JOURNAL OF CURRENT RESEARCH IN SCIENCE (ISSN 2322-5009)
CODEN (USA): JCRSDJ
2013, Vol. 1, No. 5, pp:286-293
Available at www.jcrs010.com

REVIEW ARTICLE

A BRIEF REVIEW ON PROBIOTIC BACTERIA

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ABSTRACT: Recent years have seen a growing interest in health beneficial bacteria, including commensally inhabitants of the gastro-intestinal tract (GIT) and probiotics. The historical, cultural and economical, importance of many LAB in the fermentation of products as diverse as yoghurt, cheese, kimchi or sausages, allowing long-term storage and contributing to the organoleptic properties of food, led to an extensive study of their biological properties.
KEYWORDS: Probiotics, Lactobacillus, Bifidobacterium.

GENERAL COMMENTS

Recent years have seen a growing interest in health beneficial bacteria, including commensally inhabitants of the gastro-intestinal tract (GIT) and probiotics. Probiotics are "living microorganisms which when administered in adequate amounts confer a health benefit on the host" (WHO, 2002). Both animals and human beings are considered as potential beneficiaries of probiotics ingested with food or as food supplements. The majority of probiotic bacterial strains belong to the group of lactic acid bacteria (LAB), a terminology referring to the main end product (lactic acid) of their catabolic activity in the presence of fermentable sugar. LAB have traditionally been used for the transformation of food, and notably members of the *Lactococcus, Streptococcus* and *Lactobacillus* genera have a long history of safe use in human alimentation. Among other bacteria with alleged probiotic properties considered here are members of the genera *Bifidobacterium* and *Propioni bacterium,* isolated from the gut and from fermented dairy products, respectively (Ashida *et al.,* 2011; Leverrier *et al.,* 2003). The historical, cultural and economical, importance of many LAB in the fermentation of products as diverse as yoghurt, cheese, kimchi or sausages, allowing long-term storage and contributing to the organoleptic properties of food, led to an extensive study of their biological properties. During the past 30 years, many studies increased our knowledge on central and secondary metabolism, adaptation to environmental parameters, phage resistance mechanisms, regulatory networks and genomics of these domesticated bacteria (Kok *et al.,* 2005). They contributed to the understanding of important properties related to their industrial implementation like the acidification rates or the production of secondary metabolites important for the organoleptic properties of the final products.

More recently, the knowledge accumulated on these species, associated with the social desire to characterize health-promoting species, led to the exploration of the mechanisms sustaining their probiotic activity, where extended knowledge will allow a more rational evaluation of health benefit claims. In addition to their alimentary and probiotic application, LAB also have an attractive potential as delivery vehicles for recombinant protein vaccines and the proof of concept for these novel uses has been extensively delivered during the past years (Bermudez-Humaran *et al.,* 2005). The methodological innovations and conceptual advances made in the analysis of probiotic functions should benefit the development of strains of biotechnological relevance, and will also contribute to the functional analysis of the complex intestinal micro biota (metaproteomics) (Ventura *et al.,* 2009).

A large population of probiotic bacteria is needed to carry out their beneficial effect and to repel the harmful microorganisms causing disease. Indeed, some probiotic strains are rapidly killed by acid and bile, releasing active intracellular components (De Vrese *et al.,* 2001). They may mediate a variety of health effects through numerous proposed mechanisms: inhibition of undesirable bacteria (El-Nagger, 2004; Karska-Wysockib *et al.,* 2010), neutralization of toxins, increase of the immune response (Medici *et al.,* 2004; Ghafoor, 2005) anti mutagenic and anti-carcinogenic activates (Liong, 2008; Davis *et al.,* 2009) reduction of cholesterol levels (Baldwin *et al.,* 2010) controls diarrhea (Zhang *et al.,* 2008); alleviation of

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lactose intolerance (Dylewski *et al.,* 2010), inflammatory bowel diseases (Guarner *et al.,* 2005). They are also a source of vitamins, especially of the B group (Kruis *et al.,* 2004). In order to carry out their beneficial effects, probiotic strains must survive passage through the upper gastrointestinal tract (GIT), by tolerating gastric acidity and bile toxicity (Crittenden *et al.,* 2003), and colonizing the GIT by adhering to mucin or intestinal-derived epithelial cells (Del Piano *et al.,* 2006). Moreover, probiotic strains antibiotic susceptibility should be investigated to assess their safety before their use as food additives (Parvez *et al.,* 2006).

