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Probiotics and the multitude of health benefits

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ABSTRACT:

Present day lifestyle accompanied by numerous occupational health hazards; make us susceptible to a near infinite list of health issues. Probiotics have been in use for a long time. These confer the host with health benefits. The human intestine hosts a number of organisms. These organisms influence overall health in many ways, which can be both degrading or improvising. *Lactobacilli* are the natural inhabitants of the gut and hence the most favorable probiotic organisms. Recent studies have emphasized on the use of probiotics as a complementary therapy against hypercholesterolemia. Hypercholesterolemia ranks high as a major health concern. More rampant among the aged peers, this metabolic derangement is the chief cause of coronary heart diseases. Prolonged elevated levels of serum cholesterol can lead to atherosclerosis. Treatments in the current time frame include statins and other chemotherapeutic agents, which help delaying, but fail to ward off the inevitable. Probiotic treatments, with negligible or rather no adverse side effects are gaining ground. Several lactic acid bacteria have been subjected to scientific scrutiny and their utility in treating this menace has been proven. Besides hypercholesterolemia, probiotics aid in alleviating lactose intolerance, hypertension and allergies, promote general intestinal health and alleviate gastrointestinal disorders and have also been found effective in certain cases of cancer. This review is dedicated to throw lighton the various health benefits associated with the use of probiotics.

Keywords:
Atherosclerosis, Coronary heart diseases, Hypercholesterolemia, *Lactobacilli*, Probiotics, Lactose intolerance, Hypertension

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INTRODUCTION

The currently adopted definition of the FAO/ WHO defines probiotics as "Live microorganisms which when administered in adequate amounts confer a health benefit on the host". An age old quote by Hippocrates "Let food be thy medicine and medicine be thy food", correlates to the present use of probiotics.

Probiotics are "living microorganisms which upon ingestion in certain numbers exert health benefits on the host beyond inherent basic nutrition" (Guarner and Schaafsma, 1998). Although there are many proposed definitions, the most widely accepted one is: "a live microbial food supplement that beneficially affects the host animal by improving its intestinal microbial balance" (Fuller, 1989). The use of probiotics is not new. The Samburu and Masai warriors consumed milk fermented by a wild *Lactobacillus* strain, with significant decrease in serum cholesterol levels (Sharper *et al*., 1963, Mann and Spoerry, 1974). Bacteriocins produced from the probiotic *Lactobacillus brevis* helps to kill the pathogens in gut (Karthick Raja et al, 2011). Recent studies have highlighted an array of health benefits associated with the use of fermented dairy products. Probiotics help alleviating lactose intolerance, reduce serum cholesterol levels, strengthen mucosal immunity and are potentially the safest therapeutic agents for cancer and AIDS afflicted individuals. Use of probiotics in treating gastrointestinal and urinary tract infections has shown a positive result (Gill and Guarner, 2004; RatnaSudha et al., 2009).

Multitude of benefits and virtually no adverse effects make probiotics an alluring alternative to chemotherapy. The use of Amax, a product from probiotic *Saccharomyces cerevisiae* helps in the reduction of ammonia and urea excretion (Mohamad Lashkarbolouki et al, 2011).

Use of probiotics as a complementary therapy to treat hypercholesterolemia has received a great deal of attention recently. Hypercholesterolemia and obesity are major health concerns in both developed and developing countries (RatnaSudha *et al.,* 2009).A limited amount of cholesterol is vital to body functioning. High density lipids translocate excess cholesterol to the liver. The American Academy of Pediatrics identifies hypercholesterolemia as the chief reason of many health problems, such as coronary heart disease, atherosclerosis, diabetes, arthritis and a few types of cancers. Hypercholesterolemia correlates to increased serum cholesterol levels. Low density lipids are found to be in high levels in hypercholesterolemia patients, than the high density lipids. Accumulation of low density lipids on arterial walls decreases their capacity by narrowing them, which in turn, leads to several cardiac problems, and ultimately cardiac failure. A lot of efforts have been made on developing chemotherapeutic agents to treat hypercholesterolemia in humans (McNamara and Sabb, 1989). Drugs mostly inhibit HMG-CoA reductase, the key enzyme in cholesterol biosynthesis. A decrease in the intracellular cholesterol concentration in hepatocytes lead to further increase in its clearance from the bloodstream (Lutgens et al., 2004; RatnaSudha et al., 2009). Pharmaceuticals have failed to sustain, due to the adverse effects of their prolonged use. Increasing health consciousness in the society has led to the development of probiotics as preventive substitutes (Perdigon et al., 1991).

