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ADVANCED ROLES OF PROBIOTIC BACTERIA IN FERMENTED FOODS FOR THEIR HEALTH RELATED EFFECTS ON HUMANS

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ABSTRACT

Probiotics are microbial food supplements that have gain increasingly popular reputation due to the improved scientific evidences of their safe health effects. Food industries have promoted and worked at a broad level to apply them. Probiotics are found to improve nutritional values of food and produce flavored compounds to enhance tastes. From nutritional point of view mainly Lactic acid producing species, *Lactobacilli* and *Bifidobacteria* are considered significant and are available for human use. The non-pathogenic, correctly identified strain with no possible antibiotic resistant gene must be selected for human use. Probiotics having Lactic acid bacteria are accessible in the form of fermented dairy products i.e. yogurt, fermented milks and other foods. Probiotics are considered as a part of a healthy diet for improved immune system and intestinal tract health but in some conditions like immunocompromised individuals, the probiotic testing is limited on the immune system and more confirmation is needed to be done for recommendation of probiotics to such patients. Their benefits can be attained either directly through ingestion of live microorganisms or indirectly by the metabolites produced by these microorganisms. The best use is seen in conditions like bowel disorders, lactose intolerance, antibiotic-associated diarrhea, allergies and some other conditions. In this report, beneficial effects of probiotics on human health, their efficacy in treatment, prevention from diseases, mechanism of action and their availability in different ingestible forms is reviewed.

KEYWORDS: Probiotic Bacteria Health Effects Fermented foods Probiotics.

INTRODUCTION

Probiotics are living microorganisms which improve intestinal microflora when ingested. Probiotic microorganisms are reported to have health-promoting effects on consumers.[1] Good nutrition, health and consumption of 'probiotics' provides balanced microflora in intestine. It is said that 100 g/day of bio-yogurt (106 cfu ml^{-1}) should be consumed. *Lactobacillus* and *Bifidobacterium* are frequently used in commercial products.[2] *Lactobacillus* species including *L. acidophilus, L. johnsonii, L. casei, L. rhamnosus, L. gasseri* and *L. reuteri* have been used to isolate probiotic strains whereas, *Bifidobacterium* species include *Bifidobacterium bifidum, Bifidobacterium longum,* and *Bifidobacterium infantis*. Lactic acid bacteria and yeasts (*saccharomyces*) are usually used to produce fermented dairy products.[3] In common fermented products such as yogurt, the starter culture bacteria are used to produce lactic acid. Probiotics can be ingested in various ways i.e. fermented dairy products, probiotic bacteria enriched foods and consumption of pharmaceutical products. Various studies suggested that probiotics and their fermented products have nutritional benefits to the consumers.[4] The role of probiotic bacteria in dairy products is to add nutritional value to foods and provide special therapeutic properties.[5] Some of the effects and uses of probiotic strains in fermented foods are indicated in Table 1. Most fermented dairy products contain probiotic bacteria especially lactic acid bacteria for lactose fermentation.[6,7] The micro-organisms used in preparation of cultured foods have improved ability to digest some dietary nutrients. A wide range of products with probiotics are available for the use of consumers, dairy products or nondairy products.

Dairy products include fermented milks, yogurt, cheese, ice cream, buttermilk and milk powder whereas, nondairy products include soy based products, nutrition bars, cereals and juices. They are also available in the form of tablets and powders. Fermented milks, cheeses (less frequently) have long been used for intake of probiotics, cheeses may offer more advantages than fermented milks as they have relatively high pH, solid consistency and more fat content.[8,9] Microorganisms might also produce bioactive metabolites called biogenics that enhances health-promoting characteristics in food.[10] Antimicrobial metabolites of bacteria associated with fermented foods are of real concern nowadays.

