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Probiotics as a Strategy to Improve Overall Human Health in Developing Countries

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Abstract

Probiotic strains can be successfully incorporated and manufactured into highly acceptable food products while retaining their viability and functionality. The development of successful probiotic products depends on the selection of probiotic strains for human consumption, proof of a therapeutic effect, strain survival, viability at the time of consumption and storage requirements. Dairy products have proven to be an excellent vehicle for the delivery of probiotics. Developing countries are reeling under the problems of acute and antibiotic associated diarrhea, HIV/AIDS and poor nutritional status due to improper hygiene, sanitation, unavailability of safe drinking water and lack of awareness. Results of this review suggest a promising role of probiotic products in the inhibition of pathogenic microorganisms, reduction of antibiotic-associated diarrhea, alleviation of acute diarrheal diseases especially in infants and children, protection against HIV/AIDS, management of lactose intolerance, lowering blood cholesterol levels, improving the nutritional status of the population, allergy prevention and as a vaccine adjuvant in developing countries. Educational campaigns to inform the population and policy makers about the health benefits of probiotics could help alleviate these problems in a safe way without great effort and with minimal increase in the cost of such probiotic products.

Keywords: Probiotics, Developing nations, Diarrhea, HIV/AIDS, Lactose intolerance, Cholesterol

Introduction

According to the United Nations Development Programme report in 2010, many developing countries in Africa, Southeast Asia and the Middle East are considered to have a gross income and a quality of life index below average [1]. People in developing countries not only suffer from malnutrition but also from enteric infections due to weakened immunity and lack of proper hygiene, sanitation, clean drinking water and access to proper medical care [2,3]. Every year more than a million children in these regions suffer and die from diarrhea alone [1].

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 [4]. 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 [5]. 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 [6]. In addition to these major problems; there are other nutritional related disorders such as lactose intolerance or 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 [4]. Probiotic interventions could provide an invaluable opportunity to ameliorate this current situation. This review will thus outline the potential health benefits of probiotics, and will examine the rationale for the introduction of probiotics into the developing world with particular attention to probiotic dairy products.

Probiotic Concept

Probiotics have been defined as “live microorganisms which when administered in adequate amounts confer a health benefit to the host” [7]. This definition applies only to products containing live microorganisms, and requires an adequate dose of microorganisms in order to exert the desirable effect [8]. Also the probiotic bacteria should remain viable during preparation, use and storage of the food product and it must be able to survive the intestinal environment to benefit the host [9].

The scientific basis for the use of live microbes in the prevention and treatment of infections dates back to over 100 years, when the Russian scientist Elie Metchnikoff in 1907 hypothesized that bowel health and prolongation of life could be possible by replacing or reducing the number of ‘putrefactive’ bacteria in the gut with lactic acid bacteria [10]. Gut microbiota has been defined as an organ composed of atleast 10^{13} microorganisms and mainly dominated by anaerobic microorganisms comprising of approximately 500-1000 different species that have evolved to perform functions such as digestion of indigestible fraction of food and are required to maintain good health [11]. In the last three decades, research in probiotics has advanced tremendously resulting in selection and characterization of specific probiotic cultures and the evaluation of health benefits attributed to their continuous consumption. Furthermore, advances in molecular techniques allows the possibility of tracking changes in gut microbiota after consumption of probiotic and prebiotic products and thus enabling a better understanding of their function and potential for the prevention and management of infectious diseases and gastrointestinal disorders.

Developed and developing countries differ in their perspectives regarding probiotics. In developed countries, probiotic foods are considered revolutionary and are viewed as a means for maintaining a balanced gut flora and gut health. In developing countries however, probiotics are still in question and are a dilemma for scientists, clinicians and consumers [12]. This might be in part due to lack of product availability because of limited infrastructure and funding for this area of research [1].

Probiotic Selection and Dose Requirement

The criteria for the selection of probiotic strains for human consumption depends on safety, functionality and technological aspects. The safety aspect suggests that the isolated strains should preferably be of human origin, isolated from healthy human gastrointestinal (GI) tract, non-pathogenic, have no history of association with infective diseases, do not deconjugate bile salts, and do not carry antibiotic resistance genes [13]. However, origin of the strain is not as important as viability at the target site [8]. Functional properties include acid tolerance to survive digestion, bile tolerance to survive in the small bowel, adherence, colonization and persistence in the GI-tract, viability at the target site, immune stimulation, antigenotoxic activity and inhibition of pathogens [13]. Technological aspects include the ability to be manufactured under industrial conditions, heat tolerance, survival and retention of their functionality during storage, sensory properties, and phage resistance [13,14]. Technological and sensory properties such as taste, texture, appearance and palatability of probiotic food are specifically important because by satisfying consumer demands, the food industry will succeed in promoting and encouraging the consumption of functional probiotic products [13].

Probiotic bacteria have been increasingly included in yogurts and other cultured milk products during the past three decades as a result of perceived health benefits. Members of the genera *Lactobacillus* and *Bifidobacterium* are the principle probiotic microorganisms generally used though not exclusively [8]. A summary of identified probiotic bacteria and yeast strains are presented in (Table 1). The conditions that need to be met for probiotic microorganisms to achieve their potential health benefits include being delivered at a high dose through food vehicles (especially dairy products such as yogurt, cheese, and ice cream); and being able to remain viable when they reach the intestine. The food industry and the United States Food and Drug Administration (US FDA) have adopted the minimum viable probiotic count of 10^6 CFU (Colony Forming Units)/mL at the time of consumption of probiotic foods. This standard appears to have technical and cost associated benefits [14]. A regular intake of 10^8 to 10^9 CFU/day of probiotic microorganisms is required for the probiotics to exert their health benefits [14,15]. This might vary depending on the best-before date and the amount of probiotic food ingested [14]. In addition, repeated administration of probiotic bacteria ensures adequate population levels over time [16]. These bacteria play an important role in digestion of complex polysaccharides that help in production of short chain fatty acids that serves as a source of energy for colonocytes. Also they are able to protect us from a load of external microbes due to colonization resistance that they offer by displacing gas-producing and bile salt deconjugating bacterial species. The probiotics maintain this barrier function by the production of antimicrobial peptides, immunoglobulin A and by acidification of the colon. Beyond these beneficial properties they are also involved in synthesis of vitamins such as folate, vitamin K and biotin, biotransformation of drugs and xenobiotics and metabolism of bile acids [17,18].

