Metagenics

Ultra Flora LGG

Researched, Authentic LGG

LACTOBACILLUS RHAMNOSUS LGG®

Lactobacillus rhamnosus GG (LGG®) is an exclusive and clinically trialled probiotic strain that has applications in multiple conditions. Importantly, the wide-ranging therapeutic benefits of LGG® are attributed to the ability of the strain to adhere to the mucous lining of the gut, which is dependent upon the strain's fimbria-like appendages known as pili. Pili allow the strain to persist in the human digestive tract to effectively orchestrate its beneficial host interactions.

When taken during pregnancy and infancy, LGG® may reduce the incidence of eczema in infants at high risk for its development.[1] In those infants who have developed eczema and food allergy, LGG® can reduce the severity of symptoms, thereby making it an excellent option for the prevention and treatment of this common complaint. LGG® may also be suitable in the treatment of acute infectious diarrhoea, where it may be used for reducing the frequency and severity of symptoms, and also for the prevention of gastrointestinal infection and diarrhoea.

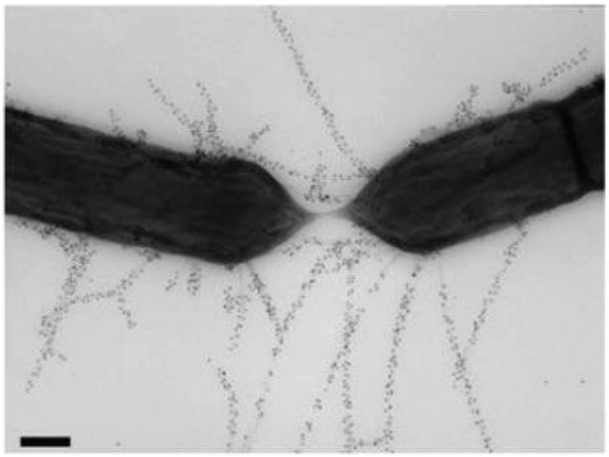

Figure 1: The strong adhesive capacity of L. rhamnosus LGG® is attributed to the strain's long pili.[2]

Actions
- Immune modulation
- Support of intestinal barrier function

Clinical Applications
- Prevention of eczema
- Reduction in the severity of atopy
- Acute gastroenteritis
- Antibiotic-associated diarrhoea
- Healthy intestinal microbiota

Dosing Considerations*

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 coadministration is considered beneficial. Separate administration of antibiotics and lactobacillus preparations by at least two hours.[71,72]

Co-prescribing considerations: refer to page 7

Breastfeeding ✓

Pregnancy ✓

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

BACKGROUND TECHNICAL INFORMATION

Gut Microbiota and Probiotics

The disruption of gastrointestinal (gut) microbiota, the vast array of microbes residing in the gut, has consequences that are far reaching, both physically and mentally. These consequences may be gut-based, for example the improper development of the gut immune system and the development of gut symptoms such as changeable stool, abdominal pain and bloating. The consequences can also be systemic, resulting in increased risks of inflammation and infection in the skin, vagina, respiratory tract and oral cavity.[3,4,5,6]

Probiotics are defined as 'live microbial ingredients that, when ingested, confer health benefits on the host'[7]. They have been shown to influence the development, maturation and maintenance of the crosstalk between the microbes within the gut microbiota. The gut microbiota will, in turn, affect the innate and acquired immune systems via the interaction of their components and/or metabolites, for example the production of the energy-producing short chain fatty acids (SCFA).[8]

