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Research Article

Probiotics: A Medieval To Modern Era Prospective

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ABSTRACT

Probiotics have been perceived as a solution to many of the life style related problems. In modern era the quality of water and food supply may affect the intestinal micro flora. Chlorinated water and preservatives added to foods may lead to an alteration in the normal micro biota of intestine. Probiotics, however, lead to reversal of this altered microbial picture back to normal. They tend to maintain the delicate balance exiting between the gastro intestinal tract and the immunological system of the body. Whenever this balance is disturbed, a disease develops. Probiotics competitively inhibit the over stimulation of immune system by pathogenic bacteria by adhering themselves to the gastro intestinal mucosa in place of pathogenic bacteria and thus inhibiting their colonization. They have proved to be beneficial in the case of allergies/eczema, diarrhoea, hyperlipidaemia, Acquired Immune Deficiency Syndrome, liver cirrhosis, gastric ulcer, hypertension, inflammation, arthritis, inflammatory bowel disease, peptic ulcer and cancer etc. It is also beneficial in case of antibiotic resistance or antibiotic associated side effects. The present review deals with the updated information about the role of probiotics in health and disease.

Key words: Probiotics, *Lactobacillus, Bifidobacterium, Streptococcus, Saccharomyces*, Healthcare

INTRODUCTION

Pharmaceuticals have not been able to completely control the global morbidity and mortality in case of both acute and chronic diseases. Hence, search for the other alternatives has always been there[1]. The old age quote of Hippocrates becomes most pertinent in the current health scenario i.e. “let food be thy medicine and medicine be thy food”[2]. In the late 90’s, microbiologists identified the difference between the micro flora of the diseased human beings and those of normal human beings. The beneficial micro flora were termed as “probiotics”[3]. There are billions of bacteria present in human Gastro Intestinal Track (GIT) forming about 1 kg of the human weight, which includes both harmful as well as beneficial bacteria. Together they are called as gut flora. Delicate balance between the harmful and the beneficial bacteria is responsible for maintenance of health. When this balance is disturbed, the person becomes diseased. One of the ways to regain this balance is the external administration of probiotics (beneficial bacteria) into the body of the diseased person. Probiotics include a large number of different types of bacteria that are normal inhabitants of human GIT. The most common among them are various species of *Lactobacilli* and *Bifidobacteria*. They reside in small intestine and colon. Probiotics have been able to attract the maximum attention among several food supplements as they have additional benefits beyond their nutritional value [4]. In 1965, Stillwell and Lilly introduced the term “probiotics”[5]. The term is made up of two words Latin preposition *pro* means "for" and the Greek adjective *βιωτικός* means “biotic”. Hence, it means “for favour of life”. According to World health organisation (WHO) and Food and Agriculture Organization (FAO) it is defined as “living microorganism intended for administration into the host body in adequate amount so as to confer health benefits”[6].

History: It has been known since long that there are benefits of using fermented milk products and poultices of bread moulds. But Ellie Metchnikoff started the probiotic therapy via fermented milk products in 1907. In 1915, the therapy was used for the treatment of urogenital infections. However, in the intertwining period of 7-8 decades less study is reported on probiotics due to an increased interest in antibiotics. These were labelled as “alternative medicines”. Recently there has been a resurgence of probiotics due to demand of consumers for better treatment. This resurgence can also be attributed to development of resistance against antibiotics[6].

Probiotic criteria: An organism must fulfil the following criteria in order to be considered as probiotics: There should be high cell viability, and should be able to survive in low pH. Even if strain cannot colonize in gut, it should have the ability to persist. They should have the ability to adhere to the epithelium of GIT so as to overcome the flushing effect due to peristalsis. They should have the ability to interact or to send signals to the immune cells associated with GIT. They should be capable of being isolated from humans. They should have processing resistance. They should be non-pathogenic. They should have positive influence on local metabolic activities.

A dose of five billion colony forming units are generally recommended for adequate health benefits. Probiotics should be Generally Recognized as Safe (GRAS). Probiotics preparations involve the use of both single as well as mixture of microorganisms[6].

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Mechanism of action of probiotics: To explain the effects of probiotics several mechanisms have been proposed. The effects can be attributed to a number of activities and their action is proposed to be multipronged. Probiotics stimulate the intestinal lactase activity. They partially digest the lactose and can be used in the case of lactose intolerance and in certain types of diarrhoea[7]. Various fermented milk industries use lactobacilli in order to decrease the lactose concentration in the dairy products which ultimately affects the severity of osmotic diarrhoea[7]. Lactic acid bacteria inhibit the growth of various pathogenic microorganisms present in dairy products by producing various metabolites such as free fatty acids, bacteriocins and hydrogen peroxide etc[8].

