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Case study

CLINICAL APPLICATIONS OF PROBIOTICS

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ABSTRACT
For some decades now, bacteria known as probiotics have been added to various foods because of their beneficial effects for human health. Examples of foods containing probiotics are yogurt, fermented and unfermented milk, miso, tempeh, soy beverages and some juices. Lactic acid bacteria (LAB) and bifidobacteria are the most common types of microbes used as probiotics; but certain yeasts and bacilli may also fit the bill. These can also be formulated into drugs and dietary supplements. Probiotics are also called "friendly bacteria" or "good bacteria". They are gaining importance because of the innumerable benefits, e.g. treating lactose intolerance, gastroenteritis infection, allergies, dental caries, inflammatory bowel disease and hypercholesterolemia. With the current focus on disease prevention and the quest for optimal health at all ages, the probiotics potential could reign high. This article discusses the summary of research on the health benefits of probiotics and offers practical information to help health professionals and even the layman.

KEY WORDS: Probiotics, lactic acid bacteria, infections, disease management, health benefits.

INTRODUCTION

Each day, every human being ingests a large number of living microorganisms, predominantly bacteria. For several decades now, bacteria called probiotics have been added to some foods because of their beneficial effects for human health (Parvez *et al*., 2006). Although these organisms are naturally present in food and water, they can also be deliberately added during the processing of foods such as sausages, cheese, yogurt and fermented milk products. The bacteria in yogurt and fermented milk products constitute the most important source of probiotics for humans. In the industrialised world, many infectious diseases are treatable and no longer the predominant cause of premature morbidity. Nevertheless, diseases associated with microorganisms are far from resolved by current therapeutics and the discovery of new and antibiotic resistant pathogens further justifies the search for new strategies to coantrol them. This is exacerbated by the continuous emergence of novel variants of established pathogens. Recent research has revealed a potential therapeutic role for the manipulation of the microbiota in the maintenance of human health and treatment of various mucosal disorders. Probiotic microorganisms can shape the immune system both at the local and systemic level which will allow future probiotics as treatments for many diseases. The benefits include either a shortened duration of infections or decreased susceptibility to pathogens (Antoine, 2010).

Advances in the field of medicine and public health during the last decades have increased the survival rate of children in their early life; however, every 15 seconds one child still dies from diarrheal disease mostly associated with contaminated food, water or HIV/AIDS (Reid *et al*., 2005). It was also found that out of approximately 8.795 million deaths in the world among children below 5 years of age, 68% was due to infectious diseases, with 49% of these deaths taking place in developing countries such as India, Nigeria, Democratic Republic of Congo, Pakistan and China (Black *et al*., 2010). The World Health Organization (WHO) also predicts that by 2025 there will still be around 5 million deaths among children below 5 years of age and 97% of these deaths will be in developing countries (WHO, 1998). In addition to these major problems; there are other nutritional related disorders such as lactose intolerance and high cholesterol levels that affect people in developing countries. Therefore, urgent and sustainable measures are required to be undertaken by developing nations to improve the health of their people. Probiotic interventions could provide an invaluable opportunity to ameliorate this current situation. This review will thus outline the potential health benefits of probiotics, health improvement, infection control and disease management, which could be eliminated by the use of different types of direct uses of probiotics or by the use of foods containing probiotics.

Probiotic Concept

The word “probiotic” (origins: Latin *pro* meaning “for” and Greek *bios* meaning “life”) was first used in 1954 to indicate substances that were required for a healthy life. Out of a number of definitions, the most widely used and accepted definition is that proposed by a joint FAO/WHO panel (FAO/WHO, 2001): *“Live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host”*. There are a large number of probiotics currently used and available in dairy fermented foods, especially in yogurts. Lactic acid bacteria (LAB)

constitute a diverse group of organisms providing considerable benefits to humankind, some as natural inhabitants of the intestinal tract and others as fermentative LAB used in food industry, imparting flavour, texture and possessing preservative properties. Beyond these, some species are administered to humans as live microbial supplements, which positively influence our health mainly by improving the composition of intestinal microbiota. For this reason, they are called probiotics. Some selected strains of *Lactobacillus, Bifidobacterium, Streptococcus, Lactococcus* and *Saccharomyces* (Table 1) have been promoted in food products because of their reputed health benefits.

