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Probiotics in the Management of Diseases: A Review

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A B S T R A C T

In recent years, there has been an increase in the application of probiotics for the treatment of some diseases and to alleviate the symptoms of many others. Diseases and ailments such as diarrhea, pouchitis, cancer, ulcerative colitis, irritable bowel disease, and a host of others have experienced an increase in the use of certain probiotics bacteria to combat them. The complete mechanisms of action of probiotics in disease management and enhancement of the health of the host remain largely unknown, but the major activity thus appear to be via modulation of immune responses (immunomodulations) and colonization competitive shielding off of pathogens. This paper is set to review some of the various ailments for which probiotics have been used. With an upsurge in the use of probiotics, also comes an increase in skeptism on the safety of their use for medical purpose, the safety concerns that may obstruct effective usage and thus judicious application of probiotics in disease management warrants further investigations.

Introduction

Probiotics are defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host (FAO/WHO, 2002). They are live nonpathogenic preparation administered to improve and restore the microbial balance of gastrointestinal tract. Probiotics, as biological factors, control the gut microbiota and result in its progression. They are organisms which are generally regarded as safe (GRAS) and consumed without the risk of infections (FAO/WHO, 2002). Most organisms used as probiotics belong to the lactic acid bacilli, Lactobacillus and Bifidobacterium, a nonpathogenic *E. coli* strain (*E. coli* Nissle 1917), *Saccharomyces boulardii*, *Clostridium butyricum*, and *Streptococcus salivarius* subspecies *thermophilus*, genetically engineered bacteria that secrete immunosuppressive substances such as interleukin-10 (IL-10) have been studied (Sartor, 2004).

Probiotics are commonly consumed as part of fermented foods with specially added active live cultures, such as in yogurt, soy yogurt, cheese or as dietary supplements. Probiotics may beneficially affect the host by augmenting its intestinal microbial population beyond the amount already

existing, thus possibly inhibiting pathogens. Specific attributes that position an organism to be an effective probiotics include acid tolerance, bile tolerance, cell surface hydrophobicity, protoplast regeneration, antimicrobial activity, cholesterol removal and bile salt deconjugation, gut colonization, lactose removal, protease and amino peptidase activity (Sartor, 2004; Sudah *et al*., 2009; Scaldaferri *et al*., 2013). To be functional in the intestinal tracts, probiotics are expected to be viable and in a certain number. As such the modes of delivery and production should be targeted towards maintaining the viability of the organism after production and even during storage.

Probiotic organisms may be naturally occurring microbes (as is the case for all used in food), or microbes that have been genetically altered for a specific effect. The complete mechanism of action of probiotics in disease management is not known, however, the major activity thus appear to be via colonization competitive shielding off of pathogens and immunomodulations. Several research effort have explained these mechanism of activities to include improving gastrointestinal tract health via modifying gut pH, antagonizing pathogens through production of antibacterial compounds, competitive exclusions of pathogens at the binding and receptor sites, enhancing the immune system, synthesizing and enhancing the bioavailability of nutrients, competing for available nutrients, reducing the symptoms of lactose intolerance, decreasing the prevalence of allergy in susceptible individuals, and reducing risks of certain cancers through binding of deleterious mutagens and carcinogens (Hirayama and Rafter 2006; Jain *et al.,* 2010).

In the present review article we highlight some of the diseases for which probiotics have been used to manage and ameliorate conditions with a view to steering interests for further probe into specific mechanisms of activity of probiotics and its possible use in the management of diseases hitherto not perceived/conceived. For more in-depth view on the diseases highlighted, the reader is kindly asked to refer to specific publications.

Probiotics in the treatment/ management of diarrheal diseases

Diarrhea has been defined as the passage of 3 or more loose or liquid stools per day, or more frequently than is normal for the individual. It is usually a symptom of gastrointestinal infection, which can be caused by a variety of bacterial, viral and parasitic organisms, diarrhea could also be antibiotic associated (WHO, 2013). Diarrhea leads to fluid loss, and may be life-threatening, particularly in young children and people who are malnourished or have impaired immunity (WHO, 2013). Reports abound on the use of probiotics for treatment of antibiotic associated diarrhea (AAD) and the management of chronic and acute enteric infections and their associated diarrheal complexes.

The rationale for using probiotics for treatment of diarrhea is based on the observation that they act either by modifying the composition of colonic microbial flora or by modulating the immune response. Lemberg *et al*. (2007) penned that probiotics modify the composition of microbial flora by several mechanisms which include: Competing with pathogens for nutrients and receptors; Inducing hydrolysis of toxins and receptors; Inducing production of antimicrobial substances including peptides of the innate immune system; Inducing production of organic acids and modulation of nitric oxide synthesis. Seth *et*

al. (2008) opined regulating intestinal permeability by modulating the epithelial tight junctions as a mechanism of action while Walker (2008) noted the exerting of a tropic action on the intestinal mucosa, which leads to brush border enzyme activation, stimulation of glucose absorption and anti-apoptotic effects on the enterocyte as one of the action mechanisms of probiotics in the management of diarrhea.