Besides hypercholesterolemia, probiotics find use as anti-cancer agents (Suvarna and Boby, 2005). They alleviate lactose intolerance (Jiang *et al.*, 1996), provide relief from constipation (Walker and Duffy, 1998), protect from pathogens (Casas and Dobrogosz, 2000), and positively stimulate the immune system (Aattouri *et al.,* 2002). In a study by Goldin and Gorbach, 1992, the importance of *Lactobacilli* in preventing the intestinal seeding and growth of pathogenic bacteria, was realized. *L. acidophilus* is the dominating species amongst all inhabiting the gut (Sandine, 1979).Several lactobacilli exhibit the unique

capability of respiring oxygen, though devoid of respiratory mechanisms. *L. plantarum* has been used to reduce soy allergy (Frias et al., 2008).The therapeutic effect of probiotics can be due to the production of anti-microbial compounds (Dodd and Gasson, 1994), increase in gut pH (Langhendries, 1995). Probiotics also compete with pathogenic organisms for the binding sites (Kailasapathy and Chin, 2000) and stimulate the immune effectors (Rolfe, 2000) and thereby provide protection against the invasive microbes in the gut.

Selection of Probiotic Organisms:

Properly assessed criteria for screening of microbes for probiotic potential are important to establish probiotics as alternatives to chemotherapy. With increasing evidences in support of various organisms, it is difficult to propose a definite list of attributes.

- A probiotic strain should be preferably of human origin.
- Probiotic strains must be tolerant to bile, acids and stable against common digestive enzymes.
- A probiotic strain must colonize in the gut. Adherence to the gut is thus of prime importance.
- It should confer significant health benefit to the consumer, without any side effects.
- The probiotic organisms should remain viable throughout the shelf life in case of functional foods.

Common Probiotic Organisms

Lactobacilli*:*

- *L. acidophilus*
- *L. casei*
- *L. delbruckeii subsp. bulgaricus*
- *L. reuteri*
- *L. brevis*
- *L. cellobiosus*
- *L. curvatus*
- *L. fermentum*
- *L. plantarum*

Gram positive cocci:

- *Lactococcus lactis subsp. cremoris*
- *Streptococcus salivarius subsp. thermophilus*
- *Enterococcus faecium*
- *Staphylococcus diacetylactis*
- *Staphylococcus intermedius*

Bifidobactera:

- *B. bifidum*
- *B. adolescentis*
- *B. animalis*
- *B. infantis*
- *B. longum*
- *B. thermophilum*

(Adapted from "Probiotics, prebiotics and synbiotics: approaches for modulating the microbial ecology of the gut", M David Collins and Glenn R Gibson, Am J Clin. Nutr, 1999, 69 (suppl), 1052S-1057S). On the grounds of fermentation behavior, the dominant probiotic genus *Lactobacillus* has been classified into three groups (Holzer *et al.,* 2003):

Obligate homofermentive

- *L. acidophilus*
- *L. delbruckeii*
- *L. helveticus*
- *L. farciminis*
- *L. lactis*
- *L. bovis*

Facultative heterofermentive

- *L. alimentarius*
- *L. casei*
- *L. curvatus*
- *L. sakei*
- *L. paralimenterius*
- *L. plantarum*
- *L. pentosus*

Obligate heterofermentive

- *L. brevis*

- *L. buchneri*
- *L. fermentum*
- *L. reuteri*
- *L. fructivorans*
- *L. sanfranciscensis*

