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Therapeutic Impacts of Probiotics – as Magic Bullet

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Abstract

Probiotics are the live microbial food/feed supplements which benefit the host when administered in a certain number. Probiotics have been within our domestic use for as long as people have consumed fermented milk, curd, butter milk, but their association with health benefits dates only from the turn of the last century, when Metchnikoff drew attention to the health promoting effects of some gut microflora on the host, and suggested that ingestion of fermented milk products ameliorated this so called auto-intoxication. Species of *Lactobacillus, Bifidobacterium, Bacillus, Streptococcus, Lactococcus* and *Saccharomyces* are commonly used as Probiotics. Recently, probiotics are immensely showing fruitful results for the treatment of various diseases and to alleviate the symptoms of many others like diarrhea, pouchitis, cancer, ulcerative colitis, irritable bowel disease, and a host of many others. The complete mechanisms of action of probiotics in disease management and enhancement of the health of the host remain largely unknown, but the major activities appear to be via modulation of immune responses and colonization and competitive shielding off of pathogens. This paper is set to review some of the ailments for which probiotics have been tested. With an upsurge in the use of probiotics, also comes an increase in skeptics on the safety of their use for medical purpose, the safety concerns that may obstruct effective usage, therefore cautious applications of probiotics in disease management necessitate further investigations.

Keywords: Probiotic, Lactic acid bacteria, Health, Infection, Disease management.

1. Introduction

The human gastrointestinal tract is house to diverse and enormous communities of microorganisms representing over 400 cultivable species. The colonization of the gastrointestinal tract commences instantly after birth. In a healthy adult, the gastrointestinal tract contains 10 times

as many bacteria (10^{14} bacteria) as eukaryotic cells in the entire body [1]; the combined genome of the intestinal flora is estimated to be 50–100 times the size of the human genome [2]. As these organisms are metabolically active and interact continuously with their environment (including other bacteria, the gut epithelium, mucosal immune system, the central nervous system, and the endocrine system), they are able to wield a significant influence on the postnatal development and the host physiology [3]. While a majority of the indigenous flora exhibit health promoting properties, some possess the potential to cause diseases. For example, lactobacilli and bifidobacteria are associated with health, while clostridia are considered detrimental to health. However, when this delicate ecological balance between pro health and anti health is perturbed by environmental or physiological factors, predisposition to infectious and immunoinflammatory disease is enhanced.

Probiotics represent the new buzz word in human dietary portfolio and are currently the major focus of attention across the world due to their enormous health potentials [4]. Probiotics are defined as live micro-organisms which when administered in adequate amounts confer a health benefit on the host most probably by recovering and restoring the microbial balance of gastrointestinal tract [5]. (SENTENCE REMOVED). Most organisms used as probiotics are *Lactobacillus* and *Bifidobacterium*, and a few tested strains of nonpathogenic *E. coli* strains, *Saccharomyces boulardii, Clostridium butyricum*, and *Streptococcus thermophilus* and genetically engineered bacteria that secrete immunosuppressive substances such as interleukin-10 [6]. Specific traits that place an organism to be an effective probiotics include acid tolerance, bile tolerance, cell surface hydrophobicity, antimicrobial activity and colonization of gastrointestinal tract [7, 8]. Several research efforts are going on to explain the mechanism of action of probiotics including improvement of gastrointestinal tract health via modifying gut pH; antagonizing pathogens through production of antibacterial compounds and/or 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 and hypocholesterolemic activity [9, 10].

A recent study paper by Probiotic Association of India presented a good competition of work done in India including the clinical applications. Several studies demonstrating health effects by *in vitro* tests, animal feeding tests and human clinical trials were reported [11, 12]. In the present review article we highlight a number of the diseases for which probiotics have been used to manage and ameliorate diseased conditions.

2. Antidiarrhea effects

Diarrhea is signal of gastrointestinal illness, which can be rooted by a variety of bacterial, viral and parasitic organisms and it could also be antibiotic associated [13]. Probiotics increases IgA level and other immunoglobulin secreted cells in the intestinal mucosa and stimulate local discharge of interferon which aids antigen transfer to principal lymphoid cells that serve to enhance antigen uptake in Peyer's patches [14]. Probiotics benefit viral diarrhea through increasing antibody secretion and lowering viral shedding, prevent selected intracellular mechanisms involved in viral replication (such as MEK, PKA, p38 MAPK) suggesting an immunological mechanism [15-17].

