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REVIEW

Probiotics - the versatile functional food ingredients

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Abstract Probiotics are live microbes which when administered in adequate amounts as functional food ingredients confer a health benefit on the host. Their versatility is in terms of their usage which ranges from the humans to the ruminants, pigs and poultry, and also in aquaculture practices. In this review, the microorganisms frequently used as probiotics in human and animal welfare has been described, and also highlighted are the necessary criteria required to be fulfilled for their use in humans on the one hand and on the other as microbial feed additives in animal husbandry. Further elaborated in this article are the sources from where probiotics can be derived, the possible mechanisms by which they act, and their future potential role as antioxidants is also discussed.

Keywords Probiotics · Versatile · Functional food · Ingredients

Introduction

The concept of functional foods was introduced in Japan during the 1980s (De Sousa et al. 2011), and it is connected with considering food not only as a means of providing basic nutrition (Alissa and Ferns 2012) which is necessary for living but also as a source of mental and physical well-being, contributing to the prevention and reduction of risk factors responsible for several diseases or enhancing certain physiological functions (Lobo et al. 2010) like immuno-potentiation, the improvement of system circulation, and control of aging (Al-Sheraji et al. 2013). Thus, a food can be regarded as functional if it satisfactorily demonstrates to beneficially affect either one or more target functions in the body beyond adequate nutritional effects; in a way that is relevant to maintenance or promotion of a state of well being and health or reduction in the risk of a disease (Lobo et al. 2010).

"Health Canada defines functional foods as products that resemble traditional foods but possess demonstrated physiological benefits". Improvement of heart health, enhancement of immune system, enhancement of gastrointestinal health, preservation of urinary tract health, anti-inflammatory influences, diminution of blood pressure, protection of vision, antibacterial and antiviral activities, decline of osteoporosis and anti-obese influences, being some of the desired physiological benefits. The functionality of functional foods is based on the bioactive components often contained naturally in the product but usually requiring the addition of a specific ingredient in order to optimize the beneficial properties. Included in the category of functional foods are: (i) usual foods with naturally occurring bioactive substances (e.g., dietary fiber), (ii) foods

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supplemented with bioactive substances (e.g., probiotics, antioxidants), and (iii) derived food ingredients introduced to conventional foods (e.g., prebiotics). Today, functional food ingredients consists of probiotics, prebiotics, vitamins and minerals; which are currently used for human consumption in the form of fermented milks and yogurts, sports drinks, baby foods, sugar-free confectionery and chewing gum (Figueroa-Gonzalez et al. 2011; Al-Sheraji et al. 2013).

This article summarizes the potential health benefits that probiotics can provide and the versatility of their applications ranging from the humans to the ruminants, pigs and poultry, and also in aquaculture practices.

Probiotics – the concept and definition

The concept of probiotics evolved at the turn of the 20th century from a hypothesis first proposed by the Russian scientist and Nobel Laureate, Elie Metchnikoff, who suggested that the long, healthy life of Bulgarian peasants; resulted from their consumption of fermented milk products. He believed that consumption of the fermenting *Lactobacillus* positively influenced the microflora of the gut, decreasing the toxic microbial activity of the pathogenic bacterial population (Figueroa-Gonzalez et al. 2011; Sharma et al. 2012).

The term *probiotic* was derived from a Greek word meaning “for life” and it was first coined by Lilly and Stillwell in 1965 to describe “substances secreted by one microorganism which stimulates the growth of another” and thus, was contrasted with the term *antibiotic* (Sharma et al. 2012). The definition of probiotics was later refined by Fuller in 1989 as “live microbial cultures which beneficially affect the host by improving its intestinal microbial balance” (Khan and Naz 2013). Then subsequently in 2001, a group convened by FAO/WHO Expert Consultation adopted the current definition of probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (Singh et al. 2011).

Microorganisms frequently used as probiotics in human and animal welfare

To be used as probiotics, it is essential that the organisms must be considered as GRAS (generally recognized as safe); which is a status used to address the problem of pathogen colonization in different ecosystems (Bouchard et al. 2013). Some of the important microorganisms considered as probiotics have been listed in Table 1.

In human nutrition, the most frequently used probiotic microorganisms include *Lactobacillus* spp., *Bifidobacterium* spp., *Enterococcus* spp.; whereas yeast especially *Saccharomyces cerevisiae* plays a major role in ruminants; while *Bacillus* spp., *Enterococcus* spp. and *Lactobacillus* spp. are more likely to be efficient in pigs and poultry (Bernardeau and Vernoux 2013); and in aquaculture practices the commonly used being *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Enterococcus*, *Carnobacterium*, *Shewanella*, *Bacillus*, *Aeromonas*, *Vibrio*, *Enterobacter*, *Pseudomonas*, *Clostridium*, and *Saccharomyces* species (Nayak 2010). But, it is important to note that the health benefits provided by probiotics are strain specific and not species or genus specific (Figueroa-Gonzalez et al. 2011).

Furthermore, with regards to specific use in humans, probiotics should be able to provide health benefits; promote or maintain the state of well being; and safety assessment should integrate long-term effects and also consider possible chronic effects.

In contrast, microbial feed additives used in animal husbandry must produce a quick response; as because the typical industrial life-spans are for example 42–80 days for a broiler chicken, around 120–200 days for shrimps, 6 months for pigs, 18–24 months for fish, a few months for calves and a few years for beef cattle. This duration being <5 % of the entire life expectancies of the corresponding animal species, which are generally >10 years except for fish and shrimp which ranges between 5 and 7 years. Further, microbial feed additives should be authorized as ‘zootechnical additives’ which means that their use should affect favorably the performance of animals in good health and also affect favorably the environment. Then, microbial feed additives should also enhance the performance characteristics which include feed efficiency through improvement of feed conversion ratio, average daily weight gain through improvement of body weight gain (BWG), milk or egg production, improving carcass composition by increasing protein and muscle deposition while reducing fat deposition, and improving herd performance by bringing about improvement in the reproductive performance of the breeding females, lowering disease incidences, lowering the culling rates in case of dairy cattle, etc. (Bach et al. 2008; Jacela et al. 2009; Bernardeau and Vernoux 2013).