McFarland (2009) submitted that antibiotic associated diarrhea (AAD) is a common complication of most types of antibiotics, especially for broad-spectrum antibiotics such as clindamycin, beta-lactams and 3rd generation cephalosporins. The non-selective action of antibiotics perturb the normal microbial flora of GIT, which leads to overgrowth and multiplication of pathogenic microorganisms i.e, *Clostridium difficle, Clostridium perfringens, Staphylococcus aureus, Klebsiella oxytoca, Candida spp* and *Salmonella spp.*, which ultimately result in the production of toxin, leading to diarrhea (McFarland, 2009). .
Perturbation of normal microbial flora leads to the decrease in the number of bacteria involved in the production of short chain fatty acids. These fatty acids are important for the nutrition of the enterocyte and for water and electrolyte absorption, and their decrease may result in watery diarrhea. Erythromycin is special case of antimicrobial agents which directly stimulate the motilin and induce the diarrhea (McFarland, 2009).

Kotowsha *et al*. (2005) observed that oral administration of selected probiotics strain along with antibiotics can be the better option to handle the situation of antimicrobial associated diarrhea. In a clinical study, Kotowsha *et al*. enrolled 269 children who were taking antibiotics for ear or respiratory infections and randomized them to either *Saccharomyces boulardii* (500 mg/d) or placebo for the duration of the antibiotic treatment. Even though the follow-up time was short (two weeks post-antibiotic), the frequency of diarrhea in the probiotic group was significantly less (3.4%) compared to 17.3% in the placebo group (Kotowsha *et al*., 2005).

Clostridium difficile–associated diarrhoea (CDAD) is most often caused by clindamycin, cephalosporins, ampicillin, and amoxicillin. *Clostridium difficile* has been associated with symptomatic diarrhoea since being identified as the pathogen responsible for pseudomembranous colitis (Santosa *et al*., 2006). Total flora replacement or faecal bacterio therapy has been described as an effective treatment alternative in severe *C. difficile* infections. It is based on transfer of faecal flora from a healthy individual to a severely ill patient. Total flora replacement has also been used to manage severe constipation, irritable bowel syndrome, and inflammatory bowel disease. Homologous faecal enemas have been used in recalcitrant cases of CDAD usually with stool donated by the patient's partner. *L. acidophilus* and *L. rhamnosus* are probiotics that have been detected in these fecal samples. It is an adjunctive therapy in sporadic clinical use. (Borody *et al*., 2003; 2004).

Traveler's diarrhea occurs in about half of travelers who visit high-risk areas. Although most cases are mild and self-limiting, there is considerable morbidity. Antibiotics are an effective means of prophylaxis but are not recommended for widespread use. Hence there is a need for cost-effective alternative treatments. The efficacy of probiotics in traveler's diarrhea has been reported with *Saccharomyses boulardii* and *Lactobacillus rhamnosus* GG shown to have significant effects. *S. boulardii* seems to

prevent bacterial diarrhoea more effectively, while *Lactobacillus rhamnosus* GG has been shown to be more effective against viral and idiopathic diarrhea (Goldin and Gorbach, 2008).

Infective diarrhea due to Rotavirus is the leading cause of infantile diarrhea worldwide and rapid oral rehydration is the primary treatment. Several potential mechanisms have been proposed for how lactobacilli reduce the duration of rotavirus diarrhea through competitive blockage of receptor sites in which lactobacilli bind to receptors, enhanced immune response, and signal(s) from lactobacilli that regulates the secretary and motility defenses designed to remove perceived noxious substances and lactobacilli that produce substances meant to inactivate the viral particles. The probiotics most frequently studied for treating acute diarrhea include *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri* (Santosa *et al*., 2006, Goldin and Gorbach, 2008).

Probiotics in inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is a collective term, used for ulcerative colitis (UC), Crohn's disease (CD) and Pouchitis. IBD is an abnormal immune response against luminal antigen of commensal bacteria in genetically predisposed individuals (Sartor, 2004; Fedorak *et al.*, 2004; Gionchetti *et al.*, 2005; Marteau *et al.*, 2009). Traditionally known medication used in IBD includes 5-aminosalicylic acid (5-ASA) and corticosteroids. Limited clinical trials suggest that selected probiotics species, alone or in combination, can prevent recurrent intestinal inflammation and possibly treat active IBD, with best results in pouchitis, and, to a lesser extent, ulcerative colitis and Crohn's disease (Table 1 adapted from Sartor, 2004).

Several probiotics mechanisms of action, relative to inflammatory bowel disease, have been elucidated: (1) competitive exclusion, whereby probiotics compete with microbial pathogens i. e. colonization resistance-occupy ecologic niche. ; (2) immunomodulation and/or stimulation of an immune response. Alter immunoregulation by induce IL-10, transforming growth factor expression and secretion, stimulate secretory immunoglobulin A production, decrease tumor necrosis factor expression ; (3) antimicrobial activity and suppression of pathogen growth, inhibit pathogenic enteric bacteria via decrease luminal pH, secrete bacteriocidal proteins,; (4) enhancement of barrier activity. Improve epithelial and mucosal barrier function, (Produce short chain fatty acids, including butyrate. Enhance mucus production and increase barrier integrity; and (5) induction of T cell apoptosis, block epithelial binding— induction of MUC 2 inhibit epithelial invasion (Rioux and Fedorak, 2006; Marteau *et a*l., 2009; Scaldaferri *et al*., 2013).

Fujmori *et al*.(1997) reported that in Crohn's disease, commensal *E. coli* strain stimulates the release of tumor necrosis factor–α (TNF- α) and interleukin-8 (IL-8) by inflamed mucosa. However, some *lactobacilli* strains including *L. casei* down regulate the spontaneous releases of TNF- α and the inflammatory response induced by *E.coli*. Therefore, it makes sense either to eliminate some bacteria with antibiotics or to alter the gut flora, in favor of more beneficial bacteria, by the use of probiotics and prebiotics (prebiotics are dietary substances usually non-digested carbohydrates that stimulate the growth and metabolism of protective commensal enteric bacteria) (Fujmori *et al*., 1997; Scaldaferri *et al*., 2013).