Table 1. Effects and uses of some probiotic strains

Sr. No.	Bacteria	Probiotic effects	Properties	Use	Reference
1.	*Lactobacillus acidophilus*	fight intestinal infection, reduces intestinal transit time, may prevent colon cancer, may be hypocholesterolemiic	Survives GI transit well. Grows slowly in fermented products	Used in acidophiulus milk and in kefir; may be used in yogurt.	[11]
2.	*Lactobacillus GG*	prevents growth of pathogens, delays tumor development, prevents traveller's diarrhea, antibiotic-associated diarrhea and infant diarrhea	Implants and colonizes the intestinal tract. However, the colonization isn't permanent.	Must have adequate number of cells for colonization in dairy products, enteric tablets and capsules.	[12]
3.	*Lactobacillus casei*	alters activity of intestinal flora, reduces diarrhea, can increase immunoglobulins, γ-interferon, and phagocytic activity, decreases risk of colon cancer	Some strains survive intestinal transit. Does not colonize.	Used in kefir and cheeses (parmesan and cheddar), new yogurt-like products.	[13,45]
4.	*Bifidobacteria*	alters composition of intestinal flora, restrict growth of pathogens, reduces diarrhea, reduces intestinal transit time, reduce colon cancer, increase secretory immunoglobulins	Produce both lactic acid and acetic acid.	May be used in yogurt.	[14]

'PROBIOTICS'

The word 'probiotic' means 'for life'.[15] Probiotics are live micro-organisms with health benefits and have different mode of actions to affect microbiota.[16] The microbial balance of the intestinal tract can be improved using probiotics in the form of food or a supplement.[17] Previously, the general definitions used for probiotics were unsatisfactory as they described probiotics as 'growth stimulating substances produced by protozoa' or 'substances maintaining intestinal microbial balance', the term 'substances' subjected a conflict because substances performing this function are may be antibiotics. Later on, with further investigations probiotics were defined as 'Mono/mixed live culture used to improve indigenous microflora of consumers.[18] The intestinal flora of humans can protect from infectious diseases, a slight disorder of delicate balance of flora can lead to infections such as diarrhea (traveler's diarrhea, antibiotic-associated diarrhea, intestinal infections), gastroenteritis, irritable bowel syndrome, constipation, inflammatory bowel disease (ulcerative colitis and Crohn's disease), food allergies, and certain cancers.[19,20,21] The intestinal immune system is stimulated when enteric microflora compete with pathogenic organisms.[22] Enteric flora is an effectiveness barrier against pathogenic and opportunistic microorganisms.[17] Probiotics have multiple antimicrobial properties against microorganisms i.e. *Escherichia coli*,[23] *Salmonella*,[24] *Listeria* species[25] and *Helicobacter pylori*.[26] The human intestinal tract constitutes more than 400 bacterial species, forming a complex ecosystem of microorganisms.[27] Large intestine has higher bacterial population, considerably lower in small intestine and stomach (due to the low pH). When composition of the intestinal flora is disturbed, pathogens dominate in the intestine and cause infectious diseases. Along ageing, extrinsic factors (bacterial contamination, stress, drugs, diet) and constipation are also responsible for such changes in microflora.[28]

Delivery of probiotic can be done through food products to establish intestinal micribiota. In order to maintain balance of microflora, a huge variety of bio-products are being produce to be consumed as probiotics and most frequently available are fresh milk, fermented milk, beverages, cottage cheese, powdered milk, health foods, ice cream and dairy desserts.[29] Nutritional value of foods can enhanced by using probiotic organisms for example, folic acid is increased by Lactic acid bacteria in fermented foods for instance yogurt and bifidus milk. Similarly, with fermentation niacin and riboflavin levels can be increased in yogurt. While using probiotic bacteria for obtaining beneficial results from fermented foods (bio-yogurt), several factors must be considered. Primarily, to achieve the desired benefits of the probiotics, a viable amount must be consumed. The dose depends upon the type of strain and the product to get the benefits of the probiotic microorganism. A dairy product that is to be consumed must contain 6-7 log cfu g^{-1} viable cells of probiotic. The estimation of ideal amount of probiotics consumption is not easy to determine, different strains have different effects and different quantities are required to get the intended results.

