Metagenics Institute™

Probiotic strains to support Immunity:

Lactobacillus plantarum HEAL9, Lactobacillus paracasei 8700:2 and Lactobacillus rhamnosus LGG®

Herbs And Nutrients That May Assist

Lactobacillus plantarum HEAL9

Lactobacillus paracasei 8700:2

Lactobacillus rhamnosus (LGG®)

Actions

- Support underactive immune response
- Support innate immune defences
- Support adaptive immune defences
- Induce T regulatory cells

Clinical Applications

- Prevention of cold and flu
- Prevent recurrent infections
- Reducing respiratory illness in children

Formulas to consider

***Dosing regimens should be determined by appropriate assessment and monitoring.**

Lactobacillus plantarum HEAL9, Lactobacillus paracasei 8700:2 and Lactobacillus rhamnosus (LGG®) are three unique probiotics for patients requiring immune stimulation, particularly for those with immune insufficiency, chronic recurrent infections, post viral immune depletion and other conditions associated with low immunity. The probiotic strains *Lactobacillus plantarum* HEAL9, *Lactobacillus paracasei* 8700:2 and *Lactobacillus rhamnosus GG* (LGG®), are proven to help restore immune control and support under active immune responses.

These probiotics support both innate and adaptive immunity and have been clinically demonstrated to reduce the frequency, severity and duration of upper respiratory infections such as colds and influenza.

Background Technical Information

Infection

One of the most common infectious diseases in humans is the common cold, an infection caused by human rhinoviruses. The symptoms associated with common viral infections, which cause colds and flu, are not caused by the viruses themselves but rather the body's inflammatory response towards them.[1] A targeted approach to downregulate the inflammatory response may, therefore, reduce the duration and severity of common cold symptoms.

It is equally important to reduce the incidence of recurrent infection, particularly in those whose immune function is compromised. During the cold and flu season, common human rhinoviruses are easily transmitted and are responsible for most absences from work and school annually. Supporting those who are vulnerable and susceptible is in the best interests of both personal and public health.

As we age our susceptibility to infection increases and overall immune function declines. Age-related changes include a reduction in naïve T cells, a predisposition toward T helper 2 (Th2) cell production and a decrease in natural killer cell activity.[2] The higher propensity toward Th2 cells leads to a suppression of the T helper 1 (Th1) mediated response required for a robust immune response and resistance to infection.

Chronic illness further contributes to the dysregulation of the immune system. Chronic illness is associated with compromised immunity and elevated levels of inflammatory cytokines, impaired ability of antigen presenting cells (APCs) to stimulate T cells and a weakened antibody response of T cells. Human studies have demonstrated this is associated with a reduced capacity to trigger interferon type II (IFN-γ) or interleukin-10 (IL-10) from specific influenza virus T cells, as well as reduced production of the pro-inflammatory cytokine IL-12, needed to directly stimulate a Th1 response.[3]

The immune system

Innate immunity

Innate / nonspecific immunity is the first line of defence against infection. It discriminates between harmful and innocuous signals, as well as between self and non-self, generating an immune response only when required.

This branch of the immune system is activated immediately upon exposure to a virus or bacteria and needs to be supported to protect against infection. The response elements of the innate immune system are triggered by the release of cytokines, which have three major effects:

- Production of acute phase proteins to activate complement or phagocytosis.
- Elevation of body temperature to inhibit the growth of the pathogen whilst enhancing host resistance.
- Induction of local inflammation, activating natural killer[*] (NK) cells and cytotoxic T-cells.

Adaptive immunity

Adaptive / acquired immunity is the second line of defence against infection. This branch of the immune system is activated whe the innate immune response has been unsuccessful at controlling the infection.

Dendritic cells, macrophages and B-cells are the main cell types involved in the initial presentation of foreign antigens to naïve T cells. Naïve T lymphocytes become sensitised in lymphoid organs by antigens taken up by dendritic cells. The phase in which a naïve T cell becomes either a T helper type 1 (Th1) or type 2 (Th2) cell has a crucial impact on the outcome of the adaptive immune response, influencing whether it will be dominated by macrophage activation and cell-mediated immune response or by antibody production.[4]

The adaptive immune response may tend towards activation of Th1 (cell-mediated immunity) or Th2 cells (humoral immunity). Different pathogens will determine which response is elicited. For example, when immune function is normal, allergens or parasitic infection generally provokes a Th2 response, whilst mycobacterial infections tend to cause a Th1 response. Ideally, the adaptive immune response eliminates the infectious agent and provides the host with a state of protective immunity against reinfection with the same pathogen.[5],[6] The health of the immune system is essentially reliant upon the balance of Th1 and Th2 cells, which is kept in check by the Tregulatory (Treg) cells.