Table.1 Randomized Double-Blind Trials of Probiotic Agents in IBD

Author (date)	Probiotic	Clinical situation	Result
Crohn's disease			
Plein, Hotz (1993)135	*Saccharomyces boulardii*	Maintenance of remission	↓ diarrhea vs. placebo
Malchow (1997)93	*E. coli* Nissle 1917	Maintenance of remission	↓ relapse vs. placebo
Guslandi (2000)136	*S. boulardii*	Maintenance of remission (probiotic mesalamine vs. mesalamine alone)	↓ relapse vs. mesalamine alone
Prantera (2002)94	*Lactobacillus GG*	Postoperative prevention	No benefit
Ulcerative colitis			
Kruis (1997)85	*E. coli* Nissle 1917	Maintain remission	Equal to mesalamine (1.6 g)
Rembacken (1999)86	*E. coli* Nissle 1917	Maintain remission	Equal to mesalamine
Kruis (2001)87	*E. coli* Nissle 1917	Maintain remission	Equal to mesalamine
Ishikawa (2003)88	Bifidobacteria-fermented milk	Maintain remission	Superior to placebo
Pouchitis			
Gionchetti (2000)77	VSL#3	Maintain remission chronic pouchitis	Superior to placebo
Mimura (2002)83	VSL#3	Maintain remission chronic pouchitis	Superior to placebo
Gionchetti (2003)84	VSL#3	Prevention after ileostomy closure	Superior to placebo

The proposed mechanisms of action of probiotics in the management of Crohn's disease include changes in short chain fatty acids (SCFA) production patterns; reduction in pro-inflammatory cytokine secretion, improving Th1/Th2 ratios; Eliminating pathogens; enhancement of barrier function (Fujmori *et al*., 1997).

In a study by Malchow, 28 patients of active CD were treated with a tapering dose of prednisolone and either placebo or *E. coli* Nissle (*E. coli* Nissle is a nonpathogenic *E. coli*, which colonize the intestine and inhibits the growth of enteropathogenic and other enteric bacteria. It is proposed that this organism, by suppressing enteropathogenic bacteria, may have a long-term effect to suppress remission). The *E. coli* Nissle was given in an increasing dosage over 24 days to the final dose of $5x10^{10}$ bacteria per day for a year. The patients are assessed for the remission .There was higher relapse rate in the placebo group (63.6%) as compared to the *E. coli* group (33.3%) (Malchow, 1997).

Fujimori *et al.*(1997) treated 10 patients of Chorn's disease not responding to 5-ASA and prednisolne therapy with a synbiotic therapy, (Probiotic - *Bifidobacterium* and

Lactobacillus and Prebiotic- psyllium), for 12 months. Six patients went into remission, one had a partial response with improvement of the number bowel movements, and three patients were non-responders. There was no significant difference between C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values were observed before and after the therapy (Fujimori *et al.,* 1997).

In ulcerative colitis (UC), the composition of microflora is imbalanced associated with increased number of pro-inflammatory bacteria, including Enterobacteriaceae, and *Bacteroides fragilis* and decreased count of protective bacteria, including *lactobacilli* and *bifidobacteria*. Furrie *et al*. (2005) documented the management of ulcerative colitis via probiotics. In a double blind study for patients with active UC, employing a combination of probiotics strain, *Bifidobacterium longum*, with a prebiotic composed of an inulin-oligofructose (growth substrate) on 18 patients. Nine patients assigned to the treatment group and nine to the placebo group. Patients assessed with a clinical activity index, level of gut inflammatory markers and histological sore. The patients were treated with the synbiotic mixture (probiotics- prebiotic) of placebo twice-daily for 4 weeks. At the end of the month, the patients were reassessed. The patients receiving the synbiotic mixture exhibited reduced mucosal inflammatory markers in colonic biopsies. There was an improvement microscopically .There is significant reduction in TNF-α and IL-α levels in mucosal biopsies in patients treated with the active therapy as compared to placebo (Furrie *et al*., 2005).

Pouchitis is an idiopathic inflammatory disease of the ileal pouch that occurs in 15% – 53% of patients who undergo total abdominal colectomy with ileal pouch-anal anastomosis (IPAA) for ulcerative colitis. Fecal stasis with immunologic reactivity appears to be important in the pathogenesis of this disease (Tursi *et al*., 2004). Welters *et al.* (2002) and Kim and Hans (2004) demonstrated that using the dietary fiber Inulin (24 g/day), for the short period of 3 weeks significantly decreases the pouchitis as measured by endoscopic and histologic score. The results correlated with a significant alteration of fecal pH, fecal butyrate, and secondary bile acid concentration.

In a randomized, double-blind, placebo-controlled study 40 patients were randomized within a week after surgery to receive either VSL#3 (3 g, 9 x 10^{11} bacteria/day) or placebo for 12 months (Welters *et al*., 2002). Two of 20 (10%) of the patients treated with VSL#3 developed an episode of acute pouchitis compared to 8/20 patients (40%) in the placebo group ($P < 0.01$). Patients treated with VSL#3 and no signs of pouchitis had a median stool frequency of 5 (range, 3–9) at the end of the trial compared to 8 (range, 6 –12) in the placebo group (with no signs of pouchitis; $P < 0.001$) (Welters *et al*., 2002).

