

Review Article

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## Role of Probiotics in human health and disease: An update

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### ABSTRACT

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Probiotics are live bacteria and yeasts that are good for our health, especially our digestive system. We usually think of bacteria as something that causes diseases. But our body is full of bacteria, both good and bad. Probiotics are often called "good" or "helpful" bacteria because they help keep our gut healthy. Probiotics are naturally found in our body. We can also find them in some foods and supplements. It's only been since about the mid-1990s that people have wanted to know more about probiotics and their health benefits. Doctors often suggest them to help with digestive problems. And because of their newfound fame, we can find them in everything from yogurt to chocolate. Researchers are trying to figure out exactly how probiotics work. Here are some of the ways they may keep us healthy: When we lose "good" bacteria in our body (like after you take antibiotics, for example), probiotics can help replace them. They can help balance our "good" and "bad" bacteria to keep our body working like it should.

### Introduction

The world as we have created it is a process of our thinking. It cannot be changed without changing our thinking- Albert Einstein. About 2000 years ago, Hippocrates quoted that "Let food be the medicine and medicine be the food" is certainly the tenet of today (Sumit N *et al.*, 2011). Currently there is an increased global interest due to the recognition that 'nutraceuticals' play a major role in health enhancement. The term "nutraceutical" was coined by combining the terms "Nutrition" and "Pharmaceutical" in 1989 by Dr. Stephen DeFelice, Chairman of Foundation for Innovation in Medicine. It can be defined as a food or nutrient, which provides health benefits, including the

prevention and treatment of a disease, like joint problems, cardiovascular health, eye related problems and cancer prevention, such foods are commonly referred to as 'functional foods', signifying they are /or their components may provide health benefit beyond basic nutrition. Nutraceuticals contain health promoting ingredients or natural components that have a potential health benefit for the body (Table 1). Eastern cultures have a long history of use of traditional medicines associated with health foods in the form of recognized nutritional foods, food supplements, medicinal herbs and crude powdered drugs derived from plants, animals, marine sources. India and China are known for their

production of traditional functional food products and nutraceuticals. There is an exhaustive list, about 470 nutraceutical and functional food products are available in various combinations and it is growing day by day (Rajasekaran A *et al.*, 2008). In present review, we have tried to focus on the role of probiotics in health in general and oral health in particular.

### **Historical Perspectives**

Looking back through history, however one has forgotten the concept of using live bacteria called probiotics, beneficial to health has been resurrected and has now come under intensive research using modern study designs and methods (Esha A *et al.*, 2011). The most common problem prevailing in the field of medicine is the development of resistance to a range of antibiotics by some important pathogens. The promiscuous and heady use of antibiotics has led to the emergence of multi-resistant strains of bacteria. This unfortunate development has led scientists to shift the paradigm of treatment from specific bacteria elimination to altering bacterial ecology by use of probiotics (Vishnu HP 2012). There is a long history of health claims concerning living microorganisms in food, particularly lactic acid bacteria. In a Persian version of the Old Testament it states that "Abraham owed his longevity to the consumption of sour milk". In 76 BC, the Roman historian Plinius recommended the administration of fermented milk products for treating gastroenteritis. Elie Metchnikoff was perhaps the first researcher to propose that fermented dairy products have beneficial properties. Although there is reference to sour milk or fermented cultures as far back as the Bible, Elie Metchnikoff is regarded as the grandfather of modern probiotics. Elie Metchnikoff proposed that the regular

consumption of lactic acid bacteria in fermented dairy products, such as yogurt, was associated with enhanced health and longevity in Bulgarian peasant populations. Grigorov later demonstrated how healthy bacteria in yogurt helped digestion and improved the immune system. He asserted that some of the bacterial organisms present in the large intestine were a source of 'toxicants', toxic substances that contributed to illness and ageing. He suggested that "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes." To test the hypothesis on the health benefit of consuming lactic acid bacteria, Metchnikoff drank sour milk every day until his demise at the ripe age of 71 in 1916. The concept of probiotics was thus born and a new field of microbiology was opened (Jaddu Jyothirmai R *et al.*, 2010, Kingsley C *et al.*, 2007).