Activation of acquired immunity and the respective activation of T helper and cytotoxic cells results in an interaction with B cells which produce the effector proteins, antibodies. The cell-mediated immune response of adaptive immunity also involves the production of cytokines, which determine the inflammatory response. For example, the production of pro-inflammatory cytokines IL-2 and IFN-γ upregulate the Th1 response to clear most viral and bacterial infections.[7]

T regulatory cells

Naïve T cells can also differentiate into T regulatory cells (Tregs). Forkhead box P3 (Foxp3) is the major transcription factor that determines the fate of Tregs and its induction results in natural Treg cell development. Tregs are important for immune homeostasis.

They can suppress both innate and adaptive immune responses mainly via the anti-inflammatory effects of IL-10 and transforming growth factor-β (TGFB), thus downregulating inflammation and the severity of symptoms associated with induction of Th1 by bacteria and viruses.

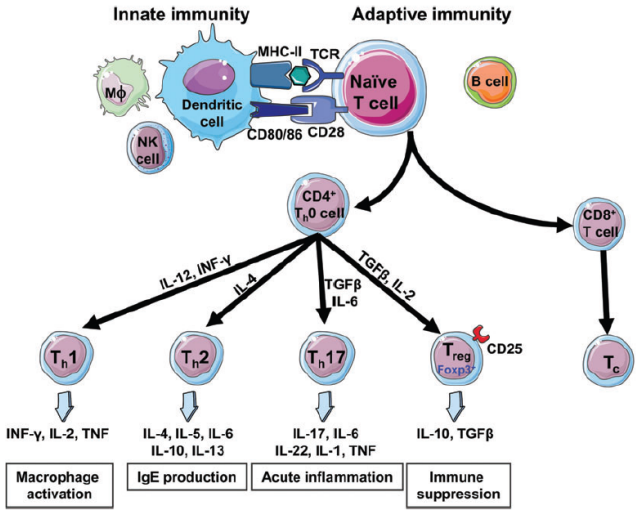

Figure 1: Cells of the innate and adaptive immune systems.[8]

The Role of The Gut In Immunity

The gastrointestinal system harbours the largest immune system in the body, with over 70% of the total immune system located in this area.[9] The gut microflora are an important constituent in the intestinal defence barrier. They elicit specific immune responses at a local and systemic level, maintain oral tolerance to antigen presentation and stimulate gut associated lymphoid tissue (GALT), including the capacity to generate IgA, important in the reduction of the number of translocating pathogenic bacteria.[10]

The GALT consists of isolated and aggregated lymphoid follicles, including Peyer's patches in the small intestine and the mesenteric lymph nodes. T and B cells, dendritic cells, macrophages and neutrophils are found in the GALT where they protect the mucosa from harmful pathogens inducing inflammatory responses to bacteria and antigens and scavenging dead cells.

Intestinal macrophages induce Tregs, essential to reduce inflammation. Following activation in the intestine, Tregs travel via lymphatic cells into the systemic circulation where they proliferate and are recruited to sites of inflammation.

The use of specific strains of probiotics to maintain healthy levels of beneficial gastrointestinal flora helps to maintain a protective barrier against the invasion of pathogens and support healthy immunity, as well as supporting the induction of Tregs to downregulate inflammation.[11],[12]

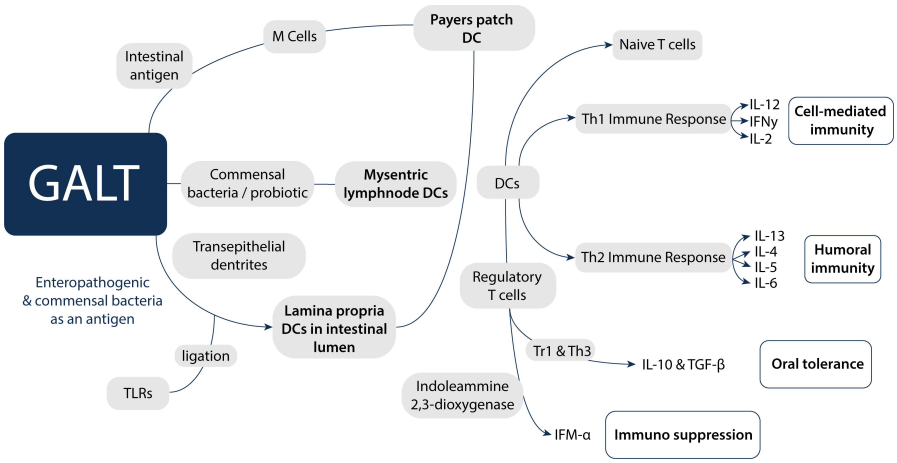

Figure 2: The role of gut-associated lymphoid tissues (GALT) in the immune system.[13]