TABLE 1. Microorganisms considered as probiotics (Toma and Pokrotnieks, 2006)

Lactobacillus	*Bifidobacterium*	*Other lactic acid bacteria*	*Non-lactic acid bacteria*
L. acidophilus	*B. adolescentis*	*Enterococcus faecalis*	*Bacillus cereus* var. *toyoi*
L. amylovorus	*B. animalis*	*Enterococcus faecium*	*Escherichia coli* Nissle 1917
L. casei	*B. bifidum*	*Lactococcus lactis*	*Propionibacterium freudenreichii*
L. crispatus	*B. breve*	*Leuconostoc mesenteroides*	*Saccharomyces cerevisiae*
L. delbrueckii subsp. *bulgaricus*	*B. infantis*	*Pediococcus acidolactici*	*Saccharomyces boulardii*
L. gallinarum	*B. lactis*	*Streptococcus thermophilus*	
L. gasseri	*B. longum*	*Sporolactobacillus inulinus*	
L. johnsonii			
L. paracasei			
L. plantarum			
L. reuteri			
L. rhamnosus			

Criteria to being Classified as a Probiotic

Among criteria for microorganisms to be included in the probiotics group are (Tomasik and Tomasik, 2003): 1) Survival on passing through gastrointestinal tract at low pH and on contact with bile; 2) Adhesion to intestinal epithelial cells; 3) Stabilization of the intestinal microflora; 4) Non-pathogenicity; 5) Survival in foodstuffs and possibility for production of pharmacopoeia lyophilized preparations; 6) Fast multiplication, with either permanent or temporary colonization of the gastrointestinal tract; and 7) Generic specifity of probiotics.

Mechanism of Action

There are several mechanisms by which probiotics are proposed to exhibit beneficial effects on the host and these can be broadly classified as microbiological, epithelial, or immunological in nature (Figure 1). Firstly, probiotic bacteria are able to modulate the composition of intestinal microbiota. This is primarily achieved through changes in the intestinal lumen environment such as lowering the pH level and competition for nutrients that result in physiologically restrictive conditions for the growth of pathogenic bacteria (Todorov *et al*., 2011). Probiotics can also compete with other microorganisms for binding to specific receptors on host epithelial cells, thereby preventing potential pathogen invasion (Setia *et al*., 2009). Modulation of colonization by probiotic bacteria can prevent harmful pathogens from persisting in the intestinal tract, thereby facilitating clearance by the immune system. In addition, some probiotic bacteria produce bacteriocins that inhibit the growth of pathogenic bacteria (Heng *et al*., 2011).

