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PROBIOTICS: LIVING MEDICINES IN HEALTH MAINTENANCE AND DISEASE PREVENTION

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INTRODUCTION

Probiotics are defined by the world health organization as live organisms, when taken in sufficient amounts; provide a benefit to human health. The beneficial microflora found in the gastrointestinal tract were termed probiotics. Probiotics, literally meaning "for life," are microorganisms proven to exert health-promoting influences in humans and animals [1].The term "synbiotics" was coined to describe the synergistic actions of pre- and probiotics [2]. In 1994, the world health organization deemed probiotics to be the next-most important immune defense system when commonly prescribed antibiotics are rendered useless by antibiotic resistance [3]. The use of probiotics in antibiotic resistance is termed microbial interference therapy. With increasing understanding that beneficial microbes are required for health, probiotics may become a common therapeutic tool used by health care practitioners in the near future.

HISTORY

Microbial cultures have been used for thousands of years in food and alcoholic fermentations, and in the past century have undergone scientific scrutiny for their ability to prevent and cure a variety of diseases. This has led to the coining of the term probiotics, or "pro-life." The first clinical trials in the 1930s focused on the effect of probiotics on constipation, and research has steadily increased since then.

The first recorded probiotic was fermented milk for human consumption. After that, probiotics became popular with animal nutrition. The role of fermented milk in human diet was known even in Vedic times. But, the scientific interest in this area boosted after the publication of the book entitled *The Prolongation of Life* by Ellie Metchinkoff1 in 1908. He suggested that people should consume fermented milk containing lactobacilli to prolong their lives. Accelerated aging is because of autointoxication (chronic toxemia), which is due to the toxins produced by gut micro flora. Bulgarian peasants who were subjected to the experiments on longevity had consumed large quantities of sour milk. The pathological reaction might be removed and life expectancy could be enhanced by implanting lactic acid bacteria from Bulgarian yogurt **[4].** Since then, researchers started investigations relating to the role of lactic acid bacteria in human and animal health. Probiotics have been used as growth promoters [**5],** for lactose intolerance [6], antitumour and anticholestrolaemic effects [7, 8].

FEATURES OF PROBIOTICS

A good probiotic agent needs to be non-pathogenic, nontoxic, resistant to gastric acid, adhere to gut

epithelial tissue and produce antibacterial substances. It should persist, albeit for short periods in the gastro-intestinal tract influencing metabolic activities like cholesterol assimilation, lactose activity and vitamin production [9].

MECHANISMS OF ACTION

Mechanisms of action of probiotics that have been suggested include receptor competition, effects on mucin secretion and/or immunomodulation of gut-associated lymphoid tissue, increased immunosuppressive and decreased proinflammatory mediators [10]. Probiotic agents exert a beneficial effect via a wide array of actions. These include resistance to colonization, production of antimicrobial substances, inhibition of pathogen adhesion, degradation of toxins, stimulation of local and peripheral immunity, stimulation of brush border enzyme activity, stimulation of secretory-IgA, and prevention of Microbial translocation. Because of these varied actions, it is unlikely pathogens will develop resistance against probiotic agents. Colonization resistance is the ability of the normal flora to protect against unwanted colonization of the GI tract by pathogens. Colonization resistance is achieved by complex interactions between the different resident bacteria of the mucosal microflora [11].

Most probiotics have the capability to produce substances which have direct antimicrobial action. Organic acids, hydrogen peroxide and bacteriocins are among the known products with inhibiting effects on pathogens. These substances can either reduce the number of pathogenic organisms directly, or in some instances can alter the metabolism of pathogens and inhibit endotoxin action [12-15].

COMPOSITION OF PROBIOTICS

Probiotics can be bacteria, moulds, yeast. But most probiotics are bacteria. Among bacteria, lactic acid bacteria are more popular. *Lactobacillus acidophilus*, *L. casei*, *L. lactis*, *L. helviticus*, *L. salivarius*, *L. plantrum*, *L. bulgaricus*, *L. rhamnosus*, *L. johnsonii*, *L. reuteri*, *L. fermentum*, *L. del brueckii*, *Streptococcus thermophilus*, *Enterococcus faecium*, *E. faecalis*, *Bifidobacterium bifidum*, *B. breve*, *B. longum* and *Saccharomyces boulardii* are commonly used bacterial probiotics. A probiotic may be made out of a single bacterial strain or it may be a consortium as well [16].