The health benefits of probiotics that are supported by adequate clinical studies and promising experimental data on animals include the prevention of diarrhea and intestinal inflammatory diseases (Jenkins *et al.,* 2005). Considering that several *lactobacilli* and *bifidobacteria* have been proven to maintain antibiotic susceptibility (Zhou *et al.,* 2005), probiotic feeding may represent an important antibiotic alternative therapy for animals and human subjects to prevent the enteropathogen infections. Several probiotics have been shown to inhibit pathogen adhesion (Forestier *et al.,* 2001). This could be the mechanism of probiotic protection against enterotoxigenic *Escherichia coli* (ETEC) infection, which should attach to mucosal surfaces to release toxins responsible for the development of diarrhea and inflammation (Jenkins *et al.,* 2005). However, there is increasing evidence that probiotics may act, not only by competing for pathogen adhesion, but also through diverse mechanisms, including maintenance of mucosal barrier integrity and modulation of mucosal immune response (O'Sullivan *et al.,* 2005).

Lactobacillus is a bacterial genus comprised of Gram-positive, rod-shaped bacteria with low percentage of guanine and cytosine bases in their genome, and they are typically aero tolerant anaerobes. Taxonomically, the *Lactobacillus* genus is diverse and it contains at least twelve individual phylogenetic groups (Felis *et al.,* 2007). More than 150 species have been named within the *Lactobacillus* genus, which were isolated, e.g., from human and animal GITs and mucous membranes and from plant surfaces. Several *Lactobacillus* strains are used in the preparation of fermented dairy products and in the production of sauerkraut, pickles, and silage. Certain *Lactobacillus* strains have been found to have beneficial effects on human health, some of which are therefore used as probiotics. One of the most important probiotic *Lactobacillus* strain is *L. rhamnosus* GG, which is probably the most intensively studied probiotic bacterium worldwide. *L. rhamnosus* belongs to an *L. casei* phylogenetic group together with *L. casei*, *Lactobacillus paracasei*, and *Lactobacillus zeae* (Felis *et al.,* 2007).

Lactobacillus rhamnosus is a bacterium that was originally considered to be a subspecies of *L. casei*, but later genetic research found it to be a species of its own. Some strains of *L. rhamnosus* are being used as probiotics. The species is sometimes used in yogurt and other dairy products. Some studies have been done on its *in vivo* effects. While frequently considered a beneficial organism, *L.rhamnosus* has been discovered to be pathogenic in certain circumstances (Avlami *et al.,* 2001). The probiotic strain *L. rhamnosus* GG (ATCC 53103) was originally isolated by Goldin and Gorbach in 1985 (Doron *et al.,* 2005). Strain was selected from a collection of *Lactobacillus* strains isolated from stool samples from healthy human volunteers, using the following criteria for an ideal probiotic strain: bile and acid resistance and the ability to persist in the harsh conditions of the GIT, adhere to human epithelial cells, and colonize the human intestine. The production of antimicrobial substances such as organic acids is also desirable, and good growth characteristics are useful in large-scale commercial production (Doron *et al.,* 2005). The most important characteristic for a probiotic is, naturally, beneficial effects on human health. The first report of positive health effects of *L. rhamnosus* was published in 1987 (Gorbach *et al.,* 1987) and more than 500 scientific articles on this probiotic strain have since been published. The health effects of *L. rhamnosus* are based on several mechanisms. *L. rhamnosus* GG colonizes the GIT efficiently and competes for adhesion sites and nutrients, such as monosaccharides, with pathogens. *L. rhamnosus* also modulates the micro ecology of the GIT, e.g., by producing short-chain fatty acids, which favor the growth of nonpathogenic organisms. In addition, *L. rhamnosus* has numerous effects on the host immune system (Doron *et al.,* 2005). A recent comparative genomics study of *L. rhamnosus* and its close relative, a dairy strain *L. rhamnosus* Lc705, revealed that *L. rhamnosus* carries unique pilus genes (*spaCBA*) in its genome (Kankainen *et al.,* 2009). Additional studies of a mutant in which the pilus gene *spaC* was inactivated showed that SpaC is essential for the adherence of *L. rhamnosus* to intestinal mucus *in vitro*, and the presence of cell surface pili was assessed to explain the ability of strain to persist longer in the human GIT than strain Lc705The best-proven health benefit of *L. rhamnosus* GG is