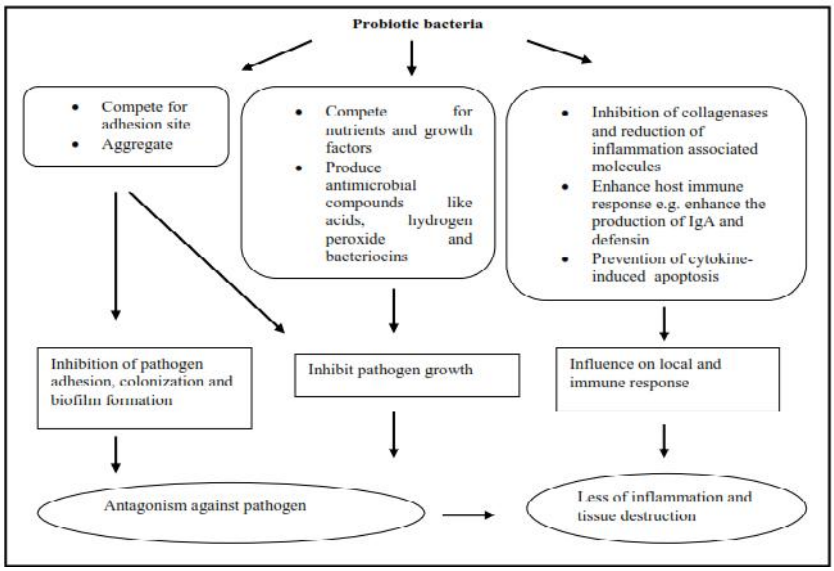

FIGURE 1: Various mechanism of action of probiotic bacteria

Another mechanism of probiotic action is directed at the epithelial surface where they modulate the integrity of the epithelial cell barrier and regulate the function and expression of tight junction proteins and mucus secretion (Caballero-Franco *et al*., 2007). Probiotics also produce significant quantities of short-chain fatty acids (SCFA) following fermentation of dietary fiber and exert potent anti-inflammatory and epithelial activities (Macia *et al*., 2012). Butyrate, a common SCFA, was found to modulate the expression of certain tight junction proteins such as cingulin, ZO proteins, and occludin to improve the epithelial barrier integrity (Peng *et al*., 2009). Various studies have found that probiotic bacteria can modulate both innate and adaptive immunity. The activation of TLRs by microbes initiates the immune response which can result in systemic and mucosal effects (Castillo *et al*., 2011). Other effects of probiotics that make them suitable for modulation of allergic disease include stimulation of mucosal IgA levels as well as allergen-specific B and T cell responses (Marschan *et al*., 2008; Maldonado Galdeano *et al*., 2011).

PROBIOTICS AND FOOD PRODUCTS

The range of food products containing probiotic strains is wide and still growing. The main products existing in the market are dairy-based ones including fermented milks, cheese, ice cream, buttermilk, milk powder, and yogurts, the latter accounting for the largest share of sales. Research has also shown potential to incorporate probiotics in non-dairy foods such as soy milk, soy cream cheese, nutritional bars, cereals, chocolate and variety of juices such as tomato, orange, grape, carrot, beet and cabbage juice (Bhadoria and Mahapatra, 2011; Nagpal *et al*., 2012). The factors that must be addressed in evaluating the effectiveness of the incorporation of the probiotic strains into such products are, besides safety, the compatibility of the product with the microorganism and the maintenance of its viability through food processing, packaging, and storage conditions. The product's pH for instance is a significant factor determining the incorporated probiotic's survival and growth, and this is one of the reasons why soft cheeses seem to have a number of advantages over yogurt as delivery systems for viable probiotics to the gastrointestinal tract (Kehagias *et al*., 2006).

Current technological innovations provide ways to overcome probiotic stability and viability issues offering new options for their incorporation in new media and subsequent satisfaction of the increasing consumer demand. Microencapsulation technologies have been developed to protect the bacteria from damage caused by external environment. By the introduction of a straw delivery system containing a dry form of the probiotic bacterium beverage manufacturers can now provide it to the consumer. In addition, viable spores of a spore forming probiotic are available in the market, offering advantages during processing. In the same time the potential of lantibiotics'—substances with antimicrobial properties—production by bifidobacteria is being explored in order to be applied in the food area (Pszczola, 2012; O'Sullivan, 2012).

ROLE OF PROBIOTICS IN VARIOUS DISEASES

Lactose malabsorption

The inability of adults to digest lactose, or milk sugar, is prevalent worldwide. Consumption of lactose by those lacking adequate levels of lactase produced in the small intestine can result in diarrhea, bloating, abdominal pain and flatulence the consumption of dairy products that are important for supplying calcium and preventing osteoporosis in people with lactose intolerance can be facilitated by probiotic bacteria**.** Hertzler and Clancy in 2003 conduct a research to determine the efficacy of Kefir in lactose digestion and tolerance in adults with lactose maldigestion. Subjects were fed test meals consisting of 20 g lactose portions of milk, plain and raspberry flavored kefir, and plain and raspberry flavored yogurt, each following an overnight (12 hour) fast. The flavoured kefir had an intermediate response. The yogurts and kefirs all similarly reduced the perceived severity of flatulence by 54 percent to 71 percent relative to milk. Abdominal pain and diarrhoea symptoms were negligible among the five treatments. Because kefir improved lactose digestion and tolerance in this study, its use may be another strategy for overcoming lactose intolerance.