### **Prebiotics and Probiotics**

Prebiotics are the substances which reach the colon in the intact form are given to the animals and beneficial for microbial growth in the intestine and normal digestion process. They act as fertilizer for probiotics for example: insulin, fructooligosaccharides. Prebiotic was first discovered by Gibson and Roberfroid in 1995 defined generally as a "Non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth activity of one or a limited number of bacterial species already established in the colon", and thus improving the host health (Nicole MR *et al.*, 2000). More specifically, prebiotics are short-length carbohydrates, such as fructo oligosaccharides, gluco oligosaccharides and inulin that resists digestion in upper gastrointestinal tract and fermented in the colon to produce short-chain fatty acids,

such as acetate, butyrate and propionate, which have positive effects on colonic cell growth and stability; (Pradeep K *et al.*, 2012, Vineet A *et al.*, 2012) whereas, the synergistic combinations of both pro and prebiotics are called Synbiotics as this approach includes a food or food supplement having both live cells of the beneficial bacteria and the selective substrate and the beneficial bacterial cells grow faster and competitively because of the presence of selective substrate and establish their predominance (Prashanthi R *et al.*, 2011, Schrezenmeir J *et al.*, 2001).

The term ‘*probiotic*’ is derived from the Latin preposition pro (‘for’) and the Greek adjective (biotic), the latter deriving from the noun (bios, ‘life’). Today, two main definitions are used. According to a WHO/FAO report (2002), probiotics are “Live microorganisms which, when administered inadequate amounts, confer a health benefit on the host”. International Life Science Institute (ILSI) Europe suggests a definition according to which a probiotic is “A live microbial food ingredient that, when ingested in sufficient quantities, exerts health benefits on the consumer. Probiotics are live microorganisms, basically bacteria that when ingested in adequate amounts would confer health benefit beyond the basic nutrition (Vineet A *et al.*, 2012). They are extensively studied for their health promoting effects because they repopulate the beneficial bacteria which can help to kill pathogenic bacteria and fight against infection (Kedar S *et al.*, 2010). Traditionally, probiotics have been associated with gut health as there is a presence of greatest concentration of commensal organisms spread over more than 400/m<sup>2</sup> of surface area. The gut flora is required rapidly just after birth and remains stable throughout the life (Bhuvaneshwari J

*et al.*, 2012). They are also called “friendly bacteria” or “good bacteria as supported by an increasing number of in vitro and in vivo experiments using conventional and molecular biologic methods (Rinkee M *et al.*, 2011).

Many microbial types are used around the world to ferment milk, plant food, meat and other products. However, much progress has been made since in terms of the fermentation of dairy products. In this regard most probiotics fall into categories of lactic acid-producing bacterial organisms, including *Lactobacillus* and *Bifidobacterium*, but also non-lactic acid organisms (Table-2). Probiotics are most often incorporated in yogurt and fermented milk, but other food lines are now available and numerous products are sold in tablet, capsule, and powder.

### **Lactobacillus Species**

Ubiquitous in nature, found in carbohydrate rich environment. They are gram positive spore forming, catalase negative appearing as rods or coccobacilli, fermentative, microaerophilic and chemo organotrophic, helpful in the production of enzymes which digest and metabolize proteins or carbohydrates, synthesize vitamin B complex, vitamin K and facilitate breakdown of bile salts. More than 100 species are identified and use in the form of gel, paste, powder and liquid forms (Patil MB *et al.*, 2006, Meurman JH 2005).

### **Bifidobacterium Species**

This species were 1<sup>st</sup> isolated and visualized by Tissier (1990) from the feces of breast feed neonates. They are strictly anaerobic, rods shaped and predominate in the large intestine. Over 30 species have been identified. They metabolize lactose, generate

lactic ions from lactic acid and synthesize vitamins. They also ferment indigestible carbohydrates and produce beneficial short chain fatty acids. (Galdeano CM *et al.*, 2007, Nicole MR *et al.*, 2000)

### **Streptococcus Thermophilus and Lactobacillus Bulgaricus**

Are primary cultures used in yogurt production. Most noted benefits are to metabolize lactose, improve lactose intolerance and antimicrobial activity (Socol C R *et al* 2010)

### **Saccharomyces Boulardii**

It is a non-colonizing lactic acid producing yeast. Most noted feature is that they secrete proteases and other substances that breakdown bacterial enterotoxins and inhibit their binding to intestinal receptors. They also enhance vitamin production and reduce serum cholesterol level (Kedar S *et al.*, 2010).

**Following are the requirements which have been identified for a microorganism to be defined as an effective probiotic.** (Azizpour K *et al.*, 2009, Behnsen J *et al.*, 2013)

The probiotic should exert positive effects on the host. It should be acid resistant, bile resistant and contain a minimum  $30 \times 10^9$  CFU/ Gram.

The probiotic should possess high survival rate & multiply faster

The adhesive capability of probiotics must be firm and faster.

Exclude or reduce pathogenic adherence.

Produce acids, peroxide and bacteriocins, antagonistic for the growth of pathogens.