Significance of Lactobacilli as Probiotics against Hypercholesterolemia

Gilliland, Nelson and Maxwell (1985) reported the direct action of some *Lactobacillus acidophilus*strains on cholesterol, based on the feeding trials performed on pigs. Anderson and Gilliland (1999), performed two controlled clinical studies, reporting an average reduction of serum cholesterol by 2.9% on regular consumption of yoghurt containing *L. acidophilus* and hence, a 6-10% decrease in cardiac complications due to hypercholesterolemia. In yet another study by Anderson and Gilliland (1999), the probiotic potential of *L. acidophilus* was related to direct cholesterol breakdown and bile salt deconjugation. The assimilation ability of six *Lactobacilli* strains in broth systems was studied by Meei-Yn Lin and Tseng-Wei Chen in 2000, reporting *L. acidophilus* ATCC 4356 to possess the highest efficiency at 57% and 71%, containing oxgall and cholic acid in the broth respectively.Kalavathy et al. (2009), studied 12 strains of Lactobacillus for their bile salt deconjugation activity, reporting the *L. reuteri* strains to be most efficient. *L. acidophilus* was reported to have the highest deconjugation efficiency and bile salt hydrolase activity, in a study by Liong and Shah (2005), which involved testing eleven strains of Lactobacilli for bile salt deconjugation, bile salt hydrolase activity and precipitation of cholesterol. *Lactobacillus plantarum* intake results in significant rooting off, of factors responsible for cardiovascular diseases, and can be used as a preventive measure against atherosclerosis in smokers (Bukowska *et al.,* 2002). In a preclinical study by Pulusani and Rao in 1983, laboratory rats fed with fermented milk were found to have lowered serum cholesterol levels. Another experiment by Grunewald (1982), where rats fed with fermented milk showed lowering of serum cholesterol levels, indicated the possible use of probiotics against hypercholesterolemia. Lin et al., (2000), examined six strains of *L. acidophilus* for their cholesterol assimilation abilities and proposed as the underlying mechanism, direct assimilation and adherence of cholesterol to *L. acidophilus* cell surface. Ziarno et al., (2007) worked on cholesterol assimilation by commercial starter cultures, reporting *L. acidophilus* monocultures to assimilate cholesterol by 49-55%. Active research in this field has shed light on the vast potential of common human gut inhabiting *Lactobacilli* as probiotics and their associated health benefits. Multitude of health benefits and safety of consumption give probiotics an edge over the market leading drugs. The probiotic potential of *L. plantarum* PHO4 was established by Nguygen et al., (2007), in a study involving hypercholesterolemic mice. The mice were fed with 107 CFU per day over two weeks. These mice had 7 to 10% lesser serum cholesterol and triglycerides than the control mice deprived of the probiotic feed. Many other bacteria other than the *Lactobacilli* have been studied for their potential as novel probiotics such as, *Bacillus coagulans*, which was patented as a composition in combination with bifidogenic oligosaccharides and other hypocholesterolemic agents (US patent 7232571), (Ratnasudha et al., 2009). *Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium infantis* strains were studied by Kim et al., (2004), for hypocholesterolemic potential. All the strains produced bile salt hydrolases that efficiently hydrolyzed major human bile salts. The assimilation efficiency depends on the strain (HodaMahrous, 2011).

Cholesterol Assimilation Mechanism:

Advancements in the field have brought to light, the array of health benefits that probiotics promise. Safety and negligible side effects are the factors that draw much attention. Several mechanisms have been

proposed to explain the hypocholesterolemic activity of probiotics. Some probiotic microbes utilize cholesterol for their metabolic needs, whereby cholesterol is catabolized. The cholesterol reduction is chiefly due to the inhibition of 3-hydroxy 3-methyl glutamyl coenzyme A reductase. Also, imbibition of cholesterol into the cell membrane and physical adherence to the cellular surface has been suggested (Hosono and Tono-Oka, 1995, Noh *et al.,* 1997). This enzyme is vital to cholesterol biosynthesis and deconjugation of bile salts. Deconjugated bile salts are poorly absorbed in the intestine (De Rodas et al., 1996). This implies the increased use of cholesterol to synthesize bile salts and excessive excretion. Some probiotics produce lipases which probably is the reason for the reduction of serum triglyceride levels.