Antibiotic associated diarrhea (AAD) is a general impediment, perturb the normal microbial flora of GIT, and ultimately result in the production of toxin, leading to diarrhea [18, 19]. Administration of probiotic strains, especially *Lactobacillus rhamnosus* strain *GG (LGG)* and *Saccharomyces boulardii*, before and during antibiotic treatment reduced the frequency and/or duration of diarrhea [20, 21]. In a clinical study, Kotowsha et al., (2005)[22] enrolled 269 children who were taking antibiotics for ear or respiratory infections; 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. Several meta-analyses have shown reduced incidences of AAD in probiotic treated patients [23, 24]. *Clostridium difficile* associated diarrhea (CDAD) is most often caused by clindamycin, cephalosporins, ampicillin, and amoxicillin. Total flora replacement or faecal bacterio therapy (using *L. acidophilus, L. rhamnosus)* has been described as an effective treatment alternative in severe *C. difficile* infections [25].

Well-controlled clinical studies have revealed that probiotics such as *L. rhamnosus* GG, *L. casei* Shirota, *L. reuteri*, and *B. animalis* Bb12 can shorten the period of acute rotavirus diarrhea [26]. Sur et al., (2011) [27] reported 14% reduction in acute diarrheal diseases in a study that evaluate the role of a probiotic milk-based beverage (Yakult) in children (aged 1-5 years) in the urban slum of Kolkata (n=3758). Basu et al., (2009)[28] tested the efficacy of *L. rhamnosus* GG in controlling acute watery diarrhea in Indian children in a randomized, controlled, hospital-based study. Dubey et al., (2008) [29] also reported a hospital based placebo-controlled study to assess the efficacy and tolerability of a commercial probiotic preparation, VSL#3 in the treatment of acute rotavirus diarrhea in children. Residents of developed countries traveling to subtropical and tropical zones suffer increased traveler's diarrhea incidence (3 times or more). Drinking a *Lactobacillus* GG strain significantly decreased the prevalence of diarrhea in travelers [30].

Prajapati and Shah (2011) [11] reviewed application of Probiotics in animals & humans and has compiled studies done in India on diarrheal diseases in gut microbiology. The results of the systematic reviews are consistent and suggest that probiotic therapy is safe and effective & shortens the duration of acute diarrheal illness in children by approximately one day.

3. Prevention of *Helicobacter pylori* infections

Helicobacter pylori is a Gram negative human gastric pathogen, which has a possible etiologic role in peptic & gastric ulcers, gastric cancer, lymphoma, and several non-gastrointestinal disorders. Although antibiotic based H. pylori eradication treatment is 90% effective, but it is expensive and causes antibiotic resistance associated with other adverse effects. In vitro as well as animal studies demonstrated that probiotic treatment is effective in reducing H. pylori associated gastric inflammation [31]. The use of probiotics to treat H. pylori infection has been proposed for improving the eradication rate, tolerability and for the compliance of multiple antibiotic regimens used for the infection [32]. About 16 studies used probiotics alone as an alternative to antibiotics for the treatment of H. pylori infection [33, 34].

Aiba et al. (1998) [35] showed L. salivarius capable of producing high amounts of lactic acid to inhibit the growth of H. pylori in the in vitro studies as well as in mice. L. johnsonii La1 was reported to demonstrate a long-time suppressive effect on H. pylori gut colonization when administered as a whey-based culture supernatant [36]. Live and heat-killed L. johnsonii La1 and L. paracasei ST11 were given to H. pylori-infected children for 4 weeks in a double blind, randomized, controlled study, resulted in a moderate decrease of infection [37]. Likewise, administration of live L. casei in milk for 3 weeks offered a slight suppression of H. pylori infection [38]. Similarly, supplementation of yoghurt containing 107 CFU of both B. lactis Bb12 and L. acidophilus La5 twice daily for 6 weeks had reduced H. pylori infection [39]. Similar studies were performed by Datta et al., (2005) [40]; Devi et al., (2007) [41] and Chaturveddi et al., (2010) [42]. Thus, long term intakes of products containing probiotic strains may have a favorable effect on H. pylori infections in humans, particularly by reducing the risk of developing disorders associated with high degrees of gastric inflammation.