For the production of probiotic products a bacterial strain should follow selection criteria: a) bacteria should have literature evidence, b) Concrete proofs of health assistance c) Ability to colonize and regulate microbial balance in gastrointestinal track, d) Stability to low pH and bile salt to sustain their viability in gastrointestinal conditions, e) Possess natural antimicrobial activity to prevent pathogen growth f) Should be safe and have no antibiotic resistance g) Should be suitable for commercialization h) Should be non-pathogenic i) Sustain processing and storage procedures.[30,31] A probiotic before administration must met a criterion to qualify for being used.[32] The quality, safety of use, characteristics of strain (to adhere, colonize, and poses

health benefits) must be taken under consideration. Probiotics in use for this purpose include lactic-acid bacteria and *Escherichia coli* strains (such as *E. coli* Nissle 1917) and yeast such as *Saccharomyces boulardii* and many others. They are well formulated, have been checked for the quality, safety and efficacy and have maximum of their health benefits to the consumers.

Mode of action

Probiotics have different mode of actions but the exact working conditions are still ambiguous. The micro-organisms improve the measure, accessibility and digestibility of dietary nutrients. They act as bacteriocin, form short fatty acid chains, reduces gut pH, maintain nutrients' competition to stimulate mucosal barrier function and immunomodulation. Antimicrobial action is observed due to the organic acids produced by the probiotics. It reduces the pH and alters the oxidation–reduction potential in the intestine. *Lactobacilli* and *bifidobacteria* shows inhibition of pathogens by producing inhibitory substances i.e. hydrogen peroxide, bacteriocins and antibiotics etc. They act as competitors for adhesion sites and nutrients. It is found that *Bifidobacteria* produces higher amounts of acetic acid than lactic acid which is a strong antagonist against gram-negative bacteria.[33] Probiotics influence some of the factors of acquired and innate immune responses by induction of phagocytosis, modulation of host metabolic activities, IgA secretion and modification of T-cell response. Fig. 1 shows different mechanisms of actions of probiotic microorganisms and their byproducts.