A randomized control trial of six weeks with *L. rhamnosus* GG versus placebo showed overall negative results in 50 children and young adults, although there was a lower incidence of perceived abdominal distension in the *L. rhamnosus* GG group (Bausserman and Michail, 2005). *L. rhamnosus* GG, but not placebo, caused a significant reduction of both frequency and severity of abdominal pain compared to baseline, and influenced intestinal permeability testing (Francavilla *et al.*, 2010). A meta-analysis demonstrated that, compared with placebo, *L. rhamnosus* GG supplementation was associated with a significantly higher rate of treatment responders in the overall population with abdominal pain-related functional gastrointestinal disorders and in the irritable bowel syndrome (IBS) subgroup (Horvath *et al*., 2011). A randomized cross-over trial with VSL#3 and placebo, comprising 59 patients for six weeks, with a two-week washout period in-between, showed a superior effect of VSL#3 compared to placebo in symptom relief, as well as in abdominal pain/discomfort, abdominal bloating/ gassiness, and family assessment of life disruption (Guandalini *et al*., 2010). Probiotics are more effective than placebo in the treatment of patients with abdominal pain-related functional gastro-intestinal disorders, especially with respect to patients with IBS (Korterink *et al.*, 2014).

GASTROENTERITITIS

Acute infectious diarrhea

Acute diarrhea is defined as more often than usual bowel movements lasting 10–14 days. The main causes of this ailment are viral infections (rotavirus, adenovirus *etc*.), bacteria (*Salmonella* spp, some pathogenic strains of *Escherichia coli, Yersinia enterocolitica, Clostridium difficile* and other) and parasitic infections (*Giardia lamblia, Cryptosporidium parvum*) (Casburn-Jones and Farthing, 2004; Guarino *et al*., 2008). A number of clinical trials have tested the efficacy of probiotics in the prevention of acute diarrhea. Probiotics are useful as

treatment of acute infectious diarrhea in children. Different strains, including *L. reuteri* SD2112, *L. rhamnosus* GG, *L. casei* DN-114 001, and *S. cerevisiae* (boulardii) Lyo, tested in controlled clinical trials decreased the severity and duration of diarrhea. Meta-analysis concludes that these probiotics are safe and effective (Szajewska *et al*., 2006). The results of clinical trials involving a group of more than 500 children, aged 3 months to 3 years indicate that, among a number of probiotic strains, the use of *Lactobacillus* GG only showed significant effect of shortening of diarrhea duration in comparison with the control group (Canani *et al*., 2007). A meta-analysis study comprising of 63 trials with 8014 people mainly infants and children, showed that probiotics shortened the duration of acute infectious diarrhea by 25 hours, showed a 59% reduction in diarrhea lasting for more than 4 days and lesser diarrheal stool on day 2 after intervention (Allen *et al*., 2010).

In 2009–2010 in Spain, an analysis of the impact of *Lactobacillus salivarius* as a milk supplement in 6-month-old infants demonstrated safety and tolerability of probiotics (Maldonaldo *et al*., 2010). Carried out in France and Lebanon in 2010, a multicenter study of the impact of milk supplementation with the probiotic *S. boulardi* administered to children with acute diarrhea showed a significant reduction in the duration of diarrhea and body weight gain after body weight loss faster than the standard milk feeding (Le Luyer *et al*., 2010). Authors of a study conducted in Brazil on 186 children aged 6 to 48 months, hospitalized for acute diarrhea, demonstrated in a double-blind trial, that the administration of the probiotic yeast *S. boulardii* to patients results in shortening of the duration of symptoms compared with the placebo group. But it is important to provide a formulation containing probiotics within 72 hours of onset of symptoms (Correa *et al*., 2011). In another study assessing community acquired diarrhea in children, 8 studies showed that diarrhea duration was reduced by 14% and stool frequency on second day treatment was reduced by 13.1% (Applegate *et al*., 2013). The effect of probiotics on the course of acute diarrhea was considered to be clinically relevant in the case of diarrhea of viral etiology and the best results were achieved through the use of supplements in the initial stage of the onset of symptoms.

