Review Article

Promising future of probiotics for human health: Current scenario

Abstract

Probiotics are nonpathogenic microorganisms mostly of human origin which, when administered in adequate amounts, confer a health benefit on the host and enable to prevent or improve some diseases. Probiotics may be a natural temporary constituent of the resident intestinal microflora, but their concentration is not sufficient for therapeutic purposes. The microbiota, the intestinal epithelium, and the mucosal immune system constitute the gastrointestinal ecosystem. All three components are essential for complete functional and developmental maturity of the system. Probiotics are defined as live microbial food ingredients that have a beneficial effect on human health. The use of antibiotics, immunosuppressive therapy, and irradiation, among other means of treatment, may cause alterations in the composition and have an effect on the gastrointestinal tract flora. Therefore, the introduction of beneficial bacterial species to GI tract may be a very attractive option to re-establish the microbial equilibrium and prevent disease. The efficacy of probiotics in acute enteric infections and post-antibiotic syndromes is now established and there is emerging evidence for a role in necrotizing enterocolitis, irritable bowel syndrome, periodontal diseases, and some forms of inflammatory bowel disease.

Key words:
Action on human health, probiotic supplements, probiotics, safety considerations

Introduction

Probiotics are defined as "live micro-organisms that confer a health benefit on the host when consumed in adequate amounts (WHO/FAO)." Probiotic bacteria should be safe for consumption, reach the intestines alive in large numbers, and impart specific health benefits to the host. These bacteria should maintain the balance of the intestinal flora by altering favorably the gut environment in such a manner that the growths of friendly beneficial bacteria are promoted and harmful disease-causing organisms are inhibited. Some of the commonly used probiotic bacteria include *Lactobacillus*, *Bifidobacteria*, and the yeast *Saccharomyces boulardii*. Apart from their use as drugs, they are most commonly used in the form of probiotic dairy products and probiotic fortified foods. Today, there is emerging evidence that probiotics offer innumerable benefits to the host by alleviating symptoms of lactose intolerance.[1] They are also known to prevent acute diarrhea, traveler's diarrhea,[2,3] antibiotic-associated diarrhea (AAD),[4,5] Rotaviral diarrhea,[6] etc. Research has also shown that probiotics help to prevent the recurrence of cancers, especially bladder and colorectal cancers.[7,8] Research is underway to evaluate their role in regulating blood pressure, lowering cholesterol, and reducing obesity in adulthood. However, probiotics do not work the same in everyone. Probiotics may be more effective in older people than in younger ones since more mature bellies may have fewer good bacteria. There is also some evidence that genetic factors, that is, how much good and bad bacteria you have in your gut, can affect your reaction to probiotics. Probiotics were first seriously studied at the Pasteur Institute in Paris at the turn of the 20th century by several leading microbiologists, including Henry Tissier and Eli Metchnikoff. Metchnikoff, who won the Nobel Prize for Medicine in 1908, hypothesized that encouraging the colonies of non-harmful gut flora by adjusting the pH

Access this article online	
Website: http://www.cysonline.org	Quick Response Code
DOI: 10.4103/2229-5186.94308	

Gaurav Tiwari, Ruchi Tiwari, Saurabh Pandey, Preeti Pandey

Department of Pharmaceutical Sciences, Pranveer Singh Institute of Technology, Bhauti, Kanpur, Uttar Pradesh, India

Address for correspondence:
Mr. Gaurav Tiwari,
Department of Pharmaceutics, Pranveer Singh Institute of Technology,
Kalpi road, Bhauti, Kanpur-208 020, Uttar Pradesh, India.
E-mail: tiwari_mpharm@rediffmail.com

of the stomach could reduce many of the health problems associated with aging. Although his idea of using fermented dairy products to manage the pH proved incorrect, the concept of his theory gained attention and further research was conducted. In 1953, the name "probiotics" was officially given to the group of bacteria strains that had been found to positively enhance the functioning of the digestive tract. Probiotics are "Live microorganisms administered in adequate amounts that confer a beneficial health effect on the host" (according to the Food and Agriculture Organization of the United Nations). Most probiotics are bacteria, which are small, single-celled organisms. Bacteria are categorized by scientists with genus, species, and strain names. They can be used as complementary and alternative medicine (CAM).[1] People use probiotic products as CAM to prevent and treat certain illnesses and support general wellness. There is limited evidence supporting some uses of probiotics. Much more scientific knowledge is needed about probiotics, including about their safety and appropriate use. Effects found from one species or strain of probiotics do not necessarily hold true for others, or even for different preparations of the same species or strain.[2]

Biological effects of probiotic bacteria

- Modulation of host immune response[5]
- Enhanced antibody production
- Enhanced natural killer cell activity
- Modulation of dendritic cell phenotype and function
- Modulation of NF-kB and AP-1 pathway
- Altered cytokine release
- Induction of regulatory T cells
- Induction of PPAR-g
- Modulation of apoptosis
- Inhibition of proteasome activity
- Enhanced epithelial barrier function
- Enhanced tight junction protein phosphorylation
- Upregulation of mucous production
- Enhanced epithelial cell glycosylation
- Increased sIgA production
- Antimicrobial effects
- Decreased luminal pH
- Stimulation of defensin secretion
- Secretion of antimicrobial peptides
- Inhibition of pathogenic bacterial invasion
- Blockade of bacterial adhesion to epithelial cells
- Release of nitric oxide

Eating bacteria is good for you

Although it may sound absolutely ludicrous to purposely ingest billions of bacteria to improve your health, that is exactly what researchers are recommending. Studies have been going on since the mid-1990s on this subject.[3] There are about 100 trillion microorganisms that represent more than 500 different species that are in each and every healthy bowel. They are there because they help keep harmful pathogens at bay, making it difficult for them to do you harm.[4]

Mechanism of action

Lactic acid bacteria produce several metabolites like fatty free acids, hydrogen peroxide, bacteriocins, etc., which prevent the growth of food-borne pathogens in dairy products [Figure 1].

