ProBio PCC™
Consumer Product Guide

Probiotic dietary supplement to help maintain a healthy gastrointestinal environment.*

Scientifically Tested for Safety and Efficacy.

Maintains a Healthy Gastrointestinal Environment*

*LACTOBACILLUS FERMENTUM PCC

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Maintaining your intestinal ecosystem is an essential, yet often overlooked part of healthy living. Both friendly and unfriendly bacteria form a delicate, yet dynamic balance as they compete to adhere and colonize the mucosa of the digestive tract. Both friendly and unfriendly bacteria can be affected by changes in the intestinal environment. Stress, traveling, alcohol consumption, certain foods, and a poor diet can disturb the delicate balance of our digestive tract. This often results in a decreased number of friendly bacteria while allowing undesirable bacteria to gain a foothold. Your body is also frequently exposed to undesirable organisms—often consumed with your food—which can cause occasional gastrointestinal (GI) discomfort, bowel irregularity, occasional diarrhea, and other digestive and non-digestive discomforts.

Bacterial colonization of the gut begins at birth as newborns are maintained in a sterile status until the delivery begins, and continues throughout life with notable age-specific changes (Mitsuoka 1992). By the time we are adults, there are more than 400 different bacterial species and over 100 trillion total bacteria in the human digestive tract (Tannock 1999). The number of bacteria found in the digestive tract is approximately 10 times the number of cells found in the rest of the body and account for nearly two pounds of body weight (Mitsuoka 1992). The density of bacteria in the intestinal flora increases dramatically from a relatively low concentration in the stomach (10⁴ CFU/ml) to a high concentration in the colon (10¹² CFU/ml). These bacteria have been estimated to account for nearly half of the volume of the contents in the colon. (Holzapfel 1998).

Gastrointestinal microflora influence our nutritional, physiological, and protective processes, providing both direct and indirect defense functions in our body. They aid digestion by breaking down proteins, carbohydrates and fats in food, and help absorption of necessary nutrients such as minerals, amino acids and vitamins. The microflora directly prevent colonization by harmful organisms by competing for essential nutrients and adherence to the mucosal epithelium of the digestive tract. In addition, by producing inhibitory substances, such as short-chain fatty acids, hydrogen peroxide, and antimicrobial compounds, the microflora also create an intestinal environment that is generally unfavorable for the growth of undesirable bacteria. These compounds may reduce not only the number of viable undesirable microbes but may also affect bacterial metabolism and toxin production (Mackie 1999).
**Probiotic efficacy**

A healthy balance of intestinal flora can be restored through the consumption of food or food supplement products that contain friendly live bacteria cultures, commonly known as probiotics (FAO/WHO 2001). Lactobacillus bacteria were first identified by Louis Pasteur, but the original observation of the positive role of probiotic bacteria is attributed to Eli Metchnikoff, the Russian Scientist working at the Pasteur Institute, who received the Nobel Prize in the early 1900s for his discoveries. Metchnikoff suggested that, “The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes” (Metchnikoff 1907). A modern day definition of a probiotic could be stated as “a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial effects in this host” (Havenaar 1992).

Probiotics containing Lactobacillus have been found in the human diet for centuries. Folk remedies since the beginning of recorded history have ascribed beneficial effects to yogurts and cheeses. Even before antibiotics became a mainstream, probiotics were studied for their ability to increase the growth rate of farm animals and impart protection to these animals against undesirable bacteria. Probiotics are used in fermented milk products and food preservatives, but it has been only during the past two decades that advances in science and technology have enabled identification of specific strains of lactobacillus with unique properties offering improved health benefits. It has been determined that different strains of probiotic bacteria may exert different effects based on specific capabilities and activities, even within one species (Ouwehand 1999, Bernet 1993).

In a recent report of a joint Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) expert consultation, guidelines for the assessment of probiotics were outlined in order to assess individual probiotic properties (FAO/WHO 2001). The consultation suggested the following guidelines regarding pH survival, colonization, identity, and dosing.