Significance of Probiotics in Gastrointestinal and Urogenitaldisorders

Diarrhea and hepatic encephalopathy:

A study by Rajkumar *et al., 2002,* showed that many *Lactobacilli,* like *Lactobacillus acidophilus, Lactobacillus bulgaricus* and some strains of *Lactobacillus rhamnosus* are effective against antibiotic-diarrhea. Another randomized controlled study by Allen SJ *et al.,* 2003, reported many *Lactobacillus, Enterococcus* and *Streptococcus* species to be effective in infective diarrhea, in people of all age groups. Goltz *et al.,* 1974*,* reported the utility of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* in treating ampicillin-induced diarrhea. *Lactobacilli* inhibit the proliferation of infectious microbes by producing compounds like lactic acid and hydrogen peroxide. Many probiotic species have been identified to be effective in children suffering from rotaviral diarrhea (Saavedra*et al.,* 2000).*Lactobacillus acidophilus* works effectively against diarrhea in cases subjected to pelvic irradiation (Marrteau *et al.,* 1990). *Lactobacilli strains* release variety of enzymes in the intestine, which has a synergistic effect on digestion, and improves intestinal absorption (Parvez*et al.,* 2006). This capability of probiotics to counter infections can be due to several reasons. Their action can be immune-modulatory but they also compete with the pathogens for binding onto epitheliocytes (De Santis et al, 2000). Another reason is the production of bacterial toxins, like nisin which ward off pathogenic bacteria. Overproduction of intestinal mucins, caused by probiotics, can hamper the adherence of enteropathogens to the intestine (Mack *et al.,* 1999). However, this hypothesis needs further elucidation. Hepatic encephalopathy results in multiple complications, such as convulsions, swings in consciousness levels, coma, which arises due to liver failure. Toxic nitrogenous wastes accumulate in the blood, which otherwise are removed by the liver. Pathogenesis of the ailment is not clearly understood. Excessive nitrogen loads, hyponatraemia, hypokalaemia, prolonged use of sedatives and alcohol intoxication potentially lead to this state of liver dysfunction. Various strains of *Lactobacilli,* viz. *L. acidophilus, L. plantarum, L. casei, L. delbruckeii, L. bulgaricus* help improving the condition. Underlying mechanisms are largely unknown.

Lactose intolerance:

Lactose is the disaccharide found commonly in milk. Lactose intolerant individuals hence cannot digest milk. Lactose intolerance in humans results due to the lack of the enzyme β-galactosidase, or lactase. Lactase catalyzes the catabolism of lactose into glucose and galactose. Lactose intolerant subjects express abdominal discomfort, flatulence and cramps (Suvarna and Boby, 2005). Also, these patients suffer from calcium deficiency, as excluding milk from the diet deprives them of the calcium. Lactic acid bacteria produce lactic acid, thereby increasing the gut pH and improving calcium absorption. Besides, most of the lactose in fermented milk is converted into lactic acid by the starter cultures and therefore, lactose intolerance is alleviated.

Urogenital infections are frequent in mid-aged peers, significantly in women. Recurrence is rather a

major problem in these cases. Commonly occurring vaginal tract infections were *Trichomonas, Candida albicans, Gardenerella vaginalis* and *Mycoplasma hominis* (Spiegel, 1991). Chemotherapeutic solutions to these infections are numerous. But often these infections have latent adverse effects. These include infertility, miscarriage, underweight infant births and of course they attract other sexually transmitted diseases. *Lactobacilli* in high populations reduce the vaginal tract pH and hence confer protection against these infections (Hawes *et al.,* 1996). *Lactobacilli* also check the recurrence of infections by *Candida* (Mallen *et al.,* 1992). Even heat killed *Lactobacilli* have been found effective in cases of *Candida* infection. Most of the studies suffered from low sample sizes and pre-completion termination of the study. But enough evidences have been obtained in support of probiotics as prophylactic therapies. Proper research in this area is essential.