Probiotics are defined as living microorganisms which, on ingestion in certain numbers, exert health benefits beyond inherent general nutrition. Mechanism of action of probiotics is seen in Figure 2. There is now good evidence that certain strains of *Lactobacilli* and *Bifidobacteria* can influence immune function through a number of different pathways including effects on enterocytes, antigen presenting cells (including both circulating monocytes and local dendritic cells [DCs]), regulatory T cells, and effector T and B cells. Importantly, however, the relationship between the various reported effects and clinical consequences of treatment are unknown. Because there are very few studies in which several allegedly probiotic strains have been compared, it is not known to what extent a finding using a certain bacterial strain is relevant for other strains, even of the same species. To date, there are only a few strains, limited to *Lactobacilli,* which have been reasonably well documented in clinical studies, mostly against infectious gastroenteritis and lactose intolerance. Locally in the gut, there is evidence that commensal gut bacteria help reduce local inflammation,[6]

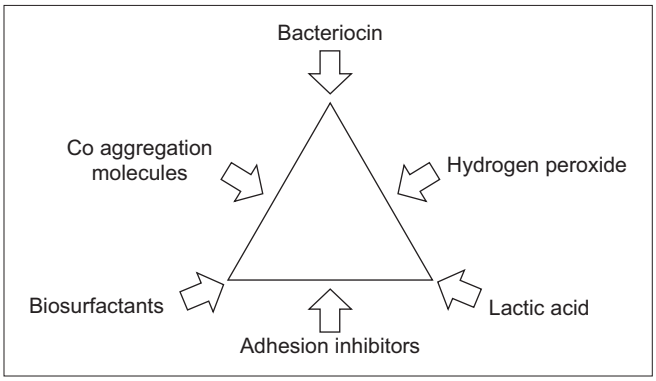

Figure 1: Metabolites of lactic acid bacteria

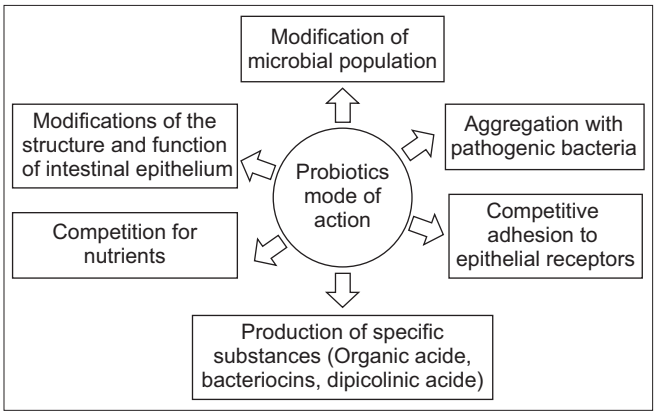

Figure 2: Mechanism of action of probiotics

and at least 1 probiotic strain has the capacity to maintain the integrity of the intestinal barrier,[7] potentially reducing systemic antigen load. At least some of the anti-inflammatory effects appear to be mediated through toll-like receptors (TLR), including TLR98 and possibly TLR2 and TLR4 expressed on enterocytes. Intestinal microbiota also promotes enterocyte production of TNF-b and prostaglandin E2, which promote the development of tolerogenic DCs.[9] Other studies have also shown that probiotics directly enhance the activity of human DC populations[10,11] to promote TH1 differentiation.[12] Consistent with notions that bacteria promote regulatory function, there is also preliminary evidence that probiotics promote immunoregulatory activity in the gut. In animal studies, probiotic supplementation can induce regulatory T-cell populations (bearing TGFb),[13] and human studies also suggest an increase in the *in vitro* production of regulatory cytokines (IL-10) after probiotic ingestion.[14]

Table 1 shows Probiotics found in randomized controlled trials to have a significant therapeutic effect. The effects may be limited to certain species, as indicated by a recent study in which *Lactobacillus reuteri* and *Lactobacillus casei*, but not *Lactobacillus plantarum*, primed monocyte-derived DCs to drive the development of regulatory T cells.[15] These regulatory T cells produced increased levels of IL-10 and were capable of inhibiting the proliferation of bystander T cells in an IL-10–dependent fashion. Interestingly, the two former species, but not *L. plantarum*, bound the C-type lectin DC-specific intercellular adhesion molecule 3–grabbing nonintegrin, and blocking antibodies to DC-specific intercellular adhesion molecule 3–grabbing nonintegrin inhibited the induction of the regulatory T cells by these probiotic bacteria. Intestinal microbiota also influences IgA production in distal sites (respiratory tract). The gastrointestinal tract makes up a critical part of the integrated common mucosal immune system, which includes mucosal surfaces across anatomically remote locations (namely the gastrointestinal tract and respiratory tract). Several mechanisms have been postulated regarding action of probiotics. Partial lactose digestion and stimulation of the intestinal mucosal lactase activity has been postulated as a possible mechanism against some types of diarrhea.[5,6] *Lactobacilli* used in the fermented milk industry have active beta-galactosidase to decrease the lactose concentration in dairy products, which may affect the severity of osmotic diarrhea due to organisms such as rotavirus.[7,8]

Probiotics can also use enzymatic mechanisms to modify toxin receptors and block toxin-mediated pathology. Probiotic agents also prevent colonization of pathogens by competitive inhibition.[9,10] The other suggested mechanisms for the effect on intestinal microflora are lowering the intestinal pH, release of gut protective metabolites, regulation of intestinal motility, and mucus production.

