HUMAN HEALTH

Your Health - Our Science

Microbiome-based probiotic health solutions







Scientific studies show that the L. CASEI 431[®] probiotic strain may support immune health

A healthy gut for a healthy immune system

With growing awareness of our immune defense, consumers are proactively looking for solutions to increase their bodies' natural defense against flu-like sickness, common colds and other immune challenges.

We know that 70-80% of the body's immune cells are located around the gastrointestinal tract¹, where they are able to interact with the bacteria present in the lumen of the gastrointestinal tract. Providing clinically documented probiotic bacteria may modulate immune responses and support the body's natural defense.²⁻⁵

Lactobacillus paracasei, L. CASEI 431[®]

The Chr. Hansen probiotic strain L. CASEI 431[®] interacts with the immune cells located in the gastrointestinal tract and may help activate immune cells and help promote immune responses.²⁻⁵

Scientific studies on the L. CASEI 431 $^{\circ}$ probiotic strain within immune health

The L. CASEI 431° strain has been investigated in four randomized, double-blinded, placebo controlled clinical studies focusing on immune health, where results show that the strain may help support the body's immune defense, help promote immune responses and reduce duration of respiratory tract discomforts.²⁻⁵

Health benefits

Scientific studies show that the probiotic strain may:

- Support the body's natural defense²⁻⁵
- Reduce the duration of upper respiratory tract discomforts⁵
- Increase the numbers of specific neutralizing antibodies produced in response to an immunization challenge²⁻⁴
- Stimulate cytokine production to promote immune responses⁶



¹ Vighi et al., Clin Exp Immunol 2008; 153 (Supp 1):3-6) |² Trachootham et al., J Func Foods 33 (2017) 1-10 |³ Rizzardini et al. Br J Nutr 2012, 107:876-884 |⁴ de Vrese et al. Eur J Nutr 2005;44:406-13 |⁵ Jespersen et al. Am J Clin Nutr 2015;101(6):1188-96 |⁶ Chr. Hansen internal in vitro data on file.

This communication, on ingredients intended for consumer goods, is only intended for business-to-business and healthcare professionals. This communication is not intended for consumers of final consumer goods.

Strong clinical documentation



- Strong clinically documented strain with four well conducted, randomized, double-blinded, placebo controlled clinical studies showing immune benefits. In three of the studies, results support immune benefits at a recommended potency of 1 billion CFU/day^{2,3,5}
- The clinical impact of the L. CASEI 431[®] strain is documented in the world's 2nd largest clinical study within probiotics (over 1,100 participants)[°]
- L. CASEI 431^e for immune health is a patented technology with patents granted in Europe and China allowing customers to differentiate their products in the market with a unique value proposition to consumers^{**}

Scientific studies on the L CASEI 431[®] strain within immune health

The L. CASEI 431[®] probiotic strain has been investigated in four randomized, double blinded, placebo controlled clinical trials all indicating that the strain may help support the body's natural defense.²⁻⁵ Results from two of the studies are illustrated below:



Randomized, double-blinded, placebo-controlled study with 115 adults consuming the L. CASEI 431[®] strain or placebo product for 6 weeks. After two weeks the subjects were exposed to an immunization challenge.

Compared to the placebo, supplementation with the L. CASEI 431[®] strain was shown to increase the level of antibodies specific to the immunization challenge and increase the number of subjects obtaining a two-fold increase in specific antibodies after the immunization challenge.³



Randomized, double-blinded, placebo-controlled study with 1,104 adults consuming the L. CASEI 431° strain or placebo product for 42 days.

The L. CASEI 431° strain was shown to significantly reduce duration of upper respiratory discomforts during a three-week period. $^{\rm 5}$

+140 years of know how

Strain combination	Dosage form	Functional ingredients	Shelf life	Potency at end of shelf life
L. CASEI 431 [®]	Capsules in vial	80 mg Vitamin C	24 months at 25- 30 °C	1 billion / Capsule
L. CASEI 431 [®]	ChewTab in vial	12 mg Vitamin C	24 months at 25- 30 °C	1 billion / ChewTab
L. CASEI 431 [®]	Bulk Capsule	80 mg Vitamin C	24 months at 2-8°C	7 billion / Capsule
L. CASEI 431 [®]	Bulk ChewTab	12 mg Vitamin C	24 months at 2-8°C	11 billion / ChewTab
L. CASEI 431 [®]	Blend		24 months at 2-8°C	100 billion / g
L. CASEI 431 [®]	Blend		24 months at 2-8°C	30 billion / g

*To our knowledge the 2nd largest probiotic clinical trial ever conducted **Patent reference: CN: ZL201510845386.0, EP 2627198 validated in DE, DK, FR, GB, IT





Taking probiotics can help reduce costs of flu-like sickness

Taking probiotics can help reduce the number of sick days

54 m	54 million days can be avoided each year if the US population takes probiotics
17 days	When people get flu-like sickness, on average they miss 1.7 days¹ of work
61%	Taking probiotics can help reduce lost work days by 61%



Flu-like sickness poses a heavy burden on the healthcare system - it is frequent and it can be severe. Each year, flu-like sickness results in a high number of visits to primary care physicians (PCPs), prescriptions of antibiotics and lost working days.

