

## 2 The Health Professional's Guide to Popular Dietary Supplements

### Acidophilus/*Lactobacillus Acidophilus* (LA)

*Lactobacillus acidophilus* (LA) is the scientific name for a heterogeneous group of lactic acid bacteria including gram-positive rods and cocci that use carbohydrates for energy and in the process produce lactic acid, hydrogen peroxide, enzymes, and B vitamins via fermentation of food and dairy products. These bacteria normally colonize the gut. LA is one of many strains of lactic acid bacteria, found in the human gastrointestinal tract, that seems to play a role in stimulating the immune response and in combating intestinal and foodborne pathogens. Within the LA species, there also exist individual strains, each with differing actions. After being ingested, LA withstands the stomach pH and travels to the lower intestine. Some portion of a bacterial load may adhere to the epithelium and thus potentially help defend the host against harmful bacteria. Antibiotics, oral contraceptives, physical stress, and malnutrition may affect the delicate balance of microflora in the intestine. Some researchers suggest that recolonizing the gut with LA and other *Lactobacillus* bacteria (via food or supplements) will create a healthy microflora and reduce gastrointestinal symptoms and vaginal infections associated with harmful bacteria overgrowth (1–3).

Media and Marketing Claims	Efficacy
Reduces lactose intolerance	NR
Prevents or reduces length of vaginal yeast infections	↔ (LA yogurt) NR (LA supplements)
Helps control rotaviral diarrhea (LA GG)	↑
Prevents antibiotic-associated diarrhea and traveler's diarrhea	↔
Controls irritable bowel symptoms	↓
Reduces cholesterol	↔
Prevents cancer	NR
Prevents or reduces severity of atopic disease (allergies, eczema, etc)	NR

### Safety

- ◆ There have been no reports of any adverse effects in human studies supplementing LA at dose levels of  $10^{10}$  or  $10^{11}$  colony-forming units/day. In addition, various LA products (milk, yogurt, sweet acidophilus milk) have been on the market for decades with no reports of bacteremic infections (4).
- ◆ Two case reports have been published of LA sepsis related to probiotic therapy among immunocompromised children, indicating a need to further monitor use of LA supplements (5). In addition, some authors suggest that immunosuppressed patients should avoid use of LA (or other probiotic) supplements (6).
- ◆ Short-bowel syndrome may predispose an individual to pathogenic infection; use LA supplements with caution.

## Drug/Supplement Interactions

- ◆ LA may have a positive effect on gut flora when administered with antibiotics.
- ◆ Separate ingestion of LA and antibiotics by at least 2 hours to avoid possibility of decreasing the effectiveness of LA.

## Caution

Some products may contain little or no LA, and some may contain other strains of lactobacilli or contaminants.

## Key Points

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- ◆ There is conflicting evidence as to whether LA-cultured dairy products may improve absorption of lactose and reduce symptoms such as cramps and diarrhea in individuals with lactose intolerance. Currently, different strains of LA are being tested for their relative effectiveness.
- ◆ There is preliminary evidence that LA-cultured yogurt (2 cups/day) may reduce episodes of vaginal infections. Evidence does not support that LA supplements either prevent antibiotic use-related vaginitis or bacterial vaginitis. However, one study demonstrated the effectiveness of yogurt cultured with LA in reducing the recurrence of bacterial vaginosis (7). Women with vaginitis may wish to try LA-cultured dairy products, not only for their potential ability to improve the infection, but also because they are good sources of calcium, which is important for women's health in general.
- ◆ As discussed in several review articles, LA and other probiotic bacteria administered in dairy products or supplements (particularly LA plantarum) may reduce diarrhea associated with antibiotic use and *Clostridium difficile* and other pathogens. Oral LA GG can prevent traveler's diarrhea, but efficacy varies depending on the country of exposure. Diarrheal events in children, including rotaviral diarrhea, seem particularly responsive to oral LA GG supplementation.
- ◆ In general, studies have not found that LA supplementation reduces symptoms associated with irritable bowel syndrome. However, in one preliminary study, *Bifidobacteria* (another probiotic often included in LA supplements) did show some benefit in people with IBS. Better controlled research in larger samples is needed before recommendations can be made.
- ◆ There is preliminary evidence that dairy products fermented with LA may reduce cholesterol levels in subjects with and without hyperlipidemia. Larger controlled trials testing LA foods and supplements are needed to verify this lipid-lowering effect.
- ◆ There is no clear evidence that LA plays a role in cancer prevention; however, theoretically maintaining a healthy gut microflora may be important to optimal immune function and gut integrity, both important to reducing cancer risk. No clinical studies have specifically tested the influence of LA dairy products or supplements on biomarkers of

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cancer in humans. Preliminary evidence suggests that LA supplementation may reduce *Helicobacter pylori* viral load and thus indirectly reduce risk for gastric cancer—further research is warranted.