Antibiotic associated diarrhea (AAD)

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. The spectrum may range from diarrhoea without mucosal abnormality to pseudo membranous colitis. The latter is a severe form of AAD (caused by *Clostridium difficile*, cytotoxic strains of which may emerge after antibiotic use). AAD occurs in 5-35% of patients under antibiotic therapy and rates vary according to the specific antibiotic, host health and exposure to pathogens (McFarland, 2008). The use of antibiotics leads to the breakdown of the colonization defence systems leading to increased infections in individuals by opportunistic pathogens such as *Clostridium difficile* (Katz, 2006). *C. difficile* invasion occurs mainly due to antibiotic therapy, but other risk factors include ageing and hospitalization (Hickson, 2011). Moreover, the *C. difficile* associated diarrhea is responsible for around 10–20% of all cases of AAD and can occur even after 6-8 weeks of antibiotic therapy termination (Katz, 2006; Hickson, 2011). There is evidence that probiotic bacteria and yeast can be effective in preventing AAD and the recurrence of C. difficile infection in both children and adults (Plummer *et al*., 2004).

Some of the probiotics most commonly used to prevent AAD are *Lactobacillus rhamnosus* GG (LGG), *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium spp*., *Streptococcus spp*., and the yeast *Saccharomyces boulardii* (Katz, 2006). A study reported that the two most effective strains in preventing AAD and *C. difficile* infections are LGG and *S. boulardii*, which are generally considered safe and well tolerated (Guandalini, 2011). The risk of developing *C. difficile* infection in hospitalized patients reduced significantly after consumption of yogurt with *L.casei* DN-114 001, *S. thermophiles* and *L. bulgaricus* (Hickson *et al*., 2007). In addition, the effects of *L. plantarum* intake showed to have a preventive effect on milder gastrointestinal symptoms such as nausea and watery stools during treatment with antibiotics (Lonnermark *et al*., 2010).

Traveler's diarrhea

Traveler's diarrhea are symptoms manifested in an acute infection of the gastrointestinal tract, characterized by the excretion of a minimum of three unformed stools per day, associated with the change of residence, such as foreign travel. In more than 80% of cases the cause of traveler's diarrhea is a bacterial infection, the most common with *E. coli enterotoxic* ETEC strain, rarely *Campylobacter*, *Shigella* and *Salmonella* (Gascon, 2006). People traveling to warmer climates and less-developed countries experience a high incidence of diarrhea, often in the 50% range.

McFarland conducted a study on the use of probiotics in the prevention of traveler's diarrhea. Observations carried out by this author using *S. boulardii* probiotic yeast showed that 29–34% of the patients receiving 5×109–1 × 1010 CFU of probiotic for three weeks had symptoms of traveler's diarrhea, whereas patients in the placebo group suffering from traveler's diarrhea ranged 39–43%. In each of the four experiments, the beneficial effect of *S. boulardii* was statistically significant. Other probiotic strains used in such studies involve *L. acidophilus*, *L. bulgaricus* and *Streptococcus thermophilus*. A mixture of bacteria taken for two weeks demonstrated efficacy in 57% of patients, while in the control group, no diarrhea was observed only in 29% of patients. Prophylactic application of the preparation containing the *Lactobacillus* GG strain in a dose of 2×109 CFU for 2 weeks also proved its effectiveness in reducing the symptoms of traveler's diarrhea in 59% of patients in comparison with the control group, which reached a value of 53%. However, not all probiotic strains are effective in preventing traveler's diarrhea. The use of both *L. acidophilus* and *L. fermentum* in very large doses of the order of 2×1011 CFU did not bring the expected results, because the effectiveness of these preparations was comparable to, or slightly lower than that in the control group (McFarland, 2007).

Prevention and treatment of allergic reactions

Recent research in mucosal immunology demonstrated interactions between microbes and host at an early age even when mucosal barrier and immune system are still immature. Probiotics have been found to enhance the innate immunity and modulate pathogen induced inflammation via toll-like receptor-regulated signaling pathways (Vanderpool *et al*., 2008).

In randomized double blind placebo-controlled studies of probiotic use, *Lactobacillus GG* or placebo was given to pregnant mothers with a strong family history of eczema, allergic rhinitis or asthma, and to their infants for the first six months after delivery. The frequency of developing atopic dermatitis in the offspring's of pregnant mothers who received *Lactobacillus GG* was significantly reduced by 2, 4, and 7 years, by 50%, 44%, and 36% respectively (Kalliomäki *et al*., 2003; Kalliomäki *et al*., 2007). *Lactobacillus acidophilus* strain was not able to produce same result in a different study suggesting the strain specificity (Taylor *et al*., 2006). *Lactobacillus GG* in combination with *B. lactis* during pregnancy and breastfeeding reduced the risk of atopic eczema and allergic sensitization in child (Huurre *et al*., 2008).