4. 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 multi factorial interventions including dietary manipulations. Several research findings [43-45], observed that in addition to risk factors such as genetic predisposition, epigenetic changes and unhealthy lifestyle, altered gut microbiota are major risk factors because that cause increased adiposity, cell dysfunction, hyperglycemia, hypercholesterolemia, dyslipidemia, metabolic endotoxemia, systemic inflammation, intestinal permeability (leaky gut) and oxidative stress associated with type 2 diabetes (T2D) and also a major risk factor in type 1 diabetes (T1D) [46].

Probiotics have emerged as the prospective biotherapeutic in improving the altered gut microbial composition and by targeting all the possible risk factors. Calcinaro et al., (2005) [46] reported that orally administered probiotic compound VSL#3 prevented autoimmune diabetes and induces immunomodulation by a drop in insulitis besides further severity in a mice. In a study conducted by Yadav et al. (2007) [47] , it was found that the administration of Dahi (an Indian fermented milk product) containing *L. 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. The probiotic Dahi supplemented diet significantly delayed the onset of glucose intolerance, hyperglycemia, hyper insulin anemia, dyslipidemia, and oxidative stress in high fructose-induced diabetic rats, indicating a lower risk of diabetes and its complications. Similarly, Ejtahed et al., (2011) [48] accounted that probiotic yogurt improved total cholesterol and LDL-C concentrations in type 2 diabetic people. The beneficial effects of co-consumption of probiotics with oral anti-diabetic sulfonylurea drug (Gliclazide) have extra beneficial pancreatic effects when insulin therapy is unsatisfactory. 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.

5. Lactose intolerance

Lactose intolerance is caused by the deficit or diminished activity of the lactose-cleaving enzyme β-galactosidase in the small intestine. It affects more than 75% of the population worldwide and causes abdominal pain, bloating, flatulence, diarrhea, nausea, and acid reflux [49]. This problem might be alleviated by the consumption of fermented dairy products having live probiotic bacteria due to their lower lactose content and the release of β-galactosidase in the GI tract that can survive digestion [50].

Yogurt found to be unique among other fermented milk products such as buttermilk and sweet acidophilus milk & well tolerated by lactose intolerant people as the presence of bacteria such as *L. delbrueckii* ssp. *bulgaricus* and *Streptococcus thermophilus* in yogurt release β- galactosidase in the intestine [51, 52]. Other fermented products such as buttermilk, kefir and ropy milk also had a 20-26% drop in lactose content [53, 54]. A clinical human study showed that supplementation with *Bifidobacterium longum* capsules and yogurt enriched with *B. animalis* was effective in alleviating lactose intolerant symptoms. In a related study on lactose maldigesting children (5-16 years), demonstrated that consumption of milk with *L. acidophilus* or a commercial yogurt containing *L. lactis* and S. *thermophilus* reduced lactose intolerance signs compared with the group of children who consumed unfermented milk [55]. Further clinical trials of specific strains and concentrations are necessary to delineate the potential therapeutic effects of probiotics in lactose intolerance.

6. Probiotics in inflammatory bowel disease

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. Several clinical trials recommend selected probiotics species, alone or

in combination, can prevent recurrent intestinal inflammation and possibly treat active IBD [56, 8].

6.1 Crohn's disease (CD)

The proposed mechanisms of action of probiotics in the management of Crohn's disease include change in the pattern of short chain fatty acids (SCFA) production; reduction in pro-inflammatory cytokine secretion, improving TH1/TH2 ratios; eliminating pathogens; enhancement of barrier function [57]. He treated 10 patients of Crohn's disease not responding to 5-ASA and prednisolne therapy with a synbiotic therapy, (Probiotic - *Bifidobacterium* and *Lactobacillus* and prebiotic- psyllium), for 12 months and concluded, six patients among twelve went into remission, one had a partial response with improvement of the number bowel movements, and the remaining three patients were non-responders. Therefore, it makes sense either to abolish some bacteria with antibiotics or to alter the gut flora, in favor of more beneficial bacteria, by the use of probiotics and prebiotics [8].

