



# HerbClip™

Mariann Garner-Wizard  
John Neustadt, ND  
Cathleen Rapp, ND

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**FILE: ■Probiotics  
■Mechanism of Action**

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**RE: Probiotics and Their Mechanisms of Action**

Michail S. The mechanism of action of probiotics. Vanderhoof JA, series editor. Probiotics: the Hope, the Hype, and the Reality, Series #2. *Practical Gastroenterology*. May 2005:29,33-34, 41-42, 44, 47.

Use of fermented foods and cultured milk products containing live microbes predates written history, but the observation that increased health and longevity of Bulgarian peasants were associated with frequent consumption of sour milk containing *Lactobacillus bulgaricus* was not made until the early 20th century. Probiotics are live microbial foods which benefit the consuming host. Successful probiotics must: 1) be able to colonize the host's intestine; 2) be able to survive and resist exposure to high pH and bile acids; 3) be able to adhere to the intestinal epithelium; 4) be nonpathogenic and nontoxic; 5) provide benefit to the host; 6) be human-specific organisms (except, one supposes, veterinary probiotics); and 7) be stable in storage.

Michail examines numerous mechanisms of action which various probiotic organisms have been observed to exert in various in vitro, animal, and human studies. These are grouped, although with some overlap, into antimicrobial effects; effects on the epithelium, mucus production, and barrier function; immune effects; effects on allergies; effects on distant mucosal sites; and antiproliferative effects (Figure 1).

Probiotics' antimicrobial effects have been most studied. The best-known effects are upon the microflora of the gut. Several probiotics seem to decrease fecal concentrations of clostridia and *Bacteroides* spp., and *Escherichia coli*, by increasing endogenous levels of lactobacilli and bifidobacteria. Many probiotics produce antimicrobial factors, for example, short chain fatty acids, which lower colonic pH, favoring the growth of less pathogenic flora. They also produce bacteriocins, antimicrobial proteins which are especially effective against gram-positive organisms. *Lactobacillus* GG inhibits growth of both gram-positive and gram-negative bacteria, producing antibacterial substances such as lactic acid, hydrogen peroxide, and pyroglutamate. *L. acidophilus* LA1 produces a non-bacteriocin, non-lactic acid antimicrobial which is effective against a wide variety of organisms. Probiotics also compete

with pathogens in adhering to the epithelium. Certain lactobacilli can even block receptors, preventing adhesion of pathogens. In addition to space on the intestinal lining, probiotics may compete with pathogens for nutrients. Consumption of monosaccharides by a probiotic, for example, may inhibit growth of *C. difficile*, which needs these sugars for growth. Finally, probiotics may modify toxin receptors through enzymatic action. Similar effects are postulated for the cholera toxin receptor. Probiotic colonies in animal studies have allowed the host to withstand "lethal doses" of pathogens such as *Salmonella enteritidis* (Table 1).

Similarly, numerous effects of probiotics on the epithelium itself, on mucus production, and on barrier function have been observed. These range from the protective effect of *L. plantarum* 299V on epithelial cells against damage from a specific *E. coli* to enhanced activation of tight junction proteins, which mitigates against leaky gut syndrome. *L. bacillus* GG can prevent inflammation and programmed cell death of epithelial cells. Both decreased mucosal permeability and increased mucus production have been observed with probiotic use. Increased *MUC2* and *MUC3* mRNA expression, in response to lactobacilli, protects epithelial cells against adhesion by pathogens. *S. boulardii* increases brush border enzymes in jejunal mucosa and, through its own production of polyamines, may enhance intestinal enzyme expression (Table 2).

Effects of probiotics on the immune system and response are quite varied. These may not depend upon colonization or upon probiotic metabolites, but be mediated by their own DNA, affecting molecular signaling within cells. In one study, probiotics both inhibited the pro-inflammatory nuclear factor kappaB pathway and triggered expression of protective heat shock proteins in intestinal cells, while simultaneously producing factors to protect these proteins. Production of proteasomes, intracellular protein destroyers, was inhibited almost as soon as colon cells were exposed to the probiotic in this study. This may be a novel method of microbial-epithelial interaction. Probiotics have shown strong, consistent ability to induce specific antibodies.

Not all probiotics have similar immunomodulatory effects, and may even act in opposing ways. Even the same probiotics, at different doses, may exert varying effects. In a study of colitis, probiotics reduced severity through increased IL-10 production and increased CD4(+)T cells bearing surface TGF- $\beta$ . Probiotics increase innate immunity. In a clinical trial involving 45 healthy volunteers, consumption of *L. casei* DN114001 increased oxidative burst capacity of monocytes as well as natural killer cells' anti-tumor activity. In healthy subjects, probiotics appear to stimulate immune response, while in hypersensitive subjects, they down-regulate response. Finally, the authors note that lactobacilli may be genetically engineered to secrete anti-inflammatory substances, such as IL-10, and deliver them to sites in the gastrointestinal (GI) tract.

Related to their immunomodulatory effects, probiotics affect allergic reactions at the level of immune cells and the intestinal lumen as well as epithelial cells. Improved barrier function, down-regulation of immune response, both at the local GI site and at distant mucosal sites, and allergic degradation all benefit allergy patients. In a double-blind, placebo-controlled study, *Lactobacillus* GG relieved atopic eczema in IgE-sensitized infants. Lactobacilli can inhibit secretion of T(H)2 cytokines (IL4 and IL5), shifting the balance to T(H)1, which

benefits those with allergies. In children with atopic dermatitis, probiotics may stabilize barrier function and reduce GI symptoms. They may reduce CD34+ hemopoietic precursor cells in subjects with systemic allergic inflammation, and increase secretion of IFN-gamma in infants who are allergic to cow milk. Some *Lactobacillus* and *Bifidobacterium* strains show promise in treating and preventing pediatric eczema and dermatitis, apparently through altered immune response rather than altered microflora population.

Probiotics can modulate intestinal functions such as detoxification, colonic fermentation, transit, and immune status, which may affect development of colon cancer. Probiotics have shown direct antiproliferative effects on tumor and immune cells. In animal studies, reduced carcinogenic enzymes, and probiotic-modulated gut and systemic immunity, have been found to be potentially significant anticancer factors.

*Lactobacillus* GG was recently reported to have "modest but consistent benefits" in preventing and reducing severity of respiratory infections at day care centers. Other effects of probiotics on distant mucosal sites are touched on only cursorily.

Side effects and contraindications to probiotics are not discussed in the article, but Michail does mention an infant study in which the colonization ability of the probiotic was reduced by prior exposure to antibiotics. Michail closes by urging continued research on probiotics' effects and mechanisms.

— *Mariann Garner-Wizard*

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