Probiotics also cause modification in the toxin receptors and thus hinder the toxin receptor mediated pathology of disease[9]. They also offer competitive inhibition during colonization to the pathogenic bacteria[10]. The other mechanisms involve lowering of pH, releasing the gut protective metabolites, production of mucous and regulation of gut motility[11]. Gastrointestinal mucosa acts as an interface between the body's immune system and the external environment. Whenever there is the decrease in gut flora the antigen transportation increases. This clearly depicts that gut flora maintain the gut defences (Figure 1)[11, 12].

The interaction between the gut epithelial cells and immune cells with non-pathogenic probiotic micro-organisms may leads to generation of immunological signals. This interaction occurs in the Peyer's patches[13]. Probiotics also modulate the immunoglobulin (Ig) production. They increase the production of IgA, a secretory immunoglobulin which plays an important role in mucosal immunity and thus act as a barrier against the various pathogenic microorganisms and viruses[13, 14]. It has also been demonstrated that probiotics also causes induction of T independent IgA[15]. Probiotics also increase the production of certain types of cytokines tumour necrosis factor- α (TNF- α), interleukins-10 (IL-10). The up and down regulation of immune response is also affected by probiotics so as to maintain the intestinal homeostasis[16].

Probiotics in health: The overall health of the person depends upon his/her eating habits and life style. In ancient time humans used to take enormous live bacteria but as the concept of hygiene developed, there has been a decrease in intake of live bacteria along with the food. The dietary habits in the western world are a cause of development of certain diseases like ulcerative colitis. Their diet lacks fruits, vegetables and omega-3 fatty acids. Due to which they have more chances of development of diseases such as heart diseases and cancer. The increase in allergic and inflammatory conditions, obesity, heart diseases and cancer has been found to be proportional to the decrease in probiotic content in the diet[17].

Probiotics in specific diseases

Allergies /Eczema: Probiotics are very effective in treatment of food allergy especially in case of infants suffering from atopic eczema or cow's milk allergy. With the use of *Lactobacillus* GG, there occurs a significant clinical improvement among the people suffering from atopic dermatitis. The clinical improvement is accompanied by reduction in inflammatory marker[18, 19].

Antioxidant activity: Bacillus coagulans RK-02 has been reported to produce extracellular polysaccharide having four hetero mono saccharides as its constituents. This has shown a significant antioxidant and free radical scavenging activity[20]. The powerful antioxidant activity is also shown by *Streptococcus thermophilus*. It protects the body from many dangerous free radicals that develop in the body due to aging, sugar, stress, antibiotics other toxins and chemicals[21]. Significant antioxidant activity is also shown by *Bifidobacterium bifidum* due to which it has been reported to produce protection to the intestinal lining from the lipid peroxidation in iron over loaded mice[22].

Antibacterial activities: Multiple probiotics via *in vitro* studies have been found to be effective against many of the pathogenic microorganisms including *Listeria monocytogenes*, *Salmonella typhimurium*, *E.coli* and *H.pylori.* Therefore, prototypic antimicrobial substances can be obtained from probiotic agents. It may prove to be useful for the pharmaceutical companies to develop new antibiotics [23,24].

Diarrhoea: Probiotics are used for prevention as well as for the cure of various types of diarrhoea. The activity of dietary probiotics against various types of diarrhoea successfully investigated. e.g.

Lactobacillus rhamnosus GG, strains of *L. Casei*, strains of *L. Acidophilus*, *L. Reuteri*, *Escherichia coli* strain, Bifidobacteria and Enterococci, and Probiotic yeast *Sacchromyces boulardii* [25].

Rota virus diarrhoea: Both preventive as well as curative probiotic treatment is available for it which has been proven with the help of randomized, double blind and placebo studies. *Bifidobacterium lactis* BB-12 and *Lactobacillus rhamnosus* GG are used for prevention whereas *Lactobacillus reuteri* SD 2222 is used for the treatment in acute cases [26-28].

Antibiotic associated diarrhoea: Although broad spectrum newer antibiotics have been developed with fewer side effects but they are liable to cause antibiotic associated diarrhoea (AAD). The chances of incidence ranges from 3.2 to 29/100 patients admitted to the hospital. The complications of AAD involve: electrolyte imbalance, dehydration, pseudo membrane colitis. Antibiotics which are used against anaerobic bacteria are supposed to cause more AAD. *Saccharomyces boulardii* can be used in the treatment of AAD [29].

Radiation induced diarrhoea: The patients who are receiving radiation therapy during cancer usually develop diarrhoea. A study of high potency probiotics preparation was done on such patients (double blind and placebo) taking VSL#3 as a preparation. It has been shown that probiotic preparation decreases the bowel movements and daily incidences of diarrhoea. From the study, a conclusion was withdrawn that lactic acid bacteria can be a safe, efficient and easy approach to treat radiation associated diarrhoea in cancer patients [30].