The most commonly utilized probiotic preparations include specific strains of — either alone or in combination — Lactobacilli, Streptococci and Bifidobacteria. These three genera are important components of the gastrointestinal flora, are considered to be harmless, and might be capable of preventing the overgrowth of pathogenic organisms. Starter bacteria used in yogurt cultures include *Lactobacillus bulgaricus* and *Treptococcus thermophilus*; however, it is not clear whether these bacteria are capable of colonization of the human GI tract. It is believed constant replenishment by periodic ingestion of yogurt might be needed for these bacteria to persist in the GI tract **[17].** Probiotics can be in powder form, liquid form, gel, paste, granules or available in the form of capsules, sachets, etc.

CLINICAL APPLICATIONS

Anti-diarrheal Effects

An extensive body of research supports a beneficial role for probiotics in the prevention and treatment of a variety of diarrheal illnesses, such as acute diarrhea caused by rotavirus infections, antibiotic-associated diarrhea and travelers' diarrhea [18-20]. Specific strains of lactobacilli have been shown to reduce the severity and duration of acute diarrhea caused by rotavirus infections in infants and young children. The most commonly studied probiotic species in these studies have been *Lactobacillus GG*, *L. casei*, *B. bifidum* and *S. thermophilus*. Probiotic bacteria have also been shown to preserve intestinal integrity and mediate the effects of inflammatory bowel diseases, irritable bowel syndrome, colitis, and alcoholic liver disease [21-23]. In addition, lactic acid bacteria may improve intestinal mobility and relieve constipation [24].

Protection against Infections

Probiotics may help prevent or treat infections such as postoperative infections, respiratory infections and the

growth of *Helicobacter pylori*, a bacterial pathogen responsible for type B gastritis, peptic ulcers and perhaps stomach cancer [25-26].

Regular intake of probiotics (i.e., a fermented milk drink containing a mixture of *L. rhamnosus GG, Bifidobacterium, L. acidophilus,* and *S. thermophilus*) has been demonstrated to reduce potentially pathogenic bacteria in the upper respiratory tract of humans [27]. Some *in-vitro*, experimental animal and limited human studies indicate that probiotics, especially lactic acid bacteria, may inhibit the growth of *H. pylori.* [28-30] Probiotics such as *Lactobacillus casei* strain *Shirota*, *Bifidobacteria* and *Lactobacillus salivarius* have been shown to inhibit the growth and/or colonization of *H. pylori* in *in-vitro* and experimental animal studies [31].

Anticancer activity

Some *in vitro* and experimental animal studies, indicates that probiotics may have the potential to reduce colon cancer risk in experimental animals, intake of yogurt and specific probiotic cultures has been shown to reduce the development of precancerous lesions (aberrant crypts) and chemically-induced tumors, although the findings appear to be both species- and strain-dependent [32,33]. Animal and *in vitro* studies indicate that probiotic bacteria may reduce colon cancer risk by reducing the incidence and number of tumors. [34] Early laboratory studies with mice identified glycopeptides from the cell walls *of L. bulgaricus* bacteria that exhibited antitumor activity [35]. *Lactobacillus GG* was later found to reduce the incidence of induced tumors in an animal model of colon cancer [36]. In humans, *L. acidophilus*, supplied via milk or supplements, reduced the levels of enzymes considered to be procarcinogenic [37]. Unlike standard chemotherapy agents, probiotic-derived agents target tumor cells without harming normal cells or causing immune suppression and other adverse side-effects [36]. Proposed mechanisms by which lactobacilli play an anticancer role include: (1) neutralizing procarcinogenic substances (e.g., nitrates) produced by harmful bacteria before they are converted into active carcinogens (e.g., nitrosamines) in the intestinal tract; (2) suppressing the metabolic action of such bacteria as *Clostridium* and certain Bacteroides, which produce higher amounts of enzymes (e.g., β-glucuronidase and β--glucosidase) that act by cleaving glucuronic acid conjugates of environmental toxins or steroidal hormones and allowing the unconjugated forms to go back into the enterohepatic circulation and by outcompeting healthy bacteria for nutrients; suppressing the induction and growth of some tumors directly [37].