***Lactobacillus* strains**
L. rhamnosus GG (LGG)
L. rhamnosus GR-1
L. reuteri RC-14
L. casei DN114001
L. acidophilus LA-1
L. reuteri SD2112
L. plantarum 299v
L. casei Shirota
L. acidophilus LB
L. rhamnosus HN001
L. salivarius UCC118
L. acidophilus NCFM
L. fermentum VRI003
L. johnsonii Lj-1
L. paracasei F19
***Bifidobacterium* strains**
B. lactis Bb 12
B. infantis 35624
B. breve strain Yakult
B. animalis DN 117-001
B. lactis HN019
B. longum BB536
***Lactococcus* strains**
Lactococcus lactis L1A
Other Bacteria and Yeast
Bacteria: *Escherichia coli* strain Nissle
Yeast: *Saccharomyces boulardii lyo*

Table 1: Probiotic bacteria and yeast shown to exert health beneficial effects [10].

Probiotic Food Products

At present, over 70 probiotic products are available all over the world commercially and include dairy products such as sour cream, ice cream, buttermilk, yogurt, milk powder and frozen desserts containing *Bifidobacteria* and *Lactobacilli* [14]. However it has been reported that viable *Bifidobacteria* counts in fermented milk products may reduce rapidly unless specific attention is given to strain selection and pH [19]. Also, it has been reported that fermented foods cannot be termed as probiotic food because there is no evidence supporting the fact that, if only the bacteria in the food is beneficial or there is also contribution of the food matrix. Also, in fermented foods, bacteria are part of a diverse community that is not well-defined in terms of strain composition and stability [7]. The incorporation of probiotic strains into cheese might be an encouraging alternative to the *Bifidobacteria* survival problem in acidic products such as yogurt and cultured butter milk. Cheese's closed matrix and low acidity, in addition to the high fat content may protect these strains during cheese manufacturing, storage and passage through the gastrointestinal tract [20]. Research has also shown potential to incorporate probiotics in non-dairy foods such as soy milk, soy cream cheese, chocolate and variety of juices such as tomato, orange, grape, carrot, beet and cabbage juice [14,21]. Probiotics are also available in the form of capsules, tablets and powders. [10,14]. Overall the incorporation of probiotics in foods and their survival ability depends on the food matrix, composition, pH, storage facilities, thus making it a challenge for manufacturers.

Probiotics and their Potential as a Health Promoting Alternative for Developing Countries

Considering that most frequent health issues in developing countries are related to intestinal health, the intervention with probiotics would greatly benefit the health of populations in these nations. Probiotics would be able to do so through their inhibitory actions against pathogens and parasites, their ability to reduce antibiotic associated diarrhea and to protect against acute and infectious diarrhea. Other benefits include protection against HIV/ AIDS infection, alleviation of lactose intolerance symptoms, lowering of cholesterol levels, improvement of overall nutritional status of people in developing regions, alleviation of allergies and ability to serve as a vaccine adjuvant.

Inhibition of pathogenic microbes and parasites

Probiotic strains have been shown to inhibit the growth, metabolic activity, and adhesion of enteropathogenic *Salmonella, Shigella*, enterotoxigenic *Escherichia coli*, or *Vibrio cholerae* to intestinal cells, thus helping to regulate intestinal microflora and exert immunostimulatory effects [22]. Suggested mechanisms involve competition for fermentable substrates, the pH lowering effect in the intestine, the production of bactericidal acids such as lactic, acetic, hippuric, butyric and citric acids [21,22], the production of H_2O_2 and the agglutination of pathogenic microorganisms inhibiting their growth [22-24]. In addition, protective functions to the host are mediated by degradation of arginine with production of nitric oxide (NO), which has shown to protect the lower intestinal tract [25] as well as the binding and metabolism of toxic metabolites (Aflatoxin M_1) and aflatoxin B1 by strains of *Lactobacilli, Lactococcus and Bifidobacterium* which make them unavailable for absorption in the intestinal tract [26,27]. Due to various anti-microbial actions, a combination of probiotics have been found to be beneficial. Colonization of *E.coli* O157: H7 was found to be reduced by consumption of *L.casei* Shirota strain [28] and *Salmonella enteritidis* was completely eliminated by consumption of *L. salivarius* [29]. In a study on pigs, levels of *Salmonella typhimurium* was reduced by using a mixture of strains *L. murinus, L. salvarius* subspp. *Salivarius*, *L. pentosus* and *Pedicoccus pentosaceous* as compared to animals treated with skim milk without probiotics [30].

Helicobacter pylori is another gram negative pathogen that was found to cause peptic ulcers, gastric cancer and type B gastritis and its infection is common in developing countries due to lack of proper hygiene, sanitation and safe drinking water [31]. Various lactic acid bacteria such as *L. johnsonii* La1 have proven to be effective against this pathogen (tested in 20 adults with mean age of 33 years) and the hypothesized mechanism is the probiotic induced decrease of urease enzyme activity which is required for their sustenance in the acidic environment of the stomach [8,32]. Other human studies have also shown reduction in *H. pylori* infection by treatment with *L. brevis* lyophilized bacteria or yogurts containing *L. acidophilus, B. lactis and L. gasseri* [33]. Moreover, the incidents of side effects produced by the use of antibiotics used to treat *H. pylori* infection was reduced by half when using a combination therapy of antibiotics and probiotics [33]. However few studies showed controversial evidence about the beneficial effects of probiotics in treatment against *H. pylori* infection and hence long term studies on the specific strain, doses and administration are required [34,35].

Other therapeutic approaches, of high relevance for developing countries, are the reduction of parasite infections by the use of specific probiotic strains. As reviewed by Marie-Agn`es Travers et al. [36], it was found that the administration of *L. reuteri* 4000 to mice, 7-15 days before infection with *Cryptosporidium parvum* bought about a 50-100% reduction in the parasite infection and the probiotics *L. acidophilus* NCFM, *B. breve* ATCC15698 or B. longum ATCC15707, *B. brevis, E. faecium and P. alcaligenes* showed similar reduction in *Cryptosporidium parvum* infection in cell culture models. Furthermore, *L. johnsonii* La 1, *L. casei* and *Enterococcus faecium* showed 75-100% reduction in *Giardia lamblia* infection in cell culture and mouse models and the probiotic *L. casei* was effective in reduction of *Babesia microti*, *Plasmodium chabaudi, Trichinella spiralis and Trypanosoma cruzi* infections in mouse models [36]. More studies and human clinical trials from developing countries are needed to demonstrate the benefits of probiotics as an anti-parasite therapeutic alternative.