Traveller's diarrhoea: It is the diarrhoea associated with the travellers. The chance of incidence ranges from 5 % to

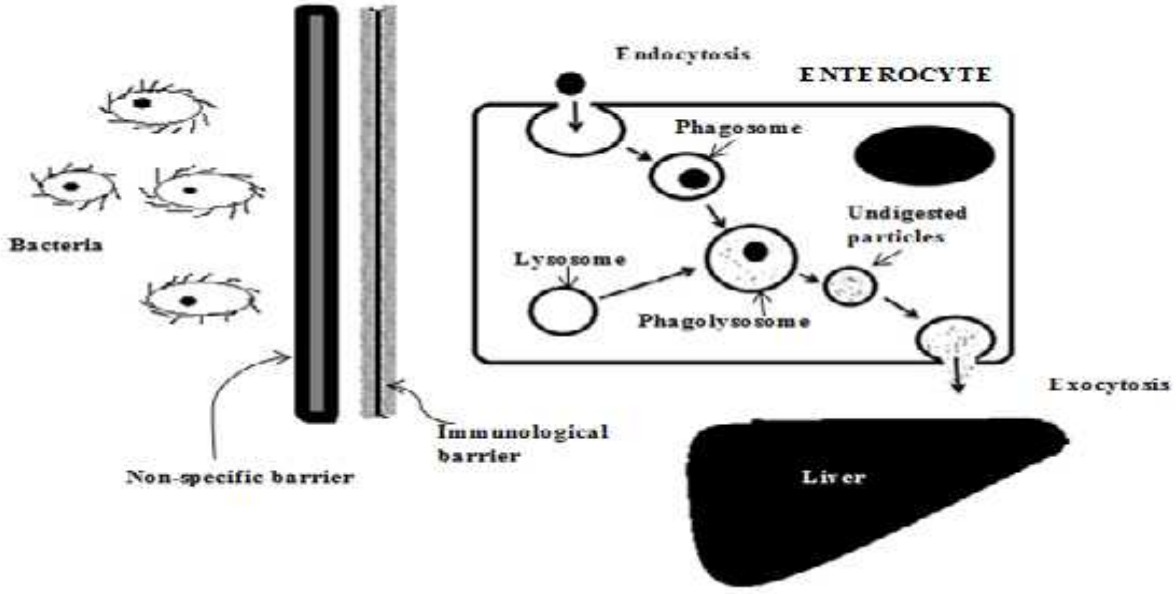

Figure 1: Barrier to antigen absorption in intestine.

15% depending on destination [31] A mixture of *Saccharomyces boulardii*, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* is found to have high efficacy in this regard [31].

Hyperlipidemia: Probiotic strains can be used to lower the body cholesterol level (especially the lactic acid bacteria). Two strains found in yogurt have been found to have significant cholesterol lowering effect. These include *Lactobacillus acidophilus* and *Bifidobacterium lactis.* When *Lactobacillus sporogenes* was given to hyperlipidemic patients over a period of three months a reduction of 32% total cholesterol level and 35% reduction in low density lipoprotein (LDL). The mechanism behind this effect is the inhibition of production of HMG CoA reductase. *L. plantarum* has also been shown to possess cholesterol lowering activities [32, 33].

Hepatic diseases: A report was published which demonstrates the role of multicultural probiotics in the treatment of liver cirrhosis. The study included first one month probiotic treatment followed by 1 month wash out period, followed again by the second probiotic treatment. During the study, blood pressure of hepatic portal vein was measured, which usually was found to decrease in case of liver cirrhosis. During the first probiotic therapy period there occurred an increase in portal vein pressure followed by decrease in that at the end of wash out period which again rise during second period of probiotic therapy. The micro-organisms present in formulation included *Streptococcus thermophilus, Bifidobacteria, Lactobacillus plantarum, L. acidophilus, L. casei, L. debrueckii bulgaricus* and *Streptococcus* faecum [34].

Hypertension: Blood pressure (BP) decrease with the consumption of fermented milk products with species of *Lactobacilli*. The antihypertensive effect of probiotic is attributed to the bacterial cell wall components. Moreover the bacteria are known to generate peptides which have angiotensin converting enzyme inhibiting property [35].