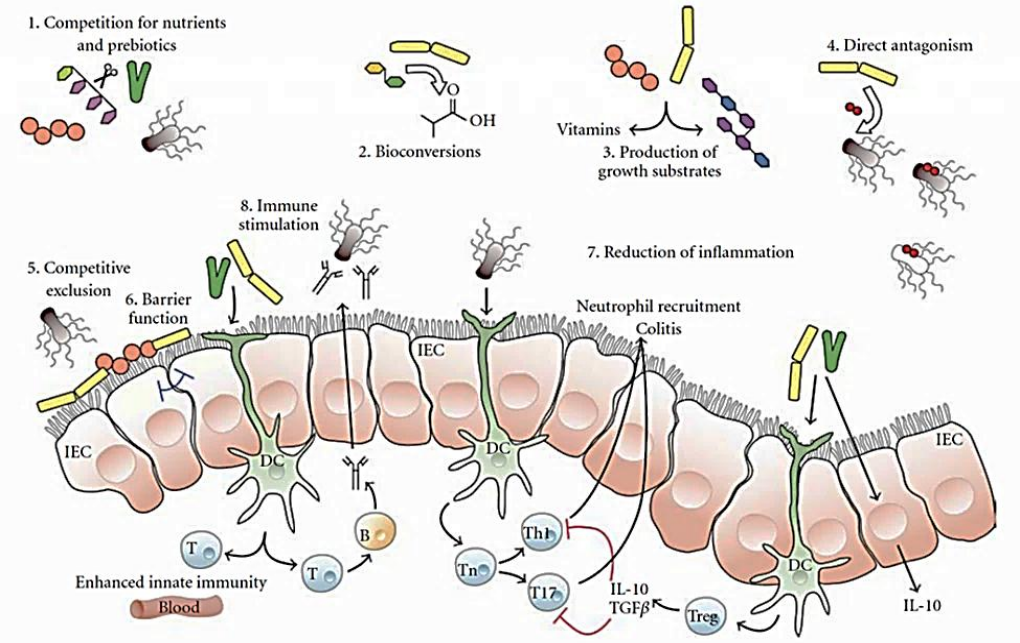

Fig.1 Schematic diagram illustration of Mechanism of action: *Competition for dietary ingredients, bacteriocins, barrier function, reduction of inflammation, stimulate innate immune response*

Important probiotic strains

Some probiotic bacteria and their different strains are listed below in Table 2. that are known and widely used in fermented products globally.

Table 2. Probiotic microorganisms used in fermented dairy products

Sr. No.	Probiotic organisms	Specific strains
1.	Lactobacillus ssp.	*L. bulgaricus, L. cellebiosus, L. delbrueckii, L. acidophilus,L. reuteri, L. brevis, L. casei, Lactobacillus curvatus, L. fermentum, L. plantarum, L. johnsonii, L. rhamnosus, L. helveticus, L. salivarius, L. gasseri*
2.	Bifidobacterium ssp.	*B. adolescentis, B. bifidum, B. breve, B. infantis, B. longum, B. thermophilum, B. lactis*
3.	Streptococcus/ Lactococcus ssp.	*L. cremoris, S. thermophilus, S. intermedius, S. lactis, L. diacetilactis*
4.	Bacillus ssp.	*B. subtilis, B. pumilus, B. lentus, B. licheniformis, B. coagulans*
5.	Pediococcus ssp.	*P. cerevisiae, P. acidilactici, P. pentosaceus*

6.	Bacteriodes ssp.	*B. capillus, B. suis,B. ruminicola, B. amylophilus*
7.	Propionibacterium ssp.	*Propionibacterium freudenreichii* ssp. *Shermanii*
8.	Leuconostoc ssp.	*Leu. Mesenteroides*
9.	Fungus	*A. niger, A. oryzae*
10.	Yeast	*S. cerevisiae, C. torulopsis*

HEALTH EFFECTS OF PROBIOTICS

A number of health effects of probiotics have been reported. Therapeutic effects of probiotics on clinical conditions i.e. diarrhea, gastroenteritis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, *Helicobacter pylori* infections, cancer, lactose intolerance, allergies, hyperlipidaemia, hepatic diseases and others have been studied widely. Only a few of them will be discussed in this paper with significant research. Fig. 2 indicates the summarized form of health effects of probiotics.