The cost of flu-like sickness to the US economy is estimated to be \$11.2 billion²

¹ Palmer et. al. 2010 | ² Putri WCWS et al. Vaccine. 2018 Jun 22



Fewer visits to primary care physicians and fewer prescriptions

Flu-like sickness often comes with direct costs to healthcare payers:

- Visits to primary care physicians (PCPs)
- Cost of medicine

Taking probiotics can help reduce the direct costs related to flu-like sickness by 17% for US health care payers.



Estimated costs of flu-like sickness: \$3.2 billion direct medical costs each year³



Expected savings from fewer visits to PCPs and fewer prescriptions: \$501 million

Taking probiotics can help reduce antibiotic prescriptions by 30%⁴



2.2 million antibiotic courses can be avoided each year in the US if the population takes probiotics.

1/3 of antibiotics prescribed to treat flu-like sickness in the US are estimated to be redundant

Antibiotic resistance is one of the biggest threats to global health, food security and development today, according to the World Health Organization.

Overuse of antibiotics can cause bacteria to become resistant, meaning current treatments will no longer work. This study provides further evidence of how probiotics and 'good bacteria' can respond to some of the world's biggest challenges.

CDC newsroom 2016

The impact of probiotics is higher in children

Children (aged 0-15) make up just below 20% of the population. However, taking probiotics can lead to proportionally higher savings in terms of lost days and total costs savings. Each of these make up 34% of the total reductions, respectively.



Children (aged 0-15)

A fever (temperature of >100°F [37.8°C]) and a cough or a sore throat

About studies

The health economic study is sponsored by Chr. Hansen, conducted and reviewed by academic and industry experts. It is published in the Journal Frontiers in Pharmacology. The underlying data used in the study came from two independent reviews: York Health Economics Consortium (YHEC) and Cochrane.

³The Cochrane Collaboration, Hao, Dong and Wu, 2015 | ⁴Hao, Quikui 2015. "Probiotics for preventing acute upper respiratory tract infections." Cochrane database of systematic reviews.King, Sarah. 2014. "Effectiveness of probiotics on the duration of illness in healthy children and adults who developcommon acute respiratory infectious conditions: A systematic review and meta-analysis." British journal of nutrition.







INFANT & YOUNG CHILDREN'S HEALTH

Help ease common childhood respiratory tract challenges

Immune system challenges impact your daily life

Young children have an immature immune system¹, making them susceptible to respiratory tract challenges² such as occasional sore throat, runny nose and ear discomfort.

Personal impact

Respiratory tract discomfort and occasional sore throat diminish quality of life and pose a burden for the affected children and their parents. Non-medical costs, such as babysitting and absence from work, also arise.³

Global impact

Occasional respiratory tract discomfort is the most common reason for visiting health care practitioners and for antibiotic use in childhood – causing a substantial economic burden on society.³ Occasional sore throat, runny nose and respiratory discomfort are the most common primary care health problem(s).^{3,4} Preschool children experience on average 3 occurrences per year. The likelihood is 2-3 times higher in children who attend day care.⁵

The solution - Bifidobacterium (BB-12®) and Lactobacillus rhamnosus (LGG®)

Many of the body's immune cells are located in the gastrointestinal tract. Bifidobacterium (BB-12[®]) and Lactobacillus rhamnosus (LGG[®]) may regulate the immune response and beneficially impact the immune function.

Health benefits

Studies within immune health show that the probiotic strains LGG[®] & BB-12[®] may reduce

- Number of children experiencing respiratory tract discomforts⁶⁻⁹
- Number of days away from day care⁶
- Number of infants with ear discomfort¹⁰
- Use of conventional therapy for ear discomfort¹⁰



How the Bifidobacterium (BB-12[®]) and Lactobacillus rhamnosus (LGG®) probiotic strains work



Reduced number of days away from day care⁶





In this randomized, double-blind, placebo-controlled study 281 children attending day care centers were included. They received 1 billion CFU/day of Lactobacillus rhamnosus (LGG®) for 3 months. The study found a reduced risk of upper respiratory discomforts and a reduced number of days away from day care in the Lactobacillus rhamnosus (LGG®) group compared to the placebo group.