Prevention of dental caries

To have a beneficial effect in limiting or preventing dental caries, a probiotic must be able to adhere to dental surfaces and integrate into the bacterial communities making up the dental bio film. It must also compete with and antagonize the cariogenic bacteria and thus prevent their proliferation. Several clinical studies have demonstrated that regular consumption of yogurt, milk or cheese containing probiotics led to a decrease in the number of cariogenic streptococci in the saliva and a reduction in dental plaque (Ahola *et al*., 2002; Nikawa *et al*., 2004). More specifically, Nikawa and colleagues reported that consumption of yogurt containing *Lactobacillus reuteri* over a period of 2 weeks reduced the concentration of *S. mutans* in the saliva by up to 80%. Comparable results were obtained by incorporating probiotics into chewing gum or lozenges (Caglar *et al*., 2006; Caglar *et al*., 2007).

Elimination of nasal pathogens

In a study of 209 healthy subjects, the consumption of a fermented milk product containing probiotics resulted in a significantly higher proportion of subjects with pathogenic bacteria eliminated from the nasal cavity, compared with consumption of a yogurt drink in the placebo group (Gluck and Gebbers, 2003). The pathogens removed included *Staphylococcus aureus, Streptococcus pneumoniae,* and b-hemolytic streptococci.

Treatment and prevention of relapses of inflammatory bowel disease

Ulcerative colitis

It is a chronic inflammatory disease of the mucous membrane of the rectum or the rectum and the colon of unknown etiology, leading in some cases to necrosis, ulceration, and perforation of the intestine as a result. It mostly affects young people between 20 and 40 years of age. In children with ulcerative colitis, administration of VSL#3 resulted in the induction and maintenance of remission of the disease (92.8%), compared with the results of the placebo group (Miele *et al*. 2009). A VSL#3 preparation consisting of 8 probiotic microorganisms – four strains of *Lactobacillus: L. acidophilus, L. casei, L. delrueckii subs. bulgaricus, L. plantarum,* three *Bifidobacterium* strains: *B. breve, B. longum, B. infantis*, and *Streptococcus salivarius* subs. *thermophilus* was tested. In a study in children aged 2–16 after a year of treatment (dose dependent on weight) in the probiotic-treated group, recurrence of symptoms was observed in 21% of patients, while in the placebo group, the rate was at 73%. As a result of VSL#3 administration to adult patients in the amount of 3.6×10-12 CFU twice daily, an improvement was reported in 43% of patients after 12 weeks of treatment. In the control group, only 16% of patients had remission of the disease (Floch, 2010). Another microorganism, whose activity in the treatment of ulcerative colitis was demonstrated in clinical trials, is *E. coli Nissle* 1917. The efficacy of this strain was compared with the standard anti-inflammatory drug used in the treatment of this disease – mesalazine. The results after a year of treatment showed that the percentage of patients taking the probiotic, who had improved health status was similar to that in patients treated with mesalazine and amounted to 64% and 66% (Kruis *et al*., 2004).

Pouchitis

Proctocolectomy with ileal pouch-anal anastomosis may be required in some ulcerative colitis patients because their disease was medically intractable or they developed secondary dysplasia or cancer. Pouchitis or inflammation of the ileal reservoir created during the procedure may develop in between 15 and 50% in patients. Trials for treating mild/ moderate pouchitis are few with small numbers of adult participants. Gionchetti *et al*. sustained VSL#3 efficacy in a study conducted on 40 patients with ileal pouch-anal anastomosis. Twenty patients received VSL#3 and 20 received placebo: only 10% of patients that received VSL#3 developed pouchitis versus 40% of placebo patients (Gionchetti *et al*., 2003). Mimura *et al*. confirmed these data (Mimura *et al*., 2004). A systematic review has also indicated that VSL#3 is effective in the primary prevention and maintenance of remission in pouchitis (Holubar *et al*., 2010).