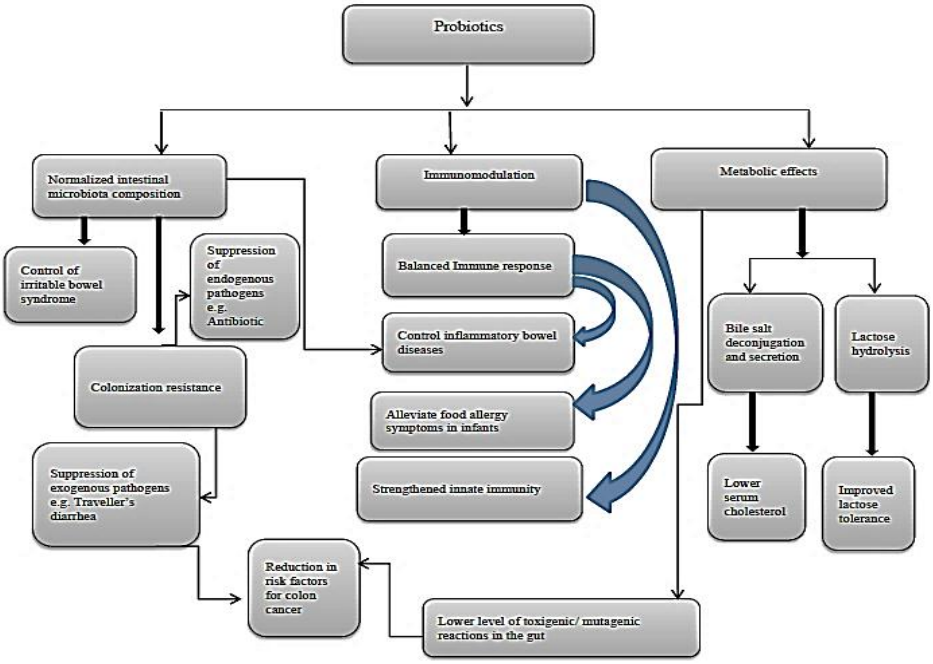

Fig. 2 Health effects of probiotics

Diarrhea infections

Probiotics are well known for diarrheal diseases prevention. *L. acidophilus* and *B. bifidum* shows inhibition towards common known food borne pathogens as they possess antimicrobial properties. Intestinal infections can be controlled by the administration of *L. acidophilus* and *B. bifidum* or both. Milk cultured with *L. acidophilus* or *B. bifidum* is known to have a preventative control against intestinal infections. Significant potential benefit of probiotics is control acute viral, bacterial and antibiotic associated diarrhea. Various enzymes are released by Lactic acid bacteria into the lumen to produce synergistic effect on digestion and are able to alleviate intestinal malabsorption. Lactic acid bacteria reduce pH within enteric tract and inhibit *Salmonella spp., E. coli* and a few major pathogens. Bacteriocins such as nisin produced by probiotics inhibit pathogens.

Strains that have significant benefits against diarrhea (travellers' diarrhea, diarrhea caused by rotaviruses) include *Lactobacillus GG, Lactobacillus reuteri, Lactobacillus casei, Saccharomyces boulardii, Bifidobacteria* spp., *Strep. thermophilus* and others. *Saccharomyces boulardi*, *Lactobacillus rhamnosus* GG and other strains are known to reduce nosocomial diarrhea, antibiotic-associated diarrhea and recurrence of *Clostridium difficile*-associated diarrhea.[19,34,35,36] *B bifidum* and *Streptococcus thermophilus* given to infant formula reduced the frequency of acute infectious diarrhea. Antibiotics may cause mild or severe diarrhea due to the disturbance of normal microflora of the intestine enabling the opportunistic or pathogenic bacteria to overcome. Antibiotic-associated diarrhea caused by *Clostridium difficile* causes diarrhea, vomiting and fever. *L. rhamnosus* and *S. boulardii* can be used for the treatment of antibiotic-associated diarrhea.[37]

Reduction of lactose intolerance

It has been observed that few people are unable to digest lactose because β-d-galactosidase enzyme is absent in the human intestine that causes abdominal discomfort. Lactase insufficiency causes inadequate digestion of disaccharide lactose. Insufficient lactase is caused when lactose-cleaving enzyme β-galactosidase (lactase) is reduced in the mucosa of small intestine. The function of

this enzyme is to hydrolyze lactose that helps to increase tolerance against dairy products.[38] It is found that fermented milk and milk products i.e. yogurt have an ability to competently improve lactose tolerance.