Reduction of Antibiotic Associated Diarrhea (AAD)

AAD occurs in 5-35% of patients under antibiotic therapy and rates vary according to the specific antibiotic, host health and exposure to pathogens [37]. Antibiotic therapy affects the fecal microflora and causes disturbance of GI micro-ecology leading to loss of colonization resistance. Colonization resistance is defined as the capacity of colon microorganisms to resist influx of external microorganisms. The mechanisms associated with colonization resistance are based on host factors such as bile acids, gastrointestinal proteases, motility, competition for adhesion sites and nutrients with production of toxic metabolites and antagonistic compounds [38]. The use of antibiotics leads to the break down of the colonization defense systems leading to increased infections in individuals by opportunistic pathogens such as *Clostridum difficile* [38,39]. *C. difficile* invasion occurs mainly due to antibiotic therapy, but other risk factors include ageing and hospitalization [40]. 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 [39,40]. 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. [41].

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* [39]. Other strains and mixtures of strains including *L. acidophilus* combined with *Bifidobacterium infantis, L. sporogens, Bifidobacterium lactis* combined with

Streptococcus thermophiles, Enterococcus faecium SF 68, *Bacillus clausii, Clostridium butyricum* seem to be effective as well [39,42]. 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 [43]. 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* [44]. 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 [45].

Another strategy to combat *C. difficile* infection might be the use of the technique faecal microbiota transplants (FMT). Few studies have shown that FMT decreased the percentage of *C. difficile* associated diarrhea [46,47]. Also, when another route of delivery of these microbes in the form of feces filled pills were given to 31 patients, it was found to cure 30 patients [47]. But this technique is expensive and far from the visual of commercialization [47]. Also, FMT is not recognized within the banner of probiotics as its procedure is not standardized and its safety is also questioned because of the unknown nature of the FMT mixture in terms of taxa including bacteria, yeasts, parasites and viruses and which microbes are bringing about the beneficial effects [7].

In general, the use of probiotic dairy products containing selected probiotic strains might be an alternative to ameliorate or prevent AAD. The growing use of antibiotics in the developing world will lead to emergence of antibiotic resistant microorganisms and probiotic foods might provide a good solution to this anticipated problem. But still, more well-designed studies are needed to demonstrate the scientific basis for the protective role of probiotics against AAD and encourage their consumption to help improve public health.

Effect of probiotics in acute and infectious diarrhea

The two major conditions responsible for morbidity and mortality in the developing world are diarrhea and HIV/AIDS [4]. Bacterial and viral pathogens are the main causes of these infections and their transmission occurs mainly through contaminated food or drinking water [48]. Estimates in 2008 suggested that diarrhea still caused 1.336 million deaths per year in children younger than 5 years of age [5] with highest rates in some countries of south Asia and Africa (Figure 1). Irrespective of the improved understanding of the pathogenesis of diarrhea and use of oral rehydration therapy (ORT), approximately 2.5 million children still die every year from acute diarrhea in developing countries [3]. It is of paramount importance that this high rate of mortality be reduced to achieve the goal set by United Nations Millennium Development goal 4 between 1990 and 2015 to bring about a two-thirds decrease in child mortality rate [48]. Probiotics can potentially help to reduce these problems. *Lactobacillus* spp. such as *Lactobacillus rhamnosus* GG (LGG), *Lactobacillus reuteri* and *Lactobacillus casei, Streptococcus thermophilus, Bifidobacterium bifidum*, and *S. boulardii* have been shown to be promising probiotic strains in treating diarrheal diseases in children [49]. Nonfood probiotics such as *E. coli* strain Nissle 1917, *Enterococcus faecium* SF68 and *Saccharomyces boulardii* in the form of powder suspensions or oral rehydration therapy were also found to be a solution in the treatment of diarrhea [22].

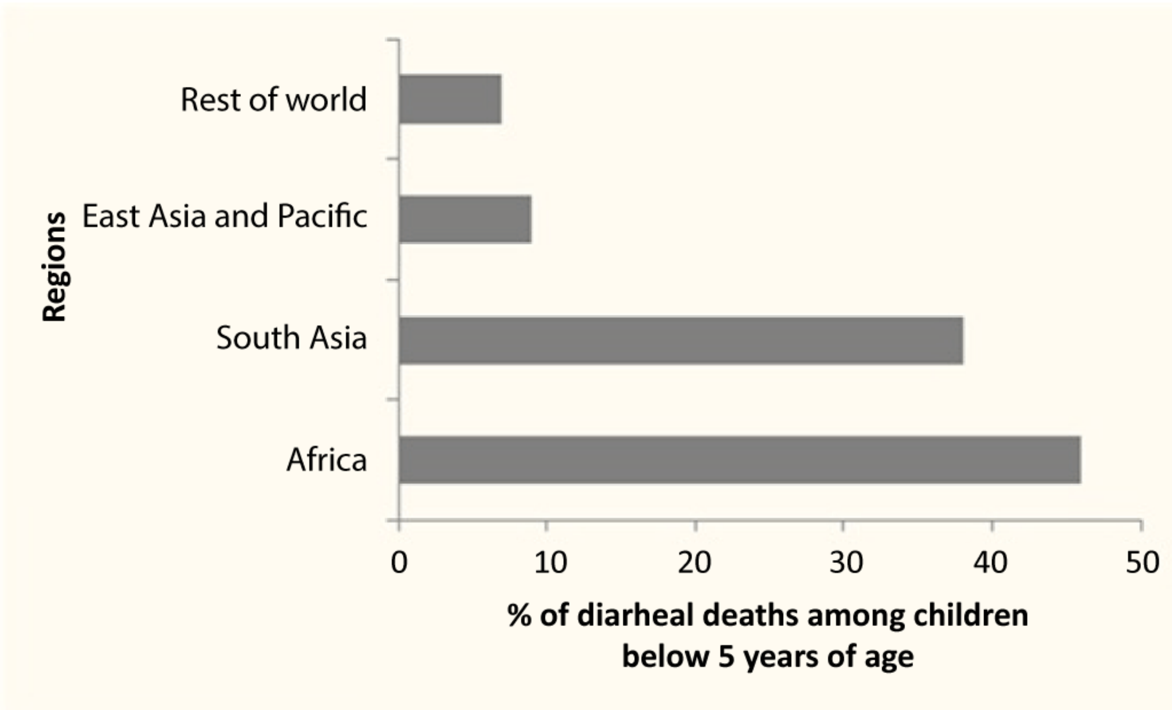

Figure 1: Rates of diarrheal deaths in children. Data is based on 10.4 million children below 5 years of age.