6.2 Ulcerative Colitis (UC)

In ulcerative colitis (UC), imbalanced microflora is associated with increased number of pro-inflammatory bacteria, including *Enterobacteriaceae*, and *Bacteroides fragilis* lead to reduce count of protective bacteria, including *lactobacilli* and *bifidobacteria*. In a double blind study for patients with active UC, Furrie et al., (2005) [58] supplied combination of probiotics strain, *Bifidobacterium longum*, with a prebiotic composed of an inulin-oligofructose on 18 patients. Nine patients assigned to the treatment group and nine to the placebo group. The patients were treated with the synbiotic mixture twice-daily for 4 weeks. At the end of the month, the patients receiving the synbiotic mixture exhibited reduced mucosal inflammatory markers (significant reduction in TNF-α and IL-α level) in colonic biopsies with the active therapy as compared to placebo. In a study comparing the effect of probiotic *Escherichia coli* Nissle 1917 versus mesalamine on induction of remission in UC, both groups had similar time to remission, demonstrating equal efficacy of treatments [59, 60].

6.3 Pouchitis

Pouchitis is an idiopathic inflammatory illness of the ileal pouch. VSL#3, a mixture of 8 probiotic bacteria, is effective in maintaining antibiotic-induced remission in patients with recurrent or refractory pouchitis [61]. In a randomized, double-blind, placebo controlled study, 40 patients were randomized within a week after surgery to receive either VSL#3 or placebo for 12 months. Two of 20 (10%) of the patients treated with VSL#3 developed an episode of acute pouchitis compared to 8 patients (40%) in the placebo group. Patients treated with VSL#3 and no signs of pouchitis and 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 [62]. Recent clinical studies further showed that VSL#3 treatment significantly increases the number of mucosal regulatory T cells in patients with IPAA, indicating a potential beneficial immunoregulatory mechanism of probiotic action in this disease [63]. Addition of VSL#3 for 6 weeks led to either remission or response in 77% of patients as measured by the disease activity index [64]. Thus, these findings suggest a potential therapeutic role for probiotics in the treatment of active IBD.

7. Probiotics in Hypercholesterolemia and Hypertension

Cholesterol is a precursor to certain hormones and vitamins and is a component 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. These cholesterol levels can be brought down using probiotics. The mechanisms can be direct or indirect. Direct mechanism is either inhibiting the *de novo* synthesis by hypocholesterolemic factors like lactose, uric acid, orotic acid, whey proteins or by decreasing the intestinal absorption of dietary cholesterol by three ways –

assimilating, binding, and degradation. The cholesterol level can be reduced indirectly by deconjugating the cholesterol by bacterial acid hydrolases to bile acids, thereby reducing the total body pool [65].

Mann (1974) [66] observed that men from the tribes of Samburu and Maasai warriors in Africa showed reduced serum cholesterol level after consumption of large amounts of milk fermented with a wild *Lactobacillus* strain. Since then, the potential hypocholesterolemic effect of fermented milk products containing lactobacilli and/or bifidobacteria has been investigated in dietary studies using humans and animals. Klaver and van der Meer (1993) [67] studied the mechanism of assimilation of cholesterol by *Lactobacillus acidophilus* and *Bifidobacterium bifidum* and concluded that removal of cholesterol was due to co-precipitation with deconjugated bile salts in an acidic environment. Lactic acid bacteria with active BSH, or cultured products containing them, are suggested to lower serum cholesterol levels through an interaction with the host bile salt metabolism [68]. Tahri et al., (1996) [69] studied assimilation of cholesterol by studying intense binding between cell surface and cholesterol, necessary for uptake of cholesterol into the cells. Consumption of probiotics points towards a decrease in cholesterol synthesis by reducing the activity of hydroxyl-methylglutaryl- coenzyme A reductase in the liver. Further, increases in the amounts of fecal bile acids suggest that there is a compensatory increased conversion of cholesterol to bile acids [70].