- ◆ Preliminary research has found that the use of *Lactobacillus rhamnosus* GG strain by women during late pregnancy and early lactation may reduce inflammatory biomarkers present in the breastmilk and the incidence of atopic eczema in newborns with a family history of these illnesses.
- ◆ Conflicting data regarding efficacy of LA may be a result of differing experimental designs, differing *Lactobacillus* strains, variations in preparation and storage of LA, and the use of nonviable bacteria in studies (8). The strongest evidence to date is related to the use of LA GG strain.

### **Food Sources**

Yogurt containing live LA cultures, kefir, and acidophilus milk

### **Dosage Information/Bioavailability**

LA supplements are sold in powders, tablets, or capsules, often with other *Lactobacilli* (*L casei*, *L delbrueckii*) or *Bifidobacteria* (*B adolescentis*, *B bifidum*, *B longum*, *B infantis*). Dosages are expressed in millions or billions of viable bacteria. Most manufacturers recommend taking 1 billion to 10 billion viable LA cells daily, but up to 100 billion live bacteria daily has been safely administered to children with diarrhea, and lower doses are sometimes ineffective. LA supplements must be used by the expiration date (usually 1 year for freeze-dried) and some require refrigeration to maintain viability.

### **Relevant Research**

#### *LA and Lactose Intolerance*

- ◆ During fermentation of yogurt and acidophilus milk, *Lactobacilli* produce lactase, which hydrolyzes milk lactose to glucose and galactose. Thus, up to 50% of lactose in acidophilus milk and yogurt is predigested by lactase during the fermentation process, which potentially reduces symptoms associated with lactose ingestion in intolerant individuals (9).
- ◆ Several studies have demonstrated that fermented dairy products (acidophilus milk, yogurt [not pasteurized or heated]) are absorbed better (as measured by breath hydrogen) and are associated with fewer intestinal symptoms than nonfermented dairy foods (2,9).

#### *LA and Intestinal Infections*

- ◆ Possible mechanisms for the protective role of LA against intestinal and vaginal disorders include (a) LA forms antimicrobial compounds such as lactic acid; acetic acid;

hydrogen peroxide; broad-range, antibiotic-like compounds, and bacteriocins that inhibit the growth of pathogenic bacteria; (b) LA byproducts such as short-chain fatty acids reduce pH and inhibit pathogenic organisms; and (c) LA competes with pathogenic bacteria for nutrients and adhesion sites (1,9).

- ◆ A detailed review in *JAMA* evaluated all available placebo-controlled, human studies of supplementation with biotherapeutic agents (*L. acidophilus*, *Bifidobacterium longum*, *Lactobacillus casei* GG, and other selected microorganisms) from 1966 to 1995. The authors concluded that these studies “have shown that biotherapeutic agents have been used successfully to prevent antibiotic-associated diarrhea, to prevent acute infantile diarrhea, to treat recurrent *Clostridium difficile* disease, and to treat various other diarrheal illnesses.” The authors noted that many of the studies included small numbers of subjects (10).
- ◆ In a double-blind, placebo-controlled study, 820 Finnish subjects traveling to southern Turkey to two destinations (Marmaris or Alayna) were randomly assigned to receive  $2 \times 10^9$  LA GG (a new *Lactobacillus* strain isolated from human intestine) powder or placebo twice daily before departure and continuing during the trip. A total of 756 subjects completed the study, with equal representation from the two groups. No significant difference was shown overall ( $P = .065$ ), but there was a destination effect, with travelers to Alayna demonstrating protection against diarrhea with supplementation (11).
- ◆ Three meta-analyses have been conducted investigating the role of LA in prevention or treatment of diarrhea. The first included 29 papers wherein intake of LA GG consistently reduced number of days with diarrhea in the setting of rotavirus (12), but did not prevent viral or bacterial diarrhea. The second analysis, focused on prevention of antibiotic-associated diarrhea in children, showed a 66% reduction in risk with supplementation (13). The third included nine studies, all of which were randomized and placebo-controlled. This analysis supported a reduction in the duration of diarrhea by a mean of 0.7 days and a mean reduction in stool frequency of 1.6 stools/day (14).
- ◆ There may be a differential effect of LA supplementation for diarrheal episodes in children vs adults. A multicenter European study showed that supplementation with LA GG (with oral rehydration therapy) significantly reduced duration of diarrhea, risk of a protracted course, and length of hospital stay among infants ( $N = 287$ ) (15). This is supported by research from Chandra et al, a placebo-controlled intervention with LA in children (16).
- ◆ However, in a study of adults ( $N = 302$ ) given LA GG or placebo, there was no significant difference in occurrence of diarrhea after antibiotic therapy (17).