Table 1: Probiotics found in randomized controlled trials to have a significant therapeutic effect

Disease	Probiotic
Antibiotic-associated diarrhea	*Lactobacillus acidophilus þ Lactobacillus bulgaricus*
	Lactobacillus rhamnosus GG
	Enterococcus faecium SF68
	Bifidobacterium longum
	Saccharomyces boulardii
Acute gastroenteritis	*Lactobacillus rhamnosus GC*
	Lactobacillus reuteri
	Lactobacillus casei strain Shirota
	Enterococcus faecium SF68
	Saccharomyces boulardii
Traveller's diarrhea	*Lactobacillus acidophilus*
	Lactobacillus acidophilus
	Lactobacillus bulgaricus
	Lactobacillus fermentum strain KLD
	Lactobacillus rhamnosus GG
	Saccharomyces boulardii

Gastrointestinal mucosa is the primary interface between the external environment and the immune system.[11] Whenever intestinal microflora reduces, antigen transport is increased indicating that the normal gut microflora maintains gut defenses. The nonpathogenic probiotic bacteria interact with the gut epithelial cells and the immune cells to start the immune signals. These bacteria must interact with M cells in the Peyer's patches, with gut epithelial cells, and with associated immune cells.[12] Probiotic bacteria have been shown to modulate immunoglobulin production. Secretory IgA plays an important role in mucosal immunity, contributing to the barrier against pathogenic bacteria and viruses. The increase in the number of IgA-producing cells was the most remarkable property induced by probiotic organisms and also by fermented milk yogurt. T-independent IgA induction has also been demonstrated. The increase in profiles of certain cytokines (TNF-α, IFN-γ, IL-10) has also been observed due to stimulation with probiotic bacteria. The release of cytokines is induced to up or down regulate the immune responses and maintain intestinal homeostasis. Interactions between probiotic microorganisms and GALT (Gut-associated lymphoid tissue), mechanisms of immunomodulation, and anti-inflammatory properties are not yet fully understood.[13]

Benefits of probiotics on human health

Characteristics of good probiotics

Fuller[10] in 1989 listed the following as features of a good probiotic: It should be a strain, which is capable of exerting a beneficial effect on the host animal, e.g., increased growth or resistance to disease; it should be nonpathogenic and nontoxic; it should be present as viable cells, preferably in large numbers; it should be capable of surviving and metabolizing in the gut environment, e.g., resistance to low

pH and organic acids; and it should be stable and capable of remaining viable for periods under storage and field conditions.

Probiotics and general health

Probiotics have traditionally been used to treat diseases related to the gastrointestinal tract. Studies suggest that probiotics may be useful in treatment of patients with hypertension, urogenital infections, lactose intolerance, and elevated levels of cholesterol. Other areas of application include probiotic effects against *Helicobacter pylori* infections in the stomach, alcoholic liver disease, small bowel bacterial overgrowth, ulcerative colitis, allergy to milk protein, juvenile chronic arthritis, antioxidative effects, asthma, hepatic encephalopathy, and their use as vaccine delivery vehicles.[11]

Probiotic strains in the oral cavity

An essential requirement for a microorganism to be an oral probiotic is its ability to adhere to and colonize surfaces in the oral cavity. Microorganisms generally considered as probiotics may not have oral cavity as their inherent habitat and, subsequently, their possibility to confer benefit on oral health is then questionable. Studies suggest that lactobacilli as members of resident oral microflora could play an important role in the micro-ecological balance in the oral cavity. The studies further demonstrated that *Lactobacilli* strains with probiotic properties may indeed be found in the oral cavity. Yet, there is no evidence whether these *Lactobacilli* strains were detected due to the frequent consumption of dairy products leading to temporary colonization only, or if the oral environment is their permanent habitat.[4]

Probiotics and periodontal disease

The oral microbiota is at least equally as complex as the gastrointestinal or vaginal microbiota. The many and varied microbial associations within the oral cavity include some that appear critical for maintaining health, according to Socransky DNA probe studies of 40 taxa of oral bacteria obtained from subgingival plaque samples of healthy individuals and others with periodontal disease indicate that several bacterial taxa, including those associated with gingival health, co-occur in the periodontal crevice. This group, designated the "green cluster," includes *Capnocytophaga* species, *Campylobacter concisus*, *Eubacterium nodatum*, and *Streptococcus constellates*. Moreover, dental biofilms are considered to be difficult therapeutic target. The current view on the etiology of plaque-related periodontal inflammation considers three factors that determine whether disease will develop in a subject: a susceptible host; the presence of pathogenic species; and the reduction or absence of so-called beneficial bacteria. In 1954, a beneficial effect of lactic acid bacteria on inflammatory infections of the oral mucosa was reported.[5] The presence of periodontal pathogens could be regulated by means of antagonistic interactions. A decrease in gum bleeding and reduced gingivitis has been observed by Krasse *et al*.[16] with the application of *L. reuteri*. Koll-Klais *et al*.[17] reported that resident *Lactobacilli* flora inhibits the growth of *Porphyromonas gingivalis* and *Prevotella intermedia* in 82 and 65%, respectively. Probiotic strains included in periodontal dressings at optimal concentration of 108 CFU ml were shown to diminish the number of most frequently isolated periodontal pathogens: *Bacteroides sp*., *Actinomyces sp*., and *S. intermedius,* and also *Candida albicans*. These authors registered a 10 to 12-month remission period after periodontal treatment by application of the periodontal dressing that comprised collagen and *L. casei*. Studies by Mohammad S. Al-Zahrani[18] have shown an inverse association between the intake of dairy products and prevalence of periodontitis. Yoshihiro Shimazaki[19] concluded that the routine intake of lactic acid foods may have a beneficial effect on periodontal disease. *C. albicans* is among the most common infectious agents in the oral cavity. The incidence of yeast infections is higher at older age and under conditions of impaired immunity. Testing the pattern of colonization of *L. acidophilus* and *L. fermentum,* Elahi *et al*.[20] showed a rapid decline in *C. albicans* in mice after the intake of probiotic strains. Continuous consumption of probiotics led to almost undetectable numbers of fungi in the oral cavity, maintaining the protective effect for a prolonged period after cessation of application. However, there is not yet any true evidence on the effect of probiotic therapy on periodontal disease, and the effect of the ingested probiotics needs further investigation.[8,4,12]

Probiotics and dental caries

The impact of oral administration of probiotics on dental caries has been studied in several experiments utilizing different test strains. *Lactobacillus rhamnosus* GG and *L. casei* have proved their potential to hamper growth of these *oral streptococci*. C. Aglar *et al*.[21,22] registered definite *S. mutans* count reduction after a 2-week consumption of yoghurt containing *L. reuteri*. A temporary reduction in *S. mutans* was observed during the period of yogurt intake and few days after cessation of consumption, indicating the necessity of continual administration of the probiotic in order to achieve an effect. However, consider the case of growing body as evidence about the role of probiotics on caries pathogens, it has been suggested that the operative approach in caries treatment might be challenged by probiotic implementation with subsequent less-invasive intervention in clinical dentistry. However, more studies are definitely needed before this goal could be achieved.[4]

