International Journal of General
Medicine and Pharmacy (IJGMP)
ISSN(P): 2319-3999; ISSN(E): 2319-4006
Vol. 2, Issue 5, Nov 2013, 17-24

International Academy of Science,
Engineering and Technology
Connecting Researchers; Nurturing Innovations

PROBIOTICS: HEALTH BENEFIT EFFECTIVENESS AND ADVERSE EFFECTS

MUSTAFA MURTAZA[1], SHAH M. JAWAD[2], LATIF M. IKRAMRUL[3] & SHAFI SAIMA[4]

[1,2,3]School of Medicine, University Malaysia, Sabah, Kota Kinabalu, Sabah, Malaysia

[4]Hospital Queen Elizabeth, Kota KInabalu, Sabah, Malaysia

ABSTRACT

Probiotics, particularly lactobacilli, lactococci and Bifid bacterium are thought to be generally safe, beneficial to health with daily ingestion by millions of individuals. Probiotics have been suggested for the treatment of infectious gastroenteritis, treatment and prevention of Clostridium difficllie associated diarrhea. Recent findings suggest that probiotics may help atopic eczema, irritable bowel disease, Helicobacter pylori infection, and recurrence of superficial bladder cancer. Probiotic are also effective in rotavirus and antibiotic associated diarrhea. Research will validate the value of probiotics for their use as growth promoters in animals. Population based studies raise concerns about the use of at least certain probiotics in vulnerable patients, particularlyimmunocompromisedhosts, patients with intravenous catheters, prosthetic material, short bowel syndrome, abnormal cardiac valves, elderly patients, and in infectious complications of acute pancreatitis reported increased mortality in probiotic treatment group. Mortality or sepsis has been reported as due to invasive Lactobacillus spp. or S. boulradi infections associated with probiotic use. Clinicians need to be aware of the risks and benefits of this treatment

KEYWORDS: Probiotics, Lactobacillus, Bacteremia, Sepsis

INTRODUCTION

Eli Metchnikoff described the beneficial effects of Lactobacilli among Bulgarian farmers. Since last century lactobacilli and bifidoobacteria have been promoted as beneficial to health. Only since 1980s have been well-designed animal experiments and human trials conducted on probiotics [1].World Health Organization (WHO) defined probiotics as live microorganisms that when administered in adequate amounts, confer a health benefit on the host [2]. Prebiotics are selectively fermented ingredients that stimulate specific changes in the colonic micro biota that benefit the health the host. At present only non-digestible oligosaccharides e.g. Inulin are classified as prebiotics. Synbiotic are combinations of prebiotics and probiotics that are designed tohave synergistic or additive effects benefiting the host. At present both bacterial, lactobacillus or biofidobacterium and fungal, Sacchromycesboularadi, probiotics are in global use [3]. The beneficial action of probiotics is attributed to: a) antagonism through production of inhibitory substances, b) competition with pathogens for adhesion sites for nutrition, c) immunomodulation of the host, d) inhibition of the toxin [4]. Probiotics, Saccharomycesboulradi have been suggested for the treatment of infectious gastroenteritis in general, and specifically for the treatment of and prevention of Clostridium difficleassociated diarrhea (CDAD). In a trial, diarrhea was resolved in 85 % of treated patients, although the number of patients treated were low [5]. Recent findings suggest that probiotics may help in atopic eczema, irritablebowel syndrome, and inflammatory bowel disease and Helicobacter pylori infections [1]. Asoet al, reported the protective effect of Lactobacilli casei strain Shirota on the recurrence of superficial bladder cancer. Although associated immune responses were not assessed in these studies, enhanced natural killer cells (NKcells) activity in adults colon cancer patients given L, caseiShirota suggests that probiotic may suppress tumor development through activation of immune system [6,7]. There is also evidence that probiotic intake is effective in acute gastroenteritis and rotavirus diarrhea, antibiotic associated diarrhea, Cohn’s disease and pediatric atopic disorders. Several

excellent reviews in immunomodulation effects of probiotic have been established. For example treatment with cocktail of lactobacilli strains significantly reduced the relapse rate and the severity of clinical symptoms in patients with pouchitis (inflammation of ileo-anal pouched formed after colectomy) compared with placebo [8].This paper reviews the health benefit and adverse effects of probiotics on the host.