Ingredients

Lactobacilli belong to a large and heterogeneous group of bacteria with widely differing properties. It is, therefore, imperative to utilise strain-specific, clinically-trialled, dose-specific organisms as prescribing an incorrect strain may fail to adequately address the condition. This is because individual species of lactobacilli interact with different antigen-presenting cells and induce the production of a specific cytokine pattern. This leads to the activation of specific immune effector pathways. Ensuring the correct pathways for a specific condition are activated increases the resolution potential. One important thing to note is that *Lactobacillus plantarum* HEAL9, *Lactobacillus paracasei* 8700:2, and *Lactobacillus rhamnosus* LGG® all have the capacity to induce a key anti-inflammatory and immunoregulatory cytokine, IL-10.[14],[15]

As important as it is to ensure strain specificity, it is equally important to know the bacteria are able to resist acid digestion and transit to the required portion of the intestine to induce the desired physiological response. *Lactobacillus plantarum* HEAL9, *Lactobacillus paracasei* 8700:2 and *Lactobacillus rhamnosus* LGG® to Support Immunity strains have been shown to do both. This has been assessed via a number of means including through the highly regarded polymerase chain reaction (PCR) analysis.[16]

- ***Lactobacillus plantarum HEAL9*** has been shown to resist acid digestion and survive to temporarily colonise the gastrointestinal tract and actively secrete antimicrobial substances that inhibit the growth of certain organisms, producing a more beneficial microbial balance.[17]
- ***Lactobacillus paracasei* 8700:2** has been shown to prevent pathogen adhesion partly by production of inhibitory substances such as bacteriocins, lactic acid, and hydrogen peroxide; and by competing for nutrient and gut receptor sites.[18],[19]
- ***Lactobacillus rhamnosus* GG (LGG®)** is one of the most extensively studied human probiotic organisms in clinical trials and human intervention studies,[20] with a well-documented safety record.[21],[22] LGG® has demonstrated resistance to acid and bile and good potential for growth and adhesion to the intestinal epithelium.[23]

Actions

Support an Underactive Immune Response

Innate immunity

Different probiotic strains have been shown to affect the immune system and also reduce the incidence and severity of infection, particularly in the respiratory system.[24] An animal study has shown that LGG® augments NK activity in the respiratory system, indicating potential protection from influenza virus infection.[25] This was corroborated by a more recent study demonstrating LGG® upregulated the pulmonary mRNA expression of genes encoding IFN-γ, thus acting as a potent immune stimulant in the fight against viral infection.[26]

***L. paracasei* 8700:2** has been shown to induce innate immune functions, including increased phagocytosis and increased levels of NK cells, which may account for its benefits in the prevention of cold and flu.[27]

Adaptive immunity

***L. paracasei* 8700:2** and ***Lactobacillus plantarum* HEAL9** have also been shown to strongly stimulate macrophages to produce high levels of interleukin IL-12, a cytokine known to promote Th1-mediated antiviral immune responses through the production of IFN-γ from T-cells and NK cells.[28],[29]

A human study was performed to investigate whether intake of ***Lactobacillus plantarum*** HEAL9 and ***Lactobacillus paracasei*** 8700:2 could affect common cold infections in healthy patients. Two hundred and seventy two healthy male and female subjects aged 18-65 were supplemented daily with either 1 billion CFU of probiotics [500 million of each strain] or a control for a 12-week period.