Probiotics and imbalanced oral ecosystem

Halitosis, the oral malodor, is a condition normally ascribed to disturbed commensal microflora equilibrium. It has recently been positively affected by regular administration of probiotics. Given that oral microorganisms, especially those on the tongue, are the primary cause of halitosis, current treatments focus on the use of chemical or physical antibacterial regimes to reduce the numbers of these

bacteria. However, most of these treatments exhibit only a temporary effect or are associated with undesirable side effects when used over a long period of time. Kang *et al*.[23] have shown a definite inhibitory effect on the production of volatile sulfur compounds (VSC) by *F. nucleatum* after ingestion of *Weissella cibaria* both *in vitro* and *in vivo*. In children, a marked reduction in the levels of H2S and CH3SH by approximately 48.2% ($P<0.01$) and 59.4% ($P<0.05$), respectively, was registered after gargling with *W. cibaria*-containing rinse. The possible mechanism in the VSC reduction is the hydrogen peroxide generated by *W. cibaria* that inhibits the proliferation of *F. nucleatum*. *Streptococcus salivarius*, also a possible candidate for an oral probiotic, has demonstrated inhibitory effect on VSC by competing for colonization sites with species causing an increase in levels of VSC. However, the few studies published on the role of probiotics in the treatment of halitosis do not entitle any evidence-based conclusions.[4,8]

Safety aspects

The issue of safety is of special concern during the past few years due to the increased probiotics supplementation of different food products. Probiotics are often regulated as dietary supplements rather than as pharmaceuticals or biological products. Thus, there is usually no requirement to demonstrate safety, purity, or potency before marketing probiotics. This can lead to significant inconsistencies between the stated and actual contents of probiotic preparations, as shown in a recent South African study. From the safety point of view, the putative probiotic microorganisms should not be pathogenic, should not have any growth-stimulating effects on bacteria causing diarrhea, and should not have an ability to transfer antibiotic resistance genes. The probiotics should rather be able to maintain genetic stability in oral microflora. The most important area of concern with probiotic use is the risk of sepsis. One theoretical concern with the safety of probiotics is that some have been designed or chosen to have good adherence to the intestinal mucosa, and this is considered important for their mechanism of action. Adherence to the intestinal mucosa may also increase bacterial translocation and virulence. The most potent probiotics, therefore, may have increased pathogenicity. The relation between mucosal adhesion and pathogenicity in *Lactobacillus spp*. is supported by the finding that blood culture isolates of *Lactobacillus spp*. adhere to intestinal mucus in greater numbers than do isolates from human feces or dairy products. *Lactobacillus* bacteremia is a rare entity, and data on its clinical significance are mainly found through case reports. For the last 30 years, there have been approximately 180 reported cases. Clinical characteristics of *Lactobacillus* bacteremia are highly variable, ranging from asymptomatic to septic shock-like symptoms. Any viable microorganism is capable of causing bacteremia, however, especially in patients with severe underlying diseases or in immunocompromised state. Nevertheless, the present literature supports the conclusion that the incidence of *Lactobacillus* bacteremia is unsubstantial and that all the cases where it has been registered are individuals with other systemic diseases such as diabetes, cardiovascular diseases, gastrointestinal disorders, malignancies, or organ transplant patients. However, it is evident that careful monitoring is needed in this regard in the future. The absence of acquired antibiotic resistances is another safety criterion to be tested in potential probiotic candidates. Some probiotics are closely related to opportunistic bacteria and this may also cause transferral of antimicrobial resistance genes in between microorganisms. Several results from antibiotic susceptibility tests claim that the test (W) and test (S) genes in some probiotic *Lactobacilli* and *Bifidobacteria* strains are responsible for gentamycin, sulfamethoxazole, polymyxin B, and tetracycline resistance. These investigations emphasize the need for a minimal safety evaluation during the selection of strains for probiotic use.[4,5]

Probiotics success strategies in food and drinks

Novel applications, future R and D, and consumer engagement-Aarkstore Enterprise Probiotics have a functional component of the health food for nearly 100 years, although there is no legal definition for the term probiotics. Probiotics are microorganisms that transfers a tiny number of congenital health benefits to the host and have numerous applications in food and medicines. Application of probiotics in a wide range of food and drink delivery format, and have multiple health extension platform enhancements that are sold. Provide additional benefits beyond the promise of taste and convenience more and more new products.

Balanced intestinal flora are primarily composed of good bacteria that work relentlessly to ensure that our body is protected against microbes and other infectious germs, maintaining a healthy digestive system.[14,15] These good bacteria stimulate the immune system, promote digestion through the production of enzymes, produce antibacterial substances, and compete against a variety of invading microorganisms.[24] Probiotics can help in maintaining and restoring balance to our intestinal flora, so that it can adequately assume its functions:

- Stimulation and modulation of the immune system
- Improve intestinal function
- Resist pathogenic invasion and growth

There are many benefits associated with regularly taking probiotic supplements. Probiotics have been shown to be helpful in treating lactose intolerance, lowering cholesterol, preventing colon cancer, improving immune system function, lowering blood pressure, and improving nutrient absorption. Individuals who suffer from Irritable Bowel Syndrome and chronic colitis have also noted that probiotic

supplements decrease the severity and discomfort of their symptoms.[25]

Action on the immune system

The immune system is a complex system comprised of cells, tissues, and organs distributed throughout the body, including the intestine. This system provides the body's protection by means of nonspecific (innate immunity) and specific (acquired immunity) defense mechanisms. Skin, mucous membranes, mucous, and hair are among the body's nonspecific defenses which constitute physical barriers used to reject foreign bodies. The inflammatory reaction is another of the body's nonspecific responses, and is characterized, among other things, by a surge of blood toward the infected region and by the recognition and destruction of the foreign body by phagocytic cells (example macrophages). The body's specific defenses initiate an acquired response targeted to the invader. This response involves the action of antibodies produced by B lymphocytes (humoral immunity) and T lymphocytes that coordinate the immune response and directly attack the infected cells (cellular immunity).[24,25]