Probiotics in Genitourinary tract infection

The genital tract of premenopausal woman mainly composed of Lactobacilli, especially *Lactobacillus crispatus* and *Lactobacillus iners*. These *lactobacilli* engaged in the production of bacteriocins, lactic acid and hydrogen peroxide, which maintain the pH acidic and keep away the pathogenic colonies from proliferating. Imbalanced microbial flora offer an opportunity for the proliferation of pathogenic microorganism such as *E. coli*, *Gardnerella vaginalis*, *Bacteroides* sp, beta-*Streptococci* , *Mobiluncus* or *Falcivibrio* spp. and *Candida albicans* (Hillier *et al.*, 1993; Cauci *et al.*, 2003; Anukam *et al.*, 2006a.b).

Unnecessary receive of broad-spectrum antibiotic (excreted out from urine), disrupt normal flora, and causes symptomatic urinary tract infections such as bacterial vaginosis and candidal vulvovaginitis ((Cauci *et al.*, 2003) Restoring the normal flora with lactobacilli may help to treat these genital infection.

The treatment of UTI usually is with oral antimicrobial regimens of clindamycin, metronidazole or nofloxacin for bacterial vaginitis and fluconazole for candidal vaginitis. Nevertheless, their nonselective antimicrobial action decrease the lactobacilli count, and alter the pH (shift to alkaline), which ultimately associated with recurrence of the infection. Use of effective probiotics could be the best option to manage the above condition and to break the cycle of recurrence.

In a clinical study conducted on 28 women suffering from recurrent candidal vulvovaginitis, Hilton *et al*. (1992) reported that administration of vaginal suppositories cantaining *Lactobacillus rhamnosus* GG twice daily for seven days, all of the women reported an improvement in vaginal symptoms and reduction in vaginal erythema and discharge.

Studies have shown that women with bacterial vaginosis (no lactobacilli) are at significantly increased risk of HIV (Falagas *et al*., 2006; Anukam *et al.*, 2006a,b).The prevention or resolution of bacterial vaginosis is particularly important in women at risk of human immunodeficiency virus (HIV) infection. Thus, treatment of bacterial vaginosis and promotion of vaginal lactobacilli may reduce a woman's risk of acquiring HIV-1, gonorrhea, and trichomoniasis. A recent publication has shown that a human vaginal probiotic strain (*Lactobacillus reuteri* RC-14) can express potent functional viral inhibitors which may potentially lower the sexual transmission of HIV (Liu *et al*., 2006).

A study constituting 13 women showed that consumption of yogurt containing *L. acidophilus* decreased the incidence of *C. albicans* yeast infections (Klebanoff *et al*., 1991). Hydrogen peroxide production is a key factor in resisting BV disease (Klebanoff *et al.*, 1991). Hydrogen peroxide producing strains of *lactobacilli* have been found in 6l% of pregnant women with normal flora and in only 5% of women with BV. Hydrogen peroxide has been shown to be toxic to BV causing organisms, namely, *Gardnerella vaginalis* and *Prevotella bivia* (Hillier *et al.*, 1993). Comparable results were obtained in open and placebo controlled studies in which lyophilized *L. acidophilus* was applied locally or *L. acidophilus* yogurt was given orally (Parent *et al*., 1996, Hallén *et al*., 1992).

In these studies, success rates for control of BV or Candida vaginitis ranged from 57% to 87% in the probiotic group and from 0 to 22% in the control group (Hallén *et al*., 1992). Various molecular methods have shown *L. crispatus* and *L. johnsonii* to be the most common vaginal isolates from "normal" women of child- bearing age (Reid *et al*., 1996) The administration of *L. rhamnosus* GR-l in combination with *L. fermentum* B-54 and RC-l4 by mouth and intravaginally has been shown to be safe and to reduce the risk of UTIs, BV, and yeast vaginitis (Reid *et al.*, 1996). As with uro-genital pathogens, lactobacilli ascend from the rectum into the vagina and subsequently alter the microenvironment and potentially modulate the immunologic status of the host such that a normal vaginal flora is more often restored and retained (Gardiner *et al.*, 2002, Cadieux *et al.*, 2002).

Probiotics in Hypercholesterolemia and Hypertension

Cholesterol is a precursor to certain hormones and vitamins and is a component of cell membranes and nerve cells. However, elevated levels of total blood cholesterol (Hypercholesterolemia) or other blood lipids are considered to be a high risk factor for coronary heart disease one of the leading causes of death. Different mechanisms by which probiotics preparations could control blood cholesterol level have been proposed to include assimilation of cholesterol in the small intestine by probiotics and incorporation of cholesterol into the cell membrane of probiotics (Noh *et al*., 1997; Taranto et al., 1999;2000; Liong and Shah, 2005a).The cholesterol-lowering effect of lactic acid bacteria (*Streptococcus, Lactobacillus, and Bifidobacterium*) is well established (Nguyen *et al.*, 2007). It has been found that the isolated lactic acid bacteria had an excellent hypocholesterolemic effect. Some strains of lactobacilli have been found to remove cholesterol via various mechanisms and can be used as a dietary adjunct to lower serum cholesterol in vivo (Liong and Shah., 2005b).

