



Intelligent Nutrition: Health-promoting Mechanisms of Probiotics

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For centuries yogurt has been regarded as a source for good health, fecundity and longevity. More than 100 years ago, Metchnikoff conducted a series of studies showing that the ingestion of microbes that ferment lactic acid improves numerous ailments including digestive and respiratory disorders. His instrumental studies introduced Balkan dairy products to many homes in Europe and North America in the belief that their consumption will promote health and serve as a natural remedy for many diseases.

Along with the evolving science of nutrition, our perception of food has also changed. In addition to the seminal role our diet has in providing the amount of energy required for the appropriate level of metabolism and growth, we expect today that food will also promote health and contribute to risk reduction of many diseases. Given the "poor" modern nutrition of westernized countries, probiotic food products may provide the elements that are lacking.

Schrezenmeir et al. [1] defined probiotics as "a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alters the microflora by implantation or colonization on a compartment of the host and by that exert beneficial health effects on the host." Microbial colonization of the intestine begins soon after birth. After weaning, the composition of the microflora resembles that of the adult flora. More than 500 different species of different bacteria exist in the intestine. Some of these species are known to be pathogenic by producing toxins, invading the mucosal layer, or enhancing carcinogenesis and inflammatory processes in the gut [2]. Probiotics are beneficial bacteria that reside within the healthy gut microflora. In addition to their proven beneficial traits, probiotic bacteria must be safe for human use, remain viable in the noxious chemical environment of the stomach and bile, and finally adhere to the intestinal mucosa. The most frequently used probiotics belong to the *Lactobacillus* and *Bifidobacterium* species.

Probiotics have been shown to be effective in myriad disorders: antibiotic-associated intestinal disorders, gastroenteritis, traveler's diarrhea, inflammatory bowel disease, irritable bowel syndrome, pouchitis and colon cancer. Moreover, probiotics confer therapeutic effects also on extraintestinal diseases, of which allergies have been the most thoroughly investigated [3,4].

The "hygiene hypothesis" proposes an association between the increase of atopic conditions in developed countries and the relatively aseptic conditions in which children live. In a prospective study of 1,035 infants followed from birth and monitored for the incidence of asthma, the results clearly showed that regular exposure to other children during the first 6 months of life, either at home or in day care, protected against the development of asthma [5]. Interestingly, another study demonstrated that the use of antibiotics by children whose parents had hay fever resulted in future higher rates for the development of allergic diseases in the children [6]. Multiple data indicate that probiotics exert their immunomodulatory effects by altering the cytokine balance towards a Th1-dominant immune system. Many strains of lactobacilli have a subtle inhibitory effect on interleukin-4 production *in vitro*, but at the same time many of them are potent stimulators of Th1 cytokines such as interferon-gamma, interleukin-12 and tumor necrosis factor-alpha [7]. Several studies indicate that yogurt consumption may be associated with enhanced IFN γ synthesis in humans. Subjects who ate any yogurt for 2 weeks had a significant rise in the activity of 2-SA synthetase activity, a specific marker of interferon synthesis [8]. In rats, diet supplementation with 350 g milk or yogurt/kg for 4 weeks resulted in increased IFN γ production and a greater response to bacteria and concanavalin A in Peyer's patches and the spleen [9].

In addition to atopic conditions, several reports tie the use of probiotics to the prevention of urinary tract infections and vaginitis. There is *in vitro* evidence that lactobacilli impede the growth and attachment of uropathogenic *Escherichia coli* to uroepithelium [10,11]. Not surprisingly, several studies found that their use may reduce the frequency of infection rates in humans [12]. Therefore, theoretically, there is a rationale for attempting to reconstitute with probiotic therapy the vaginal lactobacilli flora in women in whom they are low or absent. Another study showed that the daily consumption of yogurt containing *Lactobacillus acidophilus* resulted in a significant decrease of candidal colonization and infection of the vagina [13]. There is some evidence showing that lactobacilli

IFN γ = interferon-gamma

can reduce the risk of infection when they are applied locally, but this finding has yet to be corroborated by further investigations [14]. Hallen et al. [15] researched the effect of vaginal suppositories containing lactobacilli of human origin in 60 women with bacterial vaginosis. The women were randomized to receive two vaginal suppositories, containing either lactobacilli or placebo, or placebo every day for 6 consecutive days. Immediate cure of bacterial vaginosis was recorded in 57% of the women in the probiotic group compared to none in the placebo control group. The efficacy of this treatment modality was sustained even after the menstrual cycle of the following month, and 21% of the treated women remained free of vaginosis.

