Probiotics have been with us for as long as people have eaten fermented milk, but their association with health benefits dates only from the turn of the last century, when Metchnikoff drew attention to the adverse effects of some gut microflora on the host, and suggested that ingestion of fermented milk ameliorated this so-called auto-intoxication. In 1965, Lilley and Stillwell used the term ‘probiotic’ to describe them as beneficial micro-organisms. Finally, in 1989 Fuller defined them as ‘A live microbial food supplement which beneficially affects the host animal by improving its microbial balance’.

What is the need for probiotics?

The vast majority (> 90%) of the total cells in the body are present as bacteria in the colon, reaching $10^{12}$ for every gram of large intestinal contents. Under natural conditions, a protective gut microflora develops and there is no need for a bacterial supplement. But the changing food habits and lifestyle force us to take processed and sterile food, which affects our access to, and colonisation, by certain type of bacteria. Moreover, we also consume antibacterial substances ranging from vinegar to antibiotics.

Potential of ‘everyday standard’ food items to promote healthy GI microflora

Some standard food items, e.g., yogurt, sauerkraut, garlic, and cheese contain probiotics in the form of live lactic acid bacteria and/or probiotics in the form of fructans, a dietary fibre. Cheese contains both probiotic bacteria and the prebiotic dietary fibre inulin. The regular consumption of cheese has been associated with a reduction in the risk of Campylobacter enteritis.

Further, cheese is known to contain compounds that reduce the risk of dental caries. In a study by Ahola et al, results from logistic regression showed that short-term consumption of cheese containing Lactobacillus GG and Lactobacillus rhamnosus LC 705 showed a trend indicating that probiotic intervention might reduce the risk of the highest levels of Streptococcus mutants and salivary yeasts.

Currently used probiotics

The majority of probiotics are bacteria with the species of lactobacillus and bifidobacterium being the most common type of bacteria used. Table I shows the list of micro-organisms used as probiotics.

<table>
<thead>
<tr>
<th>A. Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. Lactobacillus: acidophilus, sporogenes, plantarum, rhamnosum, delbrueck, reuteri, fermentum, lactus, celllobiosus, brevis</td>
</tr>
<tr>
<td>ii. Bifidobacterium: bifidum, infantis, longum, thermophilum, animalis</td>
</tr>
<tr>
<td>iii. Streptococcus: lactis, cremoris, alivarius, intermedius</td>
</tr>
<tr>
<td>iv. Leuconostoc</td>
</tr>
<tr>
<td>v. Pediococcus</td>
</tr>
<tr>
<td>vi. Propionibacterium</td>
</tr>
<tr>
<td>vii. Bacillus</td>
</tr>
<tr>
<td>viii. Enterococcus</td>
</tr>
<tr>
<td>ix. E. faecium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Yeast and moulds</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. cerevisiae, A. niger, A. oryzue, C. Pintolopesii, Sacharomyces boulardii.</td>
</tr>
</tbody>
</table>

A bacteria, before being selected as a probiotic, should be non-pathogenic, non-toxigenic, should retain viability during storage and use, should have the capacity to survive and metabolise in the gut, and finally should have documented health effects. L. rhamnosus strain GG meets most of these criteria.
Table II: Indications for probiotics.

<table>
<thead>
<tr>
<th>Proven indications</th>
<th>Possible indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus diarrhoea</td>
<td>Food allergies and lactose intolerance</td>
</tr>
<tr>
<td>Reduction of antibiotic-associated side effects</td>
<td>Atopic eczema</td>
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<tr>
<td></td>
<td>Prevention of vaginitis</td>
</tr>
<tr>
<td></td>
<td>Urogenital infections</td>
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<tr>
<td></td>
<td>Irritable bowel syndrome</td>
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<tr>
<td></td>
<td>Inflammatory bowel disease</td>
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<tr>
<td></td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Traveller’s diarrhoea</td>
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<tr>
<td></td>
<td>Dental caries</td>
</tr>
<tr>
<td></td>
<td>Enhance oral vaccine administration</td>
</tr>
<tr>
<td></td>
<td>H. pylori infection</td>
</tr>
<tr>
<td></td>
<td>Various cancers</td>
</tr>
</tbody>
</table>

Probiotics in Diarrhoea

Saavedra et al showed that supplementation of infant milk formula with *B. bifidum* and *S. thermophilus* reduced rotavirus shedding and episodes of diarrhoea in children in hospital. In a study of HIV associated acute diarrhoea, Saint Marc reported that 56% of patients who were treated with *S. boulardii* had their symptoms resolved compared with only 6% of placebo treated patients. Gorbach et al demonstrated that *Lactobacillus GG* successfully eradicated *C. difficile* in five patients with relapsing colitis, when they were fed viable lactobacilli in skimmed milk daily. Further reduction in incidence of traveller’s diarrhoea has been reported by many studies.