It is believed that microbial β-galactosidase in fermented milk products sustains gastric conditions and is secreted in small intestine by bile salts which enable lactose digestion. It is also stated that short-term or long-term ingestion of the fermented milk products affects the intestinal pH, microflora and lactose fermentation, improving lactose intolerance. Lactic acid bacteria *L. acidophilus* and *B. bifidum* are known to produce β-d-galactosidase so can be used as starter cultures. The beneficial effect appears consequently due to the lactic acid bacteria that increase lactase enzyme activity in small intestine when used in fermented milk.[39,40]

Reduction of blood cholesterol levels and hyperlipidaemia

Cell membranes and nerve cells have cholesterol as major component which is essential for proper functioning of human body. It is thought to be a precursor of some hormones and vitamins. However, risk factor for developing coronary heart disease is considered to be raised in patients with elevated blood cholesterol level and several other blood lipids. Significant reduction in plasma cholesterol level reduces risk of heart attacks. It is claimed that on consumption of fermented milk, serum cholesterol level reduces significantly.[41] Various studies indicate that fermented milk contains a factor that is responsible for the inhibition of synthesis of cholesterol in the human body. *L. acidophilus* is found to deconjugate the bile acids into free acids. This new bile acid can reduce cholesterol level in the body.

Cholesterol metabolism is carried out in the liver, however, also produced in intestines in adequate amounts. Several studies claim that *L. acidophilus* strains and *bifidobacteria* species have potential to reduce intestinal cholesterol levels. In some in vitro studies bacteria eliminated cholesterol in culture media. It is now thought that bile salt hydrolase bacterial enzyme precipitated cholesterol with free bile acids and resulted in cholesterol removal from culture media.[42] Reduction of cholesterol is thought to be due to the lactic acid production by the bacteria that co-precipitates cholesterol with deconjugated bile salts at low pH.[43] The probiotics with cholesterol-lowering potential in humans are of concern for further studies.[44]

Anticarcinogenic activity

Probiotics are considered to the inhibit conversion of procarcinogens to carcinogens by bacteria, alleviate host's immune system or reduce intestinal pH to lessen microbial activity.[33] It is reported in animal models that tumor formation and proliferation is inhibited by the intake of fermented products i.e. yogurt and milks with probiotic bacteria.[43] Experimental facts suggest that recurrence of bladder tumors can be delayed by *L. casei* consumption,[45] but more confirmation evidences are required. Fecal and urinary mutagenicity have been reported to decrease by the consumption of probiotic strains including *Lactobacilli* and *Bifidobacteria*. *Lactobacilli* and *Bifidobacteria* strains reduce the metabolic activation of mutagens and carcinogens by reduction of fecal microbial enzymes; β-glucuronidase, β-glucosidase, nitroreductase, and urease. Studies showed that Lactobacillus GG reduced tumors in artificially induced colon cancer animal models,[46] *B. longum* is found to inhibit the occurrence of colon cancer, liver cancer, small intestine tumors and mammary tumors in rats.[47] Lactic acid bacteria impart important antimutagenic and anticarcinogeinc activity on consumers.

***Helicobacter pylori* infections**

H. pylori is a causative agent of gastritis, peptic ulcers and some studies have reported gastric cancer also. Use of probiotic bacteria can inhibit colonization and *H. pylori* activity within the gastric tract. In a mice model *L. salivarius* was found to produce increased lactic acid and inhibit *H. pylori* colonization.[4] *H. pylori's* urease activity was observed to be reduced due to higher lactic acid production by *Lactobacillus*. Humans consuming *L. johnsonii* showed an inhibition of *H. pylori* infection.[19] In contrast to *L. casei* and also *L. salivarius*, *H. pylori* remained uninhibited in case of *L. acidophilus* mainly due to the low lactic acid production.[48]

Inflammatory bowel disease IBD

Crohn's disease and ulcerative colitis are commonly known as inflammatory bowel disease. Inflammation of mucosa of the colon is known as Ulcerative colitis. It generally starts in rectum and leads to the large intestine. Crohn's disease has a discontinuous pattern and affects the entire gastrointestinal tract. A number of microbes are associated with its pathogenesis including *Mycobacterium paratuberculosis*, measles virus, *Listeria monocytogenes* and adherent *E. coli*. The inflammatory and functional bowel disorders can be regulated by triggering a healthy interaction between the microflora of the intestine and the gut tissues. This can be achieved by using probiotics for healthier gut physiology.[49] *Lactobacilli* may relieve constipation, IBD symptoms, pouchitis and also ulcerative colitis.[50,51] *Sacc. boulardii* decreased the incidence of diarrhea in irritable bowel syndrome whereas, other symptoms remained unchanged.[19]