Probiotics and the immune system

Consumption of beneficial bacteria such as *L. acidophilus* and *L. casei* reinforce intestinal mucous membrane immunity (mucosal immunity) as well as the body's global immunity (systemic immunity). A more detailed explanation is that human consumption of *Lactobacillus* stimulates phagocytic activity and increases production of T and B lymphocytes and production of antibodies, particularly IgM, IgA, and IgG. However, stimulation of these intestinal immune responses by commensal bacteria (specific to man) or probiotics does not readily provoke a significant inflammatory response, as it can be observed in the presence of an infectious agent. That being said, a person can safely consume probiotic bacteria on a regular basis.[26]

Intestinal immune system

The intestine is very rich in lymphocytes, which can be found under the intestinal mucous membrane. Because of its direct contact with external invaders capable of inducing infections, the intestine must be able to adequately defend the body. It plays a major role in an individual's immunity. A person's normal bacterial flora also plays a part in the immune responses through the epithelial cells of the intestine that make up the mucous membrane.[27,28]

Action on the digestive system

The food must be broken down into nutrients to be assimilated by the body. This process is called digestion. Nutrients like mineral salts (iron, calcium, etc.), vitamins, fatty acids, and fiber are essential to meet the fundamental needs of an individual. During digestion, the cells produce enzymes which break up food into increasingly smaller particles (nutrients) until they can be absorbed by the body. Without these enzymes, the body would not have access to these nutrients and would suffer from severe deficiencies.[29,30] Various digestive disorders, ranging from mild to severe, occur due to the presence of nondigested materials in the intestine. The good bacteria that colonize our intestines actively participate in digestion. They also produce enzymes which break down food in such a way that it can be absorbed and have an effect on the entire body. Consequently, the intestinal flora plays a very important role in digestion and health. *L. acidophilus* and *L. casei* are among the good bacteria that comprise the intestinal flora.[31] These bacteria improve food digestion and the body's capacity for absorption. The consumption of probiotics helps to maintain the intestinal flora's balance. As a result, they provide the body with a large quantity of good bacteria and facilitate, among other things, the digestion of food and the assimilation of nutrients while improving digestive system health.[32]

Lactose intolerant

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 B-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 108 bacteria/ml are required.[33] Milk is the richest source of calcium and Ca requirement of the body is met only through milk. Hence, a person consuming non-milk diet will naturally develop Ca deficiency, leading to osteoporosis. Birge[34] confirmed that lactose deficiency leads to calcium malabsorption and thereby to osteoporosis. Calcium malabsorption may be due to deletion of diets with milk to avoid the complications of lactose intolerance. Calcium absorption is better and more in acidic conditions; hence, if lactose is converted to lactic acid, pH of the gut decreases, i.e., it becomes acidic favoring enhanced absorption of calcium. So, if probiotics are fed to lactose-intolerant patients, then milk lactose is hydrolyzed by probiotic strains and lactose is assimilated

and calcium absorption is also favored. When a person is lactose intolerant, it means that the cells of the body are unable to produce the enzyme called lactase essential for the metabolism of lactose (found in dairy products). *Lactobacillus* produces the lactase enzyme, among others. Consequently, by consuming *L. acidophilus* and *L. casei*, we help our body break up lactose and render it much more digestible (in the form of glucose and galactose). Therefore, these bacteria can improve some individual's tolerance to dairy products.[35,36]

Action against pathogenic invasion

Pathogens are microorganisms capable of causing disease. Nowadays, the presence of pathogens in water, food, and public buildings can become a threat to our health. Moreover, taking medications like antibiotics and anti-acids can destroy intestinal flora, cause diarrhea, and increase the risk of infection. AAD and *C. difficile*-associated diarrhea are well-known side effects of antibiotic treatments and can have severe consequences on our health. The good bacteria that comprise the intestinal flora are the first line of defense against intruders. They temporarily adhere to the intestinal wall and reinforce the physical barrier against pathogens.[37] They compete with them for a spot to adhere to the intestinal wall and for the nutrients which are found there. They also produce natural antimicrobial substances called bacteriocins. These two methods of defense discourage implantation, growth, and survival of pathogens. The production of organic acids, hydrogen peroxide, and bacteriocins by lactic bacteria, particularly *L. acidophilus* and L. casei, inhibits the pathogens' actions.[38] Production of lactic and organic acids is specific to lactic bacteria. The organic acids regulate the intestinal pH to maintain it at a level that reduces the growth of infectious agents. Regular consumption of the BioK+ CL1285® formula of *L. acidophilus* and *L. casei* is a simple, effective, and inexpensive solution to preventing infections, particularly in at-risk environments (hospitals, trips, daycares, etc.) and while taking antibiotics.[39] A decrease in beneficial bacteria may also lead to development of other infections, such as vaginal yeast and urinary tract infections, and symptoms such as diarrhea from intestinal illnesses. Research has shown that certain probiotics may restore normal bowel function and may help reduce diarrhea that is a side effect of antibiotics, certain types of infectious diarrhea, inflammation of the ileal pouch (pouchitis) that may occur in people who have had surgery to remove the colon.[40,41]

Irritable bowel syndrome

This benign disease is also called functional colopathy. Well-designed clinical trials (double-blind controlled randomized trials) have been conducted. The results are not actually totally convincing and some questions issued from these trials concerned the doses, the strains, and the number of daily administration. However, in the sub-group of patients with postinfectious irritable bowel syndrome, probiotics seem to be more effective.[33]

Prevention of pouchitis recurrences

The inflammatory bowel diseases are quite frequent and required heavy treatment, sometimes with cortisone. Some probiotics have demonstrated their preventive effect on the recurrence of pouchitis. In ulcerative colitis, encouraging results have been obtained. Still, a limited number of studies have been performed in Crohn's disease.[42]

Other therapeutic applications of probiotics

Candida albicans and vaginal infections

An imbalance in the intestinal flora can have effects on the whole body, particularly the vaginal system, and involve an overgrowth of pathogens which translates into vaginal bacterial or yeast infections, such as *C. albicans*. *L. acidophilus* is one of the most important bacteria found in the vaginal and intestinal flora. These friendly bacteria create an environment that is hostile to pathogens by maintaining low pH in the flora and by producing bacteriocins. In addition, *L. acidophilus* produces hydrogen peroxide and hypothiocyanate which inhibits the growth of *C. albicans.*[43]

Cholesterol

Certain studies have demonstrated that probiotics could help to reduce bad cholesterol (low density lipoproteins). Their mechanism of action has not yet been well explained. However, probiotic bacteria could be involved in bile acid deconjugation which limits the reabsorption of cholesterol (Cholesterol is a major component of bile).[42,43]

Cancer

Many researchers are studying the question of a possible role of probiotics in the treatment or prevention of cancer. According to certain research, probiotics can have a protective role in the development of certain cancers, notably colon cancer, by inhibiting the body from producing mutagens and carcinogenic agents.