A study reported that administration of LGG in 6-24 month old children in Peru decreased the incidence of diarrhea as compared to the placebo group [50]. LGG was also shown to significantly reduce the mean duration of diarrhea (5.3 days as compared to 9.2 days in control) and stool frequency from day 4 in Indian children suffering from diarrhea [51]. *L. casei* DN-114001 strain also reduced cases of diarrheal morbidity in children from India by 40% [52]. Another study in Israel reported that healthy infants of 4-10 months of age fed with *B. lactis* BB-12 and *L. reuteri* showed reduced episodes of diarrhea as compared with control group [53]. Children between ages of 3 to 10 years from Myanmar showed reduction in the duration of diarrhea by 1.6 days when given *S. boulardii* in combination with ORT as compared to ORT alone [54]. Similar results were found in a study conducted in Pakistan with 100 children aged between 2-12 months wherein the duration of diarrhea was 3.5 days in children given *S. boulardii* in combination with ORT as opposed to 4.8 days with only ORT [55].

Rotavirus is a common cause of diarrhea and was found to affect 1 in 1.6 children under 5 years of age and the disease caused death of usually 1 in 375 in Peru [4]. The preventive and curative effects of LGG and *B. lactis* BB-12 against acute diarrhea mainly caused by rotaviruses in children has been well established by clinical studies [8,22]. Also, diarrhea caused by *E. coli* is common in developing countries especially amongst children. It was found that milk fermented with starter cultures *Streptococcus thermophilus*, *L. bulgaricus* and *L. acidophilus* produced higher levels of lactic acid and diacetyl whereas milk fermented with *L. acidophilus* produced the highest amount of hydrogen peroxide showing that milk fermented with the starter cultures was able to cure diarrhea caused by *E. coli* more effectively due to production of higher levels of antibacterial metabolites [56].

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 [57]. 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% [58].

In general, most of the positive studies demonstrating alleviation and prevention of infectious diarrhea have been performed in infants and children. Young children respond well to probiotics probably because of the immaturity of their immune system and the greater simplicity of their intestinal microflora compared to that of adults [22]. In adults there have been conflicting studies associated with probiotics and infectious diarrhea. Hence the use of probiotics as a treatment for acute and infectious diarrhea in adults, children and against diarrhea caused by other pathogens still needs to be thoroughly researched.

HIV/AIDS prevention

HIV/AIDS is very common in developing countries among women and children, especially in rural areas [4]. Globally, around 14,000 people mostly living in developing countries are in contact with HIV every day, out of which over 7000 women become infected [2,4]. It was found that one of the causes of developing HIV is the lack of *Lactobacilli* in the vagina and increased number of anaerobic organisms leading to bacterial vaginosis [59]. Hence, increasing the levels of probiotic *Lactobacilli* has been hypothesized to help prevent HIV infection. In a study on 64 women aged between 19-46 years of age it was found that oral consumption of two probiotic strains *L. rhamnosus* GR-1 and *L. reuteri* RC-14 led to significant increase in vaginal *Lactobacilli* levels as compared to placebo group after 60 days [60]. It was found that at a dose level of at least 10^8 CFU/day for 2 months, oral consumption of *L. acidophilus*, *L. rhamnosus* GR-1 and *L. fermentum* RC-14 showed an increase in probiotic levels in the vaginal tract of women suffering from bacterial vaginosis [61,62]. Additionally, an observational study over a period of three years reported that probiotic yogurt consumption, supplemented with *Lactobacillus rhamnosus*, was associated with a significant increase of CD4 among people living with HIV/AIDS [63]. CD4 cells are white blood cells that are a measure of good immune system; these cells are attacked by HIV infection which results in reduction of cell count. In another study it was found that consumption of probiotic yogurt supplemented with *Lactobacillus rhamnosus* GR-1 by consumers suffering from HIV/AIDS helped in their weight gain, they had significantly higher levels of vitamins and minerals, fewer fungal infections, fewer episodes of diarrhea and lower fatigue levels as compared to people not consuming the probiotic yogurt [64]. Also, a novel research reported that *L. jensenii* can bind to HIV type 1 (HIV-1) gp12, thus preventing the virus from causing infection [65]. Engineered probiotic strains of *E. coli* and *Streptococcus gordoni* producing HIV-gp41-haemolysin and cyanovirin-N have been found to block or inactivate HIV, thus preventing the infection [2]. Overall, the use of probiotics against HIV requires more research, but has not shown any adverse effects [4,61].

Improvement of lactose intolerance symptoms

Lactose intolerance is caused by the deficiency or decreased activity of the lactose-cleaving enzyme β-galactosidase in the small intestine [66]. It affects more than 75% of the population worldwide and causes flatulence or diarrhea [67,68]. The decreased lactase activity ranges from nearly 5% in northern Europe to more than 90% in some Asian and African countries [68]. Lactose intolerance may lead to deficiencies in the intake of protein, calcium, and other important nutrients in populations from developing countries. This problem might be alleviated by the consumption of fermented dairy products due to their lower lactose content and the release of β-galactosidase in the GI tract by live probiotic bacteria that can survive digestion [67]. Yogurt was shown to be unique among other fermented milk products such as buttermilk and sweet acidophilus milk. It is well tolerated by lactose intolerant people and enhances lactose digestion in lactase-deficient subjects due to the presence of bacteria such as *Lactobacillus bulgaricus* and *Streptococcus thermophilus* which release β-galactosidase in the intestine [67,69]. However pasteurization of yogurt eliminates this effect due to the reduction in the β-galactosidase activity [67,69]. A clinical human study showed that supplementation with *Bifidobacterium longum* capsules and yogurt enriched with *Bifidobacterium animalis* was effective in alleviating lactose intolerant symptoms [70]. A related study in lactose maldigesting children (5-16 years) demonstrated that consumption of milk with *Lactobacillus acidophilus* or a commercial yogurt containing *Lactobacillus lactis* and *Streptococcus thermophilus* reduced lactose intolerance symptoms compared with the group of children who consumed unfermented milk [67]. A study reported that lactose content decreased to 2.3 g/100 g after 11 days of storage as compared to non-fermented milk containing 4.8 g/100 g. Other fermented products such as buttermilk, kefir and ropy milk also had a 20-26% reduction in lactose content [71]. However, results showing no effects on alleviation of lactose intolerance by probiotic supplementation have also been reported [72]. These controversial results are probably due to differences in specific probiotic strains, concentrations, and preparations, as well as due to the subject's susceptibility to gas, osmotic pressure or the individual responsiveness to probiotics. Further clinical trials of specific strains and concentrations are necessary to delineate the potential therapeutic effects of probiotics in lactose intolerance [66,72] .