Safe, noninvasive, non-carcinogenic and non-pathogenic.

Coaggregate to form a normal balanced flora.

Probiotics should be durable enough to withstand the duress of commercial manufacturing, processing, packing and distribution so it can be delivered alive to the intestine.

### **Mechanisms of Action of Probiotics**

(Narwal A *et al.*, 2011, Tiwari G *et al.*, 2012, Calafiore A *et al.*, 2012, Rastogi P *et al.*, 2011, Kumar A *et al.*, 2013)

Compete for nutrients and growth factors.

Produces antimicrobial compounds like hydrogen peroxide, bacteriosin, organic acids and dipicolinic acid which inhibits the growth of pathogenic bacteria.

Compete for the adhesion sites.

Modifies microbial population by biofilm formation.

Alter the host immune response by increase IL-10, TGF- $\beta$ , decrease TNF- $\alpha$  and increase the IgA production.

Decreases production of inflammation associated molecules.

Prevents cytokines induced apoptosis.

Balances the gut and oral microbial flora thus making its colonization resistant to pathogenic bacteria.

Increases the calcium and other minerals absorption.

Modifies the structure and function of intestinal epithelium and improves the barrier function.

Inhibits the growth of pathogenic enteric bacteria by decreasing luminal pH.

Lowers the toxigenic and mutagenic reaction by its metabolic product.

Increase the turnover of enterocytes by production of butyric acid.

### **Probiotics in Oral Health and Disease**

**Dental caries** is a multifactorial disease of bacterial origin that is characterized by acid demineralization of the tooth enamel. *Streptococcus mutans* is the main microorganisms involved in causation of dental caries (Singh VP *et al.*, 2013). Probiotics can reduce the risk for a high *S. mutans* level occurrence. Bacteria administered as probiotic compete with carcinogenic microbes for adhesion sites as well as for nutrients and growth factors leading to reduced level of *S. mutans* in oral cavity. *Streptococcus thermophilus* and *Lactobacillus* species were the only ones with the capacity to integrate into a biofilm present on a hydroxyapatite surface and to interfere with development of the carcinogenic species *Streptococcus sobrinus*, *L. rhamnosus GG* and *L. reuteri* can inhibit colonization by streptococcal carcinogenic pathogens and therefore reduce tooth decay incidence in children (Kedar S *et al.*, 2010). Nikawa *et al.*, 2004 reported that consumption of yogurt containing *L. reuteri* over a period of 2 weeks reduced the concentration of *S. mutans* in saliva by up to 80%. Cagler *et al.*, in a comparative study of *S. mutans* reduction effects by several

probiotic administration forms showed a reduced *S. mutans* level in patients receiving fluid or tablet in probiotic forms (Flichy-Fernández AJ *et al.*, 2010). More recently, it was demonstrated that isolates of *W. cibaria* had the capacity to inhibit, both in vivo and in vitro, biofilm formation by *S. mutans* to prevent proliferation of this bacterial strain (Kang MS *et al.* 2006). These promising results suggest a potentially beneficial application of probiotics for prevention of dental caries.

**Periodontal diseases** can be classified into two types such as gingivitis and periodontitis. Gingivitis is characterized by inflammation limited to the unattached gingiva, whereas periodontitis is a progressive, destructive disease that affects all supporting tissues of teeth, including the alveolar bone (Houle MA *et al.*, 2003). The main pathogenic agents associated with periodontitis are *P. gingivalis*, *T. denticola*, *T. forsythia*, and *A. actinomycetemcomitans*. These bacteria have a variety of virulent characteristics allowing them to colonize the sub gingival sites, escape the host defense system and cause tissue damage (Rinkee M *et al.*, 2011). In a Russian study using probiotic tablets in complex treatment of gingivitis and different degrees of periodontitis, the effect of probiotics to the normalization of microflora was found to be higher in comparison to the controls, particularly in the cases of gingivitis and periodontitis. A decrease in gum bleeding and reduced gingivitis has been observed with the application of *L. reuteri*. Probiotics strains included in periodontal dressings at optimal concentration were shown to diminish the number of most frequently isolated periodontal pathogens like *Bacteriodes species*, *Actinomyces species* and *Staphylococcus intermedius* and *Candida albicans* (Jaddu Jyothirmai R *et al.*, 2010). Patients with various periodontal

diseases, gingivitis, periodontitis, and pregnancy gingivitis, were locally treated with a culture supernatant of a *L. acidophilus* strain. Since the primary etiological factors for the development of periodontal disease are bacteria which are present in supra and sub gingival biofilm. Patients with periodontal disease who used chewing gum or lozenges containing probiotics saw their periodontal status improve (Singh VP *et al.*, 2013).