lowered risk and reduced treatment days for acute diarrhea in children (Szajewska *et al.*, 2007) as shown, e.g., in a broad study in ten European countries, where children with acute diarrhea recovered and were discharged from the hospital faster when treated with oral rehydration solution containing *L. rhamnosus* than when treated with a corresponding placebo solution (Guandalini *et al.*, 2000). *L. rhamnosus* can also reduce the risk for antibiotic-associated diarrhea and other intestinal side effects associated with the use of antibiotics (Doron *et al.*, 2005; Cremonini *et al.*, 2002). For example, the administration of *L. rhamnosus* to children receiving antibiotic therapy for respiratory infections reduced the incidence of antibiotic associated diarrhea to one-third (Isolauri *et al.*, 2000). Substantial evidence has accumulated to support the effect of *L. rhamnosus* in treating (Majamaa *et al.*, 1997) and preventing atopic diseases in children. The preventive effect among children at high risk for atopic eczema was achieved by administering *L. rhamnosus* prenatally for 2–4 weeks and postnatally for 6 months (Kalliomaki *et al.*, 2001), and the reduced cumulative risk for developing eczema was evident even after seven years (Kalliomaki *et al.*, 2003). In a similar experiment were a mixture of *L. rhamnosus, L. acidophilus* La-5 and *Bifidobacterium animalis* subsp. *lactis* Bb-12 was given to pregnant women, the cumulative incidence of atopic dermatitis in 2-year-old children was reduced, but no effect on atopic sensitization was observed (Dotterud *et al.*, 2010). In addition, consumption of *L. rhamnosus* GG may reduce the risk and duration of respiratory tract infections in children attending day care centers (Hojsak *et al.*, 2010) and the risk for dental caries in children has been shown to be reduced by consuming strain GG (Nase *et al., 2001*).

Probiotic bacteria are exposed to several unfavorable environmental conditions during their industrial processing and ingestion by consumers. Industrial processes may include variable temperatures and pH values, and in the human GIT, probiotics are first exposed to the extremely low pH of the stomach, caused by hydrochloric acid, and then high concentrations of bile, which acts as a biological detergent in the small intestine. Proteomics has been used to study the responses of potential probiotics to several stress conditions, and a number of stress-induced proteins have been identified. (Coute *et al.*, 2007).

Most probiotic bacteria are able to adhere to intestinal epithelial cells in the GIT, and this ability is considered to be important for the beneficial effects of probiotics. In addition to other factors, probiotic bacterial adherence is often associated with the immunological effects of probiotic bacteria and with the interference of the adhesion of pathogenic bacteria. Bacterial adhesion is mediated mainly by cell surface-associated proteins, but other surface-associated factors, such as lipoteichoic acids and exopolysaccharides, could also be involved in adhesion (Velez *et al.*, 2007). In addition, in probiotic *L. rhamnosus* GG, cell wall-bound pili have been shown to be involved in adhesion to human intestinal mucus (Koskenniemi *et al.*, 2009). Probiotic bacteria also secrete proteins to the bacterial surroundings, either by active transport through the cytoplasmic membrane or by shedding from the bacterial surface. These extracellular proteins (*i.e.*, the secretome) may mediate probiotic effects in the GIT by regulating certain signaling pathways and cellular responses. The cell envelope proteome and secretome of potentially probiotic lactobacilli and bifidobacteria has been mapped in a few studies and protein localization and secretion have also been predicted by genome sequence analysis (Barinov *et al.*, 2009). The Gram-positive cell envelope consists of two main layers, the cytoplasmic membrane and peptidoglycan (or cell wall). Both of these layers are spanned by various proteins, such as transporters. There are also proteins attached on the cell surface. In cell envelope proteome studies of potentially probiotic bacteria, the cell wall protein fraction has typically been extracted by lysozyme-containing buffer (Izquierdo *et al.*, 2009; Candela *et al.*, 2010). The surface associated proteome of probiotic *L. rhamnosus* GG contained a cell wall-associated hydrolase, two oligopeptide transporter components, and two hypothetical proteins with predicted non-cytoplasmic localization. In probiotic *L. plantarum* 299v, several proteins involved in cell envelope biogenesis were identified from the cell surface-associated proteome. The cell envelope proteome of potentially probiotic *B. longum* biotype *longum* NCIMB 8809, several membrane proteins, such as ABC transporters and ATP synthase subunits were identified (Ramiah *et al.*, 2008).