### *LA and Irritable Bowel Syndrome*

- ◆ To date, studies investigating the role of LA supplementation to reduce diarrheal symptoms associated with irritable bowel syndrome generally have been negative. In a study of 12 subjects receiving LA plantarum 299V or placebo for 4 weeks in a

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crossover design, there was no significant difference in colonic fermentation or symptoms with supplementation (18). Using a similar study design in 25 subjects with IBS, no significant differences in pain, urgency, or bloating were shown between *Lactobacillus casei* strain GG and placebo (19).

- ◆ In a larger study, 77 subjects with IBS (mean age 44.3 years) were randomly assigned to (a) *LA salvarius* UCC4331, (b) *Bifidobacterium infantis* 35624, or (c) placebo for 8 weeks, with 4 weeks of follow up. There were more smokers in the group taking LA (smoking has been associated with reduced symptoms of IBS). Efficacy was assessed using both self-report of gastrointestinal symptoms and cytokine expression. Cytokine levels were compared over time and with age- and gender-matched healthy control subjects. Results showed that the bifidobacterium significantly improved symptoms and improved cytokine profiles toward reduced inflammatory response. The group taking LA had no significant improvement in IBS symptoms or cytokine profile (20).
- ◆ In a randomized, double-blind study, 64 children with IBS (12 males and 52 females; mean age 12 years) were randomly assigned to a 6-week intervention using LA GG or placebo. Twenty five children in each group completed the intervention. There was no difference between the two groups in self-reported disease-related symptoms at the start of the intervention (21). Children enrolled met Rome II criteria for IBS and completed a standardized Gastrointestinal Symptom Rating Scale to measure efficacy of the intervention. At the end of 6 weeks, 11 “responders” were identified within the intervention group and 10 within the control group, indicating no statistical difference across the two groups. However, among those with the highest abdominal pain scores at baseline, there was a significantly greater likelihood of improvement over time. This may be related to regression to the mean, as this was apparent regardless of group assignment. No objective measures of disease severity were reported. The sample size was small, given the wide range of symptoms reported, and subjects were not switched to the alternate treatment.
- ◆ In a double-blind study, 54 subjects with IBS were randomly assigned to *LA reuteri* ATCC 55730 or placebo. Efficacy was evaluated through self-report of gastrointestinal symptoms (Francis Severity score and IBS quality of life score). At the end of the 6-month intervention, there was no significant difference between groups (22). Fifteen subjects dropped out of the study, which makes interpretation of the results difficult.

### *LA and Vaginal Yeast Infections*

- ◆ A randomized, placebo-controlled, double-blind, factorial 2 × 2 study sought to test the hypothesis that oral or vaginal LA can reduce vulvovaginitis after antibiotic treatment. Two hundred thirty-five of 278 women completed the study. Women took LA orally, vaginally, or both from the start of antibiotics through 4 days after antibiotic therapy. No protective effect was shown regardless of administration route(s) (23).
- ◆ A crossover trial of six subjects assigned to one of two groups, receiving 150 mL of either pasteurized yogurt or yogurt containing live LA, studied the effectiveness of the

LA to reduce candidal yeast infections or bacterial vaginosis. Those women who received the LA-containing yogurt exhibited an increased colonization of favorable bacteria in the rectum and vagina and a decreased incidence of bacterial vaginosis (7).