Immunomodulatory Activity of Probiotics

The probiotics exert a broad spectrum of health effects. Direct effects include alleviation of various gastrointestinal disorders, altering the colonization of other gut microbes and increasing bioavailability of nutrients (Parvez *et al.,* 2006). But probiotics influence the overall health of the host in other ways too, by modulating the immune system in a variety of ways. Marrteau *et al.,* (1990) proposed that the inflammation associated with rheumatoid arthritis can be treated using probiotics. Various researchers have reported the immunological modulations on intake of probiotics that improve the innate gut mucosal defenses that are lost in cases of juvenile arthritis. Rheumatoid arthritis is an autoimmune disorder, where improper immune reactions lead to irreparable bone and cartilage damage. A random, double-blind, placebo controlled clinical trial by Mandel *et al.,* 2010, involved forty five adults randomly receiving LAB as probiotics or placebo along with the usual medication. The subjects receiving probiotic supplement reported significant relief from pain. The study reported no adverse effects of probiotic intake. The gut micro flora affects the systemic and mucosal immunity and the development and progression of rheumatoid arthritis (Hatakka *et al.,* 2003). Research indicates inflammatory cytokines to be down-regulated by probiotics, significantly by the lactic acid bacteria. Allergy or hypersensitivity is a manifestation of immune malfunction. It is quite unfortunate that allergic sensitization is increasing considerably over time, noticeably in the western countries. Change in the gut microbial constitution can lead to the development of allergies (Suvarna and Boby, 2005). The initial bacteria that inhabit the gut largely affect the immune responses (Parvez *et al.,* 2006). Probiotics are effective against food allergies. They modulate allergic responses by stimulating the gut mucosal barrier (MacFarlane and Cummings, 2002). Degradation of antigens is probably the reason behind the effectiveness of probiotics in allergies. Probiotics have also been shown to be effective in HIV positive subjects. In 2008, a randomized double blind controlled trial on 77 HIV infected children by Miura *et al.,* reported substantial increase in the CD4 cell count of subjects receiving *Bifidobacterium bifidum* and *Streptococcus thermophilus*. *Lactobacillus plantarum* 299v also exerts a positive effect in patients of immune dysfunction. A consortium of probiotic organisms might further strengthen immunity. Various animal model studies have suggested both specific and non-specific pro -immune effects of probiotics (Parvez *et al.,* 2006). This pro-immune effect are probably due to the activation of macrophages, stimulation of anti-inflammatory cytokines, increasing the NK cell activity and stimulating antibodies (Ouwehand *et al.,* 2002; Parvez *et al.,* 2006).However precise knowledge of how probiotics influence the immune system is yet to be gained, as research in this direction is still in its adolescence. Nevertheless, administration of probiotics to immuno-compromised patients presents appealing results.

Probiotics and Cancer

Cancer is the unrestricted growth of cells. Cancerous growth can be triggered by many factors, such as switching on of aberrant genes, mutagens etc., The best precautionary measure to avoid cancer is to avoid exposure to mutagens. Cancer claims a large number of lives every year. In vitro and animal studies have suggested protective potential of probiotic against colon cancer (Rowland, 2004).Intake of *Bifidobacterium longum* suppressed colon cancer induced by 2-amino, 3-methylimidazo (4, 5-f-quinoline), a food carcinogen (Rivenson and Reddy, 1993).*Lactobacillus acidophilus* considerably suppresses colon cancer induced by 1, 2-dimethyl hydrazine in rats (McIntosh *et al., 1999)*. The anti-tumor activity of *Lactobacilli* and products fermented by them was reported by Sahani and Friend, in 1984. Dietary administration of *L. acidophilus* to rats significantly diminished colon cancer in a quantitative manner (De Santis*et al.,* 2000).*L. delbruckeii* fermented milk counters carcinogenic activity of 4-nitroquinoline 1-oxide (Hosono, 1986). Probiotics help guard against cancer in several ways. They might hinder the growth of other gut microbes which convert pro-carcinogens to carcinogens, detoxify ingested carcinogens, induce apoptosis, produce anti-tumorigenic compounds, make the gut hostile for cancer inducing microbes or stimulate the body's defense against cancer.