1. **pH Survival.** Probiotics should survive passage through the digestive tract. This means they must be resistant to gastric juices and bile, or be consumed in a food vehicle that allows them to survive passage through the stomach and exposure to bile.

2. **Colonization.** Probiotics should also have the capability to proliferate and colonize in the gut and be able to grow in the presence of bile under conditions in the intestines. Probiotics must be able to exert their benefits on the host through growth and/or activity in the human body. The ability of the probiotic to remain viable in the intestines and remain effective should be verified.

   Different microorganisms express habitat preferences that may differ from person to person, resulting in varying levels of mucosal adherence (Freter 1992). Lactobacilli are among the indigenous flora colonizing the lower intestines. Bacteria colonizing such high-transit-rate sites must adhere firmly to the mucosal epithelium and must adapt to the environment of this adhesion site. The competition for adhesion receptors between probiotic and undesirable microorganisms, therefore, is dependent on such habitat preferences (Savage 1972, Beachey 1980).

3. **Identity.** The probiotics should be gram-positive bacteria, primarily in two genera, *Lactobacillus* or *Bifidobacterium*. The identity of the strain according to the International Code of Nomenclature and the viable concentration of each probiotic at the end of shelf life should be stated on the label.

4. **Dosing.** The product must indicate the dosage regimens and duration of use as recommended by the manufacturer and should be based on scientific evidence. Probiotics should be ingested regularly for the health promoting properties to persist.

**Lactobacillus fermentum PCC**

In developing ProBio PCC™ Pharmanex has followed the probiotic guidelines as established by the FAO/WHO expert consultation for pH survival, colonization, identity, and dosing (FAO/WHO 2001). ProBio PCC™ provides a proprietary strain of friendly bacteria (*Lactobacillus fermentum* PCC) that has been shown to be resistant to an acidic environment and can effectively colonize the lower digestive tract. Pharmanex’s unique strain of Lactobacillus was isolated from a Swedish woman (Gibson 1994). Researchers then developed a method in which they were able to grow *L. fermentum* commercially by using bacterial cell culture technology in a special nutrient medium. Each ProBio PCC™ capsule is guaranteed to contain a minimum of two billion CFUs (colony forming units) of the proprietary strain *L. Fermentum* PCC at the end of shelf life. Resistant starch is also provided as a non-digestible food medium, commonly known as a “prebiotic,” to promote the growth of friendly bacteria in the digestive tract.

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Health Benefits

Pharmanex’s ProBio PCC™ relieves symptoms associated with gastrointestinal (GI) complaints, bowel irregularity, occasional diarrhea, and other digestive and non-digestive discomforts. Clinical research has shown a decrease in gastrointestinal complaints and an increase in the growth of beneficial bacteria in the digestive tract after the introduction of this particular bacteria strain. ProBio PCC™ has been clinically proven to encourage the proliferation of healthy probiotic bacteria in the lower digestive tract, thus helping to fortify the natural digestive defense system (Welin 2002). By actively colonizing the lower digestive tract, ProBio PCC™ may be able to discourage the over development of undesirable bacteria and yeast. This effect may be due to direct action, modulation of local immunity, modifications of the intestinal ecosystem or a combination of these effects (Marteau 1998).

Clinical Evidence of Efficacy

The primary goal of probiotic therapy is to restore the natural balance of intestinal microflora in order to have an optimally functioning digestive defense system; this effect is well established in published research (FAO/WHO 2001). Independent research on probiotics, including Lactobacillus strains, have confirmed the following primary outcomes of probiotic therapy: (1) restoration of a healthy intestinal microflora; (2) stimulation of mucosal immunity; (3) improvement in gastrointestinal complaints, including occasional diarrhea and traveler’s diarrhea; and (4) improvement in urogenital microflora.