Lowering blood cholesterol levels

Many animal and human clinical trials have shown a relationship between cholesterol levels and increased risk of coronary heart disease. Dairy fermented products with probiotics, especially *Bifidobacterium* spp. and *Lactobacillus* spp., have the potential to help reduce serum cholesterol levels [23]. Possible mechanisms involved in the cholesterol-lowering effect of probiotics include assimilation of cholesterol by probiotic bacteria, cholesterol binding to cellular surface and incorporation into the cellular membrane, co-precipitation of cholesterol with probiotic-deconjugated bile that leads to inhibition of intestinal cholesterol absorption, inhibition of bile acid reabsorption, and production of short-chain fatty acids [23,73]. *L. acidophilus* showed cholesterol lowering properties most likely by assimilating cholesterol in the cells or by its attachment to the cells [74]. In a study performed in India, it was found that consumption of buffalo milk fermented with *L. acidophilus* showed a 12-20% reduction in serum cholesterol [75]. In another study in adults, consumption of *E. faecium* M-74 capsules enriched with selenium reduced total serum cholesterol by 12% after 56 weeks [76]. In a study on rats, administration of *L. reuteri* for 7 days was found to decrease total cholesterol and triglyceride levels by 38% and 40% respectively and increase HDL to LDL cholesterol ratio by 20% [77]. Pereira et al., also showed that *Lactobacillus fermentum* KC5b strain which was isolated from the human gut, removed 14.8 mg of cholesterol per gram of cells (dry weight) in culture medium [78]. In general, more human studies are required in developing countries to prove the effects of probiotics in lowering blood cholesterol levels [79].

Nutritional Effect

Microorganisms in fermented foods or in the gut have shown to improve the quantity, bioavailability and digestibility of some dietary nutrients [49]. Lactic acid produced during food fermentation by lactic acid bacteria leads to pH reduction, improvement of protein digestibility and calcium absorption. In addition, lactic acid bacteria was also shown to increase folic acid, niacin, and riboflavin levels in cultured dairy products with release of various enzymes and vitamins into the intestinal lumen [49].

Milk and milk products are a good source of minerals especially calcium and phosphorus, but are a poor source of iron.. Although calcium might reduce iron absorption, several studies have demonstrated the efficacy of fermented dairy products as vehicles for iron fortification. In a study it was found that there was a direct correlation between iron intake and the increase of hemoglobin levels when preschool children aged between 2-5 years old were fed with a fermented milk fortified with iron containing amino acid chelate and supplemented with probiotic *Lactobacillus acidophilus* [80]. Moreover, the Committee on Nutrition of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) has considered the supplementation of infant formula with probiotics and/or prebiotics as an important area of research. However, more clinical studies are needed to recommend the routine use of probiotics and/or prebiotics in infant formulae [81].

Role of probiotics in allergic disease prevention

Allergic diseases such as eczema, food allergy and asthma have increased in occurrence during the past few decades especially in developed countries [82,83] with nearly 20% of the world population currently affected [84]. This might also be a health concern for developing countries in the near future and probiotics could be used as a strategy in its prevention. The major populations at risk to develop allergic diseases are infants and children due to decreased microbial exposure which results in reduced microbial stimulation in the immune system at an early age [83]. In an allergic response the T-helper-2 (Th) response is activated leading to release of interleukin (IL)-4, IL-5, and IL-13 and the production of allergen-specific IgE which leads to inflammation. Studies have shown that probiotics help prevent allergic diseases by regulating the Th1/Th2 balance by modulating the immune system back to a Th1 response and by preventing inflammation by reducing TNF-α induced NF-κB activation, the major pathway causing an inflammatory response [83]. This is supported by a study demonstrating a reduced eczema severity as well as serum cytokines IL-5, IL-6, interferon (IFN)-γ, and total serum IgE levels in children between 1-13 years with a history of atopic dermatitis (eczema) when fed with a probiotic mixture of *B. bifidum, L. acidophilus, L. casei,* and *L. salivarius* [85]. In another study with 1-3 years old children, a mixture of probiotics *L. acidophilus* DDS-1, *B. lactis* UABLA-12, and prebiotic fructo-oligosaccharides (FOS) helped to significantly reduce eczema severity as compared to placebo group [86]. Moreover, probiotics have also shown to reduce eczema severity in adults fed with *L. salivarius* LS01 (DSM 22775) for 16 weeks [87].

In context to food allergy there have been studies showing inconsistent results conducted on infants and children fed with *Lactobacillus* and *Bifidobacterium* strains when suffering from allergies of cow's milk, egg or peanut [83]. Similarly, very few studies have been conducted on patients suffering from asthma and showing positive results. In a study, adults given *B. breve* M-16V and galacto or fructo-oligosaccharides showed reduction in Th-2 cytokine levels but no reduction in bronchial inflammation or improvement in lung function [88]. However in a study on school children suffering from asthma and allergic rhinitis fed with *L. gasseri A5* showed reduced cytokine levels and clinical symptoms [89]. Thus there are promising studies showing the benefits of probiotics in the prevention of eczema. However there has been conflicting data and few studies showing the benefits of probiotics in the treatment of food allergy or asthma and allergic rhinitis and hence further research is required to prove its benefits.

Probiotics as a vaccine adjuvant

A large portion of the population in developing countries do not receive vaccines because of limited access. This causes millions of deaths annually from vaccine-preventable diseases, especially among children below 5 years of age infected with pneumococcal bacteria and rotavirus [90]. Probiotics are emerging as a safe, easy to deliver, cost effective and efficient strategy in stimulating both mucosally and parenterally delivered vaccine immune responses. They might act by increasing phagocytic cell activity and production of disease specific antibodies; thus allowing safe administration of vaccines in remote areas and overcoming the requirement for multiple doses [90].

This hypothesis is supported by studies with infants showing that supplementation with *L. casei* GG increased serum levels of rotavirus specific antibodies IgA and IgM as compared to placebo group with a 8-fold higher rotavirus-specific IgM antibody secreting cell (ASC) response [91]. In another study on infants supplemented with a mix of *Bifidobacterium longum* BL999 and *Lactobacillus rhamnosus* LPR, higher serum levels of anti-HBsAg IgG concentrations were seen as compared to the placebo group following Hepatitis B vaccines [92]. Furthermore, adults immunized with live attenuated poliovirus vaccine and fed with *L. rhamnosus* GG (LGG) or *L. paracasei* CRL431 orally for five weeks showed higher levels of serum antibodies against poliovirus serotypes 1 and 2 (LGG) and serotype 3 (CRL431) [93]. In another study, adults given influenza vaccine and fed with *L. fermentum* CECT5716 showed higher levels of virus neutralizing antibodies and T-helper type 1 response [94]. Thus probiotics seem promising in alleviating vaccine preventable diseases in developing countries, however, still large randomized placebo controlled human trials are required to guarantee their benefits.