Sources of probiotics

The common sources of probiotics are yogurt, cultured buttermilk, and cheese. The other foods that are produced by bacterial fermentation are Japanese miso, tempeh, sauerkraut, beer, sour dough, bread, chocolate, kimchi, olives, and pickles. Another fermented dairy product is kefir. But among these, the dominant food vehicles for probiotics are still yogurts and fermented milks, both of which provide a relatively low pH environment in which the probiotic bacteria must survive (Anandharaj et al. 2014).

However, many studies have shown that probiotic strains are also found in nondairy fermented substrates which includes soy based products, cereals, legumes, cabbage, maize, pearl millet, sorghum, and so forth (Kechagia et al. 2013; Anandharaj et al. 2014).

Table 1 Microorganisms considered as probiotics

Lactobacillus species	Bifidobacterium species	Other lactic acid bacteria	Nonlactic acid bacteria
L.acidophilus	*B. bifidum*	*Enterococcus faecalis*	*Bacillus cereus*
	B. breve	*Enterococcus faecium*	*Escherichia coli* strain nissle
L. casei	*B. lactis*	*Lactococcus lactis*	*Propionibacterium freudenreichii*
L. crispatus	*B. longum*	*Leuconostoc mesenteroides*	*Saccharomyces cerevisiae*
L. gasseri	*B. infantis*	*Pediococcus acidilactici*	*Saccharomyces boulardii*
L. fermentum	*B. adolescentis*	*Streptococcus thermophilus*	
L. johnsonii	*B. animalis*		
L. paracasei			
L. plantarum			
L. reuteri			
L. rhamnosus			
L. bulgaricus			
L. salivarius			
L. lactis			

(Rastogi et al. 2011; Kechagia et al. 2013)

The other sources of probiotics include breast milk, the human gastrointestinal tract, and the guts of several animal species, including pigs, rats and even poultry. Recently, *L. johnsonii* CRL 1647, isolated from the *Apis mellifera* L. bee gut, was shown to exhibit a beneficial effect on honeybee colonies. Additionally, probiotic strains have also been obtained from the intestinal tracts of marine and freshwater fish, such as *Carassius auratus gibelio*, rainbow trout and shrimp (Fontana et al. 2013).

Desirable probiotic characteristics

The important criteria which are used for selecting probiotic strains includes that the organism should be: non-pathogenic and non-toxic (Singh et al. 2011); isolated from the same species as its intended host (Maurya et al. 2014); able to survive during transit through the gastrointestinal tract by being acid and bile resistant (Khan and Naz 2013; Maurya et al. 2014); able to adhere and colonize the intestinal epithelium which is an important property for successful immune modulation and competitive exclusion of pathogens (Kechagia et al. 2013; Maurya et al. 2014); able to stabilize the normal intestinal microflora (Parvez et al. 2006); able to produce antimicrobial substances like the bacteriocins against the pathogens (Kral et al. 2012); having a demonstrated beneficial effect on the host (Fontana et al. 2013); durable enough to withstand the duress of commercial manufacturing, processing and distribution (Khan and Naz 2013); and also having good sensory characteristics by not providing unpleasant flavors or textures (Parracho et al. 2007; Mitropoulou et al. 2013). The essential criteria for the use of probiotics in humans has been listed in Table 2.

Mechanisms of probiotic action

Probiotics have various mechanisms of action although the exact manner in which they exert their effects is still not fully

Table 2 Criteria for the use of probiotics in humans

Identified at the genus, species, and strain level
- The gold standard for species identification is DNA-DNA hybridization; 16S rRNA sequence determination is a suitable substitute, particularly if phenotypic tests are used for confirmation
- Strain typing should be performed by pulsed-field gel electrophoresis
- Strain should be deposited in an international culture collection

Safe for food and clinical use
- Nonpathogenic
- Not degrading the intestinal mucosa
- Not carrying transferable antibiotic resistance genes
- Not conjugating bile acids
- Susceptible to antibiotics

Able to survive intestinal transit
- Acid and bile tolerant

Able to adhere to mucosal surfaces Able to colonize the human intestine or vagina (at least temporarily)

Producing antimicrobial substances Able to antagonize pathogenic bacteria

Possessing clinically documented and validated health effects
- At least one phase 2 study, preferably independent confirmation of results by another center

Stable during processing and storage

(Borchers et al. 2009)

elucidated (Kechagia et al. 2013). Nonetheless, the possible modes of action include the following:

a. Enhancement of epithelial barrier function

Intestinal barrier function is maintained by several interrelated systems including mucus secretion, chloride and water secretion, and binding together of epithelial cells at their apical junctions by tight junction proteins (Ng et al. 2009). Integral to the gut barrier defense is mucus which is composed of mucins (MUC 2 and MUC 3) which are secreted from the goblet cells. Mucin polymerization provides the structural foundation of the mucus, granting protection from pathogens, enzymes, toxins, dehydration and abrasion. *Lactobacillus plantarum* 299v and *Lactobacillus rhamnosus* GG have been shown to upregulate production of intestinal mucins (MUC 2 and MUC 3) which subvert the adherence of the enteropathogenic bacterium *Escherichia coli* O157:H7 to intestinal epithelial cells, consequently preventing pathogenic bacterial translocation (Hardy et al. 2013).

Further, some probiotic bacteria have been found to limit chloride and water secretion, as is the case with *Streptococcus thermophilus* and *Lactobacillus acidophilus* which reversed the *E. coli*- induced chloride secretion by epithelial cells (Brown 2011).

On the other hand, intestinal barrier integrity may be increased by enhancing the expression of genes involved in tight junction signaling. On this count, some of the probiotics like lactobacilli for instance, have been shown to modulate the regulation of several genes encoding adherence junction proteins such as E-cadherin and β-catenin in T84 epithelial cells. Moreover, incubation of intestinal cells with lactobacilli modulates tight junction protein phosphorylation.