Immune Enhancement

Evidence from in vitro systems, animal models and humans suggests that probiotics can enhance both the specific and nonspecific immune response, possibly by activating macrophages, increasing levels of cytokines, increasing natural killer cell activity, and/or increasing levels of immunoglobulins. [38] Findings from experimental animal and mostly short term human studies indicate that yogurt and probiotics such as lactobacilli and bifidobacteria stimulate certain cellular and antibody functions of the immune system, which in turn may increase resistance to immune-related diseases (e.g., infections, gastrointestinal disorders, cancer, allergies) [39-42] Consumption of yogurt or lactic acid bacteria (e.g., *L. casei*, *L. rhamnosus GG*, and other strains) also modulates the production of several cytokines, which have diverse roles in regulating immune functions. [43] The greatest improvements in *B. lactis* -mediated immunoenhancement occurred in individuals with poorly functioning immune systems. [44,45]

Anti-inflammatory Effects

Because probiotics can influence the intestinal flora, they may have beneficial effects for patients with inflammatory bowel disease (IBD), which includes ulcerative colitis, Crohn's disease and pouchitis [46]. Several animal studies and a few clinical trials in humans suggest that specific probiotic bacteria may alleviate or reduce symptoms of IBD [47,48].

Prevention of Allergic Reactions

Probiotic bacteria are important in down regulating inflammation associated with hypersensitivity reactions in patients with atopic eczema and food allergy. Probiotics may exert a beneficial effect on

allergic reaction by improving mucosal barrier function. In addition, probiotic consumption by young children may beneficially affect immune system development. Probiotics such as *Lactobacillus GG* may be helpful in alleviating some of the symptoms of food allergies such as those associated with milk protein [49-52].

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 lactic acid produced by bacterial strains. Compared to milk, yogurt results in better absorption of such vitamins and minerals as calcium, copper, iron, manganese, phosphorous and zinc. Prebiotics also improve calcium bioavailability [53,54].

Cholesterol assimilation / Hyperlipidemia

Another benefit of probiotics is serum lipid reduction. Several authors have reported that *Lactobacillus acidophilus* and *L. sporogenes* were found to take up cholesterol in the presence of bile and in the absence of oxygen, both conditions present in the intestinal tract. Probiotic strains, especially lactic acid bacteria have a major role to play in the cholesterol lowering mechanism. As the cholesterol level keeps increasing in the serum, it leads to cardiac diseases. These cholesterol levels can be brought down using probiotics [55].

Lactose intolerance

Probiotic strains have also proved to solve the problem of lactose intolerance. Lactose intolerance is a physiological state in human beings where they lack the ability to produce an enzyme named lactase or β-galactosidase. This lactase is essential to assimilate the disaccharide in milk and needs to be split into glucose and galactose. Individuals lacking lactase will not be able to digest milk and it often poses a problem in newborn infants. People with lactose intolerance problem express abdominal discomfort, diarrhea, cramps, flatulence, nausea, vomiting, etc. Another problem associated with lactose intolerance is calcium deficiency. A person suffering from lactose intolerance will be advised to take non-milk diet. The resident bacteria in the colon ferment undigested lactose, producing acid and gas, causing symptoms such as abdominal pain, bloating and diarrhea. Yogurt contains less lactose than milk and delays gastric emptying, which partly explains why lactose-intolerant individuals tolerate yogurt. However, yogurt tolerance is mainly due to the supply of lactase activity from the lactic acid bacteria present in the yogurt itself. Evidence shows that bacteria must be live and present in sufficient quantity to be of benefit; yogurts containing bacteria/ml are required [56].

Hepatic Disease

A several case reports were published documenting the effect of a high potency, multicultured probiotic preparation in liver cirrhosis [57].