Conclusion and Remarks

Consumption of probiotic food products is highly recommended in developing countries because of the proclaimed health benefits which include alleviation of acute diarrheal diseases, increase in natural resistance to infectious disease in gastrointestinal tract and HIV/AIDS, improvement in lactose intolerance, reduction in serum cholesterol levels, improved nutrition, allergy treatment and serving as a vaccine adjuvant. In developing countries there is a lack of awareness about health benefits of probiotics and regulations are needed to ensure that quality and safety standards are met. In the absence of regulations, there could be production of unreliable products containing low levels of the beneficial strains that have no benefits. Hence, funding for this area of research in developing countries is very important to prove that probiotics can help to improve the nutritional and health status of people [1]. Also each nation should develop a strategy pertaining to the needs of the people, cost and compliance issues, increased awareness and consumer confidence which will ultimately lead to acceptance of probiotic products in the society. Some of the approaches could include license free inclusion of probiotics in common food vehicles such as yogurt with a minimal increase in cost, radio publicity and increased Government initiative in informing to people about the benefits of probiotics [1]. Finally, compared to normal therapeutic agents or drugs, probiotic strains are comparatively cheaper to produce, store and deliver which would overall be beneficial for developing regions [2].

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References

1. Monachese M, Cunningham-Rundles S, Diaz MA, Guerrant R, Hummelen R, et al. (2011) Probiotics and prebiotics to combat enteric infections and HIV in the developing world: a consensus report. Gut Microbes 2: 198-207.
2. Sleator RD, Hill C (2007) Probiotics as therapeutics for the developing world. Journal of Infection in Developing Countries 1: 7-12.
3. Thapar N, Sanderson IR (2004) Diarrhoea in children: an interface between developing and developed countries. Lancet 363: 641-653.
4. Reid G, Anand S, Bingham MO, Mbugua G, Wadstrom T, et al. (2005) Probiotics for the developing world. J Clin Gastroenterol 39: 485-488.
5. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, et al. (2010) Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 375: 1969-1987.
6. WHO, Global health situation and trends 1955-2025 (1998). The world health report.
7. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, et al. (2014). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 11: 506-514.
8. FAO/WHO, Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria (2001) Report of a Joint FAO WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria, American Córdoba Park Hotel, Córdoba, Argentina.
9. Gibson GR, Roberfroid MB (1995) Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 125: 1401-1412.
10. Anukam KC, Reid G (2007) Probiotics: 100 years (1907-2007) after Elie Metchnikoff's Observation. Communicating current research and educational topics and trends in applied microbiology 466-474.
11. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, et al. (2004) The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A 101: 15718-15723.
12. Hajela N, Nair GB, Ganguly NK (2010) Are probiotics a feasible intervention for prevention of diarrhoea in the developing world? Gut Pathog 2: 10.
13. Saarela M, Mogensen G, Fondén R, Mättö J, Mattila-Sandholm T (2000) Probiotic bacteria: safety, functional and technological properties. J Biotechnol 84: 197-215.
14. Bhadoria PS. Mahapatra (2011) Prospects, technological aspects and limitations of probiotics–a worldwide review. Eur J Food Res Rev 1: 23-42.
15. Ng EW, Yeung M, Tong PS (2011) Effects of yogurt starter cultures on the survival of Lactobacillus acidophilus. Int J Food Microbiol 145: 169-175.
16. Cogan TM, Beresford TP, Steele J, Broadbent J, Shah NP, et al. (2007) Invited review: Advances in starter cultures and cultured foods. J Dairy Sci 90: 4005-4021.
17. Sharma V, Garg S2, Aggarwal S3 (2013) Probiotics and liver disease. Perm J 17: 62-67.
18. Verna EC, Lucak S (2010) Use of probiotics in gastrointestinal disorders: what to recommend? Therap Adv Gastroenterol 3: 307-319.
19. Gomes AM, Malcata FX (1998) Development of probiotic cheese manufactured from goat milk: response surface analysis via technological manipulation. J Dairy Sci 81: 1492-1507.
20. Gardiner G, Ross RP, Collins JK, Fitzgerald G, Stanton C (1998) Development of a probiotic cheddar cheese containing human-derived Lactobacillus paracasei strains. Appl Environ Microbiol 64: 2192-2199.
21. Nagpal R, Kumar A, Kumar M, Behare PV, Jain S, et al. (2012) Probiotics, their health benefits and applications for developing healthier foods: a review. FEMS Microbiol Lett 334: 1-15.
22. de Vrese M, Marteau PR (2007) Probiotics and prebiotics: effects on diarrhea. J Nutr 137: 803S-11S.
23. Kumar M, Nagpal R, Kumar R, Hemalatha R, Verma V, et al. (2012) Cholesterol-Lowering Probiotics as Potential Biotherapeutics for Metabolic Diseases. Experimental Diabetes Research 2012: 14.
24. Mangell P, Nejdfors P, Wang M, Ahrné S, Weström B, et al. (2002) Lactobacillus plantarum 299v inhibits Escherichia coli-induced intestinal permeability. Dig Dis Sci 47: 511-516.
25. Bengmark S (1996) Econutrition and health maintenance--a new concept to prevent GI inflammation, ulceration and sepsis. Clin Nutr 15: 1-10.