Such interactions include, but are not limited to, a direct impact on the intestinal epithelium, including the gut associated lymphoid tissue (GALT) and intestinal lamina propria, T-cell polarisation for the production of the appropriate immune reaction, and the regulation of endogenous microbiota.[9,10,11] Probiotics also enhance the gut microbiota by replenishing levels of beneficial bacteria and inhibiting the growth of more pathogenic flora. Some of the ways this is achieved is via the occupation of receptor sites and competition for nutrients, referred to as competitive exclusion.[12,13] These mechanisms form the basis for the oral supplementation of probiotics, which ultimately aims to increase the relative numbers of beneficial bacteria colonising LGG® is one of the most extensively studied and best characterised probiotic organisms complete with a documented safety record.[14,15] LGG® has demonstrated resistance to acid and bile and has properties that allow for growth and adhesion to the intestinal epithelium.[16] It has shown good adhesion properties on intestinal mucus, various cell culture models and tissue samples from different parts of the human intestine. The strain was also recovered in biopsy samples taken from colon mucosa during administration and for at least 1 week after finishing the oral ingestion. LGG® has a balancing effect on the gut microbiota; it increases the levels of lactobacilli and bifidobacteria, increases the formation of SCFAs, and improves as well as normalises the mucosal barrier.

Quality Matters with Probiotics

The International Scientific Association for Probiotics and Prebiotics (ISAPP) recommends that probiotics be chosen from a trusted manufacturer, who sell probiotics which are backed by scientific research, and who store probiotics correctly in order to maintain optimal strength, potency and numbers of live bacteria.[17] LGG® has a long history of use and have been extensively researched - LGG® for instance is suggested to be the most researched example of bacterial strain probiotic.[18] LGG® is an example of a strain that has been genetically characterised to understand its actions, and has demonstrated acid and bile resistance, and adherence to human intestinal cells.[19]

Eczema

The incidence of infantile eczema (atopic dermatitis) is ever increasing. A full understanding of the mechanisms leading to the reddening of the skin, rash and itch is not fully understood.[21] What is known, however, is that eczema is a result of an immune system imbalance, and that re-establishing the balance is key in easing the symptoms and reducing the risk of further episodes.[22]
Maternal atopy has been shown to be a strong risk factor for the development of atopic eczema in infants.[23] The mechanisms for atopic manifestations all involve Immunoglobulin E (IgE)-mediated responses, leading to the release of inflammatory mediators into many systems, not simply the skin.[24] Prenatal probiotic supplementation has been associated with less IgE-associated allergic disease, especially in caesarean delivered children.[25]

Gastrointestinal Resilience

The concept of the 'gut as the seat of all health' is well known among those interested in health and wellbeing. The explosion of research and development relating to the human microbiome, the collection of microbes that live within and on humans and, in particular the gut microbiota, only serves to reinforce this fundamental concept.

Diarrhoea is a common digestive complaint and may be the result of an acute infection or chronic in nature. In either case, reducing the negative effects of diarrhoea, such as altered intestinal barrier and absorption functions, mineral loss, dehydration and general disruption of cellular functions, is an important treatment goal.[27]

ACTIONS

Immune Modulation

The range of LGG®'s immune-modulating mechanisms is extensive, offering far-reaching, beneficial effects from infancy to old age. These mechanisms include the reduction of atopy incidence by decreased circulating IgE levels;[28] increased transforming growth factor β2 (TGF-β2);29 increased immunoglobulin (Ig)-secreting cells, including IgM, IgA and IgG;30 and decreased oeosinophilic protein X in urine.[31] In addition, it may assist to reduce inflammation, by increasing the immune modulator, soluble cluster of differentiation 14 (sCD14)32 and serum levels of interleukin-10 (IL-10),[33,34] as well as inhibiting the synthesis of cytokines involved in inflammation, including IL-2, IL-4, IL-6, IL-12, tumour necrosis factor-α (TNF-α) and interferon-gamma (IFN-γ).[35]
Additionally, LGG can increase the immune response by increasing phagocytosis receptor expression on neutrophils.[36]
The promotion of intestinal barrier function by LGG is likely due to a decrease in α1-antitrypsin, an indicator of intestinal inflammation,[37] and a decrease of faecal TNF-α.[38] Importantly, it can also promote the growth and biodiversity of bifidobacterium and lactobacillus/enterococcus,[39,40] therefore contributing to increased microbial diversity to support overall digestive health and improve immune responses.
The adaptive immune response, once activated, may tend towards the production of T helper type 1 cells (Th1) (cell-mediated immunity) or T helper type 2 (Th2) cells (humoral immunity).[41] Different pathogens will determine which response is elicited. For example, when immune function is normal, allergens or parasitic infection generally provoke a Th2 response, whilst mycobacterial infections tend to cause a Th1 response. The phase in which a naïve T cell becomes either a Th1 or Th2 cell has a crucial impact on the immune response. The health of the immune system is, therefore, essentially reliant upon the balance of Th1 and Th2 cells, regulated by the T regulatory (Tregs) cells.
Specific strains of probiotics may be used to support the induction of Tregs. This mechanism is paramount to the ability of probiotics to regulate inflammation, maintain a protective barrier against the invasion of pathogens and antigens, and support healthy immunity.[42,43] Administration of LGG® has been associated with an increase in numbers of TGF-β secreting Treg cells, as well as nearly 2-fold up-regulation of Foxp3-expressing cells, a master regulator of transcription of Tregs in humans.[44]