Cellular immune responses were assessed by measuring the proliferation of certain cell types such as NK cells, T lymphocytes, T helper, T suppressor and T cytotoxic cells and B lymphocytes. The combination of ***Lactobacillus plantarum*** HEAL9 and ***Lactobacillus paracasei*** 8700:2 was found to significantly attenuate the rise of B lymphocytes associated with colds after a two week period. This may result in a reduction of inflammation, a key driver of the symptoms associated with colds.[30]

Lactobacillus plantarum HEAL9 and ***Lactobacillus paracasei*** 8700:2 has also been shown to efficiently induce cell-mediated function in a group of healthy volunteers.[31]

T regulatory cell support

The combination of ***L. paracasei*** 8700:2 and ***L. plantarum*** HEAL9 has been found to induce the immunoregulatory cytokine TGF-beta (TGF-β), which regulates IL-10 expression by Treg cells.[32] Figure 3 highlights the marked induction of IL-10 following the ingestion of ***L. paracasei*** 8700:2 and ***L. plantarum*** HEAL9. This increase in IL-10 may lead to a reduction in the inflammatory response associated with infective stimuli.[33]

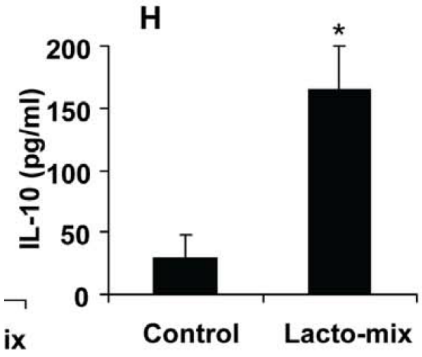

Figure 3: Combination of *L. paracasei* 8700:2 and *L. plantarum* HEAL 9 increases IL-10.[34]

The combinations of *Lactobacillus plantarum* HEAL 9 and *Lactobacillus paracasei* 8700:2 have also been found to induce Treg production in the gut mesenteric lymph nodes (MLNs). The Tregs have been shown to migrate to the periphery, including the respiratory system, and CNS. The Tregs activate the production of IL-10 and TGF-β in MLNs, spleen and blood improving both general and, in turn, respiratory immunity.[35] Figure 4 highlights the positive impact of this probiotic combination on inducing the concentration of Foxp3, an important determinant in Treg development.[36]

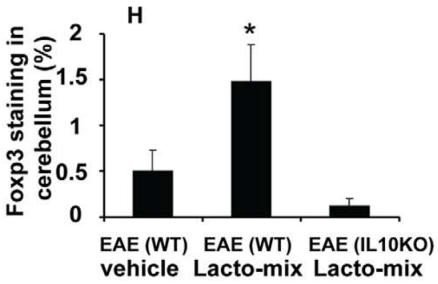

Figure 4: *L. paracasei* 8700:2 and *L. plantarum* HEAL 9 induce Foxp3 levels.[37]

LGG® has demonstrated the ability to enhance a variety of immune responses. Administration of LGG® has been associated with an increase in numbers of TGF-β secreting Treg cells in lymph nodes as well as nearly 2-fold up-regulation of Foxp3-expressing cells in lymph nodes.[38]

A study was conducted to examine the effect of five weeks of oral administration of LGG® at the cellular immune level after stimulation with a range of intestinal microorganisms, such as *Escherichia coli* and *Bacteroides fragilis*. Ten healthy adult volunteers each received LGG® (2 billion CFU/day) for 5 weeks. LGG® was shown to have a direct effect on the cellular immune system. It also activated an immunomodulatory response with an enhanced anti-inflammatory action from increased Treg and subsequent IL-10 activation (Figure 5).[39]

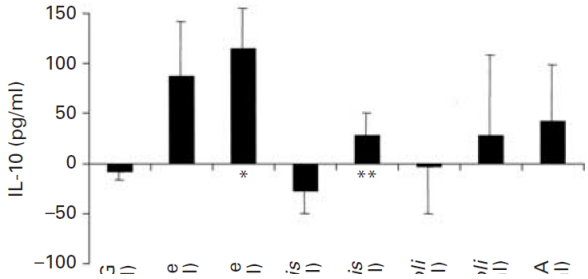

Figure 5: LGG® increases expression of the anti-inflammatory cytokine IL-10.[40]

Clinical Applications

Prevention of Cold and Flu

A randomised, controlled study was performed to investigate whether intake of ***Lactobacillus plantarum* HEAL 9** and ***Lactobacillus paracasei* 8700:2** would reduce the risk of common cold episodes, the number of days with common cold symptoms, the frequency and severity of symptoms, and the cellular immune responses in common cold. Two hundred and seventy two healthy male and female subjects aged 18-65 were supplemented daily with either 1 billion CFU of probiotics [500 million of each strain] or control for a 12-week period.[41]