Conditions of the Genitourinary Tract/ Bacterial Vaginosis

Bacterial vaginosis is one of the most common infectious disorders affecting women. It can be caused by several microorganisms, including *Gardnerella vaginalis*, *Bacteroides sp.*, β- *Streptococci* and *Mobiluncus/Falcivibrio sp.* Bacterial vaginosis is characterized by a shift in normal vaginal flora from aerobic to a predominantly anaerobic flora. In addition to the disturbing symptomatic presentation, since large numbers of pathogenic bacteria are present in the vagina, this condition can increase a woman's risk for postoperative morbidity and adverse obstetric outcome [58]. Lactobacilli are major constituents of the normal vaginal flora. Their production of bacteriocins, lactic acid, and hydrogen peroxide are mechanisms which keep pathogenic colonies from proliferating [59,60].

There is a developing role for the use of probiotics in the genitourinary (GU) system, especially for vaginitis, whether from bacterial or fungal etiology. A report on the use of *L. sporogenes* in non-specific vaginitis revealed symptomatic relief in the majority of women who used the probiotic vaginally [59]. Both oral probiotics and vaginal suppositories of probiotics have been shown to reduce the incidence of recurrent urinary tract infection [60].

Neonatal Enterocolitis

A report by Caplan and Jilling found probiotic supplementation may be effective in preventing neonatal necrotizing enterocolitis [61].

Pregnancy

Vaginal application of highly adhesive Lactobacteria to 30 pregnant women with dysbacteriosis of the birth canal resulted in correction of micro flora of this area [62]. In pregnant women with altered microflora, correction of bacterial ecology of the vagina and intestine is reported to favorably influence the course of pregnancy, labor, and the postpartum period. [63]

Nutrient synthesis and bioavailability

Fermentation of food with lactic acid bacteria has been shown to increase folic acid content of yogurt, bifidus milk and kefir and to increase niacin and riboflavin levels in yogurt, vitamin B_{12} in cottage cheese and vitamin B_6 in Cheddar cheese [64, 65] addition to nutrient synthesis, probiotics may improve the digestibility of some dietary nutrients such as protein and fat [66]. Short-chain fatty acids such as lactic acid, propionic acid and butyric acid produced by lactic acid bacteria may help maintain an appropriate pH and protect against pathological changes in the colonic mucosa.

Dysbacteriosis

Dysbacteriosis is the term used to describe the overgrowth of pathogenic organisms in the stomach or intestines. Administration of a combination consisting of *L. acidophilus* and *Bifidobacterium bifidum* resulted in restoration of duodenal bacterial flora and resolution of clinical symptoms in elderly patients with bowel disorders [67].

Other Potential Health Benefits

Some experimental animal and human investigations suggest that probiotics may reduce the risk of heart disease by their beneficial effects on blood lipid levels [68], and blood pressure [69], alleviate kidney stones [70], decrease inflammation associated with arthritis [71] and protect against dental caries.

ADVERSE EFFECTS

Generally, probiotics are considered to be very safe and well tolerated. However, 42 cases of *Lactobacillus endocarditis* have been described in the literature [72]. Larvol et al, have also reported a case of liver abscess due to *L. acidophilus* in a 39 year-old man with chronic pancreatitis who underwent a choledoco-duodenostomy. The authors suggested the choledoco-duodenostomy might have promoted biliary tract colonization [73].

FUTURE SCOPE

In Europe, Japan and Australia, probiotics and related products to improve intestinal health currently represent the largest segment of the functional foods market. The European Commission has sponsored research projects on these products' safety and efficacy. [74] Probiotics are also now among the most popular selling supplements in the United States [75] .The World Health Organization deemed probiotics to be the next-most important immune defense system when commonly prescribed antibiotics are rendered useless by antibiotic resistance [76]. The use of probiotics in antibiotic resistance is termed microbial interference therapy. With increasing understanding that beneficial microbes are required for health, probiotics may become a common therapeutic tool used by health care practitioners in the not-too-distant future. Interest continues today as recent technological advances have enabled microorganisms to be isolated and colonized to determine their specific therapeutic properties [77].

CONCLUSION

Probiotics are gaining importance because of the innumerable benefits, e.g. treating lactose intolerance, hypercholesterol problem, cardiac diseases and managing cardiac problems like atherosclerosis and arteriosclerosis. Current evidence supports the concept that oral administration of probiotic therapies may be beneficial in a multitude of disorders both inside and outside the gastrointestinal tract. Probiotic organisms can have a significant influence on the treatment and prevention of disease. With the current focus on disease prevention and the quest for optimal health at all ages, the future of probiotics is bright.

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