Support of Intestinal Barrier Integrity

The gut epithelium acts as an important barrier between the 'inside' and 'outside' world, playing an important role in the absorption of nutrients, ions and water, as well as conveying protection from potentially harmful substances such as toxins and pathogens. The integrity of the intestinal barrier depends on a complex of proteins that make up different intercellular junctions, including tight junctions (TJs). Disruption of TJs by pro-inflammatory factors elevates TJ permeability to luminal toxins, allergens and pathogens, and plays a crucial role in the pathogenesis of a number of conditions.[45] Intestinal epithelial TJs prevent the diffusion of potential injurious factors from the gut lumen into the tissue. Probiotics, such as LGG®, have been shown to support the integrity of TJ via various mechanisms,[46] which is important to protect against bacterial translocation and prevent immune dysregulation.[47]

'LGG® has been shown to provide the infant with protection from atopic eczema when administered to the mother before delivery and during breast feeding.'

Enterohemorrhagic Escherichia coli (EHEC) infection is a common infection in humans, and provides a model of intestinal dysbiosis. An in vitro study showed that EHEC causes disruption of intercellular tight junctions, leading to clinical sequelae including acute diarrhoea. A study focused on the potential therapeutic ability of LGG® to mitigate EHEC-induced changes in paracellular permeability in epithelial cell monolayers. With pretreatment, LGG® attenuated the increase in barrier permeability and protected epithelial monolayers against redistribution of certain TJ proteins, demonstrating its role in maintaining the intestinal barrier.[48]

CLINICAL APPLICATIONS

Prevention of Eczema

Maternal atopy is a clear risk factor for atopic eczema in infants. The infants most likely to benefit from maternal probiotic supplementation were those with an elevated cord blood IgE concentration, reflecting atopic sensitisation in utero. This suggests that probiotics have an effect via the early immunologic mechanisms involved in the development of atopic disease. It also highlights the complex interplay between genetic predisposition, early sensitisation and immunoprotective factors in the development of atopy.[49]

LGG® has been shown to provide the infant with protection from atopic eczema when administered to the mother before delivery and during breastfeeding. Infants with an elevated cord blood IgE concentration, considered reflective of atopic sensitisation in utero, were most likely to benefit. LGG® was also shown to

increase the amount of anti-inflammatory TGF-β2 in breast milk.[50]

A randomised controlled trial was conducted in 159 mothers who had at least one first-degree relative or partner with atopy, including eczema, allergic rhinitis, or asthma. Twenty billion CFU/day of LGG® or placebo was provided to expectant mothers from 24–28 days (mean 26 days) prior to expected delivery and for six months postnatally, either to breastfeeding mothers or directly to the infants. The frequency of eczema in the probiotic group was half that of the placebo group, 23% versus 46% (Figure 2), with the preventative effect being independent of the mode of administration.[51]

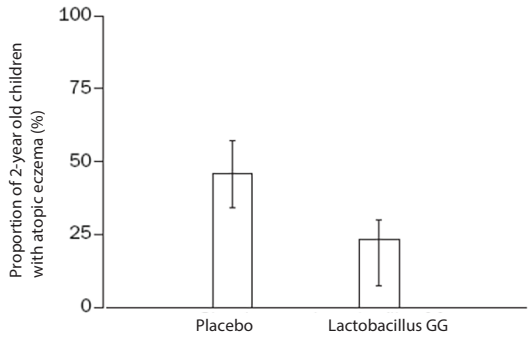

Figure 2: Treatment effect of LGG® vs. placebo on atopic disease at 2 years (Bars are 95% CI)[52]