Immune function

Interaction of the probiotics with the immune system have been broadly studied.[4,52] The immune response can be boosted by synergistic effect of two probiotics i.e. *Lactobacillus* used in combination to *Bifidobacteria*. These effects are facilitated by macrophage activation, cytokines release, enhanced natural killer cell activity and increased immunoglobulins. In a study of immunodeficient euthymic mouse model, disseminated

systemic *Candida albicans* decreased by the administration of *Lactobacillus sp.* and *Bifidobacteria*. HIV infected children are reported to have recurrent diarrhea and face malabsorption because of the bacterial overgrowth more often. *L. plantarum* 299v have been safely administrated to immunocompromised patients that positively affect the immune response, growth and development.

Hypertension

Preliminary evidence indicates that the regular consumption of probiotic bacteria and their fermented products may provide prophylactic effect against heart disease i.e. blood pressure control.[53] Consumption of *L. helveticus* and *Sacc. Cerevisiae* showed reductions in blood pressure in hypertensive patients.[54]

Hepatic disease

Hepatic encephalopathy is a life threatening liver disease. The pathogenesis of Hepatic encephalopathy is unknown but probiotics such as *Strep. thermophilus, Bifidobacteria, Lactobacillus* species and *E. faecum* have shown therapeutic effects in hepatic disorders.[55]

Arthritis

Probiotics causes balance in GI tract by colonizing bacteria and producing several vitamins. Other than GI tract they may have positive influence on joints, lungs, and skin, due to the changes in inflammatory mediators such as cytokines. It is speculated that the use of probiotics can regulate inflammation associated with rheumatoid arthritis.[19] Researchers have observed that in cases of arthritis, oral administration of *Lactobacillus* GG can help in regulation of mucosal barrier mechanisms.[56]

Allergies/Eczema

Probiotics are considered to be effective in patients with eczema and food allergies by the regulation of hypersensitive reactions.[57,58] They can control anti-inflammatory cytokines (interleukin-10) in most of the atopic children.[59] It was suggested that probiotics may provide a helpful tool in treating food allergies by enhancing endogenous mucosal barrier functions of the gut.[4,60] They are also helpful in cases of allergies associated with milk protein intolerance.

Genitourinary tract infections

It is found that vaginal health is correlated with the *lactobacilli* presence.[61] Recently, a study was conducted with cases of recurrent bacterial vaginosis, bacterial cultures were isolated from patients and antimicrobial assay with four different strains of *lactobacilli* was done. It was found that all bacterial species were inhibited by the four strains of *lactobacilli.* It is possibly done by maintenance of acidic environment within the tract. In treatment of urinary tract infections, oral and vaginal administration of probiotics showed significant reduction.[61]

CONCLUSION

There is scientific evidence against use of probiotics as human friendly agents but we are still in developmental phase to produce effective probiotics for human application. Lactic acid bacteria and their byproducts have been seen less toxic and carcinogenic and so are more effectively used. The probiotic containing products have functional benefits of probiotics on humans as well as animals. Dairy products; bio-yoghurt and fermented milks, are important delivery vehicles for probiotic bacteria. In vitro studies shows beneficial effects, but still the uncertainty of recommendation and ambiguity of mechanisms of action is of concern. Viable microorganisms and dosage necessary for health benefits must be given more attention to overcome the limitations of use. Awareness of efficacy, safety and validation of probiotics needs to be established on an international level. Further researches can signify the role of probiotics in nutrition and medicine. More evidences can increase the use of probiotics in food industry and treatment of diseases. Newest species and strains are constantly being identified and genetically modified; the safety of use of such strains should be monitored and regulated accordingly.

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