Mucosal Immunity

The digestive tract provides a protective interface between our internal environment and a constantly challenging external environment. Approximately 70% of the human immune system is localized in the digestive tract (Bengmark 2001). The surface of the intestinal mucosal membranes is protected by a local adaptive immune system, characterized by gut-associated lymphoid tissue. This gut-associated lymphoid tissue represents the largest mass of lymphoid tissue in the human body. It has been proposed that the generation of gut-associated lymphoid tissue and our intestinal immune regulation depends to a large extent on the establishment of indigenous microflora (Isolauri 2001). Probiotic bacteria have been shown to enhance humoral immune responses and thereby promote the intestine’s immunologic barrier. Furthermore, probiotic bacteria have been shown to stimulate humoral immune responses and to modulate the host’s immune responses (Kaila 1992, Perdigon 1986).

Many probiotic effects are mediated through immune regulation, normalizing mucosal function, and maintaining normal intestinal permeability (Isolauri 2001, Kalliomäki 2001).

Gastrointestinal Disturbances

According to the World Health Organization, up to 30% of the population, even in developed countries, are affected by occasional diarrhea each year (FAO/WHO 2001). Strong in vitro evidence and some animal studies show that certain probiotic strains can inhibit the growth and adhesion of a range of undesirable bacteria (Coconnier 1997, Hudault 1997, Gopal 2001, Ogawa 2001).

Urogenital Health

The urogenital microflora of a healthy woman comprises more than 50 species of organisms, which differ in composition according to reproductive stages and exposure to external factors. Studies investigating the effects of probiotics on the maintenance of a healthy urogenital microflora have had mixed results; it appears that certain properties of these strains, including adhesive ability and production of inhibitory substances are important in conferring protection to the host (Reid 2001, FAO/WHO 2001).

Pre-Clinical Studies—L. fermentum PCC

L. fermentum PCC has been shown in animal studies to have immuno-modulating activity. Pre-clinical studies have shown that L. fermentum PCC is stable and that the strain can survive transit through the digestive tract. Colonization of the human digestive tract has been demonstrated after a single dose; the duration of colonization varied between individuals with a mean value of 14 days (Gibson 1994).

Adhesion and colonization of the human digestive tract has been indicated as a key criterion for selection of probiotics. L. fermentum PCC has been shown both in vitro and in vivo to adhere to the human intestinal mucosa. An investigative study in which intestinal mucosal samples were treated with PCC-specific antiserum, showed that L. fermentum PCC was associated with the small intestinal mucosa after oral administration. The investigators proposed that “this attachment could allow prolonged colonization of the entire tract and contribute to the probiotic effectiveness of this strain. The mucosal attachment could also contribute to the observed immunomodulation observed in other studies” (Welin 2002) (see graph).
There is emerging evidence that strains of Lactobacillus bacteria that have the capacity to associate with the Peyers Patch (an area of mucosal lymphoid tissue in the small intestine) have a greater potential to trigger the mucosal immune system. Researchers have found that *L. fermentum* PCC preferentially targeted, and was recovered from, the Peyers Patch in mice; hence, *L. fermentum* PCC could have an enhanced capacity to trigger the mucosal immune system (Plant 2002).* (see graph)

**Clinical Studies—*L. fermentum* PCC**

The health benefits of *L. fermentum* PCC are documented in human, animal, and *in vitro* studies. Twelve clinical studies have been completed, or are in progress, validating the stability, colonization, and clinical efficacy of *L. fermentum* PCC. Additional clinical studies are currently in progress. This proprietary strain has been shown in clinical studies to reduce the symptoms of occasional diarrhea, constipation, flatulence, bloating, and abdominal discomfort (Conway 2002, Li 2002). Sixteen animal and *in vitro* studies have been completed on this proprietary strain, documenting similar positive results.