The preventative effect of LGG® on eczema also extends beyond infancy. The above primary study was followed up at four years and seven years. At four years (107 children assessed) there was a reduced incidence of eczema in the probiotic group.[53] These effects continued through to final follow-up visit at seven years of age. 116 children completed the seven-year follow-up: 62 of 82 (76%) in the placebo group and 53 of 77 (69%) in the LGG® group. Overall, the risk of eczema during the first seven years of life was significantly reduced in the LGG® group compared with the placebo group (Figure 3).[54]

In a double-blinded, placebo-controlled study of 62 mother-infant pairs, LGG® was given for four weeks before birth and during breastfeeding. Administration of probiotics to the pregnant and lactating mother increased TGF-β2 levels in mothers receiving probiotics compared with those receiving placebo - 2885 pg/mL vs. 1340 pg/mL. The risk of developing eczema during the first two years of life was significantly reduced in infants of the mothers who received probiotics, in comparison with that in infants whose mothers received placebo (15% vs. 47%).

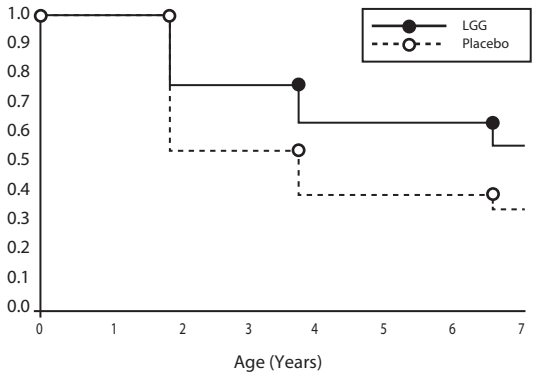

Figure 3: Kaplan-Meier curves for the proportion of children without eczema at the ages of 2, 4, and 7 years in LGG® (n = 64) and placebo (n = 68) groups (p=0.008), indicating a protective effect of LGG® on the risk of developing atopic eczema.[55]

It should be acknowledged that a published study investigating the effects of LGG® on the prevention of atopic dermatitis, taken by pregnant women and then by breastfeeding mothers or formula-fed infants, failed to find a beneficial effect for LGG®. However, the dosage of LGG® used in this study was 5 billion organisms twice daily, half that of the studies above, indicating that the lack of positive results could be due to an insufficient dose.[56]

Reduction in the Severity of Atopy

Research has shown that commencing LGG® in infancy may also be of benefit in decreasing symptoms of atopy, including food allergy and eczema. The immunological mechanisms that may be involved with this benefit have been investigated in several trials that are discussed below.

A two part randomised controlled trial first included 31 formula-fed infants, aged 2.5 to 15.7 months, with eczema and a clinical history suggestive of cow's milk allergy. Sixteen infants received extensively hydrolysed whey formula, while 15 received the same formula fortified with LGG® at a dose of 5×108 organisms per gram of formula, giving an average dose of 1 billion of LGG® daily for one month. In the second part of the study, 11 breastfed infants with eczema, aged 0.6 to 8.5 months, were continued on breast milk, and 20 billion LGG® was given twice daily for one month to the nursing mothers.

The clinical score of atopic dermatitis (SCORAD†) improved significantly during the one month study period in infants treated with the LGG® fortified formula, and in the breastfed children whose mothers received the probiotic, but not in the group on formula only. Improvements occurred in regards to the extent, intensity and subjective scoring.

† SCORing index Atopic Dermatitis: a scale widely used in clinical studies to assess atopic dermatitis / eczema.