26. Oatley JT, Rarick MD, Ji GE, Linz JE (2000) Binding of aflatoxin B1 to bifidobacteria in vitro. J Food Prot 63: 1133-1136.
27. Peltonen K, el-Nezami H, Haskard C, Ahokas J, Salminen S (2001) Aflatoxin B1 binding by dairy strains of lactic acid bacteria and bifidobacteria. J Dairy Sci 84: 2152-2156.
28. Ogawa M, Shimizu K, Nomoto K, Takahashi M, Watanuki M, et al. (2001) Protective effect of Lactobacillus casei strain Shirota on Shiga toxin-producing Escherichia coli O157:H7 infection in infant rabbits. Infect Immun 69: 1101-1108.
29. Pascual M, Hugas M, Badiola JI, Monfort JM, Garriga M (1999) Lactobacillus salivarius CTC2197 prevents Salmonella enteritidis colonization in chickens. Appl Environ Microbiol 65: 4981-4986.
30. Casey PG, Gardiner GE, Casey G, Bradshaw B, Lawlor PG, et al. (2007) A five-strain probiotic combination reduces pathogen shedding and alleviates disease signs in pigs challenged with Salmonella enterica Serovar Typhimurium. Appl Environ Microbiol 73: 1858-1863.
31. Hunt RH, Xiao SD, Megraud F, Leon-Barua R, Bazzoli F, et al. (2011) Helicobacter pylori in developing countries. World Gastroenterology Organisation Global Guideline. J Gastrointestin Liver Dis 20: 299-304.
32. Michetti P, Dorta G, Wiesel PH, Brassart D, Verdu E, et al. (1999) Effect of whey-based culture supernatant of Lactobacillus acidophilus (johnsonii) La1 on Helicobacter pylori infection in humans. Digestion 60: 203-209.
33. Lesbros-Pantoflickova D1, Corthésy-Theulaz I, Blum AL (2007) Helicobacter pylori and probiotics. J Nutr 137: 812S-8S.
34. Pacifico L, Osborn JF, Bonci E, Romaggioli S, Baldini R, et al. (2014) Probiotics for the treatment of Helicobacter pylori infection in children. World J Gastroenterol 20: 673-683.
35. Navarro-Rodriguez T Silva F, Barbuti R Mattar R, Moraes-Filho J, et al. (2013) Association of a probiotic to a Helicobacter pylori eradication regimen does not increase efficacy or decreases the adverse effects of the treatment: a prospective, randomized, double-blind, placebo-controlled study. BMC Gastroenterology13: 1-8.
36. Travers MA, Florent I, Kohl L, Grellier P (2011) Probiotics for the control of parasites: an overview. J Parasitol Res 2011: 610769.
37. McFarland LV (2008) Antibiotic-associated diarrhea: epidemiology, trends and treatment. Future Microbiol 3: 563-578.
38. Hopkins MJ, Macfarlane GT, (2003) Nondigestible oligosaccharides enhance bacterial colonization resistance against Clostridium difficile in vitro. Appl Environ Microbiol 69: 1920-1927.
39. Katz JA (2006) Probiotics for the prevention of antibiotic-associated diarrhea and Clostridium difficile diarrhea. J Clin Gastroenterol 40: 249-255.
40. Hickson M (2011) Probiotics in the prevention of antibiotic-associated diarrhoea and Clostridium difficile infection. Therap Adv Gastroenterol 4: 185-197.
41. Plummer S, Weaver MA, Harris JC, Dee P, Hunter J (2004) Clostridium difficile pilot study: effects of probiotic supplementation on the incidence of C. difficile diarrhoea. Int Microbiol 7: 59-62.
42. Weichselbaum E (2009) Probiotics and health: a review of the evidence. Nutrition Bulletin 34: 340-373.
43. Guandalini S (2011) Probiotics for prevention and treatment of diarrhea. J Clin Gastroenterol 45 Suppl: S149-153.
44. Hickson M, D'Souza AL, Muthu N, Rogers TR, Want S, et al. (2007) Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial 335: 80.
45. Lonnermark E, Friman V, Lappas G, Sandberg T, Berggren A, et al. (2010) Intake of Lactobacillus plantarum reduces certain gastrointestinal symptoms during treatment with antibiotics. J Clin Gastroenterol 44: 106-112.
46. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, et al. (2013) Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 368: 407-415.
47. Zhang S (2013) Faeces-filled pill stops gut infection. Nature.
48. Santosham M, Chandran A, Fitzwater S, Fischer-Walker C, Baqui AH, et al. (2010) Progress and barriers for the control of diarrhoeal disease. Lancet 376: 63-67.
49. Parvez S, Malik KA, Ah Kang S, Kim HY (2006) Probiotics and their fermented food products are beneficial for health. J Appl Microbiol 100: 1171-1185.
50. Oberhelman RA, Gilman RH, Sheen P, Taylor DN, Black RE, et al. (1999) A placebo-controlled trial of Lactobacillus GG to prevent diarrhea in undernourished Peruvian children. J Pediatr 134: 15-20.
51. Basu S, Chatterjee M, Ganguly S, Chandra PK (2007) Effect of Lactobacillus rhamnosus GG in persistent diarrhea in Indian children: a randomized controlled trial. J Clin Gastroenterol 41: 756-760.
52. Agarwal KN, Bhasin SK (2002) Feasibility studies to control acute diarrhoea in children by feeding fermented milk preparations Actimel and Indian Dahi. Eur J Clin Nutr 56 Suppl 4: S56-59.
53. Weizman Z, Asli G, Alsheikh A (2005) Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. Pediatrics 115: 5-9.
54. Htwe K, Yee KS, Tin M, Vandenplas Y (2008) Effect of Saccharomyces boulardii in the treatment of acute watery diarrhea in Myanmar children: a randomized controlled study. Am J Trop Med Hyg 78: 214-216.
55. Billoo AG, Memon MA, Khaskheli SA, Murtaza G, Iqbal K, et al. (2006) Role of a probiotic (Saccharomyces boulardii) in management and prevention of diarrhoea. World J Gastroenterol 12: 4557-4560.
56. Ogueke CC (2008) The effect of metabolites of lactobacillus in fermented milk on the growth of hospital isolates of E. coli. Life Sci J5: 90-94.
57. Allen SJ, Martinez EG, Gregorio GV, Dans LF (2010) Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev 10: CD003048.
58. Applegate JA, Fischer Walker CL, Ambikapathi R, Black RE (2013) Systematic review of probiotics for the treatment of community-acquired acute diarrhea in children. BMC Public Health 13 Suppl 3: S16.
59. Sewankambo N1, Gray RH, Wawer MJ, Paxton L, McNaim D, et al. (1997) HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. Lancet 350: 546-550.
60. Reid G, Charbonneau D, Erb J, Kochanowski B, Beuerman D, et al. (2003) Oral use of Lactobacillus rhamnosus GR-1 and L. fermentum RC-14 significantly alters vaginal flora: randomized, placebo-controlled trial in 64 healthy women. FEMS Immunol Med Microbiol 35:131-134.
61. Homayouni A, Bastani P, Ziyadi S, Mohammad-Alizadeh-Charandabi S, Ghalibaf M, et al. (2014) Effects of probiotics on the recurrence of bacterial vaginosis: a review. J Low Genit Tract Dis 18: 79-86.
62. Falagas M, Betsi GI, Athanasiou S (2007) Probiotics for the treatment of women with bacterial vaginosis. Clin Microbiol Infect 13: 657-664.
63. Irvine SL, Hummelen R, Hekmat S, Looman CW, Habbema JD, et al. (2010) Probiotic yogurt consumption is associated with an increase of CD4 count among people living with HIV/AIDS. J Clin Gastroenterol 44: e201-205.
64. Reid G (2010) The potential role for probiotic yogurt for people living with HIV/AIDS. Gut Microbes 1: 411-414.
65. Chang TL, Chang CH, Simpson DA, Xu Q, Martin PK, et al. (2003) Inhibition of HIV infectivity by a natural human isolate of Lactobacillus jensenii engineered to express functional two-domain CD4. Proc Natl Acad Sci U S A 100: 11672-11677.
66. de Vrese M, Stegelmann A, Richter B, Fenselau S, Laue C, et al. (2001) Probiotics--compensation for lactase insufficiency. Am J Clin Nutr 73: 421S-429S.
67. Montes RG1, Bayless TM, Saavedra JM, Perman JA (1995) Effect of milks inoculated with Lactobacillus acidophilus or a yogurt starter culture in lactose-maldigesting children. J Dairy Sci 78: 1657-1664.
68. Bulhões AC, Goldani HA, Oliveira FS, Matte US, Mazzuca RB, et al. (2007) Correlation between lactose absorption and the C/T-13910 and G/A-22018 mutations of the lactase-phlorizin hydrolase (LCT) gene in adult-type hypolactasia. Braz J Med Biol Res 40: 1441-1446.