These studies demonstrate that a probiotic can be effective in treating antibiotic induced diarrhoea, diarrhoeal disease acquired during travel, which most likely has a mixed bacterial and viral etiology, and diarrhoeal diseases in young children caused by rotavirus.

Probiotics in lactose intolerance

Kim and Gilliland found that feeding fermented milk to lactose intolerant subjects resulted in a significantly lower level of hydrogen in the breath when compared to the hydrogen level for subjects fed unfermented milk. Hydrogen in the breath is a marker for bacterial metabolism of lactose in the large bowel. A lower hydrogen level indicates that lactose has been metabolised prior to entering the large intestine.

Antimutagenic and anticarcinogenic properties of probiotics

Probiotics can be antimutagenic in several ways. The enteropathogens such as *E. coli* and *Clostridium perfringens* produce enzymes such as beta-glucuronidase, and nitroreductase. Beta-glucosidase and urease can convert procarcinogens to proximate carcinogens. The colonising cells of bifidobacterium produce lactic acid and lower the intestinal pH and create a bactericidal environment for these putative enteropathogens, and thus develop a favourable microenvironment which modulates the bacterial enzymes. Purified bifidobacterial cell wall antitumour activities and induces activation of phagocytes to destroy growing tumour cells. RAS activation represents one of the earliest and most
frequently occurring genetic alterations associated with human cancers, especially carcinoma of colon. Elevated levels of ras P-21 have been correlated with increased cell proliferations, histologic grade, nuclear aplasia and degree of undifferentiation.

Reddy et al demonstrated that dietary B. longum cultures significantly suppressed the expression of total and neonated ras P-21 in the colonic mucosa and tumours compared with control diet.

An additional mechanism of tumour suppression may involve a role for B. Longum as an immunomodulator and biological response modifier. Probiotics also stimulate apoptosis through end-product formation.

**Probiotics and immune enhancement**

The colonic microflora affects mucosal and systemic immunity in the host. Intestinal epithelial cells, blood leucocytes, B and T lymphocytes, and accessory cells of the immune system are all complicated targets for probiotics. The effect is produced either by absorption of a soluble antigen or by translocation of B lactobacilli through the gut wall into the blood stream. Lactobacilli which adhere to human intestinal epithelial cells are capable of activating macrophages.

**Probiotics and irritable bowel syndrome (IBS)**

There have been few studies involving probiotics and IBS. This may be because IBS is a multifactorial condition making it difficult to study homogenous groups of patients. Halpern et al conducted a randomised double blind cross-over trial using Lacteol Fort®, an antidiarrhoeal drug containing 5x10^10 heat killed organisms/capsule of Lactobacllus acidophilus or a placebo. They demonstrated a statistically significant difference in overall GI function, defined by clinical criteria, in the Lacteol group in comparison to those receiving placebo.

**Food allergy and probiotics**

Loskutova et al and Trapp et al in two different studies reported that administration of probiotics was associated with disappearance of food allergy manifestation with decrease in concentration of IgE in the serum and with a lower frequency of allergies. Probiotics, by their potentiating effect on the non-immunologic and immunologic defense barrier of the gut, alleviate the inflammatory response in food allergy. Bifidobacteria and lactobacilli have been shown to enhance IgA production in Peyer’s patches, and potentiate IgA response to potentially harmful antigens. Probiotics reduce the secretion of Th2 cytokines which are IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. These cytokines are responsible for strong antibody (esp IgG and IgE) responses and eosinophilia found in helminthic infections and allergic disorders. Probiotics induce the secretion of IL-12 by activated macrophages. IL-12 increases resistance to intracellular bacteriae and parasites. Lactobacilli modify the immunomodulatory properties of native food protein. Thus, probiotics influence the immune system by activating the lymphoid cells of the gastrointestinal lymphoid tissue.

**Atopic dermatitis and probiotics**

Studies have been conducted to assess the role of probiotics in atopic disease. A study was conducted by Kirjavainen PV et al to assess the efficacy of oral supplementation of viable and heat inactivated probiotic bacteria in the management of atopic disease. The study population included 35 infants with atopic eczema and
allergy to cow’s milk. At a mean age of 5.5 months, they were assigned in a randomised double blind manner to receive either extensively hydrolysed whey formula (placebo group) or the same formula supplemented with viable *Lactobacillus GG* (viable LGG group) or heat inactivated *Lactobacillus GG* (heat inactivated LGG group) respectively. Within the study population, atopic eczema and subjective symptoms were significantly alleviated in all the groups. It was concluded that supplementation of infant formulae with viable but not heat inactivated LGG is a potential approach for the management of atopic eczema and cow milk allergy.