A number of probiotic preparations have been evaluated for their efficacy in preventing traveler’s diarrhea, but those reported to date have had limited success with small improvements noted. To determine the effects of *L. fermentum* on traveler’s diarrhea, 300 Swedish soldiers travelling to Lebanon were given *L. fermentum* three days prior to departure and for four weeks on location. In this study, a statistically significant reduction (50%) in the incidence of gastrointestinal disturbances and diarrhea was noted. Furthermore, those subjects that received the *L. fermentum* PCC had less severe symptoms than those who received *L. acidophilus* or placebo (Conway 2002).* (see graph)

**Proprietary Processing**

The combination of quality ingredients, qualified manufacturers, certified independent laboratory verification, and a continuous drive to supply leading edge products, ensure our distributors and consumers the highest quality products available in the industry. ProBio PCC™ has been developed through scientific and analytical methods to ensure that the product meets label claims for live cultures (CFUs) at the end of shelf life, which is a more valid indicator of efficacy than claiming number of live cultures at manufacturing.’ Pharnanex has established an exclusive supply agreement with the supplier of *L. fermentum* PCC, making this unique strain proprietary to our company. *L. fermentum* PCC is a patent-pending strain of Lactobacillus bacteria with ten patents having been filed to date. In developing ProBio PCC™ Pharnanex has followed the probiotic guidelines as established by the FAO/WHO expert consultation for pH survival, colonization, identity, and dosing (FAO/WHO 2001).

The ingredients in ProBio PCC™ have been tested for purity, and where applicable, ingredients are certified pure by testing for unwanted microbes, including *Salmonella, E. coli,* other coliforms, and *Staphylococcus aureus.* Additional tests include total plate counts, yeasts, molds and pesticide residues. Our manufacturers go through a detailed selection and certification process to assure their compliance with Good Manufacturing Practice (GMP) standards set by the Food and Drug Administration (FDA).

**Side Effects**

There are no known side effects at the recommended dosage.

**Safety and Toxicity**

ProBio PCC™ is safe and well tolerated at the recommended dosage. Lactobacilli have a long history of use as probiotics without established risk to humans, which remains the best proof of safety (Naidu 1999, FAO/WHO 2001). Also no pathogenic or virulent properties have been found (Aguirre 1993). Probiotics containing Lactobacillus have been shown to be safe in children (FAO/WHO 2001).

**Contraindications/Drug Interactions**

If you are pregnant or lactating, or taking a prescription medication, consult a physician prior to use. There are no known drug interactions.

**Directions for Use**

ProBio PCC™ is recommended for adults who experience occasional diarrhea, constipation, or cramps as a result of distressed digestive flora, and for adults who experience occasional gastrointestinal disturbances such as gas or bloating. Take one capsule daily to maintain normal digestive health. While *L. fermentum* has been shown to actively colonize the lower digestive tract, continuous ingestion is recommended for best results.

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How Supplied

ProBio PCC™ is supplied in a 30 day supply of 30 capsules.

Storage

Store in a cool, dry place. Avoid excessive heat. Protect from light. This product does not require refrigeration.

Shelf Life

Expiration date and lot code numbers are stamped on the bottle.

Warnings

Keep out of reach of children. If you are pregnant or nursing, or taking a prescription medication, consult a physician before using this product.

References


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The Pharmanex 6S Quality Process™
Central to the Pharmanex mission of transforming time-honored, traditional preparations into health promoting botanical products with known content and consistent activity is the Pharmanex 6S Quality Process™.

| Selection | • Exhaustive scientific review of research and databases is conducted.  
| • Authenticity, usefulness, and safety standards are determined. |
| Sourcing | • Teams of experts investigate potential sources and evaluate quality.  
| • Comprehensive botanical and chemical evaluations are completed. |
| Structure | • Structural analyses of natural compounds are determined.  
| • Active ingredients are isolated and studied. |
| Standardization | • Strict standardization to at least one relevant marker molecule is required.  
| • Proprietary processing methods to increase consistency and ensure measured dose effectiveness are developed. |
| Safety | • Safety is assessed from available research.  
| • Microbial test, chemical, toxin, and heavy metal analyses are conducted. |
| Substantiation | • Documented pre-clinical and clinical studies are reviewed.  
| • Pharmanex sponsored studies are initiated when appropriate. |

For More Information:
To learn more about the Pharmanex line of natural healthcare products, please call Product Support 1-800-487-1000.

Visit our website and access information directly at www.pharmanex.com