PROBIOTICS AS NATURAL HEALTH PRODUCTS

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Probiotics

It has been nearly a century since Metchnikoff postulated that lactic acid bacteria offered health benefits leading to health and longevity[1]. Since that time, the concept of probiotics has advanced dramatically[2] and probiotics are becoming an increasingly important functional food and NHP.

Probiotics have been defined as live microorganisms that when ingested in appropriate quantities, have a beneficial effect in the prevention and treatment of specific medical conditions by improving the host's intestinal microbial balance[3]. These microorganisms are believed to exert biological effects through colonization resistance, whereby the indigenous anaerobic flora limits the concentration of potentially harmful (mostly aerobic) germs in the digestive tract. Other modes of action, such as supplying enzymes or influencing enzyme activity in the gastrointestinal tract, may also account for some of the other functions that have been attributed to probiotics.

Promising probiotic strains include members of the genera *Lactobacillus*, *Bifidobacterium*, and *Enetrococcus* and the species of most interest for efficacy testing and in the market include *Lactobacillus acidophiulus, L. johnsonii, L. Casei, L. gasseri, L. plantarum, L. rhamnosus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Enterococcus faecalis and Enterococcus faecium*[4].

Among the accepted criteria for isolating and defining probiotic bacteria[5] are:

- Human origin;
- Resistance to acidity and bile toxicity;
- Adherence to human intestinal cells;
- Colonization (even transiently) of the human gut;
- Antagonism against pathogenic bacteria;
- Production of antimicrobal substances;
- Immune modulation properties;
- Clinically proven health effects (dose-response data); and
- History of safe use in humans.

Probiotics in health maintenance and disease prevention

Probiotics have been investigated in relation to a number of health concerns, including atopic eczema[6], vaginal yeast infections[7], rheumatoid arthritis[8] and liver cirrhosis[9]. Although there is

[1] Metchnikoff E. The Prolongation of Life. New York, NY, Putnam Sons, 1908.
[2] Reid G, Jass J, Sebulsky MT, McCormick JK. 2003. Potential uses of probiotics in clinical practice. Clin. Microbiol. Rev. 16:658-672.
[3] Fuller, R. 1989. A review: Probiotics in man and animals. J Appl. Bacteriol. 66, 365-378.
[4] Kaaur IP, Chopra K, Sainni A. 2002. Probiotics: potential pharmaceutical applications. Eur. J. Pharm. Sci. 15:1-9.
[5] Brassart D and Schiffrin EJ. 2000. Pre-and probiotics. In: Essentials of Functional Foods. Schmidl MK, Labuza TP (Eds.) Aspen Publishers, Gaithersburg, MD, pp. 205-216.

some clinical evidence for the role of probiotics in lowering cholesterol, the results are conflicting[10]. The greatest clinical evidence for probiotic use is related to its use in improving gut health and stimulating immune function[11].

Probiotics and improved gut function

The intestine is the body's most important immune function-related organ: approximately 60 % of the body's immune cells are present in the intestinal mucosa. The intestine also contains extensive microflora – 100,000 billion bacteria located mainly in the colon and comprising over 400 species of bacteria[12].

Of the many functions of the intestine, immune functions are particularly important. The immune system prevents immune responses against dietary proteins - prevention of food allergies - and against pathogenic microorganisms, viruses (rotavirus, polio virus), bacteria (*salmonella*, *listeria*, *clostridium*, etc.) and parasites (toxoplasma) - prevention of chronic inflammatory diseases of the intestine.

Probiotics affect intestinal bacterial flora by increasing anaerobic bacteria and decreasing the population of potentially pathogenic microorganisms. This phenomenon can reduce the incidence of diarrhea, which is one of the most well recognized uses for probiotics and has been documented with a number of specific strains, including *Lactobacillus* GG, L. *reuteri*, *Saccharomyces boulardii*, Bifidobacteria species and others[13]. Probiotics may also reduce the risk of colon cancer, likely due to their role in suppressing the activity of certain bacterial enzymes that may increase the levels of procarcinogens[14]. Well-designed, randomized clinical studies are still required to define the role of probiotics as therapeutic agents in inflammatory bowel disease[15].