**Halitosis** or **bad breath** is a condition that affecting comparatively large section of population with multiple local and systemic etiological factors. The main local etiologies include periodontitis, poor oral hygiene, deep dental caries, tongue coating and faulty restorations. Bad breath in oral cavity is mainly ascribed to the production of volatile sulfur compounds (VSC) by gram negative and gram positive anaerobes residing in periodontal pockets and on the dorsal surface of tongue. The replacement of bacteria implicated in halitosis by colonization with probiotic bacterial strains may have potential application as adjuncts for the prevention and treatment of halitosis (Pradeep K *et al.*, 2012). A definite inhibitory effect on the production of VSC by *F. nucleatum* was observed after ingestion of *W. cibaria* both in vitro and in vivo. In children, a marked reduction in the levels of H<sub>2</sub>S and CH<sub>3</sub>SH was registered after gargling with *W.cibaria* containing rinse (Jaddu Jyothirmai R *et al.*, 2010). The possible mechanism in the VSC reduction is the hydrogen peroxide generated by *W.cibaria* that inhibits the proliferation of *F. nucleatum*, *S. salivarius* also a possible candidate for an oral probiotic which has demonstrated inhibitory effect on VSC by competing for colonization sites with species causing an increase in levels of VSC. Strains used as probiotic for mouth and gut associated halitosis include *E.coli*

Nisle 1917, *S. salivarius* k 12, *W. confusa* isolates and a lactic acid forming bacterial mixture (Haukioja A 2010).

**Oral candidiasis:** *Candida* species are part of a commensal oral flora in about 50% of healthy subjects, but able to cause a clinically apparent lesion if the immune defenses were breached either on the local or systemic level and a leading cause of infection in oral cavity (Hatakka K *et al.*, 2007). It is particularly common in the elderly and in immunocompromised patients. Hatakka *et al.*, showed a reduction in the prevalence of *C. albicans* in the elderly after consumption of probiotic cheese containing *L. rhamnosus* GG in a randomized placebo controlled trial. A concomitant feature of the probiotic activity observed in this study was diminished risk of hypo salivation and the feeling of dry mouth of the subjects. Results obtained by Koll *et al.*, when assessing the effects of various *Lactobacillus* strains in oral cavity were markedly different; most strains suppressed growth of periodontal pathogens, including *A. actinomycetemcomitans* (60 out of 67 tested strains); *P. gingivalis* (35 out of 42 strains); *P. intermedia* (26 out of 42 strains); and carcinogenic *S. mutans* (37 out of 67 strains). No inhibition was found for *C. albicans* growth (Flichy-Fernández AJ *et al.*, 2010). The authors had no explanation to this and the finding certainly needs to be confirmed in further investigations.

### **Treatment and Prevention of Diarrhoea by Probiotics**

Efficiency of the probiotics have been tested by a number of clinical trials for the prevention of acute diarrheal condition. Multiple short and long terms use of antibiotics leads to a common side effect of diarrhea. Two meta analyses (using strains *Lactobacillus acidophilus*, *Lactobacillus*

rhamnosus strain GG, *Lactobacillus bulgaricus* and yeast *Saccharomyces boulardii*) could be used to prevent antibiotic associated diarrhoea. Major problem in paediatrics hospital is the nosocomial diarrhea and it is prevalent worldwide. Prophylactic uses of probiotics (*Bifidobacterium bifidum*, *Streptococcus thermophiles* and *L rhamnosus starin GG*) are useful especially for infants for the prevention of acute diarrhea (Cremonini F *et al.*, 2002, Saavedra JM *et al.*, 1994).

### **Management of Lactose Intolerance by Probiotics**

Lactose malabsorption in adult population varies from 50%-100% in African, Asian and South American countries and 5%-15% in Northern European and American countries. Lactose digestion improvement by using bacteria as starter culture in yogurt (*Lactobacillus delbrueckii* subspecies *bulgericus* and *S. thermophilus*) is well recognized due to the presence of bacterial enzyme beta- galactosidase (Kolars JC *et al.*, 1984). Several human studies demonstrated better lactose digestion and absorption in subjects that consumed fresh yogurt (live yogurt cultures) in comparison with the consumption of pasteurized product (heat killed bacteria) (Dewit O *et al.*, 1988).

### **Anticancer Properties of Probiotics**

Several studies revealed the importance of probiotic therapy that inhibited transformation of procarcinogen to active carcinogens which further reduced the risk of colon cancer. Probiotics may also inactivate mutagenic compounds, producing antimutagenic compounds, suppressing the growth of pro- carcinogenic bacteria, reducing the absorption of mutagens from the intestine and enhancing immune function (Van't Veer P *et al.*, 1989).