L. acidophilus deconjugates bile acids into free acids that are rapidly excreted from the intestinal tract. Because free bile salts are excreted from the body, the synthesis of new bile acids from cholesterol lowers its concentration in the body. Further, it has been suggested by Andersson *et al.*(1995), that the bile flow is stimulated by regular milk consumption (l L/day). Isolates of *L. acidophilus* from human intestine are better able to assimilate cholesterol and actively deconjugate bile salts than commercially used cultures of *L. acidophilus. Lactobacillus plantarum* PH04 and *L. reuteri* showed cholesterol-lowering activities (De Smet *et al.*, 1998; Nguyen *et al.*, 2007). Clinical investigation have suggested a decrease in serum cholesterol concentrations during consumption of very large amounts (8 L/day) of yogurt or fermented milk per day (Hepner *et al.*, 1979) Hypercholesterolemia is one of the major causes for hypertension (Liong and Shah, 2005b).

Probiotics have potential to regulate blood cholesterol level in hypercholesterolemia. The elevation of blood pressure is found to be greatly induced when total cholesterol level exceeds 6.4 mmol/L. This may increase cardiac output and peripheral vascular resistance that causes an elevated blood pressure (Noh *et al*., 1997; Taranto et al., 1999; Liong and Shah, 2005b). Therefore, lipid metabolism disorders are often the causes of hypertension. A variety of in vitro experiments and in vivo trials have provided experimental evidence to support the roles of probiotics in lowering serum cholesterol and improving lipid profiles, which subsequently leads to a reduced risk of hypertension (Noh *et al*., 1997; Taranto et al., 1999; Liong and Shah, 2005b).

Probiotics in oral and dental diseases

The application of probiotics in the management of dental caries (Meurman *et al., 1995;* Näse *et al.*, 2001*;* Ahola *et al.*, 2002*;* Kang *et al.*, 2005*;* Stamatova *et al.*, 2007*;* Caglar *et al.*, 2006; 2007; 2008a,b*;* Cildir *et al.*, 2009), periodontal diseases (Grudianov *et al.*, 2002*;* Volozhin *et al.*, 2004*;*), halitosis (Kazor *et al.*,2003; Burton *et al.*, 2006*;* Kang *et al.*, 2006) and oral candidiasis (Elahi *et al.*, 2005*;* Hatakka *et al.*,2007)have been reported.

The proposed mechanisms of action of probiotics might be due to the competition

for binding sites in oral biofilms, strengthening the mucosal barrier *via* tropic effects on the epithelium, and stimulating both the innate and adaptive immune system. The ability of probiotics in the reduction of *S. mutans* and other oral streptococci with cariogenic potential abound.(Meurman et al., 1995; Kang et al., 2005; Stamatova et al., 2007; Caglar et al., 2008a, b; Çaglar et al., 2007; Çaglar et al., 2006; Cildir et al., 2009.)

A randomized, double-blind, placebo-controlled intervention study examined the effect of milk containing *L. rhamnosus* GG on caries and the risk of caries in children when compared with normal milk (Näse et al., 2001), probiotic milk was able to reduce *S. mutans* counts at the end of the trial and a significant reduction of caries risk was also observed. The putative caries prophylactic effect of probiotics has been also confirmed by daily intake of cheese containing *L. rhamnosus* GG and *L. rhamnosus* LC 705(Ahola et al., 2002). The probiotic cheese significantly reduced *S. mutans* counts in the intervention group during the post-treatment period when compared with the controls. Another probiotic species, *Bifidobacterium* DN-173 010, ingested once daily with yogurt demonstrated a significant reduction of salivary *S. mutans*, whereas no significant reduction was found in lactobacilli levels (Çaglar et al., 2005).

Periodontal inflammation has been reduced and also positively affected by the administration of two probiotic tablet forms Bifidum bacteria and lactic acid bacteria available on the Russian market (Grudianov et al., 2002). Studies have also shown that a periodontal dressing containing *L. casei* can reduce the number of most common periodontal pathogens and extend remission up to 10–12 months (Volozhin et al., 2004).

Bad breath in the oral cavity (Halitosis or *foetor ex ore}* is mainly ascribed to the production of volatile sulfur compounds (VSC) predominantly by Gram negative anaerobes residing in periodontal pockets and on the tongue dorsum. The replacement of bacteria implicated in halitosis by colonization with probiotic bacterial strains from the indigenous oral microbiota of healthy humans may have potential application as adjuncts for the prevention and treatment of halitosis. Kazor *et al.* (2003) reported that *L. salivarius* was the most predominant species detected in healthy subjects, whereas it was detected in only one of the subjects with halitosis at very low levels .The rationale of probiotic implementation in cases of halitosis has been documented in several studies. *S. salivarius* K12 taken in a lozenge after a mouthwash could reduce oral VSC levels in 85% of the subjects in the test group (Burton *et al.*, 2005). *Weissela cibaria* was also reported to being able to reduce VSC production both *in vitro* and *in vivo* (Kang *et al.*,2006a). A contributing factor to malodor reduction can be the ability of *W. cibaria* to co-aggregate with species renowned for their VSC production (*F. nucleatum*, for example), thus reducing the source for malodorous compounds in the oral cavity (Kang *et al.*,2006b).

Hatakka *et al.*(2007) reported that probiotic applications in the oral cavity have the potential to alleviate symptoms and reduce pathogenic potential of *Candida* species. They observed that a 16-week probiotic intervention study demonstrated a significant reduction by 75% of high yeast counts in the elderly and Hyposalivation reduction was also observed by the intake of *L. rhamnosus* GG containing cheese associated with control of oral *Candida*.