Chronic inflammation of the stomach

Helicobacter pylori is a bacteria responsible for chronic inflammation of the stomach. Even if the probiotics cannot eradicate this agent, they have demonstrated their ability to reduce the density of this agent in the stomach.[44]

Nosocomial infections in hospitalized patients

This benefit could be explained by an improvement of the immune defenses in transplanted patients or in those with serious underlying diseases.

Decrease infections in preterm newborn babies

In children, Prof. Yamashiro's[45] work has been fully appreciated. His studies are of interest because they are based on a large population of premature babies weighing less than 1 or 1.5 kg. The supplementation with *Bifidobacterium breve* since the first day of life showed a significant reduction of infections and mortality. The effect

on necrotizing enterocolitis is more debated. Prof. Yamashiro underlines the following two major points regarding his own experience: the importance of the breast-feeding of these babies (they will benefit from gut colonization from their mother's flora) and a very early administration of the probiotic from the first day of life.[46]

Urogenital health

Probiotics are also beneficial in maintaining urogenital health. This is due to the fact that the vagina is like the intestinal tract, a finely balanced ecosystem. The dominant *Lactobacilli* strains normally make it too acidic for harmful microorganisms to survive. But the system can be thrown out of balance by a number of factors, including antibiotics, spermicides, and birth control pills. Probiotic treatment that restores the balance of microflora may be helpful for such common female urogenital problems as bacterial vaginosis, yeast infection, and urinary tract infection. Both oral and vaginal administration of *Lactobacilli* may help in the treatment of bacterial vaginosis, although there is not enough evidence yet to recommend it over conventional approaches.

Food allergies and skin

This practice is so well known that even many MDs are recommending probiotics during and after antibiotics. But there is new evidence that probiotic benefits go beyond that. One area of investigative research concerns building the immune system's resistance to allergies that affect the skin. An obvious example of a skin's allergic reaction is eczema, which tends to occur more often with infants and toddlers. A recent Dutch study gathered over 150 pregnant women with allergic disease histories in their families. During the last six weeks of pregnancy, they were given either three strains of probiotics or an inactive placebo pill. Neither they nor the doctors involved knew who received what. After those pregnant women gave birth, most of their children were still monitored by the Dutch researchers.[47,48] The children continued to receive probiotics or placebos for 12 months. After three months, the rate of eczema occurring among the probiotic subjects was less than half of those given placebos. There were no more probiotics or placebos administered to the children after 12 months. However, many were still observed up until age two years. As they approached that age, the eczema occurrence gap between the two groups with eczema narrowed somewhat. But there was still a substantial difference. The study results provided evidence that probiotics can have an effect on offspring from allergy-prone mothers. Another recent study involved probiotics administered to mice, with a focus on food allergies. All the mice had whey intolerances, and they were fed probiotics and prebiotics while drinking milk. With the addition of probiotics, their intolerance to whey showed considerable improvement with almost no skin reactions. Today, up to 8% of children have various chronic food allergies. Extending this study to children may prove probiotics as a natural remedy for their food allergies.[49]

Reduce symptoms of flu and respiratory tract infection

Studies in both adults and children have indicated that probiotics may reduce the frequency, duration, and symptoms of flu and respiratory tract infections (Note: These studies did NOT involve the H1N1 flu virus, as they were conducted before this year's outbreak).

Prevent post-pregnancy obesity

Women who are concerned about excess weight gain post-pregnancy may want to consider taking probiotics. A new study found that women who took probiotics during pregnancy had a reduced risk of obesity after delivery than those who did not take the beneficial bacteria. Losing excess pounds after pregnancy can be a difficult task for many women. Probiotics, which are beneficial bacteria shown in many research studies to be helpful in regulating the digestive system, have also demonstrated usefulness in preventing colds and flu and in aiding weight loss after gastric bypass surgery.[50]

Treatment of autism

Probiotics have been under the spotlight by researchers questioning how beneficial they would be as a treatment for autism. Autism (Autism Spectrum Disorder) is a disease characterized by a wide group of neurodevelopment disorders, with the most common being impaired social interaction.[51] Based on this, many wonder how probiotics could play a part in the treatment of autism. However, autism consists of several physical symptoms in addition to the psychological and neurological symptoms. One major physical symptom found in many autism patients is stomach problems. This helps explain where probiotics come into play since probiotics are beneficial in the stomach and intestinal lining of the stomach.[46,50] Research has shown that children with autism have large amounts of bacterium *Clostridium* in their body, which in certain levels can produce toxins that affect the brain. Although it has not been medically determined that bacterium *Clostridium* is indeed the cause of autism symptoms, it appeared that patients that were given probiotics showed improvement. Probiotics are group of live microorganisms including strains of *Bifidobacterium* and *Lactobacillus* as well as several types of yeast, which when ingested improves the balance of the gastrointestinal tract.[51,52] In simpler terms, probiotics can help provide the stomach with enough good bacterial to prevent or minimize the stomach problems characteristic of autistic children such as bloating, stomach pains, constipation, and other bowel problems. Many parents of autistic children are finding that their children have fewer digestive problems when given a daily dose of probiotics. If probiotics can indeed help autistic children with digestive problems, this may help with other symptoms including positive psychological effects. Yeast infections are another problem that affects many children with autism. But regular doses of probiotics seem to balance out the yeast.