COMMERCIALLY AVAILABLE PROBIOTICS

There is whole range of probiotics in the market. Some products purported to contain single microbes, other comprising multiple distinct microbese.g.VSL#3 which contains eight strains of bacteria from the genera Bifidobacterium. Lactobacillus, and Streptococci and others containing multiple species ofa single bacterial genus (e.g. Lactobacillus acidophilus and Lacto bacillisrhammosus). However, studies to verify the composition of the marketed probiotic formulations have found that discrepancies are common, at least 30 to 40% of the products, between the stated and actual number of viable organisms, the concentration of the organisms, and the type organisms product compared with product labeling [3]. In addition, some marketed probiotics are labeled with taxonomically incorrect or fictitious microbial names. Thus, considerable uncertainty exists about the composition and reliability of currently available probiotic preparations. As food ingredients or dietary supplements, probiotics are not subject to minimal manufacturing standards with regulatory oversight, nor are scientifically sound studies of demonstrating efficacy required to market a probiotic product [2,3]. Hence, for most available, studies to demonstrate probiotic confers a demonstrable health benefits- are lacking and even less information is available to define the mechanism (s) by which particular products promote human health in different clinical illnesses. In the United States, probiotics may receive “GRAS” status (Generally Recognized As Safe) by the U.S. Food Drug Administration (FDA), even if no efficacy data exist. GRAS substances are those “for which are used in food has proven track record of safety based on a history of use before 1958 or published scientific evidence, and that need not be approved by the FDA prior to being used”. There are eight probiotics that currently possess GRAS status in the United States e.g. Lactobacillusreuteri strain DSM 17938, Lactobacillus caseisubsprhammosus strain GG, Lactobacillus acidophilus, Lactobacilluslactis and padiococcusacidilactici, Biofidobacteriumlactis strain Bb12 and Streptococcus thermophiles strain Th4,Biofidobacterium lomgum BB536,Sacchromyces cerevisiae strain BCMo01 with enhanced expression of urea amidolyase, S. cerevisiae strain,MI.01 carrying a gene encoding thamalalactic enzyme from Oenococcusaeni and gene encoding malate permease from Schizosacchromycespombe, and Carnobacteriummaltromaticum strain CB1. (http://www.cfsan.fda.gov/-rdb/opa-gras.html,Feb.2009).

CLINICAL TRIALS ON PROBIOTICS

Clinical trials and well-designed animal experiments were conducted in 1980s.Only about 40 studies on probiotics or synbiotics have been published to date, compared with more than 400 randomized controlled probiotic clinical trials. There has been one clinical trial in a myriad of clinical conditions. Gastrointestinal conditions, such as inflammatory illnesses (e.g. inflammatory bowel diseases, or necrotizing enterocolitis in neonates)or enteric infections, have been studied most often[9]. In addition to on specific clinical conditions, numerous studies have been conducted to evaluate the effect of individual probiotic preparations on the composition of the fecal flora, gastrointestinal barriers- function, and nutrition, as well as a variety of mucosal systemic, or cutaneous immune responses in healthy individuals and different patient populations. The reported results often differ among studies on similar topics but, overall it is unusual for available for the randomized, controlledtrials in a particular condition to have been conducted with the same probiotic agent with comparable rigor. Verification of probiotic content and viability is not current standard of reported probiotic randomized, controlled studies. For example, a recent review of 46 clinical trials of probiotic used in inflammatory bowel disease noted

that only 23 reported studies were double-blind, randomized, controlled trials and that among all reviewed trials, 32 used different probiotic products,10 used different prebiotic products and 4 used different synbiotics [10].