Enteropathogens such as *E.coli* and *clostridium perferinges* produce enzymes such as beta-glucuronidase, and nitroreductase. Beta – glucosidase can convert procarcinogens to proximate carcinogens.<sup>16</sup> *Bifidobacterium* creates a bactericidal environmental for these putative enteropathogens as colonizing cells of *Bifidobacterium* produces lactic acid and lower the intestinal pH and therefore develops a favorable environment which modulates the bacterial enzymes. Purified bifidobacterial has cell wall antitumor activities and induces activation of phagocytes to destroy growing tumor cells (Sekine K *et al.*, 1994). One of the earliest and most frequently occurring genetic alterations associated with human cancer, especially carcinoma of colon are associated with RAS activation. Elevated levels of ras P-21 have also been correlated with increased cell proliferations, histologic grade, nuclear aplasia and degree of undifferentiation.<sup>18</sup> *B.longum* cultures as demonstrated by Reddy et al suppressed the expression of total and neonated ras P – 21 in the colonic mucosa and tumors compared with control diet. *B. longum* also plays a role as an immunomodulator and biological response modifier by providing an additional mechanism of tumor suppression. Probiotics also stimulate apoptosis through end-product formation (Reddy BS, Riverson A 1993, Okawa T *et al.*, 1993).

### **Immune Enhancement by Probiotics**

Evidences suggest that specific strains of lactic acid bacteria, when consumed in certain numbers, are able to modulate aspects of both natural and acquired immune responses. The colonic microflora affects mucosal and systemic immunity in the host. It is produced either by absorption of soluble antigen or by translocation of lactobacilli through the gut wall into the bloodstream.

Lactobacilli which adhere to human intestinal epithelial cells are capable of activating macrophages, intestinal epithelial cells, blood leucocytes, B and T lymphocytes, and accessory cells of immune system are all complicated targets for probiotics (Berg RD 1983).

### **Innate Immune Response and Probiotics**

The ability of specific strains of probiotics to enhance aspects of natural immunity in human subjects is well documented. Enhanced phagocytic capacity of peripheral blood leucocytes was reported by schiffrin and colleagues in healthy human adults administered fermented milk supplemented with specific strains of probiotics (Lactobacillus johymsonii Lal or bifidobacterium lactis Bb12) for three weeks. Cessation of probiotic consumption showed improvement in phagocytic activity which were sustained for several weeks and granulocytes showed higher increase in phagocytic cell function compared with monocytes. Subjects receiving probiotics have also been reported which have shown significant increase in the expression of receptors involved in phagocytosis (CR1, CR3, FcyRI and FcαR) In neutrophils, phagocytic index and oxidative burst or microbicidal capacity. It has also been observed that complement receptor expression are been influenced by different lactic acid bacteria strains which differ in their capacity in phagocytic cells. For example, He et al revealed that complement receptors were more efficiently upregulated by Lactobacillus lactis on blood leucocytes than L rhamnosus.<sup>76</sup> Furthermore, dose of minimum  $10^9$  cfu/day was found to be necessary for the improvements in immune function as the immunostimulatory effect of probiotic intake was dose dependent (Schiffrin EJ *et al.*, 1995, He F *et al.*, 2000). Somehow ageing is also associated with a

decline in immunocompetence as to correct the age related decline in phagocytic cells especially in the elderlies, supplementation with the probiotics could be used. Subjects receiving milk without probiotics had phagocytically less active leucocytes compared to the ones receiving milk containing L. rhamnosus (HN001) or B. lactis (HN019) for three to six weeks and exhibited significantly more phagocytically active blood leucocytes (neutrophils and monocytes). Simultaneously improvements and increase in the activity of N K cells in the peripheral blood of human volunteers fed with yogurt, milk, or sausages containing probiotics have also been reported (Gill HS et al 2001, Gill HS, Cross ML et al 2001).