Other recent studies on autistic children included the role that probiotics play on behavior and mood. A group of autistic children was brought together and half of them received probiotics while the other half received "fake" probiotics (the parents were not told which one their child was getting). The result of this test was that the parents whose children were getting the real thing saw remarkable behavioral improvements in their children. They possessed better attention span, better focus, and exhibited a better mood in general.[53] Researchers were not sure if the improved mood and disposition was because of the positive psychological effects from the probiotics or if the children behaved better because they simply felt better physically. So, improved psychological effects or improved physical effects. Many feel it does not matter as long as they are showing improvement when using probiotics. There are several reasons that people are interested in probiotics for health purposes. First, the world is full of microorganisms (including bacteria), and so are people's bodies–in and on the skin, in the gut, and in other orifices. Friendly bacteria are vital to proper development of the immune system, to protection against microorganisms that could cause disease, and to the digestion and absorption of food and nutrients.[50]

Interactions between a person and the microorganisms in his body, and among the microorganisms themselves, can be crucial to the person's health and well-being. This bacterial "balancing act" can be thrown off in two major ways: by antibiotics, when they kill friendly bacteria in the gut along with unfriendly bacteria. Some people use probiotics to try to offset side effects from antibiotics like gas, cramping, or diarrhea. Similarly, some use them to ease symptoms of lactose intolerance–a condition in which the gut lacks the enzyme needed to digest significant amounts of the major sugar in milk, and which also causes gastrointestinal symptoms.[52]

Commercial strains sold as probiotics

Table 2 lists some commercial strains currently sold as probiotics. Species are listed as reported by manufacturer, which may not reflect the most current taxonomy. Note that to legitimately be called a "probiotic," strains must have undergone controlled evaluation for efficacy. The purpose of this table is to give the reader a sense of what is commercially available, not provide recommendations for probiotic strain use. Efficacy and safety dossiers should be

Table 2: Characterized probiotic strains and their manufacturers

Strain	Commercial products	Source
L. acidophilus NCFM *B. lactis* HN019 (DR10) *L. rhamnosus* HN001 (DR20)	Sold as ingredient	Danisco (Madison WI)
Saccharomyces cerevisiae (boulardii)	Florastor	Biocodex (Creswell OR)
B. infantis 35264	Align	Procter and Gamble (Mason OH)
L. fermentum VRI003 (PCC)	Sold as ingredient	Probiomics (Eveleigh, Australia)
L. rhamnosus R0011 *L. acidophilus* R0052	Sold as ingredient	Institute Rosell (Montreal, Canada)
L. acidophilus LA5 *L. paracasei* CRL 431	Sold as ingredient	Chr. Hansen (Milwaukee WI)
B. lactis Bb-12	Good Start Natural Cultures infant formula	Nestle (Glendale, CA) Chr. Hansen (Milwaukee WI)
L. casei Shirota *B. breve* strain Yakult	Yakult	Yakult (Tokyo, Japan)
L. casei DN-114 001 ("L. casei Immunitas")	DanActive fermented milk	Danone (Paris, France)
B. animalis DN173 010 ("Bifidis regularis")	Activia yogurt	Dannon (Tarrytown, NY)
L. reuteri RC-14	Femdophilus	Chr. Hansens (Milwaukee WI)
L. rhamnosus GR-1		Urex Biotech (London, Ontario, Canada) Jarrow Formulas (Los Angeles, CA)
L. johnsonii Lj-1 (same as NCC533 and formerly *L. acidophilus* La-1)	LC1	Nestlé (Lausanne, Switzerland)
L. plantarum 299V	Sold as ingredient; Good Belly juice product;	Probi AB (Lund, Sweden); NextFoods (Boulder, Colorado)
L. rhamnosus 271	Sold as ingredient	Probi AB (Lund, Sweden)
L. reuteri ATCC 55730 ("Protectis")	BioGaia Probiotic chewable tablets or drops	Biogaia (Stockholm, Sweden)
L. rhamnosus GG ("LGG")	Culturelle; Dannon Danimals	Valio Dairy (Helsinki, Finland) The Dannon Company (Tarrytown, NY)
L. rhamnosus LB21 *Lactococcus lactis* L1A	Sold as ingredient	Essum AB (Umeå, Sweden)
L. salivarius UCC118		University College (Cork, Ireland)
B. longum BB536	Sold as ingredient	Morinaga Milk Industry Co., Ltd. (Zama-City, Japan)
Lactobacillus paracasei 33	Sold as ingredient	GenMont Biotech (Taiwan)

reviewed to determine adequacy of substantiation by those interested in using these strains.[53]

Safety considerations

As probiotic supplements merely augment and replenish the supply of gut flora that naturally exists in the human body, the potential for adverse reactions is extremely low. However, a 2008 study showed that individuals who suffered from acute pancreatitis had increased rates of death when taking a regimen of probiotics.[54,55] The U.S. Food and Drug Administration do not regulate dietary supplements in the same way it regulates medication. A dietary supplement can be sold with limited or no research on how well it works or on its safety. Always tell your doctor if you are using a dietary supplement or if you are thinking about combining a dietary supplement with your conventional medical treatment. It may not be safe to forgo your conventional medical treatment and rely only on a dietary supplement. This is especially important for women who are pregnant or breast-feeding.[56,57]

When using dietary supplements, keep in mind the following:

- Like conventional medicines, dietary supplements may cause side effects, trigger allergic reactions, or interact with prescription and nonprescription medicines or other supplements you are taking. A side effect or interaction with another medicine or supplement may make other health conditions worse
- Dietary supplements may not be standardized in their manufacturing. This means that how well they work or any side effects they cause may differ among brands or even within different lots of the same brand. The form you buy in health food or grocery stores may not be the same as the form used in research
- The long-term effects of most dietary supplements, other than vitamins and minerals, are not known. Many dietary supplements are not used long-term
- The best part of probiotic therapy is that it is generally considered safe due to the fact that they are already in the digestive system. This also means that probiotics are typically free of side effects, except for people who have an impaired immune function. This is why it is important that if you are going to "self medicate" to address any of the above conditions with probiotics, you talk with your doctor or healthcare provider so that he or she is aware of what you are doing.[58]

Current challenges and future advances

In India, probiotics are often used as animal feed supplements for cattle, poultry, and piggery. This requirement is also met by importing probiotics from other countries. It is rarely used for human beings–Sporolac, *Saccharomyces boulardii,* and yogurt (*L. bulgaricus* + *L. thermophilus*) are the most common ones. Sporolac is manufactured using *Sporolactobacilli*. *Lactobacilli* solution is an example of a probiotic, usually given to pediatric patients in India. The latest and recent addition to the list of probiotics in India is ViBact (which is made up of genetically modified *Bacillus mesentericus*), which acts as an alternate to B-complex capsules. In India, only sporulating *Lactobacilli* are produced and they are sold with some of the antibiotic preparations.