**Probiotics and vaccine adjuvants**

Isolauri *et al* noted an increase in rotavirus specific IgM secreting cells when the children were given *Lactobacillus GG* as an adjuvant to an oral vaccine to rotavirus compared to placebo on 8th post-vaccination day 34. LGG also increased IgA and IgM seroconversion when measured in paired sera measured prior to vaccination, and after 30 days of vaccination.

**Probiotics in vaginitis and other urogenital infections**

Although antimicrobial therapy is generally effective in eradicating urogenital infections, there is still a high incidence of recurrence. There is good clinical evidence to show that the intestinal and urogenital microbial flora have a central role in maintaining both the health and well-being of humans.

**Bacterial vaginosis**

Essentially, bacterial vaginosis is considered as an overgrowth of anaerobic organisms combined with a loss of the protective lactobacilli normally found in the healthy vagina 35. Recently, daily oral intake of probiotic strains *Lactobacillus rhamnosus GR-1* and *Lactobacillus fermentum RC-14*, resulted in asymptomatic bacterial vaginosis patients reverting to normal lactobacilli dominated vaginal microflora 36,37. The mode of action might compromise increased ascension of probiotic and/or indigenous lactobacilli from the rectal skin to the vagina and enhancement of the intestinal mucosal immunity which effects vaginal immunity rendering the environment less receptive to bacterial vaginosis organisms.

**Urinary tract infections**

The basis for use of probiotics emerged from clinical observations in 1973, where a study of healthy women showed an association between lactobacilli presence in the vagina and no history of UTI 38. Extensive studies of various lactobacilli strains led to the selection of a two-strain combination for vaginal use. This comprises distal urethral isolate *L. rhamnosus GR-1*, selected primarily for its anti gram-negative activities and resistance to spermicide and *L fermentum B-54* replaced more recently by RC-14, for anti gram-positive cocci activities and hydrogen peroxide production. In order to optimise a consistent dose with a good shelf life in a formulation preferred by patients, the organisms are freeze dried and placed in gelatin capsules with dosage at 10⁹ per capsule higher than the total microbial content of the vagina 39. Results from various studies indicate that the recurrence rate of UTI can be significantly reduced using one or two capsules vaginally per week for a year with no side effects or yeast infections 39.

**Blood lipids and probiotics**

Since the early work of Mann and Spoerry, probiotics have been reported to have cholesterol lowering properties in humans. The proposed mechanism is that probiotics cause direct assimilation of lipids, convert them into other metabolites and end products, which affects synthesis of cholesterol 40. Many studies have been conducted since then to prove this fact but because of many limitations and confounding factors, none of the studies had sufficient statistical power to detect changes in cholesterol of < 15%. It is clear that if probiotics do have a cholesterol lowering effect, it is a relatively weak one compared with the effect of powerful cholesterol lowering drugs.

**Inflammatory bowel diseases**

The luminal bacterial flora and immunological responses play a major role in initiation and perpetuation of chronic inflammatory bowel disease. Probiotics by their immunomodulatory and bowel flora manipulating properties, show a promising effect in treatment of chronic
inflammatory bowel disease. More clinical trials are needed to evaluate the true place of probiotics within a treatment regimen for chronic inflammatory bowel disease.

**Side effects and safety profile of probiotics**

Cases of infection due to lactobacilli and bifidobacterium are extremely rare and are estimated to represent 0.05 - 0.4% of cases of infective endocarditis and bacteraemia. Of interest, increasing consumption of probiotic lactobacilli and bifidobacteria has not led to an increase in such opportunistic infections in consumers. Immunocompromised patients generally are more vulnerable to infection with pathogens and have a higher incidence of opportunistic infections. However, there is no published evidence that consumption of a probiotic that contains lactobacilli or bifidobacteria increases the risk of opportunistic infection among such individuals. In addition, 2 clinical studies have been conducted to assess the safety of probiotics in small groups of specific immunocompromised patients (e.g., patients with HIV infection), and the findings of these studies support the safety of probiotics consumed by such groups. There is no evidence that ingested probiotic lactobacilli or bifidobacteria pose any risk of infection greater than that associated with commensal strains. In quantitative terms, the existing data suggests that the risk of bacteraemia which is the most commonly reported of these infections is < 1 case per million individuals. It is virtually impossible to propose a risk of death because of the common association of infections involving lactobacilli with fatal underlying conditions or the presence of polymicrobial infections. Vigilance regarding the detection of possible rare cases of infections due to probiotics should be maintained and isolates should be sent to reference centres for molecular characterisation and confirmation.

**References**


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(January - December 2004)

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