There is additional concern is the study criteria leading to restricted enrollment in probiotic clinical trials. For example, a recent, highly publicized trial evaluating a probiotic Lactobacillus preparation to prevent antibiotic-associated diarrhea was conducted using randomized, double-blind, placebo-controlled protocol and enrolled 135 patients. The results suggested that the probiotic yielded benefit, significantly reducing both antibiotic –associated diarrhea and the number of patients who acquired diarrhea caused by Clostridium difficile. However, only8 % of potentially eligible patients were enrolled in the study, limiting the ability to generalize the results to clinical practice [11]. Cochrane reviews provide a structured (using predefined criteria), collaborative, and multinational approach to evaluation interventions for the prevention and treatment of disease. Of 15 available Cochrane reviews, 10 focus on luminal gastrointestinal conditions or infections including infectious diarrhea, antibiotic- associated diarrhea, C. difficlecolitis, inflammatory bowel disease (including pouchitis), necrotizing enterocolitis in preterm infants, collagenous colitis, and irritable bowel syndrome. Among these conditions, the studied probiotics may reduce the risk of severe necrotizing enterocolitis in preterm infants weighing more than 1000g; may have utility in the maintenance of chronic pouchitis remission status post pouch-anal anastomosis; and were suggested as useful adjunct to oral hydration therapy for infectious diarrhea (although the most effective product remain ill-defined). A recent meta-analysis evaluating the use of probiotics in acute, likely infectious diarrhea noted that the majority of the data was derived from hospital-associated studies, with a paucity of community-based trials of probiotic use in acute diarrhea and only one trial available from a developing world setting [12].

MODE OF ACTION AND EFFECTIVNESS OF PROBIOTICS

The mechanism of action of probiotics from the data predict that each person has a unique colonic microbiome comprising predominantly two bacterial lineage, the Firm cutes (mostly Clostridiaspp) and the Bacteriodes (mostly Bacteriodesspp) Further, the composition and structure of the individual's micro biome is important to health but may also contribute to disease risk. Detailed murine studies of common bacterial members of the micro biome such as Bacterioidesfragilis or Bacteriodesthetaiotaoute to health or disease. For example, select strains of B. fragilis through expression of surface polysaccharides A, can serve to diminish mucosal inflammation or even promote systemic adaptive immune responses, whereas B. the taiotaomicr on is thought to play an important role in nutrition through glycan foraging in the colonic lumen [13-16]. However, the disruption of the balance between Firmicutes and Bacterioides has suggested to contribute to the development of obesity and inflammatory bowel disease [17,18]. It is within this scientific framework aimed at understanding the fundamental mechanisms by which the micrbiome influences mucosal innate and adaptive immunity as well as the health or disease of the host that investigations are being conducted to define the mechanistic and biological basis for health benefits of probiotics [19].

The mechanism of most probiotic remain unexplored, it is generally presumed the molecular mechanisms of probiotics are triggered by microbe-epithelial interactions at the site of probiotic application (e.g. .gut, vaginal) with modulation of one or more mucosal or systematic immune response. The mechanisms by which probiotics act should be presumed to differ among probiotics. Recent experimental studies in vitro and vivo beginning to provide clues to how probiotics may act, with preponderance of information suggesting that certain probiotics dampen nuclear factor- kB activation and hence, proinflammatory mucosal or systematic immune responses[19,20,21].Additional data suggest that select probiotics augment antibody responses, to immunization and infecting pathogens. In some instances, cell free supernatants of studied probiotics similarly dampen inflammatory responses, suggesting the possibility that probiotics may

cell free anti-inflammatory molecules [22]. Isolation and characterization of these molecules provide an approach to the development of new therapeutic agents in the future. Although it has widely presumed that probiotics, through mucosal adherence, displace pathogens and prevent their ability to colonize and initiate disease, there no firm data confirming this concept and in fact, experimental studies have reported conflicting results on the ability of probiotics to displace pathogens from epithelial cells or the mucosa [23]. In human studies, distinct strains of probiotics have shown differing capacities for colonization based on fecal studies. Further, detection of changes in innate and adaptive immune-responses has varied with different probiotics and differing study populations. Modest enhancement of systematic proinflammatory responses has been demonstrated, for example in allergy-prone infants [24,25].