Most of the identified proteins in these studies were “new surface proteins”, or proteins that have a cytoplasmic function but that also occur on the cell surface. These proteins are called “moonlighting proteins”, and they may have more than one separate role in an organism. One group of these surface proteins was glycolytic proteins. Their function in a central sugar metabolizing route, glycolysis, inside the cell, but

they have also been found to localize to the cell surface. Glyceraldehyde -3- phosphate dehydrogenase (Gap) was found in the cell envelope proteomes of most of the studied potential probiotics (Ruiz *et al.,* 2007; Candela *et al., 2010*). Gap is also surface-associated in other bacteria, such as pathogenic streptococci and staphylococci, and it has been shown to have several functions on the cell surface. Gap acts as an adhesin and binds to several human proteins, such as fibronectin and plasmin. Gap is also involved in the acquisition of transferring-bound iron and has a role in cell-to-cell communication (Jin *et al.,* 2005). Cell surface Gap has also been shown to be mandatory for the virulence of group a *streptococci.* The virulence of *Streptococcus* strains was completely attenuated by inhibiting the exportation of Gap to the cell surface by inserting a hydrophobic tail in the Gap protein. In lactobacilli, cell surface Gap adheres to fibronectin and human colonic mucin (Kinoshita *et al.,* 2008) and activates human plasminogen (Hurmalainen *et al.,* 2007). In addition, the association of Gap with the cell surface is pH-dependent (Antikainen *et al.,* 2007) and related to plasma membrane permeability. Gap has also been suggested to be involved in adhesion in *L. plantarum* because the highly adhesive strain WHE 92 expressed more Gap on its cell surface than the less adhesive strains 299v and CECT 4185 (Izquierdo *et al.,* 2009). All of the other glycolytic proteins (seven proteins), except phosphofructokinase, have also been detected from the probiotic cell envelope enolase and phosphoglycerate mutase are putative plasminogen-binding proteins in *Bifidobacteria* (Candela *et al.,* 2010). In *lactobacilli*, enolase binds to human fibronectin (Castaldo *et al.,* 2009) and enhances the activation of human plasminogen (Hurmalainen *et al.,* 2007) and thus it seems to be involved in bacteria–host interactions. Another group of "moonlighting proteins" found on the cell surface of potentially probiotic bacteria are the elongation factors. Elongation factors are usually cytoplasmic enzymes that play a central role in protein synthesis, elongation factors EF-Tu[134] EF-Ts (and a few other elongation factors were found in the cell envelope proteomes of potentially probiotic *lactobacilli* and *bifidobacteria*. In probiotic *L. johnsonii* NCC533, EF-Tu is cell-surface exposed and binds to intestinal epithelial cells. In addition to acting as an adhesin-like factor, EF-Tu can induce a proinflammatory response (Granato *et al.,* 2004). *L. crispatus* strain and its non-aggregative mutant, EF-Tu was also implicated in adhesion because it was more abundant in the aggregative strain than in the mutant. Several stress-response proteins that normally function in the cytosol, such as the chaperones GroEL and DnaK, were found in the cell envelope protein fractions of a couple of potentially probiotic *lactobacilli* and *bifidobacteria.* In probiotic *L. johnsonii* NCC533, GroEL is also present on the cell surface, as demonstrated using a whole-cell enzyme-linked immunosorbent assay, and it has been shown to bind to mucins and human intestinal epithelial cells. In addition, GroEL has immunomodulatory eff ects and mediates the aggregation of the gastric pathogen *H. pylori* (Bergonzelli *et al.,* 2006). In potentially probiotic *B. animalis* subsp. *lactis* BI07, the DnaK protein was verified to be surface exposed by immune electron microscopy. The *dnaK* gene of *B. animalis* subsp. *lactis* BI07 was cloned and expressed in *E. coli*, the His-tagged DnaK was purifi ed, and using a solid-phase plasminogen-binding assay, DnaK was shown to bind to plasminogen, suggesting a function as a human plasminogen receptor (Candela *et al.,* 2007). Ribosomal proteins are part of ribosomes, which are at the core of protein synthesis, but individual ribosomal proteins may have other functions in the cell (Ruiz *et al.,* 2007). In a few probiotic bacteria, ribosomal proteins have been found in the cell envelope proteome. Four different ribosomal proteins occurred on the cell surfaces of both probiotic *L. rhamnosus* GG and *L. plantarum* 299v whereas 41 of the 52 predicted ribosomal proteins were found in the membrane and cell envelope protein fractions in potentially probiotic *B. longum* NCIMB 8809. The bacterial cell wall is decorated with cytoplasmic proteins, such as ribosomal proteins, as a result of the lysis of a subpopulation of the cells during culture (Tjalsma *et al.,* 2008). The possible functions of surface-localized ribosomal proteins remain to be clarified. Proteomic analyses of potentially probiotic bacteria also include studies in which potential probiotic traits are touched. A high serum cholesterol level is a risk factor for human disease, and the ability of potentially probiotic *L. acidophilus* strains to reduce cholesterol levels was analyzed in two proteomic studies. In *L. acidophilus* A4, the cholesterol-reducing ability was found to be related to the catabolite control protein CcpA, which was shown to regulate production of several proteins whereas in *L. acidophilus* ATCC 43121 the cholesterol-reducing component was suggested to be a secreted protein (Kim *et al.,* 2005). Potentially probiotic *Bifidobacterium* and *Lactobacillus* strains were investigated to evaluate properties that are required for viability in the GIT. The interaction of potentially