Elahi *et al.*(2005), Wagner *et al.*(2000) *in vivo* studies on mice have shown that lactobacilli might indeed be effective in controlling oral candidiasis. A higher clearance of *C.albicans* in mice fed with *L. acidophilus* compared to control group was demonstrated, however, no noticeable delay in colonization of the oral cavity by *C. albicans* of immunocompromized mice was achieved when heat killed *L. casei* and *L. acidophilus* cells were given

Stamatova and Meurman, (2009) in randomized controlled trials have nevertheless shown that probiotics may control dental caries in children due to their inhibitory action against cariogenic streptococci. They observed that less evidence exists on their role in periodontal disease or oral yeast infections.

Probiotics in Kidney diseases

The number of patients with chronic kidney disease (CKD) is rising worldwide and it is now being recognized as a major public health concern. Natarajan *et al.* (2009; 2010) observed oral administration of a probiotic formulation of selected microbial strains extend renoprotection via intraintestinal extraction of toxic waste solutes in patients with chronic kidney disease (CKD). The main outcomes of this investigation include a significant reduction of BUN (blood urea nitrogen, serum creatinine, and uric acid.), enhanced well-being, and absence of serious adverse effects (Natarajan *et a.l.,* 2010), thus supporting the use of the chosen probiotic formulation for bowel-based toxic solute extraction.

Lieske *et al.*(2005), Hoesl and Altwein,(2005) noted that a probiotic preparation able to degrade oxalate in vitro was shown to reduce oxalate fecal excretion. A high level of oxalate in the urine is a risk factor for development of kidney stones. Several probiotics preparations induce protective cytokines, including IL-10, and suppress proinflammatory cytokines, such as TNF-α and IL-6. Intestinal microflora is deranged in hemodialysis (HD) patients as an increase in aerobic bacteria such as *E. coli* and a decrease in anaerobic bacteria such as Bifidobacterium. One study reported that oral administration of *Bifidobacterium longum* in a gastroresistant seamless capsule decreases the the pre-HD serum levels of homocysteine and indoxyl sulfate. It has also been shown that synbiotics containing lactobacilli can reduce serum level of p-Cresol in HD patients. High-serum p-cresyl sulfate and indoxyl sulfate levels were associated with renal progression. Serum concentrations of p-cresol are independently associated with overall mortality and cardiovascular disease in HD patients.

In-vitro and in-vivo investigations undertaken by Kibow Biotech (2012) suggest that oral administration of a probiotic formulation comprised of selected microbial strains may extend renoprotection via intra intestinal extraction of toxic solutes in patients with CKD stages 3 and 4. They opined that science has defined more than 100 uremic toxins that may be involved in Chronic Kidney Disease and as well in CKD Stage 5, also known as end-stage renal disease (ESRD), and that certain probiotic microorganisms can utilize urea, uric acid and creatinine and other toxins as its nutrients for growth. Overloaded and impaired kidneys have a buildup of these poisonous wastes in the bloodstream, probiotics microorganisms multiply, thereby creating a greater diffusion of these uremic toxins from the circulating blood across the lining of the intestinal walls into the bowel. This increased microbial growth is excreted along with the feces (which is normally 50% microbes by weight) (Kibow Biotech, 2012)

Probiotics in Chronic fatigue syndrome (CFS)

CFS is a medically unexplained illness, characterized by persistent and relapsing fatigue, in addition to cognitive dysfunction, headaches, joint pains, and central nervous system disturbances (Komaroff *et al*., 1996). Aaron *et al.*(2000) observed that many CFS patients also complain of gastrointestinal (GI) disturbances and are more likely to report a previous diagnosis of irritable bowel syndrome (IBS), meet diagnostic criteria for IBS and experience IBS related symptoms. Whitehead *et al.* (2002) noted that while CFS is neither a gastrointestinal nor psychiatric disorder per se, over 50 percent of patients with CFS meet the diagnostic criteria of IBS, and anxiety itself is often a hallmark symptom in those with IBS. This corroborate the discovery that gut pathogens in the GI tract can communicate with the central nervous system and influence behavior associated with emotion, anxiety in particular, even at extremely low levels and in the absence of an immune response (Lyte *et al.*, 1998; Goehler *et al.*, 2007).

Probiotics, or live microorganisms which confer a health benefit on the host, have the potential to influence mood-regulating systemic inflammatory cytokines, decrease oxidative stress and improve nutritional status when orally consumed (Logan *et al.*, 2003). Several researches indicate that there are marked alterations in the intestinal microflora of CFS patients, including a lowered level of bifidobacteria and small intestinal bacterial overgrowth (Butt *et al*., 1998; Logan *et al.*, 2003; Rao et al. 2009) It has been observed that the oral administration of *Lactobacillus casei* strain Shirota (LcS) caused a significant rise in fecal *Bifidobacteria spp* and *Lactobacillus spp* in CFS and the administration of *Lactobacillus casei* strain Shirota (LcS) or placebo to otherwise healthy adults, reveals probiotics helped for mood regulation. Those with the lowest scores in the depressed/elated dimension at baseline had significant improvement in mood scores after taking the probiotic compared to the placebo group. The probiotic bacteria and placebo were unable to make a difference in those with the highest baseline mood scores (Benton *et al.*, 2007; Rao *et al*., 2009). In a similar study using the animal model of depression, the oral administration of a probiotics was shown to increase plasma tryptophan levels, decrease serotonin metabolite concentrations in the frontal cortext and dopamine metabolite concentrations in the amygdaloid cortex (Desbonnet *et al.*, 2008).