Other health benefits

The list of health benefits mediated by probiotics is not limited to the ones mentioned so far and includes a range of promising effects that require however further human studies in order to be substantiated. There is evidence that probiotic bacteria are dietary components that may play a role in decreasing cancer incidence. The exact mechanisms are under investigation, but studies have demonstrated that certain members of *Lactobacillus* and *Bifidobacterium* spp. decrease the levels of carcinogenetic enzymes produced by colonic flora through normalization of intestinal permeability and microflora balance as well as production of antimutagenic organic acids and enhancement of the host's immune system (Kumar *et al*., 2010).

Furthermore, evidence suggests that food products containing probiotic bacteria could possibly contribute to coronary heart disease prevention by reducing serum cholesterol levels as well as to blood pressure control. Proposed mechanisms include interference with cholesterol absorption from the gut, direct cholesterol

assimilation, and production of end fermentation products that affect the systemic levels of blood lipids and mediate an antihypertensive effect. Antaie *et al*. (2009) compared the effect of consuming probiotic yogurt with that of ordinary yogurt on serum cholesterol level in mildly to moderately hypercholesterolemic subjects. Results indicate a significant decrease in serum total cholesterol. Comparison of other blood lipid indices did not show any significant differences between these two. Yogurt containing two probiotic bacteria strains, *L. acidophilus* and *B. lactis*, had a cholesterol-lowering effect in hypercholesterolemic subjects. Ejtahed *et al.* (2011) investigated the effects of probiotic and conventional yogurt on lipid profile in type 2 diabetic people. Participants consumed daily 300 g of probiotic yogurt containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 or 300 g of conventional yogurt for 6 wk and found that probiotic yogurt improved total cholesterol and LDL-C concentrations in type 2 diabetic people and may contribute to the improvement of cardiovascular disease risk factors. Last but not least, probiotic strains administered in dairy products have shown to improve the therapeutic outcome in women with bacterial vaginosis, most probably by supporting the normal vaginal lactobacilli microbiota (Falagas *et al*., 2007). Nevertheless, these probiotic effects are still a matter of debate as further research is needed in long-term human studies.

DOSAGE OF PROBIOTICS

One to two billion colony forming units (CFU) per day of a mixed strain supplement probiotic are considered to be the minimum amount for the healthy maintenance of intestinal microflora. To get adequate amount of health benefits, a dose of 5x109 CFU/d has been recommended for at least five days. According to Earl Mindell, an expert on nutrition, healthy persons should take 2 to 5 billion CFU of probiotics per day and those with problems in the gastro intestinal tract can take up to 10 billion CFU per day. The current daily intake recommended by the Natural Health Products Directorate of Canada, for prescription probiotics, is 5-10 billion CFU (Chakraborti, 2011).

CONCLUSION

This study reviewed the concept, mechanisms of action and clinical application of probiotics. Several important mechanisms underlying the antagonistic effects of probiotics on various microorganisms include the following: modification of the gut microbiota, competitive adherence to the mucosa and epithelium, strengthening of the gut epithelial barrier and modulation of the immune system to convey an advantage to the host. Probiotics are becoming an important part of the complex world of foods that are good for health. They are foods that contain live bacteria. It is the bacteria and metabolites which they produce that give these probiotics their health-promoting properties. These can boost the immune system, heal the intestine, prevent allergies and beneficial in oral health. A good diet, supplemented with a high quality probiotic will improve the balance between good and bad bacteria and have nutritional and therapeutic properties. In spite of the problems with dosage and viability of probiotic strains, lack of industry standardization and potential safety issues, there is obvious considerable potential for the benefits of probiotics over a wide range of clinical conditions. Ongoing basic research will continue to identify and characterize existing strains of probiotics, identify strain-specific outcomes, determine optimal doses needed for certain results and assess their stability through processing and digestion. Available data from clinical use clearly state that probiotics have great health potential, particularly today with the increasing threat of antibiotic over-usage and prevalence of antibiotic resistant microorganisms. With the current focus on disease prevention and the quest for optimal health at all ages, the future of probiotics is bright.

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