Probiotics have also been indicated to initiate repair of the barrier function after damage. For example, *Escherichia coli* Nissle 1917 not only counteracted the disruptive effects of enteropathogenic *E. coli*, but also restored the mucosal integrity in T84 and Caco-2 cells. This effect is achieved by increasing expression and repartition of tight junction proteins of the zonula-occludens (ZO-2) and altering protein kinase C signaling (Goudarzi et al. 2014).

b. Increased adhesion to intestinal epithelial cells

The effective performance of a probiotic depends on their strong adhesion and colonization of the gut, which in turn improves the host immune system. *Lactobacillus plantarum* 299v has been shown to exhibit a mannose-specific adhesion by which it can adhere to human colonic cells. Once the probiotic adheres to the cell, various biological activities take place, which primarily include the release of cytokines and chemokines. These then exert their secondary activity such as stimulation of mucosal and systemic host immunity (Hemaiswarya et al. 2013).

c. Competitive exclusion of pathogenic microorganisms

Probiotic bacteria are able to exclude or reduce the growth of pathogens by any one of the following ways which includes creation of a hostile microenvironment like the lowering of the pH of the gut below than what is essential for the survival of pathogenic bacteria such as *E. coli* and *Salmonella*, by producing organic acids like acetic acid and lactic acid (Brown 2011; Bermudez-Brito et al. 2012; Goudarzi et al. 2014). The others include physical blocking of available bacterial receptor sites (Goudarzi et al. 2014); compete with pathogenic bacteria for essential nutrients and energy source (Brown 2011); secretion of antimicrobial substances and release of selective gut-protective metabolites like arginine, glutamine, short-chain fatty acids and conjugated linoleic acids (Bermudez-Brito et al. 2012; Hemaiswarya et al. 2013).

d. Production of antimicrobial peptides

Many lactic acid bacteria produce well characterized inhibitory peptides which include, but are not limited to lantibiotics (class I), peptide bacteriocins (class II), and bacteriolysins (class III) (Saulnier et al. 2009). Bacteriocins are antimicrobial compounds with a molecular weight of >1,000 Dalton. Bacteriocins produced by gram-positive bacteria usually the lactic acid bacteria include lactacin B from *L. acidophilus*, plantaricin from *L. plantarum* and nisin from *Lactococcus lactis*. These have a narrow activity spectrum and act only against closely related bacteria, but some bacteriocins are also active against food-borne pathogens. The common mechanisms of bacteriocin-mediated killing include the destruction of target cells by pore formation and/or inhibition of cell wall synthesis (Bermudez-Brito et al. 2012).

The probiotic bacteria *Lactobacillus reuteri* produces an antimicrobial agent reuterin which has broad-spectrum activity against a variety of pathogens including bacteria, fungi, protozoa and viruses, and can be differentially expressed by various *L. reuteri* strains (Saulnier et al. 2009).

Defensins are a family of highly conserved small cysteine-rich antimicrobial peptides particularly abundant at mucosal sites where they contribute to the host defense by disrupting the cytoplasmic membrane of susceptible microorganisms (Hardy et al. 2013). The probiotic *E. coli* Nissle strain has been shown to induce expression of human beta- defensin 2 in Caco-2 intestinal epithelial cells and this type of effect may contribute to an improved mucosal barrier and provide a means of limiting access of enteric pathogens (Ng et al. 2009).

e. Modulation of the immune system

There are growing evidences that probiotics have immunomodulatory properties and that these properties of probiotics are strain-dependent. Some of these probiotic immunomodulatory properties are as listed below:

i. Increasing the phagocytic capacity of macrophages

Many probiotic strains have been shown to influence innate defense mechanisms such as phagocytosis. It has been demonstrated that *L. acidophilus* La1 increased the phagocytic capacity of leucocytes isolated from the blood of humans who had consumed probiotics and this was consistent with the adhesion potential of this bacterium. But it has also been found that even *Bifidobacterium lactis* Bb12 which exhibits slightly less adhesion is also able to increase phagocytosis substantially (Delcenserie et al. 2008).

ii. Enhancing natural killer cell activity

Consistent evidences point to the fact that a number of probiotics enhance natural killer (NK) cell activity in vitro and there is some supportive evidence that this also occurs in vivo. Probiotic strains whose cell walls are resistant to digestion appear to be particularly potent enhancers of NK cell activity. It is suggested that monocytes phagocytose the probiotic bacteria and the insoluble cell wall components induce the production of interleukin-12 (IL-12), which augments NK cell activity. In a particular study, it was found that when neonatal and infant mice were administered with *Lactobacillus casei* Shirota by stomach tube for 3 weeks prior to infection with influenza; the mice demonstrated a lower rate of accumulated symptoms, a greater survival rate and lower titres of influenza in nasal washings taken a few days after infection. These correlated with an increase in NK cell activity and production of IL-12 (Yaqoob 2014).

iii. Stimulating IgA production

Many probiotic strains are apparently able to stimulate the production of IgA by B cells, which help maintain intestinal humoral immunity by binding to antigens, thereby limiting their access to the epithelium. Study subjects who consumed fermented milk containing *Bifidobacterium bifidum* and *L. acidophilus* La1 following vaccination against *Salmonella typhi* Ty21 showed a significant increase in IgA serum concentration.

In addition, children who were 2 to 5 years old and who received *L. rhamnosus* GG concomitantly with a rotavirus vaccination showed an increased number of IgA secreting cells.

A study conducted to examine IgA production by intestinal mucosal lymphoid cells in mice showed that *B. bifidum* significantly induced IgA production in Peyer's patches and mesenteric lymph nodes, and that optimal secretion was obtained with probiotics encapsulated in alginate microparticles. Surprisingly, rather than inducing a specific humoral immune response, *B. bifidum* apparently had a more systemic immune effect.

Another study demonstrated that a peptide fraction derived from *Lactobacillus helveticus*- fermented milk contributed to induce local mucosal and systemic IgA immune responses in mice that were infected with *E. coli* O157:H7 (Delcenserie et al. 2008).

iv. Modulation of cytokine production

Probiotics have also been demonstrated to modulate cytokine production in a strain-dependent manner. These immunomodulatory capacities of probiotic strains have been extensively studied using various in vitro co-culture assays that employ different types of immune cells such as human monocyte-derived dendritic cells, human peripheral blood mononuclear cells and mouse bone-marrow-derived dendritic cells and use cytokine production profiles as a functional read-out. Interleukin-10 (IL-10) which is associated with T helper 2 (T_H2) cell or T regulatory (T_{Reg}) cell stimulation is typically used as a marker for anti-inflammatory effects, whereas the p70 IL-12 heterodimer and tumor necrosis factor (TNF), which are associated with both T_H1 cell stimulation and the induction of interferon-γ (IFN- γ) production by T cells and natural killer (NK) cells, are commonly measured as markers for pro-inflammatory responses (Bron et al. 2012).