HEALTH BENEFIT OF PROBIOTICS

The mechanism of clinical benefit is postulated to be via GI immune mechanism. Colonization bacteria interact with cells, including immune cells of the gut epithelium, and probiotic bacteria could enhance mechanisms such as natural killer cell activity, cytokines production, macrophage activation, and secretory IgA activity [26]..Probiotics might also be effective by a simple no nimmunologic mechanism, preventing pathogen adherence and invasion of gut tissues [26]. The ideal probiotic would survive stomach acid and intestinal bile, multiply within the human intestine and attach to human epithelial cells, and also produce antibacterial substances. Lactobacillus GG, for example, was chosen for probiotic intervention specifically because it survives passage in the upper GI system, multiplies in the intestine, adheres well to epithelial cells in vitro and prevent adherence of E. coli 0157-H7,and produces a substance effective against some pathogenic bacteria [27]..

Probiotic have been used for acute diarrhea, allergies colitis, inflammatory bowel disease, and irritable bowel syndrome, the strongest evidence for efficacy is in the treatment and prevention of acute diarrhea [28]. Approximately 300 European children aged 1 to 36 months with acute diarrhea predominantly caused by rotavirus were randomized between treatment with oral rehydration solution plus L.GG (10^{10} CFU/250 ml) or oral rehydration solution plus placebo. The duration of diarrhea was 58 hours for the Lactobacillus group versus 72 hours for placebo group [29]. In another study approximately 60 6-to 36 month –old Finish children with rotavirus diarrhea were randomized to Lactobacillus reuteri at a high dose (10^{10} CFU/250ml), L. ruteri at low dose (10^{7} CFU/25ml), or placebo. Duration of diarrhea was 1.5 days in the high dose group,1.9 days in low-dose group, and 2.5 days in the placebo group [30].Conversely, a low dose of L.GG (10^{8} CFU/250ml.per day) did not decrease the duration of rotavirus diarrhea in 300 Indian children, mean age 1 year [31].

In another study comparing the efficacy of several probiotics thought to be effective treatment for diarrhea in Italian children aged 3 to 36 months. Each probiotic was administered at approximately 10^{10} CFU/day. Compared with the duration of diarrhea for oral rehydration solution alone (115 hours), L.GG demonstrated a statistically significant improvement (72 hours) but Saccharomycesboulardi and Enterococcus faceium did not [32]..L.GG was effective prophylaxis in Peruvian children; 160 undernourished 6- to 24 month-old children [33].

PROBIOTICS AS GROWTH PROMOTERS IN ANIMALS

Since 1950 and 70, most classes of antibiotics were used as growth promoters, primarily in pigs and poultry, at application rates of about 50 ppm in feeds. The responses in production were consistently of the order of 10 to 15 per cent and improvements in feed averaged 5 per cent. The level of response depend on environmental factors and, of course the pathogen loads present [34]. Indiscriminate use of antibiotics of all classes for growth promotion, as well as concerns about residues in animal products intended for human consumption, led to a series of inquires globally between 1969 and 1975 [35, 36]. In 1969, Sweden decided to ban the use of antibiotics as animal growth promoters. Detection of