Hemolytic uremic syndrome: This syndrome is usually develops in children taking antibiotic therapy for *E.*coli [36] In this syndrome, epithelial injury occurs due to drop in trans epithelial electrical resistance. Such injury can be prevented by pre-treatment of intestinal (T84) cells with lactic acid producing bacteria (69). *E.coli* produces vero cytotoxin which causes haemorrhagic colitis and haemolytic uremic syndrome in humans. This can be inhibited by the use of probiotic containing *Bifidobacterium longum*, which produces substances that can bind to vero cytotoxins [37]. *Bifidobacterium longum* also offers protection against *Salmonella* typhimurium [38].

Inflammation /Arthritis: Probiotics produce both direct as well as indirect effects. The direct effects produce locally with in the GIT includes vitamin production etc. The indirect effects which are produced outside the GIT occur in joints, skin and lungs. Amongst the indirect effects it exerts its influence on immunity and alters the level of inflammatory mediators. Modulation of inflammatory response can be localized within the GIT or it may be systemic. It is postulated that inflammation associated with rheumatoid arthritis can be modulated with the help of probiotics. In chronic juvenile arthritis, there is a disturbance in the gut defence mechanism and an alteration in the permeability of GIT which may account for the inflammation associated with arthritis. The effects of Lactobacillus GG administration to the patients for two weeks shows remarkable improvement [39].

Inflammatory Bowel Disease (IBD): IBD involves two chronic diseases: Ulcerative colitis and Crohn's disease

The available clinical data shows the role of intestinal micro biota in the pathogenesis of IBD and there by provides an evidence that alteration in the intestinal micro biota with the help of probiotics can be helpful in the treatment of disease. E.g. *Bifidobacteria infantis* has been found to reduce the inflammatory response of the gut lining by inhibiting the bacteroides. *Lactobacillus plantarum* has also been reported to be used in IBD. A

probiotic formulation containing no of microbes (VSL#3) used in case of ulcerative colitis although its clinical efficacy is not certain. *E. coli* has also been used in case of ulcerative colitis but its clinical efficacy depends upon its dose [40-44].

Kidney stones: Kidney stones develop as the result of increased concentration of oxalate in the urine. *Oxalobacter formigenes* is responsible for degrade oxalate with the help of enzyme oxalyl-CoA People with renal stone are found to have less *Oxalobacter formigenes* which ultimately leading to increased oxalate in the urine (hyperoxaluria). *Bifidobacterium breve* has also been reported to be beneficial in case of kidney stones as it also exhibits oxalate degrading property [45,46].

Neonatal enterocolitis: Caplan and Jilling reported that supplementation with probiotics can be helpful in preventing the neonatal enterocolitis. They developed murine model explaining different characters of neonatal enterocolitis that are clinically and pathologically important. *Bifidobacterium infantis* was found to be effective in this case[47].

Cancer: There are several hypotheses which explain the mechanism of action of probiotics in treatment of various types of cancers. These include: Detoxification of ingested carcinogens. Inhibition of bacterial growth and/or production of their metabolites those are carcinogenic in nature. Inhibition of tumour cells growth via production of specific compounds. Immune system stimulation against tumour cells. Metabolite production (e.g. butyrate) which improve apoptosis [48]. *Lactobacilli* have been reported to prevent establishment and growth of tumour cell and their metastasis [49]. With increase in consumption of products containing *Lactobacilli* or *Bifidobacterium* the chances of breast and colon cancer reduces [50-51]. The recurrence of superficial bladder cancer has been found to be significantly reduced with the consumption of *Lactobacillus* casie [52].

Peptic ulcers: According to a report *Lactobacillus salivarius* has been found to be useful in *H.pylori* induced peptic ulcers as it produces lactic acid which can completely inhibit *H.pylori* growth, this in turn, inhibits the inflammatory response associated with it. The first bacteriocin (natural antibiotic substance) was isolated from *Lactobacillus* salivarius. *L. casei* (strain Shirota) can also be used in case of *H.pylori* induced peptic ulcer 53-54.

Lactose intolerance: Probiotics relieve the symptoms associated with intolerance as well as they decrease oro-cecal transit. Those individuals who have such intolerance can tolerate 12 to 15g of lactose when probiotic therapy is given. Yogurt is used in case of such patients as it contains less lactose as compare to milk. Moreover, it contain lactase enzyme and delay gastric emptying time [55-58].

CONCLUSION

Probiotics are gaining importance because of its immense benefits in treatment of various ailments. The basic hindrance in use of probiotic as therapeutic agent is the lack of scientific data (preclinical and clinical report). According to experts there is the need of further research to show preventive and therapeutic health benefits, to elucidate mechanism of action, therapy duration, optimal intake, selection of specific strains, etc. Probiotic as dietary supplements have no labelling requirements which often confuse the consumer to use them. Therefore education of the public regarding the probiotics is necessary. According to experts there should be greater understanding of the concept that how they work. Probiotics must undergoing critical scientific evaluation procedures before they are to be launched into the market.

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