presence of molecular receptors in the membrane of the target cell, although this has not been demonstrated [58]. Class II peptides have a helical amphiphilic structure that allows them to be inserted into the target cell membrane, leading to depolarization and death [59]. The initial interaction with the heads of anionic membrane phospholipids takes place at the hydrophilic N-terminus of peptides. The C-terminus of peptide is more hydrophobic than the N-terminal and is thought to be involved in hydrophobic interactions with the membrane.

CONCLUSION

Probiotic LAB play an important role to maintain gut homeostasis and prevent microbial infections by producing organic acids, H_2O_2, CO_2, diacetyl, acetaldehyde, D-isomers of amino acids, reuterin and bacteriocins. Importance of probiotics is evidenced by their ubiquitous occurrence in natural food products, due to their GRAS (Generally Recognized as Safe) status and their ability to exert health benefits beyond basic nutrition. Their growth lowers pH which inhibits the growth of most of other microorganisms.

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