### **Humoral Immune Response and Probiotics**

Possible mechanisms of functioning of the immune system influenced by the probiotics are not fully understood. A large number of human studies have also shown that humoral immune response to natural infections and systemic or oral immunization is been potentiated by intake of specific strains of lactic acid bacteria. Lactobacillus GG fed infants had significantly higher IgG, IgA and IgM IMMUNOGLOBULIN secreting cells compared to those given a placebo. Further it was also observed that IgA specific antibody secreting cells to rotavirus and serum IgA response was more efficiently stimulated by lactobacillus GG than L casei subspecies rhamnosus or a combination of S thermophilus and L delbrueckii subspecies bulgaricus (Majamaa H *et al.*, 1995). Immunogenicity of mucosal and systemic vaccines enhanced by the effect of probiotics has also been reported. Fourfold increase (0.04) in serum IgA antibody response to salmonella typhi immunization was reported by Link-Amster

and colleagues in volunteers consuming yogurt containing *B. bifidum* and *L. acidophilus* La 1 compared with a 2.5 –fold increase in the control group (Link-Amster H *et al.*, 1994). Pattern recognition receptors (such as toll like receptors) present on the surface of immunocompetent cells (monocytes, macrophages, dendritic cells, etc), present in the peyer's patches, lamina propria or other sites recognizes the probiotic associated molecular patterns (for example, peptidoglycan, lipotechoic acid, bacterial DNA) and triggers the release of a range of cytokines that shape the developing immune response or active immune response. Increased transport of antigenic materials across the gut and improved antigen presenting cell function (upregulation of antigen presenting molecules and co-stimulatory molecules induced by proinflammatory cytokines and/or increased B-cells) somehow potentiate humoral immune responses but the exact mechanism is not known (Gill HS 1998, Meydani SN, Ha WK 2000).

### **Irritable Bowel Syndrome and Probiotics**

Bloating, flatulence, abdominal pain and diarrhea are common symptoms which are seen in patients with irritable bowel syndrome. These symptoms are difficult to treat and have a significant impact on lives of patients. Intestinal gas can produced by gut flora but they also consume gas and probiotics might reduce gas accumulation and improve the balance within the bowel.

Pain and flatulence in patients with irritable bowel syndrome is decreased by administration of a *L. plantarum* strain in a double blind clinical trial. VSL#3 probiotic mixtures is very useful for the relief of abdominal bloating in patients with diarrhea concluded in a recent placebo controlled trail. 28 patients with high volume diarrhea

caused by food intolerance for 12 weeks administered  $10^{10}$  cfu/d of *Enterococcus faecium* PR88 by Hunter et al and there was a symptomatic improvement in 19 of the 28, and a significant decrease in faecal weight (Nobaek S *et al.*, 2000, Kim HJ *et al.*, 2003)

### **Allergy and Probiotics**

Probiotics associated with disappearance of food allergy manifestation with decrease in concentration of IgE in the serum and with a lower frequency of allergies was reported by Loskutova et al and Trapp et al in two different studies (Loskutova IE 1985, Trapp CL *et al.*, 1993). Inflammatory response in food allergy is alleviated by the potentiated effect of the probiotics on the non-immunologic and immunologic defense barrier of the gut. Potentiate IgA response to potentially harmful antigens and IgA production in peyer's patches have been shown to be enhanced by *Bifidobacteria* and *Lactobacilli* (Yasui H *et al.*, 1992). Secretion of Th2 cytokines which are IL-4,IL-5,IL-6,IL-9, IL-10,IL-13 are reduced by the probiotics. Further these antigens are responsible for strong antibody (esp IgG and IgE) responses and eosinophilia found in helminthic infections and allergic disorders (Sutas Y *et al.*, 1996).

Efficacy of whey formula supplemented with *Lactobacillus* GG in infants with atopic eczema and cow's milk allergy was extensively examined by Majamaa and Isolauri and Significant improvement in clinical symptoms and markers of intestinal inflammation was seen in subjects receiving formula with *Lactobacillus* GG (Majamaa H *et al.*, 1997). Immunomodulatory properties of native food protein modified by *lactobacilli* thus probiotics influenced the immune response of human by activation of lymphoid cells present in lymphoid tissues of gastrointestinal tract.

**Table.1** Classification of Nutraceuticals

S. No	Class/Components	Sources
1	Probiotics/Prebiotics/ Synbiotics	Curd, yogurt, Whole grains, onions.
2	Plant based antioxidants a. Polyphenol b. Saponin c. Phytoestrogen c. Carotenoids d. Vitamins E/C	Fruits, Tea, babul pods, mustard cake, rape seed, salseed, Citrus, Fruits, vegetables, soya bean. Soyabean, GNC, Lucerne, chick pea Soybean, flax, lentil seed, Maize, berseem, lucerne, Flax, rye, vegetables. Berseem, lucerne, oat, maize fodder, carrots, vegetables, fruits, Vegetables, Egg, Citrus, Corn. Sunflower oil, Olive oil, Almond oil, Beet green, Spinach, Turnip. Lemon, Orange, Rose hips, Papaya, Garlic.
3	Omega 3 fatty acids	Milk & meat, fish oil, berseem, maize, fodder, mustard, linseed, rapeseed
4	Dietary fibers	Oats, Barley, Legumes, Carrot, Broccoli, Root Vegetables.