Randomized, double-blind, placebo-controlled study including 81 infants receiving Lactobacillus rhamnosus (LGG®) and Bifidobacterium (BB-12®) daily until the age of 12 months. The study found a reduced number of infants with ear discomfort and a reduced use of conventional therapy for ear discomfort in the probiotic group compared to the placebo group.

+140 years of know how

Strain name	Active ingredients	Dosage forms	Shelf life	Potency at end of shelf life
BB-12®	With and without Vit. D	Oil drop	24 months	1 billion CFU/dose
BB-12®	-	Blend for infant formula	24 months	30 or 100 billion CFU/g
LGG®	-	Oil drop	24 months	1 billion CFU/dose
LGG®	With and without Vit. D	Oil drop	24 months	5 billion CFU/dose
LGG®	-	Blend for infant formula	24 months	30 or 100 billion CFU/g
BB-12® + LGG®	-	Oil drop	24 months	1 billion CFU/dose
BB12® + LGG®	-	Blend for infant formula	24 months	30 billion CFU/g

¹Ygberg and Nilsson, Acta Paediatrica, 2012 Feb; 101(2):120-7 |² Tregoning and Schwarz Clin Microbiol Rev 2010 Jan; 23(1): 74–98 |³Lenoir-Wijnkoop et al. PLoS One, 2015; 10(4):e0122765 | ⁴ Zoorob et al. Am Fam Physician. 2012 Nov 1;86(9):817-822 | ⁵Lu et al. Child Care Health Dev 2004; 30: 361-8 | ⁶Hojsak et al. Clin Nutr, 2010; 29:312-316 | ⁷Hojsak et al. Pediatrics, 2010;125:e1171-e1177 | 8 Taipale et al. Br J Nutr, 2011; 105:409-41 | 9 Taipale et al. Pediatric Research, 2016; 79:65-69 | 10 Rautava S et al. Br J Nutr, 2009; 101:1722-1726







INFANT & YOUNG CHILDREN'S HEALTH

Reduce excessive crying and fussing

Excessive crying and fussing

Worldwide, up to 25% of all infants under 3 months of age suffer from excessive crying and fussing.¹ Up to one in five infants visits the doctor because of excessive crying during the first months of life.²

Personal impact

Excessive crying and fussing is usually self-limiting; however, it is a source of distress for the infants, parents and caregivers.³ Excessive crying and fussing is associated with parental guilt, frustration, sleep problems and visits to the doctor.³

Global impact

Excessive crying and fussing is one of the challenges of parenthood. It is one of the common reasons parents seek doctors' advice during their child's first 3 months of life.⁴

Infants who cry and fuss excessively need more good bacteria

Infants who cry and fuss excessively have lower counts of good bacteria and increased concentrations of undesirable bacteria in their digestive tracts.^{3,5}

The solution can be Bifidobacterium (BB-12®)

Bifidobacterium (BB-12[®]) in oil drops and blends for infants colonizes the digestive tract and positively modulates the composition of the intestinal microbiota.⁶ Bifidobacteria are found in the milk of breastfeeding mothers and Bifidobacterium (BB-12[®]) has been shown to support the infant's digestive comfort.^{6,7}

Clinical evidence

Bifidobacterium (BB-12 $^{(8)}$) has been investigated in a randomized, double-blind, placebo-controlled trial in infants who cry and fuss excessively.⁸

Health benefits

Clinical study in infants with excessive crying and fussing shows that Bifidobacterium (BB-12®) may help

- Reduce crying duration⁸
- Reduce number of daily crying episodes⁸

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How Bifidobacterium (BB-12[®]) may help ease excessive crying and fussing in infants



Intestinal Lumen

Mucus

Intestinal Cells

Immune Cells **Jur Science**

Scientific evidence on Bifidobacterium (BB-12®) within excessive crying and fussing in infants⁸

- In this randomized, double-blind, placebocontrolled trial 80 breastfed infants (≤ 7 weeks) with excessive crying and fussing were included.
- They received either 1 billion CFU/day of Bifidobacterium (BB-12[®]) or placebo for 28 days.
- The study found an increased number of infants with a ≥50% reduction in crying after 28 days in the Bifidobacterium (BB-12®) group compared to placebo. Furthermore, a reduced number of daily crying episodes was observed in the Bifidobacterium (BB-12®) supplemented group.⁸

80% of infants in the Bifidobacterium (BB-12[®]) and 33% of infants in the placebo group reached the target of \geq 50% reduction in duration of crying after 28 days⁸