Hypertension

A large proportion of the western population suffers from hypertension. Role of probiotics in hypertensive individuals is not yet concrete. Clinical studies proposed the production of peptides from the milk protein digestion by bacteria, to have blood pressure suppression ability in hypertensive subjects (Takano, 1998, Mary Ellen Sanders, 2000). Studies on hypertensive rats (Nakamura *et al.,* 1995 and 1996) and a clinical human trial (Hata *et al., 1996)* reported the two active tripeptides: valine-proline-proline and isoleucine-proline-proline, which inhibit the enzyme acting on

Some probiotics in the indian market

Trade Name	Producing Company	Formulation
Eubioz	Lupin	*L. acidophilus* *L. rhamnosus* *B. bifidum* *B. longum* *Streptococcus thermophilus* *Saccharomyces boulardii*
Bifilac	Tablets, India	*L. sporogens* *Streptococcus faecalis* *Clostridium butyricum* *Bacillus mesentericus*
Becelac	Dr. Reddy's Lab	*L. acidophilus*
Equipro	CadilaPharma	*L. acidophilus* *Streptococcus faecalis* *Clostridium butyricum* *Bacillus mesentericus*
Lactobacil	Infar	*L. acidophilus*
Actigut	Alembic	*L. acidophilus* *L. rhamnosus* *B. longum* *B. bifidum* *Saccharomyces boulardii* *Streptococcus thermophilus*
Prepro	Fourrts	*L. acidophilus* *Streptococcus faecalis* *Clostridium butyricum* *Bacillus mesentericus*
Lactisyn	Franco-Indian	*L. acidophilus* *L. lactis* *Streptococcus thermophilus* *Streptococcus lactis*
Goodlac	Biomilcom	*L. acidophilus* *L. rhamnosus* *B. longum* *Saccharomyces boulardii*
Econove	Glenmark	*L. reuteri* RC-14 *L. rhamnosus* GR-1

(Adapted from the review "Emergence of Probiotics in Therapeutic Applications", Barun K. Bhattacharyya, International Journal of pharmaceutical Sciences and Nanotechnology, 2(1), 2009, 383-389)

angiotensin and hence reduce blood pressure. Studies on hypertensive rats by Nakamura *et al.,* in 1995 and 1996, were the first reports in this field. Sawada *et al.,* reported the wall fragments of *L. casei* strain to possess hypotensive activity. Further research is needed to establish probiotics as an antihypertensive therapy. But preliminary research indicates positive results.

Future Perspectives

Rigorous scientific research backs probiotics to be of remarkable therapeutic efficacy. Probiotics, because of the large number of health benefits and consumer safety, will see a tremendous demand and development. Various scientific studies provide unrivalled evidence in support of probiotics as complementary therapeutic agents. Probiotics provide a natural way of controlling serious health issues. Identification of a myriad of probiotic organisms only adds to the development of these functional foods. Advanced molecular biology techniques and genetic engineering will come handy to the development of well-defined and more efficient probiotics. Involvement of several pharmaceutical giants across has provided a major thrust to the development of "magic pills". Probiotics will provide a safer way to treat the once before incurable, deleterious ailments like cancer. Advanced delivery techniques, such as microencapsulation, add to the efficacy of probiotic action. Increased drug resistance and evolution of multi drug resistant species, emphasizes on the need of probiotics. Multi-facet developments will increase the market presence of probiotics in the future. It will not be an exaggeration to say that probiotics in the future will be the reigning therapeutic agents

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