**Table.2** Proven Probiotic Microorganisms

Lactobacillus Species	Bifidobacterium Species	Non-lactic acid Species
<i>L. rhamnosus</i> GG (LGG)	<i>B. lactis</i> Bb 12	<i>Escherichia coli</i> strain nissle
<i>L. rhamnosus</i> GR-1	<i>B. infantis</i> 35624	<i>Saccharomyces boulardi</i> lyo
<i>L. reuteri</i> RC-14	<i>B. breve</i> strain Yakult	<i>S. salivarius</i> subsp. <i>thermophilus</i>
<i>L. casei</i> DN114001	<i>B. animalis</i> DN 117-001	<i>S. cremoris</i>
<i>L. acidophilus</i> LA-1	<i>B. lactis</i> HN019	<i>S. intermedius</i>
<i>L. reuteri</i> SD2112	<i>B. longum</i> BB536	<i>Leuconostoc</i>
<i>L. plantarum</i> 299v	<i>B. bifidum</i>	<i>Pediococcus</i>
<i>L. casei</i> Shirota	<i>B. thermophilum</i>	<i>Propionibacterium</i>
<i>L. acidophilus</i> LB	<i>Bifidobacterium</i> DN-17301	<i>W. cibaria</i>
<i>L. rhamnosus</i> HN001	<i>B. breve</i>	<i>E. faecium</i>
<i>L. salivarius</i> UCC118	<i>B. infantis</i>	<i>Lactococcus. lactis</i> subsp. <i>cremoris</i>
<i>L. acidophilus</i> NCFM	<i>B. longum</i>	<i>S. diaacetylactis</i>
<i>L. fermentum</i> VRI003	<i>B. lactis</i>	
<i>L. johnsonii</i> Lj-1	<i>B. adolescentis</i>	
<i>L. paracasei</i> F19		
<i>L. sporogenes</i>		
<i>L. lactus</i>		
<i>L. cellobiosus</i>		
<i>L. brevis</i>		
<i>L. gasseri</i>		

Table references - (Esha A *et al.*, 2011, Kingsley C *et al.*, 2007, Nicole MR *et al.*, 2000, Kedar S *et al.*, 2010, Bhuwaneshwari J *et al.*, 2012)

### **Lowering of Blood Cholesterol**

Consumption of fermented milk associated with reduced serum cholesterol level was reported by Mann and Spoerry (Mann GV, Spoerry A 1974). Mechanisms showing effect of probiotic on the cholesterol levels include assimilation of cholesterol by bacterial cells, deconjugation of bile acids by bacterial acid hydrolases, cholesterol binding to bacterial cell walls and inhibition of hepatic cholesterol synthesis and redistribution of plasma to the liver (Lovegrove J, Jackson K 2003). However studies in human subjects revealed conflicting results like reduction in serum cholesterol from 5.7 to 5.3mmol/l was reported by Lin et al after 7 weeks and in subjects receiving *L. acidophilus* and *L. bulgaricus* serum cholesterol reduced to 5.4mmol/l after 16 weeks whereas the levels remain unchanged in the control subjects (Lin SY *et al.*, 1989).

### **Role of Probiotics in Bacterial Vaginosis and Urinary Tract Infections**

There is a high incidence of urogenital infections though antibiotics are generally effective. Microflora of the intestinal and urogenital tract have a central role in maintaining both the health and well - being of humans.

### **Urinary Tract Infection**

Two strain combination for vaginal use was selected due to the extensive studies on the various lactobacilli strains. Combination comprises distal urethral *L. rhamnosus* GR-1, primarily for its anti gram negative activities and resistance to spermicide and for anti gram -positive cocci activities, *L. fermentum* B-54 was replaced recently by RC-14 which was also responsible for hydrogen peroxide production. To formulate

a good shelf life for patients, consistent doses are made as the gelatin capsule containing  $10^9$  freeze dried organisms which is higher than the total microbial content of vagina.39.using one or two capsules vaginally per week reduced recurrence rates of UTI for a year with no side effects or yeast infections (Reid G *et al.*, 1995).

### **Bacterial Vaginosis**

Overgrowth of anaerobic organisms combined with a loss of protective lactobacilli is considered as bacterial vaginosis, normally it is found in the healthy vagina. Asymptomatic bacterial vaginosis reverted to normal lactobacilli in patients with the daily oral intake of probiotic strains *Lactobacillus rhamnosus* GR-1 and *lactobacillus fermentum* RC-14. Probiotic intake in patients suffering from vaginosis increases the lactobacillus count in vagina from rectal skin and enhancement of intestinal mucosal immunity effects vaginal immunity renders the environment less favourable to bacteria which are causing vaginosis (Reid G, Bruce AW *et al.*, 2001, Reid G, Charbonnaeau D *et al.*, 2003).