antibiotic residues is not the concern; rather, it is the fear about the development of gastrointestinal bacteria with drug resistance. The proposed banning of antibiotics for growth stimulants, at least in Europe, has led to an urgent search for reliable alternatives. Those currently considered, developed and evaluated included somatotrophins (BTs for dairy-cattle milk production and PsT for pig meat) [37]. Probiotic bacteria principally various species of Lactobacillus and Enterococcus faecium have been used extensively in pigs, poultry and calves since 1970.Responses have been variable depending on the quality and nature of the probiotic preparation used and the disease status of the animals. Studies have shown weight gains occurred, they averaged around 5 per cent [38]. However such gains are inconsistent and that probiotic treatment even reduce weight gain and feed conversion. Similarly indeterminate results have been found with broiler and layer poultry [39]..Probiotics have consistently improved the survival of chicks and to lowering of Salmonella and Campylobacter loads. A competitive exclusion (CE) treatment is the name usually reserved for treatment of day-old chicks with micro flora, resulting in colonization resistance towards potentially pathogens [39,40]. With bans on antibiotic use in animals will necessitate research and development to determine and validate the value of probiotics for use as growth promoters in animals [41].

ADVERSE EFFECTS OF PROBIOTICS

Probiotics, particularly lactobacilli, lactococci, and Bifido bacterium are thought to be generally safe based on a long history of extensive use with likely daily ingestion by millions of individuals and limited toxicity [42]. In fact, ingestion of L.rhamnosus GG is reported to have increased tremendously in Finland from 1990 to 2000 [42]. Population- based studies appear reassuring about the toxicity of probiotic use, other data raise concerns about the use of at least certain probiotics in vulnerable patients, particularlyimmunocompromisedhosts, the severely ill those with serious co morbidities, patients with intravenous catheters, prosthetic material or hardware, short bowel syndrome, or abnormal cardiac valves, and the elderly [43]. In particular, a recent randomized, double blind, placebo-controlled trail designed to evaluate the effectiveness of a probiotic preparation (6 different Lactobacillus or Bifidobacterium. Strains; total daily dose 10^{10} bacteria) on infectious complications of acute pancreatitis reported increased mortality in probiotic treatment group (16% in 152 patients treated with probiotics Vs 6 % in 144 patients treated with placebo; relative risk 2.53,95% confidence intervals 1.22-5.25) without any measureable impact on infectious complications [44].

Further, bowel ischemia was significantly increased in in the patients with acute pancreatitis treated with probiotic. The mechanisms that could for this striking imbalance in adverse outcomes are unknown. Bacteremia, endocarditis, and liver abscess have been reported as due to Lactobacillusspp. Infection including L rhamnosus GG, with enhanced concern in individuals with short gut syndrome, central venous catheters, intestinal feeding tubes, or serious co morbidities [42].

Similarly, although Saccharomyces boulradi (a subtype of Saccharomyces cerevisiae, or brewer’s yeast) is an infrequent fungal bloodstream isolate, in one series 86% of S.boulradifungemia episodes were identified in children or adults who ingested S. boulradi as a probiotic [45]..Land, et al.reported a pediatric case of invasive disease attributable to a Lactobacillus strain .Molecular DNA fingerprinting analysis showed that Lactobacillus strain isolated from blood samples was indistinguishable from the L rhamnosus GG administered to the infant [46]. Mortality or sepsis with shock has been reported as due to invasive Lactobacillus spp. or S.boulradi infections associated with probiotic use. Other concerns about probiotic use, such as precipitating lactic acidosis, toxicity to the gastrointestinal tract, and transfer of antibiotic resistance within the gastrointestinal tract, remain theoretical in the absence of substantiation in clinical studies [42]. In view of the increasing use of probiotics as health supplements and therapeutic agents, clinicians need to be aware of the risks and benefits of these treatments [47].

CONCLUSIONS

Probiotics are widely used for their health benefits. Probioticsare safe for use in healthy individuals, but their use in certain clinical conditions must be with caution. Their effects may vary in health, various diseases, and different age groups and populations. Medical professionals need to be aware of the benefits, and side effects of these treatments.

ACKNOWLEDGEMENTS

We wish to thank Vice Chancellor, University Malaysia Sabah, KotaKinabalu, Sabah Malaysia and the Dean School of Medicine, UMS for the permission to publish this article.

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