It has been proposed that probiotics fall into two main categories: those which are 'immunostimulatory' characterized by their ability to induce IL-12 and therefore augment host defense via enhancement of NK cell activity and T_H1 pathways, and those which are 'immunoregulatory' characterized by their ability to induce IL-10 and the T regulatory pathway. In general, lactobacilli tend to fall in the immunostimulatory category, whereas bifidobacterium tend to fall in the immunoregulatory category (Yaqoob 2014).

It has been revealed that lactobacilli, such as *Lactobacillus casei* Shirota or *Lactobacillus reuteri* ATCC 23272, induce T_H1 cells via the induced production of IL-12 generated by macrophages and dendritic cells, and *Bifidobacterium bifidum* W23 and *Bifidobacterium longum* W52 inhibit the production of cytokines generated by T_H2 cells via the production of IL-10 generated by monocytes (Chiba et al. 2009). Another study also demonstrated that T cell-derived IL-10 suppresses T cell-dependent intestinal inflammation in *Bifidobacterium breve*-treated severe combined immunodeficient (SCID) mice (Jeon et al. 2012).

f. Interference with quorum sensing signaling molecules

Bacteria communicate with each other as well as with their surrounding environment through chemical signaling molecules called auto-inducers. This phenomenon of communication is known as quorum sensing and one of its characteristics is that it can control the gene expression of the entire community in response to changes in cell number.

Probiotic bacteria such as lactobacillus, bifidobacterium and *Bacillus cereus* strains degrade the auto-inducers of pathogenic bacteria by enzymatic secretion or production of auto-inducer antagonists and thereby control the virulence gene expression in pathogenic bacteria. *L. acidophilus* secretes a compound that inhibits the quorum sensing signaling or interferes with the bacterial transcription of the *E. coli* O157 gene which is involved in colonization and thus helps prevent bacterial toxicity. Similar results have also been reported from studies using *B. cereus* and *Bacillus toyoi* probiotic bacteria (Brown 2011; Goudarzi et al. 2014).

Probiotics in human health and disease

Probiotics have been shown to promote a variety of biological effects in a number of physiological conditions and pathologies, and the overall health benefits of probiotic microorganisms has been depicted in Fig. 1.

a. Intestinal-related diseases

i. Antibiotic-associated diarrhea

Mild or severe episodes of diarrhea are common side effects of antibiotic therapy as the normal microflora tends to be suppressed, encouraging the overgrowth of opportunistic or pathogenic strains. Treatments with *Bacillus* spp., *Bifidobacterium* spp., *Lactobacillus* spp., *Lactococcus* spp., *Leuconostoc cremoris*, *Saccharomyces* spp., or *Streptococcus* spp., individually or in combination were shown to have a protective effect in preventing antibiotic-associated diarrhea (Fontana et al. 2013; Kechagia et al. 2013). A meta-analysis consisting of 34 studies which included 4138 patients reported that the pooled relative risk (RR) for antibiotic-associated diarrhea (ADD) in the probiotic group versus placebo was 0.53 [95 % CI: 0.44-0.63] which in terms of the risk reduction corresponded to a number needed to treat (NNT) of 8 [95 % CI: 7–11]. Further, the pooled RR from 6 studies during *Helicobacter pylori* treatment was 0.37 [95 % CI: 0.20-0.69] corresponding to a NNT of 5 [95 % CI: 4–10], while the pooled RR excluding studies during *H. pylori* treatment was 0.56 [95 % CI: 0.46-0.67] corresponding to a NNT of 9 [95 % CI: 7–12], which clearly indicates a greater risk reduction in the pooled analysis of studies having *H. pylori* eradication regimens (Videlock and Cremonini 2012).

ii. Rotavirus diarrhea

Rotavirus is the most common cause of acute infantile diarrhea in the world and a significant cause of infant mortality. Clinical studies have shown that probiotics such as *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri*, *Lactobacillus casei* Shirota, *Bifidobacterium animalis* Bb12 can shorten the duration of acute rotavirus diarrhea with the strongest evidence pointing to the effectiveness of *L. rhamnosus* GG and *B. animalis* Bb12 (Kechagia et al. 2013).

iii. Travellers' diarrhea

People traveling to warmer climates and less-developed countries experience a high incidence of diarrhea, often in the 50 % range (Goldin and Gorbach 2008). With regard to this, a meta-analysis by Guarino et al. (2008) revealed evidence of a protective effect by *Saccharomyces boulardii* and by a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*.

iv. Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic condition affecting 3-25 % of the population for which no curative treatment is available. Accordingly, therapy is aimed at reducing the symptoms (Fontana et al. 2013). A study by Drouault-Holowacz et al. (2008) reported an increase in patients with satisfactory relief of overall IBS symptoms after receiving a probiotic mix of *Bifidobacterium longum* LA101, *Lactobacillus acidophilus* LA102, *Lactococcus lactis* LA103, *Streptococcus thermophilus* LA104. Another study by Enck et al. (2008) reported that the use of the bacterial lysate of *Enterococcus faecalis* and *Escherichia coli* as being effective in reducing the typical symptoms of IBS. The combined data from a meta-analysis of 14 randomized placebo controlled trials suggested a modest improvement in the overall symptoms of IBS after several weeks of probiotics treatment with the overall odds ratio (OR) of 1.6 [95 % CI: 1.2-2.2] for the dichotomous data from seven trials (895 participants); and for continuous data from six trials (657 participants), the standardized mean difference (SMD) was 0.23 [95 % CI: 0.07-0.38] (Hoveyda et al. 2009).

v. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is an umbrella term comprising different conditions of the gut, of which the two main types are ulcerative colitis and Crohn's disease; that are characterized by chronic or recurrent mucosal inflammation. The nonpathogenic strain *E. coli* Nissle 1917 has proved to be effective in preventing relapse in Crohn's disease patients and