Only 55% of those in the probiotic group experienced one or more cold episodes compared with 67% of those in the control group. In addition, the number of days with common cold symptoms was significantly reduced from 8.6 days in the control group to 6.2 days in the probiotic group, a reduction of 28%, during the 12-week period (Figure 6). The total symptom score was reduced by 24% during the study period from a mean of 44.4 for the control group to 33.6 for the probiotic group (Figure 6). The reduction in pharyngeal symptoms such as a scratchy, sore throat and hoarseness was also significant.[42]

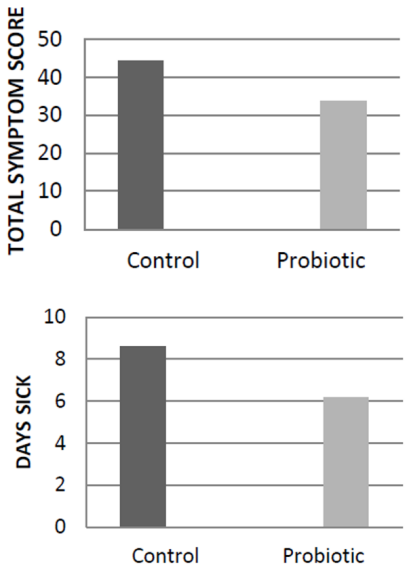

Figure 6: The reduction in number of sick days and total symptom score in probiotic group compared to control.[43]

Prevent Recurrent Infection

In a similar trial the combination of ***Lactobacillus plantarum* HEAL9** and ***Lactobacillus paracasei* 8700:2** was administered to patients who had an increased risk of infection (defined as a minimum of two episodes of common cold during the last six months) for 12 weeks.

The intensity of 13 cold symptoms, including general illness symptoms (e.g. headaches, joint pain), nasal symptoms (runny nose, congested nose, yellow or bloody secretion, sneezing), bronchial symptoms (cough, yellow or other secretion) and pharyngeal symptoms (sore throat, difficulty swallowing, hoarseness) were evaluated daily by the subjects on a four-point rating scale (0 = complaint free, 1 = slight, 2 = moderate, 3 = severe) during an episode for a period of seven days.

Treatment with the probiotic blend throughout the 12 weeks was found to produce a statistically significant 33% reduction of the total sum score (75.2 vs. 113.4) of the common cold symptoms in the probiotic group compared to placebo. In addition, a statistically significant 16% reduction of the duration of the common cold episodes was seen in the probiotic group compared to placebo, from 6.7 days to 5.6 days (Figure 7).[44]

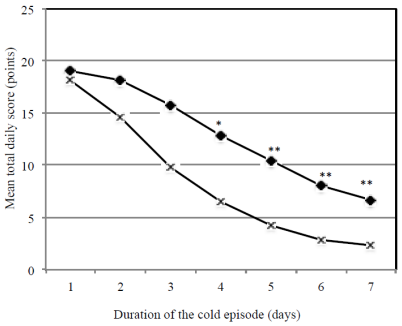

Figure 7: Daily common cold symptom scores over seven days.[45]

Key: '<>" placebo, 'X" probiotic

Reducing Respiratory Illness In Children

A number of studies have demonstrated positive results with the use of **LGG®** in the prevention and reduction of respiratory illness in children.[46],[47] An excellent example is a study conducted with children attending day care centres. 281 children were randomly allocated to receive either LGG® (10 billion CFU/day) or placebo for a three month period.[48]

Children receiving LGG® had a significantly reduced risk of upper respiratory infections (Figure 8), a reduced risk of respiratory infections lasting longer than three days and a significantly reduced number of days with respiratory symptoms, compared to the placebo group.[49]

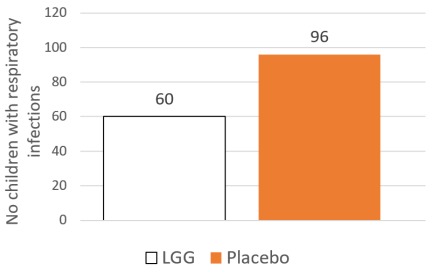

Figure 8: Number of children with respiratory infections administered LGG® or placebo.[50]

In another study conducted on 571 children aged 1–6, the intake of LGG® during a seven month period resulted in a relative reduction in the number of children suffering from respiratory infections.[51]

Cautions and Contraindications

Contraindications

- None of note.