Probiotics and immune modulation

One of the putative effects of probiotics is the modulation of immune function. Specific cellular components in lactic acid bacteria strains seem to induce strong adjuvant effects including modulation of cell-mediated immune responses, augmentation of cytokine pathways and regulation of interleukins, and tumor necrosis factors. Probiotics such as *Lactobacillus acidophilus* and *Bifidobacterium bifidum* have been shown to influence select aspects of immune function involving one or several components of an immune response, e.g., humoral, cellular or

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[6] Kalliomäki M, Salminen S, Poussa T, *et al.* 2003. Probiotics and prevention of atopic disease: 4-year follow-up of a randomized placebo-controlled trial. The Lancet 361: 1869-1871.

[7] Reid G, Jass J, Sebulsky MT, McCormick JK. 2003. Potential uses of probiotics in clinical practice. Clin. Microbiol. Rev. 16:658-672.

[8] Hatakka K, Martio J, Korpela M et al. 2003. Effects of probiotic therapy on the activity and activation of mild rheumatoid arthritis--a pilot study. Scand J Rheumatol. 32:211-215.

[9] De Santis A, Famularo G, De Dimone C. 2000. Probiotics for the hemodynamic alterations of patients with liver cirrhosis. Am. J. Gastroenterol. 95: 323-324.

[10] De Roos NM, Katan MB. 2000. Effects of probiotic bacteria on diarrhea, lipid metabolism, and carcinogenesis: a review of papers published between 1988 and 1998. Am. J. Clin. Nutr. 71:405-411.

[11] Farnworth ER. 2001. Probiotics and prebiotics. In: Handbook of Nutraceuticals and Functional Foods. Wildman REC (Ed.), CRC Press, Boca Raton, FL, pp. 407-422.

[12] Tuohy RM, Probert HM, Smejkal CW, Gibson GR. 2003. Using probiotics and prebiotics to improve gut health. Drug Disc. Today 8: 692-700.

[13] Drisko JA, Giles CK, Bischoff BJ. 2003. Probiotics in health maintenance and disease prevention. Alternative Med. Rev. 8:143-155.

[14] Rafter J. 2003. Probiotics and colon cancer. Best Pract. Res. Clin. Gastroenterol. 17:849-859.

[15] Tamboli CP, Caucheteux C, Cortot A *et al.* 2003. Probiotics in inflammatory bowel disease: a critical review. Best Pract Res Clin Gastroenterol.17:805-820.

nonspecific immunity. Although several in vitro and in vivo studies on probiotic effects on immunity have been reported, the specific mechanisms of the observed changes remain unclear and very few human intervention studies have been reported[16].

Some dietary substances, the so-called "**prebiotics**" can favor the growth of beneficial bacteria over that of harmful ones. The concept of prebiotics is relatively new and has recently been defined as nondigestible food ingredients that beneficially affect host health by selectively stimulating the growth and/or activity of bacteria in the colon[17]. The prebiotic, fructooligosaccharide (FOS), is found naturally in many foods, such as wheat, onions, bananas, honey, garlic, or leeks. They can also be isolated from chicory root or synthesized enzymatically from sucrose.

Fermentation of FOS in the colon results in a large number of physiologic effects including increasing the numbers of bifidobacteria in the colon, increasing calcium absorption, increasing fecal weight, shortening of gastrointestinal transit time, and possibly lowering blood lipid levels. The increase in bifidobacteria has been assumed to benefit human health by producing compounds to inhibit potential pathogens, by reducing blood ammonia levels, and by producing vitamins and digestive enzymes. A **synbiotic** product exerts both a prebiotic and probiotic effect.

NHP Approval of Probiotics

The *NHP Regulations* define a probiotic as a monoculture or mixed-culture of live micro-organisms that benefit the microbiota indigenous to humans[18]. A probiotic is limited to non-pathogenic microorganisms. An example is *Lactobacillus acidophilus*.

Although the safety of traditional lactic acid bacteria is not in question, the more recent use of intestinal isolates of bacteria delivered in high numbers to consumers with potentially compromised health has raised the question of safety. Generally, the safety of lactobacilli and bifidobacteria has been reviewed and their pathogenic potential deemed to be quite low. This is based on the prevalence of these microbes in fermented food, as normal colonizers of the human body, and the low level of infection attributed to them[19].