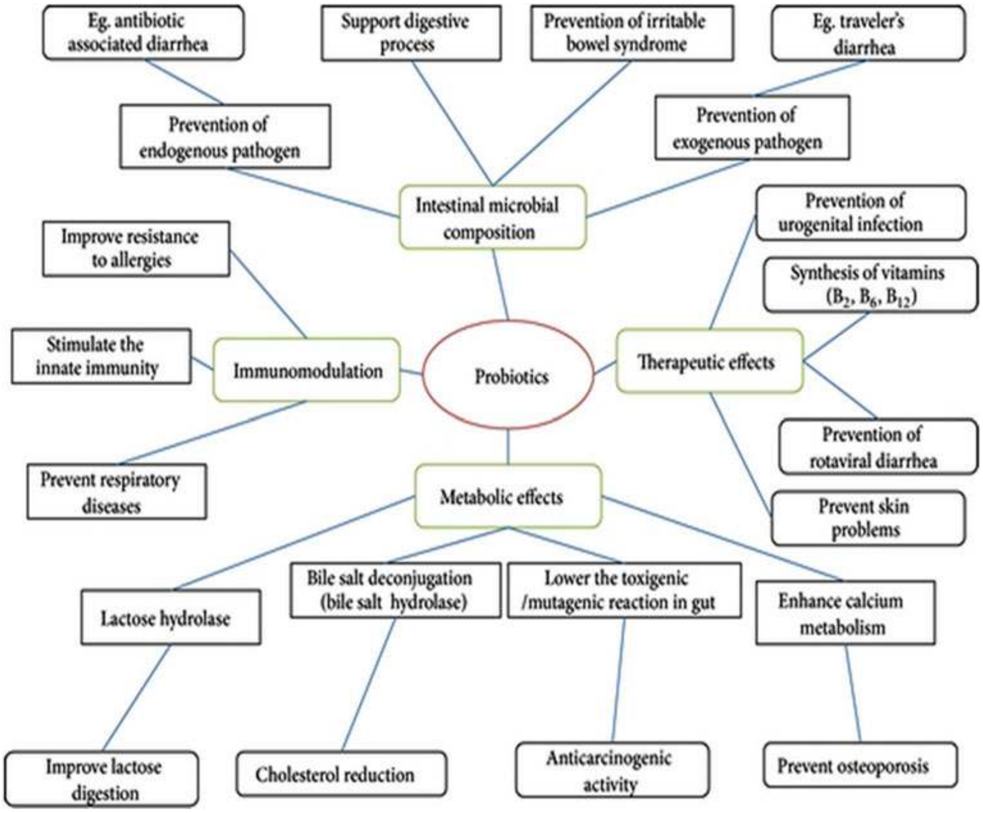

Fig. 1 Overall benefits of probiotic bacteria on human health (Anandharaj et al. 2014)

S. boulardii has shown some success in relieving the symptoms of active Crohn's disease and also in reducing the risk of a relapse (Maurya et al. 2014).

vi. Lactose intolerance

Lactose intolerance is a genetically determined beta-galactosidase (lactase) deficiency resulting in the inability to hydrolyze lactose into the monosaccharides glucose and galactose. Lactose intolerant individuals develop diarrhea, abdominal discomfort, and flatulence after consumption of milk or milk products. The use of *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus* has been effective in this direction, partly because of higher beta-galactosidase (lactase) activity (Kechagia et al. 2013).

In general, probiotics are beneficial in the treatment and prevention of gastrointestinal diseases; but before choosing a probiotic for the purpose, the type of disease and probiotic species (strain) are the most important factors to be taken into consideration. This is according to the conclusion from a meta-analysis which included randomized controlled trials in humans that used a specified probiotic in the treatment or prevention of pouchitis, infectious diarrhea, irritable bowel syndrome, *Helicobacter pylori*, *Clostridium difficile* disease, antibiotic associated diarrhea, traveler's diarrhea or necrotizing enterocolitis. This meta-analysis which contained 74 studies, 84 trials and 10,351 patients showed that in general probiotics were found to have a beneficial effect on the treatment and prevention of all eight gastrointestinal diseases with a relative risk of 0.58 [95 % CI: 0.51-0.65]. But out of the eight diseases, only six showed positive significant effects; whereas in the case of traveler's diarrhea and necrotizing enterocolitis, probiotics showed no efficacy. This effect may be due to the low number of studies on these diseases, or in the case of traveler's diarrhea where the underlying mechanism of the disease is often not bacterial. Further, out of the eleven species and species mixtures which were analyzed, majority showed positive significant effects except for *Lactobacillus acidophilus*, *Lactobacillus plantarum*, and *Bifidobacterium infantis* (Ritchie and Romanuk 2012).

b. Allergy

A limited number of strains have been tested for their efficiency in the treatment and prevention of allergy in infants (Kechagia et al. 2013). A study on breast fed infants suffering from atopic eczema reported that *Bifidobacterium lactis* and *L. rhamnosus* GG were found to be effective in decreasing the eczema severity. Furthermore, *L. rhamnosus* GG was found successful in preventing the occurrence of atopic eczema in high risk infants (Isolauri et al. 2000). Probiotics however have not been very successful in alleviating symptoms of asthma (Kechagia et al. 2013). This is in agreement with a meta-analysis observation which included seventeen studies reporting data from 4755 children (2381 in the probiotic group and 2374 in the control group) and which reported that infants treated with probiotics had a significantly lower risk ratio (RR) for eczema compared to controls (RR 0.78 [95 % CI: 0.69-0.89], $p=0.0003$), especially those supplemented with a mixture of probiotics (RR 0.54 [95 % CI: 0.43-0.68], $p<0.00001$). But no significant difference in terms of prevention of asthma (RR 0.99 [95 % CI: 0.77-1.27], $p=0.95$), wheezing (RR 1.02 [95 % CI: 0.89-1.17], $p=0.76$) or rhino-conjunctivitis (RR 0.91 [95 % CI: 0.67-1.23], $p=0.53$) was documented. The results of this meta-analysis indicate that probiotic supplementation prevents infantile eczema; thus suggesting a new potential indication for probiotic use in pregnancy and infancy (Zuccotti et al. 2015).

As far as food allergy is concerned, it is described as an immunologically mediated adverse reaction against dietary antigens leading to secondary intestinal inflammation and disturbances. The mechanism of the immune modulating effect of *L. rhamnosus* GG are not entirely understood but it seems to be related with the antigen's transport across the intestinal mucosa (Kechagia et al. 2013).

c. Reduction in serum cholesterol

An in vivo study on the cholesterol-lowering potential of *Lactobacillus casei* subsp. *casei* in rats reported that the cholesterol levels were lower in the plasma of groups fed fermented milk by 2 – 11 % and by 15 – 25 % in groups fed lyophilized culture as compared to the group fed skim milk (Mishra et al. 2015).