Probiotics in Diabetes

Diabetes mellitus has been described as a metabolic disease associated with a series of multiple risk factors that can be effectively managed by multifactorial interventions including dietary manipulations. Several research findings (Esteve *et al.*, 2011; Kootte *et al.*, 2012; Panwar *et al.*, 2013; Stachowicz and Kiersztan,2013), observed that in addition to risk factors such as genetic predisposition, epigenetic changes and unhealthy lifestyle, altered gut microbiota is a major risk factor because it cause increased adiposity, β-cell dysfunction, hyperglycemia, hypercholesterolemia, dyslipidaemia, metabolic endotoxemia, systemic inflammation, intestinal permeability (leaky gut), defective secretion of incretins and oxidative stress associated with type 2 diabetes (T2D). It is also a major risk factor in type 1 diabetes (Calcinaro *et al.*, 2005).
The influence of gut microbiota on health and disease has been established (Ulisse *et al*., 2001; Schultz *et al*., 2002; Vaarala, 2003; Sing *et al*.,2009), results from several

genomic, metagenomic and metabolomic studies have provided substantial information to target gut microbiota by dietary interventions for the management of T2D (Panwar *et al.,* 2013). Probiotics particularly lactobacilli and bifidobacteria have emerged as the prospective biotherapeutics with proven efficacy to abrogate progression and development of diabetes through improving the altered gut microbial composition and by targeting all the possible risk factors.

Calcinaro *et al.* (2005) reported that orally administered probiotic compound VSL#3 (a probiotic compound containing 3×10^{11}/g viable lyophilised bacteria, including bifidobacteria (*B. longum, B. infantis and B. breve*), lactobacilli (*L. acidophilus, L. casei, L. delbrueckii* subsp. *L. bulgaricus* and *L. plantarum*) and *Streptococcus salivarius* subsp. *thermophilus*.) prevented autoimmune diabetes and induces immunomodulation by a reduction in insulitis severity in a mice. They opined that the results provide a sound rationale for future clinical trials of the primary prevention of type 1 diabetes in man by oral VSL#3 administration. Similarly, Matsuzaki *et al.*(1997) reported that oral administration of heat killed *Lactobacillus casei* to non-obese diabetic (NOD) mice reduces the incidence of diabetes, but the mechanism underlying this finding has not been elucidated.

The consumption of probiotics was reported to prevent or delay the onset of diabetes and subsequently reducing the incident of hypertension. In a study conducted by Yadav *et al.* (2007), it was found that the administration of Dahi (an Indian fermented milk product) containing *Lactobacillus acidophilus*, *L. casei* and *L. lactis* to high fructose-induced diabetic rats for eight weeks decreased the accumulation of glycogen in the liver of rats compared to the control that was not fed the probiotics. High fructose diets induce type II diabetes that is associated with insulin resistance, hyperinsulinemia, hypertriglyceridemia and hypertension. This caused by the mobilization and accumulation of fructose in the liver that increases the rate of lipogenesis and synthesis of triacylglycerol. The probiotic dahi-supplemented diet significantly delayed the onset of glucose intolerance, hyperglycemia, hyperinsulinemia, dyslipidemia, and oxidative stress in high fructose-induced diabetic rats, indicating a lower risk of diabetes and its complications. The catabolism of fructose ultimately induces insulin resistance (Yadav *et al.*, 2007). Similarly, Eitahed *et al* (2011) reported 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.

The beneficial effects of co-consumption of probiotics with diabetic drugs on controlling diabetes have been reported. Gliclazide is an oral anti-diabetic sulfonylurea drug that has beneficial extra pancreatic effects when insulin therapy is insufficient. Such findings, point toward the beneficial effects of probiotics for treating diabetes in synergism with other diabetes drug and thereby reduces the incidence of diabetes related hypertension. Amar *et al.* (2011), Cani *et al*. (2007) reported that dietary modulation of gut microbiota with a view to increasing bifidobacteria reduced endotoxaemia and improved glucose tolerance and insulin secretion, as well as reducing inflammation development in high fat-diet-fed mice. Together, these findings suggest that the gut microbiota contribute to the pathophysiological regulation of endotoxaemia and set the tone of

inflammation, glucose tolerance and insulin secretion. Thus, specific strategies for modifying gut microbiota in favour of bifidobacteria could be useful tools for reducing the impact of high-fat feeding on the occurrence of metabolic diseases.

Probiotics in Cancer

Cancer is a complex disorder, characterized by the uncontrolled growth and spread of abnormal cells. There is not yet a cure for cancer largely because the exact causes of most types of cancer are still not known but however, it is a combination of various metabolic and physiologic disturbances in the cell, which are directly or indirectly related to the involvement of genetic makeup (Giovannucci, 2007; Jain *et al.*, 2010;). It has been reported that diet makes an important contribution to cancer, e.g., up to 75% of colorectal cancer cases are thought to be associated with diet, implying that risks of cancer are potentially reducible. Evidence from a wide range of sources supports the view that the colonic microflora is involved in the etiology of cancer (Hirayama and Rafter, 2006). This has led to intense interest in factors such as probiotics that can modulate gut microflora and its metabolism.