Such toxicology and safety issues have been recognized within the *NHP Regulations* and the NHPD does require evaluation unique to probiotics. According to the *Regulations*, unlike other NHPs, conventional toxicology and safety evaluation is not sufficient to evaluate the safety of probiotic microorganisms as noted[20]:

A probiotic is meant to survive or/and grow in order to benefit humans, which makes the use of these tests ineffective for probiotics. Therefore, a multi-disciplinary approach is necessary to examine the pathological, genetic, toxicological, immunological, gastro-enterological, and microbiological aspects of the safety of probiotic strains. These requirements were mainly based

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[16] De Roos NM, Katan MB. 2000. Ibid.

[17] Gibson G.R., Beatty E.B., Wang X., Cummings J.H. 1995. Selective stimulation of *bifidobacteria* in the human colon by oligofructose and inulin. Gastroenterology. 108: 975-982.

[18] Food and Drugs Act. Natural Health Product Regulations. http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpdpsn/regs_cg2.pdf

[19] Reid G, Jass J, Sebulsky MT, McCormick JK. 2003. Potential uses of probiotics in clinical practice. Clin. Microbiol. Rev. 16:658-672.

[20] Food and Drugs Act. Natural Health Product Regulations. Additional Requirements for Probiotics. http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/overview_nhp_regs_e.html#1

on FAO/WHO's "Guidelines for the evaluation of probiotics in food-Report of a joint FAO/WHO working group on drafting guidelines for the evaluation of probiotics in food."[21]

Certain probiotic bacteria have been associated with human illnesses and/or have a high risk of developing antibiotic resistance and are not suited for use as probiotics. Products containing the following strains or species will be rejected as NHPs without further consideration:

- *Bacillus cereus*
- *Bacillus clausii* CNCM MA23/3V & CNCM MA66/4M
- *Enterococcus spp.*
- *Bifidobacterium dentium*
- *Lactobacillus plantarum* CNCM MA40/5B-p
- *Parascardovia denticolens*
- *Pediococcus acidilactici* CNCM MA28/6B
- *Scardovia inopinata*

Within the *NHP Regulations*, there are a number of safety considerations that must be addressed with regard to probiotics.

A. Antibiotic resistance profile

As with any bacteria, antibiotic resistance exists among some probiotic bacteria. The resistance may be related to chromosomal, transposon or plasmid genes. Bacteria containing transmissible resistance genes, especially to antibiotics important in human medicine, should not be used as probiotics.

B. Production of antibiotics

Bacterial strains confer resistance to antibiotics by producing enzymes that chemically modify structures of certain antibiotics; develop antibiotic resistance by mutation in the presence of the drug and may produce antibiotics. Such strains should not be used as probiotics.

C. Pathogenic potential

Organisms not commonly used or without a long history of use need to be tested for pathogenic potential and should be demonstrated to be free of virulent factors and toxin production. If the strain under evaluation belongs to a species with known hemolytic potential, determination of hemolytic activity is required.

D. Metabolic activities

Certain strains produce metabolites such as D-lactate and bile salt deconjugase which may cause problems in human physiology so these strains should not be used as probiotics.

Efficacy Considerations

As with other NHPs, pre-clinical experiments using animal models are encouraged before proceeding to human clinical trials. In order for probiotic strains to be efficacious, it is important for them to meet and maintain certain criteria, including minimum daily dose, acid and bile stability, intestinal mucosal adhesion properties, and viability throughout product shelf life. Special technologies are required to prevent loss of viability and may include freeze drying, selected excipients to control water activity, enteric coating for protection against gastric acidity and microencapsulation.

[21] FAO/WHO. 2002. Guidelines for the evaluation of Probiotics in Foods. www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf

Dietary Recommendations for Probiotics

The amount of probiotics necessary to replenish the intestine varies according to the extent of microbial depletion and the presence of harmful bacteria. One to two billion viable organisms per day of acidophilus is considered to be the minimum amount for the healthy maintenance of intestinal microflora[22].

[22] Reid G, Jass J, Sebulsky MT, McCormick JK. 2003. Potential uses of probiotics in clinical practice. Clin. Microbiol. Rev. 16:658-672.