The potential hypocholesterolemic effects of probiotics sparked much interest based on evidence from animal work and from human studies. A randomized feeding trial comprising 27 human volunteers with both normal lipid profile and hyperlipidemia was conducted by Ashar and Prajapati (2001) [65] by feeding 200 ml of stirred acidophilus milk (5×10^8 live lactobacilli) for 20 days and observed significant reduction by 7.6% in total cholesterol and 15.7% in LDL cholesterol. In a study evaluating the effect of *L. plantarum* PH04 on cholesterol, Nguyen et al., (2007) [71] administrated 4×10^8 cfu/ml dose per mouse daily to twelve male hypercholesterolemic mice for 14 days and found reduction in total cholesterol and triglycerides (by 7 and 10%, respectively) compared to control. Batish et al., (2010) [72] studied anti-hypercholesterolemic effects of *L. plantarum* LP91 (>1.0×10^8 cfu/g) on SD rats for 3 weeks and revealed 23.26% , 21.09% and 38.13% reduction in total cholesterol, TAG and LDL cholesterol, respectively. Hu et al. (2013) [73] studied two NS *lactobacillus* strains, *L. plantarum* NS5 and *L. delbrueckii* NS12 for their cholesterol lowering effects on male SD rats fed a high cholesterol diet. In a recent study, Mohania et al. (2014) [74] showed antihypercholesterolemic effect of LaVK2 Dahi in 21 male Wistar rats with diet induced hypercholesterolemia, where plasma total cholesterol, LDL+VLDL and TAG levels found to be significantly decreased significantly at 22.6%, 89% and 64.2%, respectively.

A variety of *in vitro* experiments and *in vivo* trials have provided experimental evidence to support the roles of probiotics in lowering serum cholesterol which subsequently leads to a reduced risk of hypertension [75]. Many of the proposed mechanisms and experimental evidence specifically targeting cholesterol lowering effects remain controversial. Thus, more properly designed *in vivo* trials may disclose additional understanding and knowledge to define the role of probiotics and their mechanism of action in this regard.

8. Anticancer effects

Probiotics, due to their ability to modulate the colonic microflora and encourage local and systematic immunity, could be one of the great interests to employ as therapeutics against various types of cancer by preventing the establishment, growth, and metastasis of transplantable and chemically induced tumors [76, 77]. An inverse relationship between the consumption of fermented dairy products, containing lactobacilli or bifidobacteria, and the incidence of cancer has been reported in epidemiological and population based case-control studies [78-80].

Short chain fatty acids (SCFA) produced by probiotic bacterial fermentation of indigestible polysaccharides and oligosaccharides have been shown to induce apoptosis of damaged cultured cells of colonic crypts [called aberrant crypts (AC), enlarged and elevated preneoplastic structures]. Butyrate also reduces the number of aberrant crypt foci in rats treated with the carcinogen azoxymethane [81]. Early laboratory studies using *Lactobacillus GG* was found to reduce the incidence of induced tumors in an animal model of colon cancer [82]. Unlike standard chemotherapy agents, probiotic-derived agents target tumor cells without harming normal cells or causing immune suppression and other adverse side-effects [83, 84]. Aso & colleagues (1992) [85] revealed the protective effect of *L. casei* Shirota on the recurrence of superficial bladder cancer in a randomized, controlled, multicentre study. After a year, tumor recurrence rate was significantly lower in subjects receiving *L. casei* (57%) compared with the control group (83%). Increases in the percentage of T-helper (TH) cells and Natural Killer (NK) cells in adult colorectal cancer patients suggest that stimulation of the immune system by *L. casei* Shirota may have an important role in the suppression of tumor development [86]. Similar meta-analysis was performed by Bogdanov et al., (1975) [87] and Ayebo et al., (1981) [88]. Hosoda et al., (1996) [89] demonstrated that administration of *L. acidophilus* LA-22 showed remarkable decrease (71.9%) in faecal mutagenicity.