It is known that the risk of developing many types of cancer can be reduced by adopting certain lifestyle changes, such as quitting smoking and eating a nutritional balanced diet. The environment delivers risk factors that cause mutations and initiate cancer or enhance growth by genetic and epigenetic mechanisms (Ferguson, 1999). Nutrition may supply products that may counteract the causative factors (Johnson *et al*., 1994) and that can be recommended on the basis of a wholesome and complete diet (Pool-Zabel, 2005). Much attention has focused on decreasing cancer risk through diet alterations, particularly consumption of probiotics and increasing intake of dietary fiber (prebiotics). Several case control studies of cancer has reported inverse association for yogurt, cultured milk and other fermented milk (Le *et* al., 1986; Young and Wolf, 1988; Veer *et al*., 1989; Peters *et al.,* 1992; Boutron et *al.*, 1996;). However, Kampman *et al.* (1994a, b) reported a weak non significant inverse association for fermented dairy products and colorectal cancer and no association for intake of dairy products and decreased risk of colon cancer. Reports abound on reduction of mutagenic activity by *L. acidophilus*, *L. casei* and *Bifidobacterium bifidum* cultures (Biasco *et al.,* 1991; Lidbeck *et al.*, 1992*;* Aso and Akaza 1992; Hayatsu and Hayatsu, 1993; Aso *et al.*, 1995)

It has been reported that ingestion of probiotics, prebiotics, or combinations of both (synbiotics) plays an important role in the prevention of colorectal cancer (Jain *et al.*, 2010). Goldin and Gorbach have demonstrated that dietary administration of some specific lactobacilli strains significantly decreased the incidence of 1, 2-dimethylhydrazine-induced experimental colon cancer (Goldin et al., 1996; Goldin and Gorbach, 2008). The microbial flora and the immune system of the body play an important role in the modulation of carcinogenesis. Both may be influenced by the probiotics. The overall mechanism of probiotic action in the regulation of cancer is not known, however, some of the deduced mechanisms (Hirayama and Rafter, 2006; Jain *et al.*, 2010) include:

- Decreasing the exposure of microbial flora to chemical carcinogens
- Detoxifying ingested carcinogens,/ inhibition of carcinogens and/or procarcinogens

- Decreasing the population or metabolic activity of bacteria that may generate carcinogenic compounds ie inhibition of bacteria that convert pro- carcinogens to carcinogens
- Producing compounds that inhibit the growth of tumor cells
- Stimulating the immune system to defend better against cancer cell proliferation
- Producing metabolic products (e.g. butyrate) which improve programmed cell death (apoptosis).
- reduction of intestinal pH to reduce microbial activity
- alteration of colonic motility and transit time.

The preventions or delay in development of intestinal tumors by lactobacilli is ascribed to its binding to mutagenic compounds in the intestine and suppressing the growth of causative bacteria, which convert procarcinogens into carcinogens. The ability of lactobacilli to reduce the risk of cancers has also been based on their ability to modify gut microflora and to decrease B-glucoronidase and other carcinogen levels (Hirayama and Rafter, 2006; Jain *et al.*, 2010). Reddy *et al*. (1997) developed azoxymethane-induced aberrant crypt foci in colon of rats and found that a stimulated growth of bifidobacteria in the colon could lead to the inhibition of colon carcinogenesis. The authors suggested pH-lowering effect of bifidobacteria in the colon, which subsequently inhibited the growth of *E. coli* and clostridia.

A decrease in growth of such pathogenic microorganisms may also produce the modulation of bacterial enzymes such as beta-glucuronidase that can convert pro-carcinogens to proximate carcinogens. There has been evidence that some probiotics produce butyric acid and that this molecule can influence the rate of apoptosis in enterocytes. Probiotics also neutralize the activity of mutagens such as 4-nitroquinoline-N-oxide, 2-nitrofluorene, and benzopyrene (Wollowski *et al.*, 2001). Some probiotics may decrease the fecal concentration of enzymes, mutagens, and secondary bile salts that may be involved in colon carcinogenesis. *L. casei* Shirota strain is reported to possess promising potential for cancer chemoprevention (Morotomi, 1996). *L. rhamnosus* GG can protect against the formation of dimethylhydrazine-induced colon cancer in rats (Goldin *et al.*, 1996).

Conclusion

Various *in vitro*, animal model and case control studies proved the potential for and prebiotics to exert therapeutic effects. Certain combinations of pro- and prebiotics (synbiotics) have revealed greater efficacy than either treatment alone, although there is, however, few randomized controlled clinical trials and epidemiological studies demonstrating the “anti-disease” effects of probiotics in human, ie studies in humans have been less definitive, the few clinical studies do provide evidences that dietary probiotics interact with the host and possibly with the intestinal microbiota and dietary content to exert protective effects in the etiology of some diseases. Great care must be exercised in extrapolating the results of *in vitro* and animal studies to the human system. It also must be kept in mind that the composition and metabolic activities of intestinal flora of experimental animals are significantly different from those of humans. Indeed, it has been demonstrated that human intestinal microflora had different effects than mouse microflora concerning DNA adduct formation after exposure to mutagens (Hirayama *et al.*,2000).Further research is required to be done to identify the specific

strains and strain characteristics responsible for specific disease treatment, antitumor effects and the mechanisms by which these effects are mediated. However, even with the above reservations in mind and mindful of the limited number of human studies available, the use of probiotics for human disease management and cancer suppression is interesting, holds promise, and certainly deserves more scrutiny. Research works to identify which probiotic, prebiotic, or synbiotic will be most efficacious for a specific treatment should be a research focus for the future, the safety of their use for medical purpose and the safety concerns that may obstruct effective usage and thus judicious application of probiotics in disease management warrants serious investigations.

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