probiotic *B. longum* NCIMB 8809 with human intestinal mucus was explored using 2-D GE, and the mucus was shown to induce the production of bacterial proteins that mediate interactions with mucus. *B. longum* NCIMB 8809 was also shown to metabolize the mucus, and the addition of mucus to the growth medium altered the carbohydrate preferences of this strain (Ruiz *et al.,* 2007). In the GIT, *Bifidobacteria* are able to metabolize sugars that are not absorbed or metabolized by the host. Using a 2-D DIGE method, probiotic *B. animalis* subsp. *lactis* Bb-12 was proposed to metabolize non-digestible xylo-oligosaccharides using a multistep mechanism consisting of specific transport and degradation systems (Nakanishi *et al.,* 2011). A synthetic sugar alcohol, lactitol, is also a carbohydrate that is not metabolized by the host and has been found to stimulate the growth of *lactobacilli* and *bifidobacteria*. In a 2-D DIGE experiment, the response of probiotic *L. acidophilus* NCFM to lactitol was explored, and the production of several enzymes involved in the metabolism of the carbohydrate moieties of lactitol was elevated, supporting the presence of an effective lactitol metabolism in this probiotic bacterium. Potentially probiotic *B. longum* NCC2705 was shown to metabolize several monosaccharides using a single primary metabolism route (called the bifid shunt), but the end products of pyruvate metabolism changed with the fermented sugar, possibly reflecting differences in the redox balance under different growth conditions.

Microbial interactions between pathogenic *E. coli* O157:H7 and potentially probiotic *B. longum* subsp. *longum* JCM 1217 were studied using a broad mapping of the transcriptome-, proteome-, and metabolome-level changes in both monoculture and a co-culture of these strains. The pathogen benefited from co-cultivation by receiving extracellular nutrients, such as serine and aspartate, from the *B. longum* strain. The presence of *B. longum* in the culture also down-regulated the chemotaxis system of the pathogen due to the increase in the level of nutrients produced by *B. longum* (Nakanishi *et al.,* 2011). The effect of co-culture has also been studied in two *Bifi dobacterium* strains, *B. breve* NCIMB8807 and potentially probiotic *B. longum* NCIMB8809. In this experiment, the *B. longum* strain seemed to benefit from co cultivation and up-regulate its energy metabolism, whereas *B. breve* was inhibited to some extent by *B. longum* and its stress responses were activated in the co-cultivation conditions (Ruiz *et al.,* 2007). In three additional studies concerning the proteomics of potentially probiotic bacteria, the ability of selected strains to metabolize Selenium (Lamberti *et al.,* 2011) and to resist stress caused by antibiotics (Candela *et al.,* 2007) and tannic acids (Curiel *et al.,* 2011) were elucidated. Selenium is an important micronutrient for humans, and selenium deficiency causes several health problems. Potentially probiotic *L. reuteri* Lb2 BM was shown to metabolize selenium by utilizing the enzyme selenocysteine lyase and thus enhance the bioavailability of organic selenium for the host (Lamberti *et al.,* 2011). The rifaximin antibiotic resistance of potentially probiotic *B. infantis* BI07 was studied to assess the use of an antibiotic–probiotic combination for the clinical management of intestinal disorders (Candela *et al.,* 2007). Rifaximin induced both common and targeted stress responses in the studied strain, but no biodegradation of the antibiotic was observed, and it was therefore estimated that rifaximin and bifidobacteria could be used simultaneously. The response of potentially probiotic *L. plantarum* WCFS1 to tannic acids was studied to understand how this tannin-degrading, potentially probiotic strain resists the antimicrobial effects of tannins, which are common components of all plant-based food (Lamberti *et al.,* 2011). Proteomic analysis suggested that *L. plantarum* WCFS1 responds to tannic acid challenge by conserving energy and maintaining the integrity of the cell wall. The harmful oxidative effects caused by the autooxidation of tannins were resisted by producing proteins involved in DNA repair and the inactivation of toxic radicals. The ability to respond to the antibacterial effects of tannic acid is probably beneficial for *L. plantarum* WCFS1 because it may improve its competitiveness against other less resistant microbiota in the GIT (Curiel *et al.,* 2011).

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