Intake of LAB in fermented milk or other products influence gut flora enzymes, like β-glucuronidase, nitroreductase, and azoreductase as these enzymes convert procarcinogen to carcinogen [90]. A daily intake of *L. acidophilus* and *B. bifidum* for 3 weeks decreased the activity of nitroreductase but increased the activity of β-glucosidase [91]. This could be an advantage since β-glucosidase may release flavonoids which have antimutagenic, antioxidative and immune stimulatory effects [92, 83]. Similar effects were observed by *L. acidophilus* NCFM and N-2 [82].
Other mechanisms by which probiotics may act as anti-tumorigenic factors are: enhancement of local and systemic immune response and produce molecules that neutralize or block mutagens; or these molecules may be directly anti-tumorigenic by nature [82]. The need for cautiously designed, long term studies in human is necessary in prevention of the earliest stages in the onset of evolution of cancer.

9. Probiotics in prevention of allergic disease

The prevalence of allergic diseases have increased considerably in recent decades, especially in countries with western lifestyle that characterized by high standard of hygiene, delivery mode, antibiotic use in the newborn and infant, and non-breast-milk diets, reduced exposure to microbes in daily environments, reduced consumption of fermented food [93-95]. Assessment of various strains of lactic acid bacteria can restore the normal intestinal permeability thereby improving intestinal processing of antigens ingested in the diet, reducing intestinal inflammation by producing IgE, potentiating of regulatory T cell cytokines, consequently reducing symptoms of atopic dermatitis [96].

Probiotics have been studied as possible dietary interventions to interrupt progression of eczema to rhinitis and rhinitis to asthma [97]. Moroi et al., (2011) [98] corroborated that, 22 to 24% reduction in the incidence of allergic dermatitis is due to the administration of strains of *Lactobacillus* in the first months of the child life, demonstrating the prevention capacity. In a randomized, double blind, placebo controlled study by Isolauri (1994) [99] investigated cow's milk sensitive infants with atopic dermatitis assessed their response to a hydrolyzed whey formula alone or in combination with LGG. At the end of one month the probiotic group had a significantly greater improvement in the extent and intensity of their eczema by decrease in the concentrations of fecal α-trypsin and TNF-α. The authors speculated that the LGG produced enzymes that can act as a suppressor of lymphocyte proliferation and also aided to generate protein breakdown products that result in IL-4 down regulation. Furthermore, the LGG-stimulated increase in secretary IgA help in increased elimination of antigen and overall down regulation of hypersensitivity reactions. In

a similar report, after 2 months, infants received whey formula with probiotic LGG showed significant improvement in extent and severity of atopic eczema by reducing the concentrations of soluble CD4 in serum and eosinophilic protein X in urine [100]. These findings have also been recently confirmed by Rosenfeldt et al., (2003) [101], in which 56 percent of patients experienced improvement in eczema by having diet containing *L. rhamnosus* and *L. reuteri* compared to 15% in placebo group. Similar outcomes were observed for *L. rhamnosus GG* [102] and *L. fermentum* [103]. Some studies have also shown that 80% of the patients with acne that used probiotics had a reduction in acne inflammation [104, 105].

10. Probiotics in Respiratory diseases

Recently probiotics have being exploited in the prophylaxis of different respiratory tract ailments such as sinusitis, rhino sinusitis, pharyngitis, otitis. The strains of *Lactobacillus plantarum* & *L. casei*, *L. fermentum* VRI-003, *Bifidobacterium breve* 99, *B.longum* SP 07/3 among others were used in a combined or single action of respiratory infections viewing satisfactory results the drop of acute episodes of the diseases mentioned above as well as a reduction in the duration of the episode in chronic diseases [106, 107].

Latest study evaluated the use of *Lactobacillus* in patients with cystic fibrosis that are chronically colonized by *Pseudomonas aeruginosa* [108]. Some probiotic strains such as *Lactobacillus plantarum* and *Lactobacillus rhamnosus* aids in prophylaxis and can avert nosocomial pneumonias characterized as respiratory tract colonization by pathogenic bacteria, chiefly *Pseudomonas aeruginosa* [109]. Further studies are needed to better explain the probiotics action and mechanism for treatment [110].

11. Probiotics in Urogenital diseases

Bacterial vaginosis is one of the most common infectious disorders affecting women. Lactobacilli are major constituents of the normal vaginal flora. Their production of bacteriocins, lactic acid, and hydrogen peroxide are mechanisms which keep pathogenic colonies of several anaerobic floras, including *Gardnerella vaginalis*, *Bacteroides sp.*, β- *Streptococci* and *Mobiluncus/Falcivibrio sp*. from proliferating [111, 112].