### *LA and Cholesterol*

- ◆ Several hypotheses have been offered to explain how LA might help reduce serum cholesterol. For example, LA may (a) inhibit 3-hydroxy-3-methylglutaryl CoA reductase, a rate-limiting enzyme in endogenous cholesterol synthesis; or (b) bind with cholesterol in the intestinal lumen, thus reducing absorption into the blood (1,9).
- ◆ According to two review articles of more than 25 animal and in vitro studies, isolated LA and lactic acid bacteria found in fermented dairy products were associated with hypocholesterolemic effects (1,9).
- ◆ In a double-blind, placebo-controlled crossover study, 40 subjects with hypercholesterolemia were randomly assigned to receive 200 mL yogurt containing live cultures of LA or placebo daily for 4 weeks each, with a 2-week washout. LA yogurt (strain L-1) was associated with a significant 2.9% reduction of serum cholesterol (24).
- ◆ In a double-blind, placebo-controlled crossover trial, 30 healthy male subjects with borderline elevated cholesterol levels were randomly assigned to receive 125 mL yogurt fermented with LA and added fructooligosaccharides (2.5%) or a traditional yogurt fermented only with yogurt strains. Subjects consumed 3 × 125 mL yogurt daily for 3 weeks, each with a 1-week washout period. Blood samples were taken before the study and at the end of both treatments. Compared with the control product, LA yogurt resulted in significantly lower values for serum total cholesterol, LDL cholesterol, and the LDL-to-HDL ratio (values were decreased by 4.4%, 5.4%, and 5.3%, respectively). Serum HDL cholesterol, triglycerides, and blood glucose levels were unaffected (25). In a separate crossover design study using control yogurt and yogurt supplemented with LA 145 and *B longum* 913, 29 women with (N = 15) or without (N = 14) elevated serum cholesterol consumed the assigned yogurt for 7 weeks each. Total and LDL cholesterol did not change, but HDL cholesterol increased by a mean of 0.3 mmol/L in the LA-supplemented group, and the ratio of LDL to HDL decreased from 3.24 to 2.48 (26). In a study of 78 healthy adults with normal or borderline serum cholesterol levels, LA strain L-1 in the form of yogurt (or control yogurt) for 2 weeks did not alter lipid levels. However, 2 weeks of intervention may be inadequate, and it is less likely that normolipidemic individuals would respond (27).

### *LA and Cancer*

- ◆ Several possible mechanisms of the potential anticarcinogenic action of LA have been hypothesized. These include the production of compounds that inhibit tumor cell growth, antagonistic action against organisms that convert procarcinogens into carcinogens, and degradation of carcinogens (1) or immunomodulation (28).
- ◆ Observational studies have suggested that consumption of fermented dairy products is correlated with a lower prevalence of colon cancer (1).

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- ◆ According to a review article of several animal studies, orally administered LA (fermented dairy products and single preparations) may slow tumor development in animals. However, the researchers stressed that there is currently no proof in humans that *Lactobacilli* or their fermented products can prevent cancer (9).
- ◆ A study of mice with induced mammary tumors showed that neither the initiation nor the promotion phase of cancer was affected by supplementation of LA, *bifidobacteria*, or fermented yogurt powder (29).

### *LA and Atopic Disease*

- ◆ Among infants at risk for atopic disease (asthma, allergic rhinitis, eczema) due to family history, there is preliminary evidence that supplementation with LA GG in the final weeks of pregnancy and 3 to 6 months postpartum can reduce disease in the newborn (administered via breastmilk or in formula). A blinded Finnish study was conducted among 159 pregnant women with a family history of atopic disease. Compared with placebo, daily administration of LA GG ( $2 \times 10^{10}$  colony forming units during the final 4 weeks of pregnancy and during the first 3 months of lactation significantly reduced inflammatory biomarkers profile (increased TGF- $\beta$ 2 anti-inflammatory growth factor) in the infants. Infants with elevated cord blood IgE were most responsive to the LA GG supplementation (30). In a follow up analysis, LA GG or placebo was given to the infants for 6 months after birth. Eczema incidence at age 2 years was shown to be 23% in for the LA GG group vs 46% for the control group, indicating that risk of eczema was significantly reduced with supplementation (31).

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