1. Probiotics are well-defined bacterial types administered to the host in sufficient numbers at the end of product shelf life, to confer defined and proven physiological benefits. They are not commensal organisms found in the human gut[56]
2. Probiotics are not genera or species, such as *L. acidophilus* or *L. rhamnosus*. These are simply bacterial types, not probiotics until proven to confer a specific benefit. Products are often called "acidophilus," but *L. acidophilus* is not only reclassified into *Lactobacillus gasseri*, *Lactobacillus crispatus, L. acidophilus, Lactobacillus gallinarum, Lactobacillus amylovorus, and L. johnsonii*, it is neither the dominant constituent of the intestinal microbiota, nor the main *Lactobacillus* species at that site. Furthermore, a review of PubMed and dairy literature fails to show convincing evidence that any strain of *L. acidophilus* meets the FAO/WHO standards of being a probiotic by conferring proven physiological benefits on human beings. *L. acidophilus* NCFM, an organism used extensively in the USA as a "probiotic" in dairy products, has been purported to benefit patients with lactose intolerance, but this is not supported conclusively by human studies. One trial shows alleviation of small bowel bacterial overgrowth, but this needs to be repeated. A *L. acidophilus* strain R0052 used with some success to prevent nectrotizing enterocolitis in newborns is actually a *L. helveticus*. The strain *L. acidophilus* La5 has been shown to confer health benefits, but only in combination with other strains. Meanwhile, *L. acidophilus* L1 lowered serum cholesterol in one treatment period but not the next[57]
3. Viable numbers of probiotic organisms used in a product must be consistent with those tested successfully in a clinical trial. In other words, one cannot add 1 000 colonies of *L. reuteri* SD2112 or another known probiotic which has been shown at a dose of 1 billion colonies to confer benefits, then call the new product a probiotic. If strains are combined, such as *L. rhamnosus* GR-1 and *L. reuteri* RC-14, addition of the second strain must be justified clinically[58]
4. The literature is strewn with experiments on "probiotic" strains, many using *in vitro* adhesion or inhibition assays that do not prove functionality *in vivo*. Until these strains have been shown to fulfill the guidelines and confer health benefits on a host, they should be termed potential probiotic strains or simply bacterial strains[59]
5. Genetically engineered bacteria can be probiotic, if

properly documented. Studies have shown that a vaccine produced using constructs combining epitopes from mutans streptococcal glucosyltransferases and glucan-binding protein B has great potential to interfere with the development of caries. The creation of a *Lactococcus lactis* LL-Thy12 strain expressing human interleukin-10 (IL-10) is a development of potential clinical significance (Braat *et al*., 2006).[60] The replacement of the thymidylate synthase gene with a synthetic sequence encoding mature human IL-10 provides a means to treat inflammatory bowel disease as well as contain the organism due to its inability to survive without exogenous thymidine added. *L. jensenii* recombinants secrete 2-domain CD4 proteins to competitively bind human immunodeficiency virus (HIV), precluding it from attaching to host cells, and secrete Cyanovirin-N, a microbicide designed to inhibit HIV binding. The use of *L. jensenii* 1153 has been claimed to be preferable to *L. lactis, L. plantarum, or L. gasseri*, which have been used by others to secrete cyanovirin-N. However, neither *L. lactis nor L. plantarum* are common inhabitants of the vagina, whereas *L. gasseri* is. In contrast, *L. reuteri* RC-14 has been shown to persist in the vagina for several weeks and 12 recombinant strains have been created, the first using chromosomal integration rather than plasmid expression. These strains secrete three microbicides, PRO 542, a recombinant CD4-immunoglobulin G2, macrophage inflammatory protein 1b (MIP-1b), the normal ligand for CCR5, and T-1249, the "next generation" T-20-like peptide fusion inhibitor that retains activity against T-20-resistant HIV-1. *In vitro* studies showed inhibition of viral entry and killing of the virus. None of the three approaches to anti-HIV recombinants included a suicide gene system, and thus containment is not assured. This raises the question of whether or not all genetically modified bacteria created for human use should have a containment system[61]

6. In order to attain more widespread credibility among the scientific and clinical communities, products must contain speciated strains, sufficiently viable at end of shelf life, and with appropriate label claims. Differences in growth parameters and stress responses are observed among probiotic strains of the same species. Heat and oxygen tolerance, stress resistance, and other factors affect viability. Studies are needed to assess the contributions that different delivery vehicles make to the efficacy of products. For example, dairy foods in which probiotic strains grow will contain metabolic end-products, and it could be these substances, or prebiotic compounds in the milk, that induce biological effects. Likewise, for prebiotics, the necessary quantity and type of substance needed to confer health benefits must be defined in each case. At present, many products contain small amounts of inulin or fructo-oligosaccharides, without the clinical data to show if such amounts are sufficient for health benefits[62]

Conclusions

Probiotic therapy has already made its way in the treatment of number of conditions–infectious, inflammatory, neoplastic, and allergic. There is a long list of potentials of giving probiotics in a number of these conditions. But before bringing probiotics into routine usage, proper evaluation of these products is essential. Several important criteria and standards regarding quality and reliability have to be met. Thus, future well-designed placebo-controlled studies with validated results are required for ascertaining the true health benefits of these products. The important point is careful selection of the probiotic agent, its dose standardization, and a thorough knowledge of its beneficial effects over and above the toxic effects, so that this traditional therapy proves to be an effective tool for medical therapy.

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How to cite this article: Tiwari G, Tiwari R, Pandey S, Pandey P. Promising future of probiotics for human health: Current scenario. Chron Young Sci 2012;3:17-28.

Source of Support: Nil, **Conflict of Interest:** None declared