There is a developing role for the use of probiotics (both oral and vaginal suppositories) in the genitourinary (GU) system, especially for vaginitis, whether from bacterial or fungal etiology. Reid et al., (2003) [113] showed consumption of yogurt containing *L. acidophilus* decreased the incidence of *Candida* yeast infections. In one open clinical trial, 40 female patients restore the physiological pH of vagina by controlling symptoms of bacterial vaginosis after the treatment with *L. rhamnosus* [114]. In another randomized, double blind placebo controlled study in ninety women after treatment of Candidiasis and Vaginosis with probiotic *L. gasseri, L. casei, L. fermentum, P. acidilactici*, results showed delay in recurrence of symptoms of vaginosis with prevention in vaginal colonization by pathogens [115]. In a parallel study by (Ya et al., 2010) [116], *L. rhamnosus, L. acidophilus, S. thermophilus* showed reduction in frequency of bacterial vaginosis in 120 women.

12. Additional health benefits of Probiotics

12.1 Assisting Vitamin and Mineral Uptake

Probiotics increase the bioavailability of vitamins and protein in the GI tract as a result of increased acidification of the gut pH by the production of lactic acid. Compared to milk, yogurt results in better absorption of such vitamins and minerals as calcium, copper, iron, manganese, phosphorous and zinc [117].

12.2 Pregnancy

Vaginal application of highly adhesive Lactobacilli to 30 pregnant women with dysbacteriosis of the birth canal resulted in correction of bacterial ecology of vagina and intestine [118] with favorably influence the course of pregnancy, labor, and the postpartum period [119].

12.3 Oral health

Lactobacilli have the ability to inhibit the growth of periodontopathogens including, P. gingivalis, P. intermedia and A. actinomycetemcomitans [120, 121]. Comelli and colleagues investigated the 23 bacterial strains used in the dairy industry, among them Streptococcus thermophilus and Lactobacillus lactis ssp. lactis were the only ones with the ability to form biofilms present on a hydroxyapatite surface and to interfere with development of the cariogenic species Streptococcus sobrinus [122]. This concept prompts a new horizon on the relationship between diet and oral health.

12.4 Obesity

Obesity is a growing problem in the population and affects all age groups. There are several studies that make a direct relationship between abdominal fat deposition and the imbalance of the gut microbiota [123, 124]. Therapeutic efforts indicate that probiotics help in maintaining the balance of intestinal microflora and recommended for the treatment of obesity-related disorders following the nutritional and pharmacological treatments [125, 126].

12.5 AIDS

HIV infection can upset the natural balance of healthy bacteria in the intestine, which can be restored by adding probiotics in diet. Many evidences available that shows the probiotics help in re-establishment of CD4 (T helper cells) counts so that the immune system is more prepared to battle against HIV linked infections [127].

12.6 Hypertension

High levels of blood cholesterol, diabetes, and improper modulation of rennin, imbalanced sexual hormones, and obesity are risk factors causing hypertension [128]. Studies suggest that consumption of certain lactobacilli (specially L. helveticus), or their formulation, may reduce serum cholesterol and improve lipid profiles, subsequently attenuating the risk of hypertension [129-131].

13. Conclusion and outlook

Probiogenomic, Nutrigenomics and Metabolomics are rapidly developing new bodies of knowledge that will change future research and practice in human nutrition. Probiotics have been shown to promote a variety of biological effects in a number of physiological conditions and pathologies, including allergy, intestinal and liver diseases, urinary and upper respiratory infections, AIDS and metabolic diseases. These effects are strain specific and primarily mediated through changes in the faecal microbiota and immune modulation. In addition, multi-centered and replicate studies are necessary to evaluate the actual role of probiotics in the amelioration of symptoms for many diseases. Most of the clinical studies are still targeted to general health benefits or especially on gastrointestinal tract disorders. In coming years, India will have more systematic multicenter clinical trials on foreign as well as indigenous probiotic strains to combat diseases.

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