On this aspect, a number of cholesterol lowering mechanisms by *Lactobacillus* strains have been proposed including assimilation of cholesterol by growing cells, binding of cholesterol to cellular surface, incorporation of cholesterol into the cellular membrane, deconjugation of bile via bile salt hydrolase, and coprecipitation of cholesterol with deconjugated bile. But the exact mechanisms still remain unclear and controversial (Anandharaj et al. 2014).

A meta-analysis of 13 randomized controlled trials which included 485 participants with high, borderline high and normal cholesterol levels reported that the pooled mean net change in total cholesterol for those treated with probiotics compared to controls was −6.40 mg dl^{-1} [95 % CI: −9.93 to −2.87], the mean net change in low-density lipoprotein (LDL) cholesterol was −4.90 mg dl^{-1} [95 % CI: −7.91 to −1.90], the mean net change in high-density lipoprotein (HDL) cholesterol was −0.11 mg dl^{-1} [95 % CI: −1.90 to −1.69] and the mean net change in triglycerides was −3.95 mg dl^{-1} [95 % CI: −10.32 to −2.42]. These results indicate that a diet rich in probiotics decreases total cholesterol and LDL cholesterol concentration in plasma for participants with high, borderline high and normal cholesterol levels (Guo et al. 2011).

d. Prevention of dental caries formation

Streptococcus mutans is the main microorganism involved in causation of dental caries. The use of probiotics like *L. rhamnosus* GG has been reported to inhibit oral colonization by cariogenic pathogens and thereby reduce tooth decay incidence in children (Goel et al. 2014). Twetman and Keller (2012) reported that a search for retrieving papers containing relevant clinical trials on the use of probiotic bacteria as a potential and clinically applicable anti-caries measure yielded 2 animal and 19 human studies. Out of the 19 papers reviewed, 12 papers reported a significant reduction of *Streptococcus mutans* in saliva or plaque following daily intake of probiotic lactobacilli or bifidobacteria; whereas 3 papers reported an increase of lactobacilli. But it was also outlined that a high degree of heterogeneity among the included investigations hampered the analysis. There were further three caries trials in preschool children and the elderly which demonstrated prevention of caries formation between 21 % and 75 % following regular intakes of milk supplemented with *L. rhamnosus*. But in their conclusion the authors noted that large-scale clinical studies with orally derived specific anti-caries candidates are still lacking.

e. Prevention of respiratory infections

A meta-analysis that included ten randomized controlled trial (RCT) comparing probiotics with placebo to prevent acute upper respiratory tract infections reported that probiotics were more effective than the placebo in reducing the number of participants experiencing episodes of acute respiratory infections, the rate ratio of episodes of acute upper respiratory tract infections and reducing antibiotic use.

Another meta-analysis consisting of five randomized controlled trial (RCT) showed that the administration of probiotics is associated with lower incidence of ventilator-associated pneumonia compared with the placebo (Fontana et al. 2013).

f. Urinary tract infections

Urinary tract infections (UTI) are common among women and frequently have a tendency to recur. The causative organisms include *E. coli*, *Proteus* spp., *Klebsiella* spp., *Staphylococcus* spp., which are mainly intestinal uropathogens. The depletion of vaginal *Lactobacilli* is associated with UTI risk, which suggests that repletion might be beneficial (Fontana et al. 2013; Maurya et al. 2014). It has been found that high level vaginal colonization with *Lactobacillus crispatus* probiotic was associated with a significant reduction in recurrent UTI (Stapleton et al. 2011). Data from a random-effects model meta-analysis comparing incidence of recurrent UTI in 294 adult women patients across five studies showed no statistically significant difference in the risk for recurrent UTI in patients receiving *Lactobacillus* versus controls, as indicated by the pooled risk ratio of 0.85 [95 % CI: 0.58-1.25, p=0.41]. But when a sensitivity analysis was performed which excluded studies using ineffective strains and studies testing for safety; and included data from 127 patients in two studies, observed a statistically significant decrease in recurrent UTI in patients given *Lactobacillus* denoted by the pooled risk ratio of 0.51 [95 % CI: 0.26-0.99, p= 0.05] with no statistical heterogeneity (I^2=0 %). These results indicate that probiotic strains of *Lactobacillus* are safe and effective in preventing recurrent UTI in adult women. But the authors in their conclusion stated that more randomized clinical trials (RCTs) are required before a definitive recommendation can be made; since the population contributing data to this meta-analysis was small (Grin et al. 2013).

g. Prevention of osteoporosis

One of the main bone diseases which is associated with aging and postmenopausal condition is osteoporosis; with one of the most serious problems among women over 50 years of age being hip fracture due to osteoporosis. The possibility of wrist, hip, or spine fracture is estimated to be parallel to the risk of heart disease (approximately 15 %). In this regard, a few animal studies and a particular study on humans demonstrated a positive effect of probiotics on bone metabolism and bone mass density. In the human study, twenty postmenopausal women with a mean age of 65 years and a mean body mass index (BMI) of 26 were assessed for the effects of probiotics on bone. The study was a double-blind randomized crossover study with the subjects being segregated into two groups; in which the group consuming *Lactobacillus helveticus* fermented milk was compared to the control milk consumption group. The results from this study confirmed the reduction of parathyroid hormone (PTH) followed by an increase in serum calcium levels in the group that consumed *Lactobacillus* fermented milk and as a consequence of which there was reduced bone resorption. Further, the ionized serum calcium, total calcium, phosphate, and urinary calcium were higher in the group that consumed *L. helveticus* fermented milk as compared to the control group.

Although the exact mechanisms by which probiotic bacteria exert their effects on bone health in humans is still unclear; nonetheless the principal mechanisms by which probiotic bacteria increase the bioavailability of minerals include (i) increasing mineral solubility by the production of short chain fatty acids; (ii) producing phytase enzyme that overcomes the effects of depressed mineral availability due to phytate; (iii) reducing intestinal inflammation which in-turn increases bone mass density; and (iv) hydrolyzing the glycosidic bonds of estrogenic food in the intestines (Parvaneh et al. 2014).

h. Anticancer effects

Several animal studies have shown that supplementation with specific strains of lactic acid bacteria (probiotics) could prevent the establishment, growth, and metastasis of transplantable and chemically induced tumors. Studies in human subjects have also revealed that probiotic therapy may reduce the risk of colon cancer by inhibiting transformation of procarcinogens to active carcinogens, binding/inactivating mutagenic compounds, producing antimutagenic compounds, suppressing the growth of pro-carcinogenic bacteria, reducing the absorption of mutagens from the intestine, enhancing immune function, have anti-proliferative effects via regulation of apoptosis and cell differentiation, fermentation of undigested food which helps generate short-chain fatty acids (SCFA), and inhibition of tyrosine kinase signaling pathways (Gill and Guarner 2004; Uccello et al. 2012). An inverse relationship between the consumption of fermented dairy products, containing lactobacilli or bifidobacteria, and the incidence of colon and breast cancer has also been reported in epidemiological and population based case–control studies.