The concentration of α1-antitrypsin, an indicator of intestinal inflammation, decreased significantly in the whey formula with LGG® (p=0.03) but not in the group receiving the whey formula alone (p=0.68). In parallel, the median concentration of faecal TNF-α decreased significantly with LGG® from 709 pg/g to 34 pg/g (p=0.003), but not in the control group (levels in the breastfed group were very low at baseline).[57]
A subsequent study found similar benefits from the use of LGG® in breastfeeding infants with eczema. In a randomised, double-blind, placebo-controlled study, 18 infants with a mean age of 4.6 months, who manifested eczema during exclusive breastfeeding, were weaned to LGG® in an extensively hydrolysed whey formula, or the same formula without probiotics. After two months, a significant improvement in skin condition occurred in patients given LGG® compared to the unsupplemented group: the SCORAD score decreased from 16 (7-25) [median (interquartile range)] during breastfeeding, to 1 (0.1-8.7) in the LGG® group vs. 13.4 (4.5-18.2) in the unsupplemented group (p=0.01). These improvements occurred in parallel with a reduction in the concentration of eosinophilic protein X in urine, which further supports the reductions in allergic inflammation with LGG® supplementation.[58]

LGG® has also been shown to down-regulate milk-induced immune-inflammatory response in hypersensitive individuals.59 A study demonstrated that milk increased expression of phagocytosis receptors‡ in milk-hypersensitive adults, whereas healthy adults did not experience such a response. When these same groups were given milk with LGG®, expression of phagocytosis receptors was stimulated in the healthy group and attenuated in the milk-hypersensitive group. LGG®, therefore, modulated the immune response differently in healthy and hypersensitive individuals, indicating that it can stimulate the immune system when an increased response is needed, and down regulate when attenuation is required.[60]

Acute Gastroenteritis

A 2013 meta-analysis of 15 randomised, controlled trials incorporating 2963 participants, showed that LGG® significantly reduced the duration of diarrhoea episodes caused by acute gastroenteritis, compared with placebo or no treatment (mean difference, MD -1.05 days, 95% CI -1.7 to -0.4) (Figure 4). It was determined the positive effect was most notable in daily doses of ≥1010 colony forming units (CFU) per day.[61]
In children aged between 3 and 36 months with acute diarrhoea, including rotavirus diarrhoea, LGG® has been shown to be more effective in reducing the duration of diarrhoea than other probiotic preparations.[62,63] Just one day after first probiotic administration, a dose of 6 billion twice daily reduced the daily number of stools to a level significantly lower than other single probiotics or placebo. LGG® therapy was also found to be associated with an enhanced serum immune response to rotavirus.

Additionally, improving gut health with probiotics such as LGG® at a dose of just 2 billion CFU a day has been shown to reduce the risk of gastrointestinal infection in adults.[64] An example of a mechanism via which LGG® may exert its anti-infectious activity has been demonstrated in vitro, where LGG® prevented changes to epithelial cell morphology and attachment by E. coli.[65]

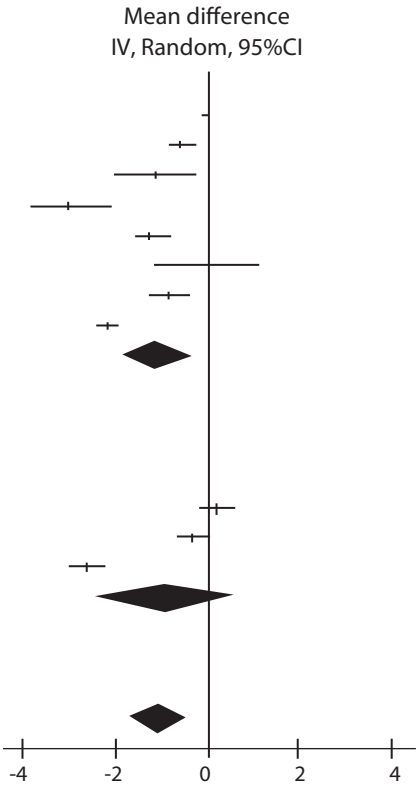

Figure 4: Duration of diarrhoea from acute gastroenteritis: Lactobacillus GG vs. control.[66]

‡ Phagocytosis receptors mediate the process of phagocytosis and are responsible for the early activation of the inflammatory response, prior to antibody production.