### **Helicobacter Pyroli Infection and Probiotics**

Probiotics in *Helicobacter pylori* infection of the gastric mucosa has been tested as a new strategy. Growth of *H pylori* is known to be inhibited by some strains of lactic acid bacteria in vitro by several mechanisms (stimulating specific and non-specific immune responses and producing antimicrobial substances) and prevents infection (Wendakoon CN *et al.*, 2002).

### **Systemic Infection and Probiotics**

Immune system is boosted by translocation of viable or dead bacteria in minute

amounts. Several complications have been shown to occur in several pathological conditions like sepsis, severe acute pancreatitis, liver cirrhosis and multi system failure by bacterial translocation due to bacterial translocation (Lichtman SM 2001). Sepsis is prevented in patients with severe acute pancreatitis with the use of probiotics. Patients treated with *L. plantarum* and incidence of pancreatic abscesses and necrosis were observed at a significant lower rate than in the control group in a randomized double blind trial (Olah A *et al.*, 2002). Incidence of infection involving 95 liver transplant patients were further divided into 3 groups and submitted to different prophylaxis procedure: selective bowel decontamination with antibiotics, fermentable fibres with administration of live *L. plantarum* and the fibre supplement with the administration of heat killed *L. plantarum*. 15 out of 32 patients (48%) were recorded for postoperative infection in antibiotic group, 4 out of 31 (13%) in the live *L. plantarum* group and in the heat killed *L. plantarum* group (34%) that is 11 out of 32, being significant the difference between antibiotics and *L. plantarum* groups (Raves N *et al.*, 2002).

### **Gut Microbiome and Aging**

Assembly of genomes from microorganisms inhabiting the gut is defined as the intestinal microbiome. Investigation of what gut microbes are actually doing can be done from faeces through a combination of metatranscriptomics, metaproteomics, and metabolomics approaches to analyze RNA, protein and small metabolite pools which are further identified by comparing against appropriate databases (Gosalbes M J *et al.*, 2011, Marcobal A *et al.*, 2013). Role of human microbiota in health and disease requires understanding of the cross talk between microbiota and host as well as

integration of taxonomical and metabolic features. Dietary interventions effects on gut microbiota composition/functionality and host metabolic outcomes are provided through the basis of metabolomics but still there is a challenge to develop computational tools to integrate results from multiple levels (Franzosa E A *et al* 2014). Extremes of life in terms of microbiota modulation have not yet been taken into account for probiotic or prebiotic selection to date the specific needs of defined population. Specific and nutritionally adequate products are required to satisfy the particular requirements of these population groups. Development of a new generation of highly adapted functional food products should now be integrated or shared as knowledge.

### **Risks Associated with Clinical use of Probiotics**

Endocarditis , liver abscess , pneumonia in adult and sepsis in children caused by *Lactobacillus* species are rare but well recognized in the absence of probiotic supplementation. It was also reported by Rautio *et al* in a 75 year old woman who developed *Lactobacillus* GG (LGG) liver abscess and pneumonia after 4 months due to daily consumption of LGG (Rautio M *et al.*, 1999). Similarly Mackay *et al* reported the case of a 67 yr old man who suffered from *L. rhamnosus* endocarditis after a dental extraction by taking probiotic capsules daily (Mackay AD *et al.*, 1999).

Many cases of probiotic bacteremia or fungemia have occurred in patients with underlying immune compromise, chronic disease, or debilitation, and no reports have described sepsis related to probiotic use in otherwise healthy persons. Most cases of probiotic sepsis have resolved with appropriate antimicrobial therapy, but in

some cases patients have developed septic shock (Hennequin C *et al.*, 2000).

### Conclusion and Future Prospective

There is no doubt that we will witness a significant increase in the role of probiotics in nutrition and medicine over the next decades. Their application in the prevention and treatment of various disorders should be considered by medical professionals as well as should be promoted by the food industry. Newly developed probiotic strains should be thoroughly evaluated for safety before being marketed. Although much remains to be learned regarding the mechanisms of action and the appropriate administration of probiotic strains, it is clear that different strains can have very specific effects. Moreover their effects may vary in health and disease, in different disease states, and in different age groups. Thus, clinical trial results from one probiotic strain in one population cannot be automatically generalized to other strains or to different populations. Further studies are needed to explore mechanistic issues and probiotic interactions. 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.

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