However, there is little “direct experimental evidence” regarding the anticancer effectiveness (tumor suppression) of probiotic therapy in humans (Gill and Guarner 2004). But as of the moment, there is a completed phase 2 trial assessing the role of probiotics on gut microbiota and colorectal cancer but the results have not been published yet. Furthermore, the role of the VSL#3 probiotic combinations in rectal cancer is being investigated in a phase 3 clinical trial and the results are also due (Whyand and Caplin 2014).

Probiotics for ruminants

In adult ruminants, probiotics have mostly been selected to target the rumen compartment, which is the main site of feed digestion, and the most common probiotics for ruminants being the live yeast (*Saccharomyces cerevisiae*). In dairy ruminants, live yeasts have been shown to improve performance with respect to increasing the dry matter intake and milk production. Further in beef cattle, growth parameters (average daily gain, final weight, intake, feed to gain ratio) has been reported to be improved by daily live yeast supplementation.

There is also an increasing amount of evidence through in vitro studies that live yeast stabilizes ruminal pH and decreases the risk of acidosis by limiting lactate production by *Streptococcus bovis* and favoring lactate uptake by *Megasphaera elsdenii* (Chaucheyras-Durand and Durand

2010). Regarding the use of lactate-producing bacteria like *Enterococcus* and *Lactobacillus*, the underlying principle behind it is that by providing a constant supply of lactate in the rumen, lactate-utilizing bacteria are stimulated and the overall microflora can adapt to the presence of a higher concentration of lactate (Chiquette 2009). Alternately, lactate users like *Megasphaera elsdenii* or *Propionibacterium* spp., could be administered as direct-fed microbials to avoid ruminal lactate accumulation.

Regarding the strategy to reduce digestive carriage by adult ruminants of human pathogens, certain strains of *Lactobacillus acidophilus* have been shown to decrease the numbers of *E. coli* O157 and also appear to reduce shedding of *Salmonella enterica*.

In young pre-ruminants, bacterial probiotics such as *Lactobacillus* spp., *Bifidobacterium* spp., *Enterococcus* spp., *Propionibacterium* spp., or *Bacillus* spores, represent an interesting means of stabilizing the gut microbiota and limiting the risk of pathogen colonization by generally targeting the small intestine as the rumen is not yet developed (Chaucheyras-Durand and Durand 2010).

Probiotics for pigs

The most common probiotics for monogastric animals are the yeasts (*Saccharomyces boulardii*), and bacteria (*Lactobacillus* spp, *Enterococcus* spp., *Pediococcus* spp., *Bacillus* spp.) which target the hindgut (cecum, colon) that harbors an abundant and very diverse microbial population mainly composed of bacteria and archaea (Chaucheyras-Durand and Durand 2010).

Studies suggest that certain microbial supplements are useful in protecting the young pigs particularly from intestinal infections around weaning. This period and other stressful mixing events during their lives is probably important because it is at these points that pigs pick up important zoonotic pathogens like *Salmonella enterica* and *Streptococcus suis* (Kenny et al. 2011). It is in this context that performance benefits have been reported after weaning by using *S. boulardii*. Similar findings have been reported with *Pediococcus acidilactici* - based probiotic supplementation. The benefits of intestinal IgA secretion and reduction of translocation of enterotoxigenic *E. coli* have also been observed with *S. boulardii* or *P. acidilactici* given to piglets (Chaucheyras-Durand and Durand 2010).

Furthermore in a recent study, Mishra et al. (2014) indicated that dietary supplementation with *S. cerevisiae* or *L. acidophilus* had a positive effect on the performance of weaned piglets.

Probiotics for poultry

Probiotic species belonging to *Lactobacillus*, *Streptococcus*, *Bacillus*, *Bifidobacterium*, *Enterococcus*, *Aspergillus*, *Candida* and *Saccharomyces* have been shown to have a beneficial effect on broiler performance with evidences of increased resistance of chickens to *Salmonella*, *E. coli* or *Clostridium perfringens* infections (Chaucheyras-Durand and Durand 2010; Kral et al. 2012). La Ragione et al. (2001) reported that oral inoculation of *Bacillus subtilis* spores could reduce intestinal colonization of *E. coli* O78:K80 in chickens. Probiotics have also been reported to increase feed efficiency and productivity of laying hens with an improvement in egg quality (decreased yolk cholesterol level, improved shell thickness, egg weight) (Chaucheyras-Durand and Durand 2010).

Probiotics in aquaculture practices

The gastrointestinal microbiota of aquatic species is particularly dependent on the external environment due to the flow of water which passes through the digestive tract. Thus, the majority of bacteria are transient in the intestine due to constant intake of water and food, together with the microorganisms present in them. Apart from the potentially pathogenic bacteria such as *Salmonella*, *Listeria*, and *E. coli*, probiotic bacteria and other microorganisms have also been identified in the gastrointestinal tract of aquatic animals which include the gram-positive bacteria such as *Bacillus*, *Carnobacterium*, *Enterococcus*, and several species of *Lactobacillus*; gram-negative, facultative anaerobes such as *Vibrio* and *Pseudomonas*, as well as certain fungi, yeasts, and algae of the genera *Debaryomyces*, *Saccharomyces*, and *Tetraselmis*, respectively.

The use of probiotics in aquaculture is relatively recent and the initial application had been to test their ability to increase growth of hydrobionts (organisms that live in water). Then subsequently probiotics were used for the purpose of improving water quality and control of bacterial infections. Furthermore, there are also documented evidences that probiotics can improve the digestibility of nutrients, increase tolerance to stress, and encourage reproduction.