Antibiotic-Associated Diarrhoea

LGG® is also effective in reducing the incidence of antibiotic-associated diarrhoea. Two randomised placebo-controlled studies in children have shown LGG® to reduce the incidence of diarrhoea when co-administered with antibiotics for the duration of the treatment. The first study was in children with a median age of four years and acute infectious disorders such as respiratory, skin or urinary tract infections, at a dose of 10 to 20 billion CFU daily.[67] The second trial was in children with acute respiratory infections and a mean age of 4.5 years, at a dose of 20 billion CFU twice daily.[68]

In fact, a meta-analysis of probiotic treatment for antibiotic-associated diarrhoea has found that LGG® was one of only two single probiotic strains for which there was significant evidence for a reduction in the risk of antibiotic-associated diarrhoea. Six trials of LGG® were reviewed, giving a combined relative risk of 0.31 (95% CI 0.13–0.72, p=0.006).[69]

Healthy Intestinal Microbiota

As previously noted, LGG® has a balancing effect on the intestinal ecosystem; it increases the level of lactobacilli and bifidobacteria, promotes the formation of SCFAs, and normalises the mucosal barrier.[70]

A study cohort comprised 53 mothers with 53 newborn breastfed infants. The mothers were divided into two groups: mothers receiving LGG® (n=29) and mothers receiving placebo (n=24). Mothers started consumption of the preparation four weeks prior to labour and continued for three weeks after birth (seven weeks in total). Faecal samples were collected from mothers once before and once after delivery and from infants at five days and three weeks of age. LGG® had a significant effect on the infants' bifidobacterium microbiota when the probiotic was given to mothers (Figure 5). Disturbances in the microbiota, such as low levels of bifidobacteria, have been reported to precede the development of certain health conditions. This indicates the likely importance of initial microbiota establishment to an individual's health and wellbeing later in life.[71]

		B. longum		*B. infantis*		*B. breve*		*B. bifidum*		*B. catenulatum*		*B. adolescentis*	
Subject	Treatment	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Mother	Placebo*	40.9	45.8	9.1	20.8	9.1	12.5	4.5	8.3	36.4	41.7	31.8	20.8
	LGG*	62.1	58.6	17.2	20.7	17.2	17.2	13.7	6.9	34.5	34.5	34.5	27.6
		5 days	3 weeks	5 days	3 weeks	5 days†	3 weeks	5 days	3 weeks	5 days	3 weeks	5 days†	3 weeks
Infant	Placebo*	15.3	25.0	15.4	6.3	0.0	12.5	7.7	12.5	15.4	12.5	30.8	12.5
	LGG*	9.1	30.4	18.2	8.7	27.3	39.1	0	17.4	36.3	13.0	0.0	13.0

*No statistically significant differences ($P > 0.05$) were found between both sampling times for any of the analyzed bifidobacterial species neither in mothers nor in infants.
†Statistically significant difference ($P < 0.05$) between treatment groups (placebo vs. LGG).

Figure 5: Percentage of subjects positive for the Bifidobacterium species tested at the different sampling times in mothers (before and after delivery) receiving Lactobacillus rhamnosus GG (LGG®) or placebo, and their infants (5 days and 3 weeks of age).[72]

Cautions and Contraindications

Contraindications	• None of note
Moderate Level Cautions	• None of note
Low Level Cautions	• Severely ill and/or immunocompromised patients: Severely ill and/or immunocompromised patients may develop Lactobacillus bacteraemia and sepsis, though this is a very rare finding. Use only under medical supervision in hospitalised patients.[73,74] • Short bowel syndrome: Patients with short bowel syndrome might be predisposed to pathogenic infection from lactobacilli. This might be due to impaired gut integrity in patients with short bowel syndrome. Use only under medical supervision in patients with this condition.[75,76]

Pregnancy and Breastfeeding

• Safe to use in pregnancy and breastfeeding

Dosing Considerations

Antibiotics: Concomitant administration of antibiotics might decrease the effectiveness of probiotics. However, concomitant use of probiotics reduces the likelihood of gastrointestinal and genitourinary side effects and co-administration is considered beneficial. Separate administration of antibiotics and probiotic preparations by at least two hours.[77,78]

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