In this issue of *IMAJ*, Colodner and associates [16] report on the failure of *Lactobacillus rhamnosus* GG to propagate and colonize in the vaginal microflora following the intake for 1 month of yogurt containing the bacteria. As the authors noted, LGG has the ability to synthesize hydrogen peroxidase, which confers their antibacterial effect. However, LGG were found to bind weakly to the uroepithelium [17]. In addition, LGG did not abrogate the adherence of pathogenic bacteria to susceptible sites in the uroepithelium. Yet LGG bound strongly to enterocytes and competed with the binding of pathogenic strains of *E. coli* and *Salmonella* species to the intestinal epithelium [18]. In their study, Colodner et al. [16] chose to use a surrogate marker and the results they present should be regarded accordingly. The clinical data on the use of LGG imply that LGG probably has role in allergic conditions, where it was reported to abrogate casein-induced production of interleukin-4 and to significantly improve the clinical outcome of patients with atopic dermatitis [19].

The mounting evidence on the use of probiotics for different conditions yields numerous and puzzling contradictory results. We have come to acknowledge that probiotics is probably advantageous in different diseases, however we still have a long way to go to fully understand its mechanism of immunomodulation and the multiple chain of events that lead to a sound immune response. The influx of studies expected in the coming years, many of which will be sponsored by the food industry, will most likely clarify some of these issues.

References

- Schrezenmeir J, de Verse M. Probiotics, prebiotics and symbiotic approaching a definition. *Am J Clin Nutr* 2001;73(Suppl):361-4s.
- Salminen S, Bouley C, Boutron-Ruault MC, et al. Functional food science

and gastrointestinal physiology and function. *Br J Nutr* 1998;80(Suppl): S147-71.

- Marteau PR. Probiotics in clinical conditions. *Clin Rev Allergy Immunol* 2002;22:255-74.
- Chermesh I, Eliakim R. Probiotics – scope and promise in inflammatory bowel disease. *IMAJ* 2002;4:353-6.
- Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;343:538-43.
- Droste JH, Wieringa MH, Weyler JJ, Nelen VJ, Vermeire PA, Van Bever HP. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy* 2000;30:1547-53.
- Borchers AT, Keen CL, Gershwin ME. The influence of yogurt-Lactobacillus on the innate and acquired immune response. *Clin Rev Allergy Immunol* 2002;22:207-30.
- Solis-Pereyra B, Aattouri N, Lemonnier D. Role of food in the stimulation of cytokine production. *Am J Clin Nutr* 1997;66:521-5S.
- Aattour N, Bouras M, Tome D, Marcos A, Lemonnier D. Oral ingestion of lactic-acid bacteria by rats increases lymphocyte proliferation and interferon-gamma production. *Br J Nutr* 2002 87:367-73.
- McGroarty JA Reid G. Detection of a Lactobacillus substance which inhibits *Escherichia coli*. *Can J Microbiol* 1988;34:974-8.
- Velraeds MC, van der Belt B, van der Mei HC, Reid G, Busscher HJ. Interference in initial adhesion of uropathogenic bacteria and yeasts silicone rubber by a Lactobacillus acidophilus biosurfactant. *J Med Microbiol* 1998;49:790-4.
- Reid G, Bruce AW, Taylor M. Instillation of Lactobacillus and stimulation of indigenous organisms to prevent recurrence of urinary tract infections. *Microecol Ther* 1995;23:32-45.
- Hilton E, Isenberg HD, Alperstein P, France K, Borenstein MT. Ingestion of yogurt containing Lactobacillus acidophilus as prophylaxis for candidal vaginitis. *Ann Intern Med* 1992;116:353-7.
- Reid G, Burton J. Use of Lactobacillus to prevent infection by pathogenic bacteria. *Microbes Infect* 2002;4:319-24.
- Hallen A, Jarstrand C, Pahlson C. Treatment of bacterial vaginosis with lactobacilli. *Sex Transm Dis* 1992;19:146-8.
- Colodner R, Edelstein H, Chazan B, Raz R. Vaginal colonization by orally administered *Lactobacillus rhamnosus* GG (LGG). *IMAJ* 2003;5:767-9.
- Velraeds MM, van de Belt-Gritter B, Busscher HJ, Reid G, van der Mei HC. Inhibition of uropathogenic biofilm growth on silicone rubber in human urine by lactobacilli – a teleologic approach. *World J Urol* 2000;18:422-6.
- Lee YK, Puong KY. Competition for adhesion between probiotics and human gastrointestinal pathogens in the presence of carbohydrate. *Br J Nutr* 2002;88(Suppl)1:S101-8.
- Sütas Y, Hurme M, Isolauri E. Downregulation of antiCD3 antibody-induced IL-4 production by bovine caseins hydrolysed with *Lactobacillus* GG-derived enzymes. *Scand J Immunol* 1996;43:687-9.

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