Currently, there are commercial probiotic products prepared from various bacterial species such as *Bacillus* spp., *Lactobacillus* spp., *Enterococcus* spp., *Carnobacterium* spp., and the yeast *S. cerevisiae* among others, and their use is regulated by careful management recommendations (Cruz et al. 2012).

Regarding the role of probiotics as growth promoters, Lara et al. (2003) reported that when the diet of Nile tilapia (*Oreochromis niloticus*) was amended with a probiotic *Streptococcus* strain, there was a significant increase in crude protein, crude lipid content, together with an increase in the weight of the fish. Further, Balcazar (2003) demonstrated that the administration of a mixture of bacterial strains (*Bacillus* and *Vibrio* spp.) positively influenced the growth and survival of white shrimp juveniles.

In the context of disease control, Rengpipat et al. (2000) had reported that the use of *Bacillus* spp. (strain S11) provided disease protection by activating both cellular and humoral immune defenses in tiger shrimp (*Penaeus monodon*). Further, it has also been demonstrated that oral administration of *Clostridium butyricum* bacteria to rainbow trout enhanced the resistance of fish to vibriosis by increasing the phagocytic activity of leucocytes (Pandiyan et al. 2013).

In relation to improvement of water quality, it had been observed that when *Streptomyces* was applied as a probiotic in the laboratory culture of *Penaeus monodon*, there was a marked improvement in the water quality parameters accompanied by an increase in the length and weight of the tiger shrimp (Lakshmi et al. 2013).

As agents for improving nutrient digestion, Tovar et al. (2002) reported that the probiotic yeast *Debaryomyces hansenii* HF1 has the ability to produce spermine and spermidine, the two polyamines involved in the differentiation and maturation of the gastrointestinal tract in mammals. In addition, this yeast secretes amylase and trypsin enzymes that aid digestion in sea bass larvae. Probiotics have also been used in the case of European bass larvae (*Dicentrarchus labrax*) (Cruz et al. 2012).

With regard to increasing the level of stress tolerance, Carnevali et al. (2006) reported that supplementation of *Lactobacillus delbrueckii* subsp. *delbrueckii* in the diet of European sea bass (*Dicentrarchus labrax*) significantly lowered the levels of cortisol in fish tissues.

Regarding the effect on the reproductive performance of fishes, Ghosh et al. (2007) reported that using a strain of *Bacillus subtilis* isolated from the intestine of *Cirrhinus mrigala* and its subsequent incorporation at different concentrations to four species of ornamental fishes: *Poecilia reticulata*, *Poecilia sphenops*, *Xiphophorus helleri*, and *Xiphophorus maculates*, led to an increase in the gonadosomatic index, fecundity, viability, and production of fry from the females of all four species. It was further proposed that the complex B vitamins synthesized by the probiotic, especially thiamine (vitamin B1) and vitamin B12, contributed to reduce the number of dead or deformed alevins.

Future prospects of probiotics as antioxidants

Various studies during the recent times have focused on the antioxidative property of probiotics and a few patents on the use of *Bifidobacterium lactis* BS05, *Lactobacillus acidophilus* LA06, and *Lactobacillus brevis* LBR01, have been recently granted in this area. There are also strong evidences emerging for the antioxidative activity of *Lactobacillus plantarum*, *L. helveticus*, *L. acidophilus*, *Lactobacillus fermentum*, *L. casei*, *L. rhamnosus* GG, and a few bifidobacteria and foods containing these organisms. Although the mechanisms of antioxidative action has not been properly understood; but the production of bioactive peptides has been considered an effective mode of antioxidative activity in foods containing probiotic bacteria. Peptides obtained from hydrolyzed food proteins have been shown to possess antioxidative activities, which can impart protection against the peroxidation of lipids or fatty acids. It has been observed that the peptic digest of casein liberates small peptides with radical scavenging activity. The antioxidant ability was considered due to the presence of histidine and some hydrophobic amino acids in high concentrations. Increased antioxidant activity of milk during fermentation with commonly used dairy starter cultures which include *Leuconostoc mesenteroides* subsp. *cremoris* strain, *L. jensenii*, and *L. acidophilus* has also been observed. Further, *L. rhamnosus* GG was reported to have potent antioxidative activity by down-modulating the reactive oxygen species (ROS) production and phagocytic capacity of neutrophils. It has also been reported that some probiotics increased the activity of antioxidative enzymes like glutathione S-transferase, glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase or modulate the circulatory oxidative stress which in turn protects cells against carcinogen-induced damage. However, it should be noted that the antioxidative property of probiotics is strain specific.

The manifestations that probiotics have antioxidant attributes is significant in the sense that this can help diversify the potential sources of antioxidants which can be safely used; which until now has been the property of substances mostly available in plant material only; including garlic, broccoli, green tea, soybeans, tomatoes, carrots, Brussels sprouts, kale, cabbages, onions, cauliflower, red beets, cranberries, cocoa, blackberries, blueberries, red grapes, prunes, and citrus fruits. This is highly desirable as because reactive oxygen species (ROS) - mediated oxidative stress is known to play a vital role in the development of chronic diseases such as cancer, diabetes, heart disease, stroke, Alzheimer’s disease, rheumatoid arthritis, cataract, and aging (Mishra et al. 2015).

Conclusion

There are numerous scientific evidences supporting the incorporation of probiotics in nutrition as a means of derivation of health benefits. In humans, the best documented effects are for bowel disorders such as lactose intolerance, antibiotic-associated diarrhea and infectious diarrhea; allergy; and a large number of evidences are still emerging concerning their potential role in various other conditions (Kechagia et al. 2013). Even in animal health and nutrition, probiotics can expect a promising future because of the fact that they offer a viable alternative for the generation of a higher-quality livestock product in terms of size, production time, and health (Chaucheyras-Durand

and Durand 2010; Cruz et al. 2012). All these become more important since there is a worldwide concern over the present state of antimicrobial resistance among zoonotic bacteria that potentially circulate among food-producing animals including poultry, beef and dairy cattle, goats, sheep and aquaculture. This has resulted in the general public perception that antibiotic use by humans and in food animals, selects for the development of antimicrobial resistance among food-borne bacteria that could complicate public health therapies. Consequently, there is a need for developing novel intervention methods to deal with this situation and, on this count a potentially efficient and versatile option being the use of probiotics to selectively target pathogenic organisms while avoiding killing of beneficial organisms (Seal et al. 2013).

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