69. Savaiano DA, AbouElAnouar A, Smith DE, Levitt MD (1984) Lactose malabsorption from yogurt, pasteurized yogurt, sweet acidophilus milk, and cultured milk in lactase-deficient individuals. Am J Clin Nutr 40: 1219-1223.

70. He T, Priebe MG, Zhong Y, Huang C, Harmsen HJ, et al. (2008) Effects of yogurt and bifidobacteria supplementation on the colonic microbiota in lactose-intolerant subjects. J Appl Microbiol 104: 595-604.

71. Alm L (1982) Effect of fermentation on lactose, glucose, and galactose content in milk and suitability of fermented milk products for lactose intolerant individuals. J Dairy Sci 65: 346-352.

72. Levri KM, Ketvertis K, Deramo M, Merenstein JH, D'Amico F (2005) Do probiotics reduce adult lactose intolerance? A systematic review. J Fam Pract 54: 613-620.

73. Zhuang G, Liu XM, Zhang QX, Tian FW, Zhang H, et al. (2012) Research advances with regards to clinical outcome and potential mechanisms of the cholesterol-lowering effects of probiotics. Clinical Lipidology 7: 501-507.

74. Lin MY, Chen TW (2000) Reduction of cholesterol by Lactobacillus acidophilus in culture broth. Journal of Food and Drug Analysis 8: 97-102.

75. Khedkar CD, Mantri GRD, Kulkarni JM, Khedkar SA e tal. (1993) Effect of feeding Acidophilus milk on serum cholesterol in human volunteers of 50-60 years. Journal Of Dairying Foods & Home Sciences 12: 33-38.

76. Hlivak P, Odraska J, Ferencik M, Ebringer L, Jahnova E, et al. (2005) Bratisl Lek Listy 106: 67-72.

77. Taranto MP, Medici M, Perdigon G, Ruiz Holgado AP, Valdez GF (1998) Evidence for hypocholesterolemic effect of Lactobacillus reuteri in hypercholesterolemic mice. J Dairy Sci 81: 2336-2340.

78. Pereira DI1, Gibson GR (2002) Cholesterol assimilation by lactic acid bacteria and bifidobacteria isolated from the human gut. Appl Environ Microbiol 68: 4689-4693.

79. Richelsen B1, Kristensen K, Pedersen SB (1996) Long-term (6 months) effect of a new fermented milk product on the level of plasma lipoproteins--a placebo-controlled and double blind study. Eur J Clin Nutr 50: 811-815.

80. Silva MR, Dias G, Ferreira CL, Franceschini SC, Costa NM (2008) Growth of preschool children was improved when fed an iron-fortified fermented milk beverage supplemented with Lactobacillus acidophilus. Nutr Res 28: 226-232.

81. Braegger C, Chmielewska A, Decsi T, Kolacek S, Mihatsch W, et al. (2011) Supplementation of infant formula with probiotics and/or prebiotics: a systematic review and comment by the ESPGHAN committee on nutrition. J Pediatr Gastroenterol Nutr 52: 238-250.

82. Savilahti E1, Kukkonen K, Kuitunen M (2009) Probiotics in the treatment and prevention of allergy in children. World Allergy Organ J 2: 69-76.

83. Toh ZQ, Anzela A, Tang ML, Licciardi PV (2012) Probiotic therapy as a novel approach for allergic disease. Front Pharmacol 3: 171.

84. Michail S (2009) The role of probiotics in allergic diseases. Allergy Asthma Clin Immunol 5: 5.

85. YeÅŸilova Y, Ã‡alka Ã–, Akdeniz N, BerktaÅŸ M (2012) Effect of probiotics on the treatment of children with atopic dermatitis. Ann Dermatol 24: 189-193.

86. Gerasimov SV, Vasjuta VV, Myhovych OO, Bondarchuk LI (2010) Probiotic supplement reduces atopic dermatitis in preschool children: a randomized, double-blind, placebo-controlled, clinical trial. Am J Clin Dermatol 11: 351-361.

87. Drago L, Iemoli E, Rodighiero V, Nicola L, De Vecchi E, et al. (2011) Effects of Lactobacillus salivarius LS01 (DSM 22775) treatment on adult atopic dermatitis: a randomized placebo-controlled study. Int J Immunopathol Pharmacol 24: 1037-1048.

88. van de Pol MA, Lutter R, Smids BS, Weersink EJ, van der Zee JS (2011) Synbiotics reduce allergen-induced T-helper 2 response and improve peak expiratory flow in allergic asthmatics. Allergy 66: 39-47.

89. Chen YS, Jan RL, Lin YL, Chen HH, Wang JY (2010) Randomized placebo-controlled trial of lactobacillus on asthmatic children with allergic rhinitis. Pediatr Pulmonol 45: 1111-1120.

90. Licciardi PV, Tang ML (2011) Vaccine adjuvant properties of probiotic bacteria. Discov Med 12: 525-533.

91. Isolauri E, Joensuu J, Suomalainen H, Luomala M, Vesikari T (1995) Improved immunogenicity of oral D x RRV reassortant rotavirus vaccine by Lactobacillus casei GG. Vaccine 13: 310-312.

92. Soh SE, Ong DQ, Gerez I, Zhang X, Chollate P, et al.(2010) Effect of probiotic supplementation in the first 6 months of life on specific antibody responses to infant Hepatitis B vaccination. Vaccine 28: 2577-2579.

93. de Vrese M, Rautenberg P, Laue C, Koopmans M, Herremans T, et al. (2005) Probiotic bacteria stimulate virus-specific neutralizing antibodies following a booster polio vaccination. Eur J Nutr 44: 406-413.

94. Olivares M, Díaz-Ropero MP, Sierra S, Lara-Villoslada F, Fonollá J, et al. (2007) Oral intake of Lactobacillus fermentum CECT5716 enhances the effects of influenza vaccination. Nutrition 23: 254-260.