Cautions

- Severely ill and/or immunocompromised patients: Lactobacillus bacteraemia and sepsis have been reported in severely ill and/or immunocompromised patients, though this is a very rare finding.[52],[53] Use only under medical supervision in severely ill, hospitalised patients.
- Short bowel syndrome: Patients with short bowel syndrome might be predisposed to pathogenic infection from lactobacillus. This might be due to impaired gut integrity in patients with short-bowel syndrome. Use only under medical supervision in patients with this condition.[54]

***Note: Antibiotics:** Concomitant administration of antibiotics might decrease the effectiveness of lactobacillus. However concomitant use of probiotics reduces the likelihood of gastrointestinal and genitourinary side effects and co-administration i considered beneficial. Separate administration of antibiotics and lactobacillus preparations by at least two hours.[55],[56]

Pregnancy and Breastfeeding

- **Pregnancy:** A review did not identify any concerns for use during pregnancy, however safety has not been conclusively established in humans.
- **Breastfeeding:** Likely safe when used at recommended doses.

Footnotes

[*] Natural killer cells are innate lymphocytes with powerful cytotoxic activity which is vital for the immune response to microbial and viral infection.

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Formulas to consider

Metagenics

UltraFlora® Immune Booster

Targeted Probiotic Support for Healthy Nasal, Sinus & Respiratory Function

- Provides a blend of highly viable, pure strains of "friendly" bacteria, *Lpa* 8700:2 and *Lp* Heal9, which support healthy nasal, sinus, and respiratory function.

1 capsule contains	
A 50:50 Blend of: Lactobacillus paracasei 8700:2 Lactobacillus plantarum HEAL9	1 billion CFU††

Other Ingredients: Starch, capsule (hypromellose, gellan gum), and magnesium stearate (vegetable).

Directions: Take one capsule once daily or as directed by your healthcare practitioner.

This product is non-GMO, gluten-free, and vegetarian.

†Vegetarian capsule

††At date of expiration

Application:

- Targeted support for healthy respiratory function
- Suitable for short term and long term use

Ultra Flora LGG®

Researched LGG®

- The LGG® strain has been clinically demonstrated in studies to reduce the frequency and severity of diarrhoea. LGG may also reduce the symptoms of eczema and allergic rhinitis in children

1 capsule contains	
Lactobacillus rhamnosus (LGG®)	10 billion CFU (Organisms)

Directions:

Adults: Take 2 capsules daily

To maintain healthy gut flora: Take 1 capsule daily.

This product is non-GMO, gluten-free, and vegetarian.

Storage: Store at 25°C. Activ-Vial™ desiccant lined bottle guarantees live and effective probiotics without refrigeration.

LGG® is a registered trademark of Chr. Hansen A/S.

Application:

- Immune modulation
- Support of intestinal barrier function
- Prevention of eczema
- Reduction in the severity of atopy
- Acute gastroenteritis
- Antibiotic-associated diarrhoea

MetaKids Baby Probiotic

Probiotic Support for Babies and Young Children

- Features a unique blend of probiotics to help support a healthy intestinal environment.

1 drop contains	
A Blend of: Bifidobacterium animalis ssp. lactis, Lactobacillus rhamnosus GG	1 billion CFU†

Other Ingredients: Sunflower oil, D-alpha-tocopherol, and citric acid

Directions: Shake well before use. Administer 6 drops of oil onto a spoon or into milk/food once daily or as directed by your healthcare practitioner.

This product is non-GMO, vegetarian, and gluten free.

Caution: Keep out of the reach of children. Discard 4 weeks after opening.

†At date of expiration.

Application:

- Support for a healthy intestinal environment
- May be beneficial for immune support

UltraFlora BiomePro

Multistrain. Clinically effective doses.

- This multidimensional formula features 105 billion CFUs per capsule†.

1 capsule contains	
A Proprietary Blend of: Lactobacillus acidophilus NCFM ††† Lactobacillus rhamnosus GG Lactobacillus plantarum Lp-115 Bifidobacterium lactis Bl-04 Bifidobacterium lactis Bi-07††† Lactobacillus paracasei Lpc-37 Lactobacillus rhamnosus HN001 Bifidobacterium lactis HN019	105 billion CFU††

Other Ingredients: Microcrystalline cellulose, capsule (hydroxypropylmethylcellulose), magnesium stearate (vegetable), and silica.

Directions: Take one capsule daily or as directed by your healthcare practitioner.

This product is non-GMO, gluten-free, and vegetarian.

†Vegetarian capsule

††At date of expiration.

†††Bi-07® and NCFM® are registered trademarks licensed by DuPont.

Application:

- Healthy respiratory function
- Healthy intestinal microbiota