+140 years of know how

Strain name	Other active ingredients	Dosage forms	Shelf life	Potency at end of shelf life	Recommended daily use
Bifidobacterium (BB-12®)	With and without Vit. D	Oil drops	24 months at <30°C	1 B CFU/dose	1 B CFU (6 drops)
Bifidobacterium (BB-12®)	_	Blend for infant formula	24 months at 2-8 °C	30 and 100 B CFU/g	1 B CFU
Bifidobacterium (BB-12®)	_	Blend for infant sticks	24 months at 2-8 °C	4 B CFU/g (1 stick)	1 B CFU (1 stick)

¹ Wolke et al. J Pediatr, 2017;185:55-61.e4 | ² Alvarez et al. Paediatr, 1996; 85:463-466 | ³ Zeevenhooven et al. Nat Rev Gastroenterol Hepatol, 2018;15:479-496 | ⁴ Kheir et al. Ital J Pediatr, 2012;38:34 | ⁵ Mayer et al. J Clin Invest, 2015;125:926-38 | ⁶ Jungersen et al. Microorganisms, 2014;2:92-110 | ⁷ Fernandez et al. Cell Mol Biol, 2013;59:31-42 | ⁸ Nocerino et al. Alimentary Pharmacology & Therapeutics, Dec 2019 | ⁹ Pärtty et al., PLoS ONE, 2012; 7(3):1-5





GUT HEALTH

Reduce risk of upset stomach while travelling

What causes stomach upset while traveling?

When travelling to foreign regions, we are exposed to different foods, hygiene levels and environments. This can cause an upset stomach. A disruption of the gut microbiota with *Escherichia coli* is the most common cause globally of an upset stomach while traveling¹

Travel-related stomach upset is common

The prevalence of travelers' loose stools varies according to destination, but is up to 50% in high-risk countries^{4,5}

Good bacteria go with good travel

Experiencing an upset stomach while traveling is annoying and potentially dangerous. Studies have shown that supplementing one's diet with good bacteria before, during and after traveling may reduce the risk of acquiring an upset stomach^{2,3}

The solution - QuatroCap*

Chr. Hansen's QuatroCap^{*} is a unique formulation of four probiotic strains: BB-12[®], LA-5[®], STY-31[™] and LBY-27[™]. These strains may help you maintain regularity and avoid stomach upset when you are on the move and in foreign regions

Scientific evidence on QuatroCap* and gastrointestinal health during and after travel is promising

QuatroCap* has been investigated in randomized, double-blind, placebo-controlled trials of adult travelers

Health benefits

Scientific evidence suggests that the probiotic solution QuatroCap* may:

- Reduce the risk of acquiring an upset stomach while travelling^{2,3}
- Reduce occurrence of loose stools after returning home³

¹ Barrett et al, BMJ, 2016; 353:i1937 | ² Black FT et al, Travel Medicine, 1989; 333-335 | ³ Black FT et al, unpublished data, 1988 | ⁴ Steffen et al, JAMA, 2015; 313:71-80 | ⁵ Steffen et al, J Travel Med, 2004; 11:231-237 *QuatroCap is a unique formulation of the four probiotic strains BB-12[®], LA-5[®], STY-31[™] and LBY-27[™]



How QuatroCap* works

Strains in QuatroCap* can transiently colonize the mucosal surfaces in the intestine and thereby increase the possibility for delivering beneficial health effects

- Strains in QuatroCap* modifies dysbiosis e.g. by producing antimicrobial substances and competing with the harmful bacteria for adhesion sites in the intestine
- 2. Strains in QuatroCap* **support the intestinal barrier** function e.g. by stimulating intestinal cell growth
- Strains in QuatroCap* regulate the immune response and may beneficially impact the immune function e.g. by maturating and activating immune cells

Scientific evidence on QuatroCap* and

gastrointestinal health while traveling

Randomized placebo controlled study with 94

during a 2 week trip to a high risk country

be recommended to all travelers¹

Black FT et al. Travel Medicine, 1989: 333-335

• Upset stomach defined as three or more watery

Study conclusion: QuatroCap* can without any risk

travelers consuming QuatroCap* or placebo capsules

is promising

stools/24h



QuatroCap* reduced the number of travellers with an upset stomach¹



*QuatroCap is a unique formulation of the four probiotic strains BB-12®, LA-5®, STY-31™ and LBY-27™

Scientific evidence on QuatroCap* and gastrointestinal health after travel is promising

- Randomized double-blinded placebo controlled study with 101 travelers consuming QuatroCap* or placebo capsules before, during and after a 15 day trip to a high risk country
- QuatroCap* was shown to reduce risk of an upset stomach while traveling and none of the travelers consuming QuatroCap* acquired an upset stomach after returning home

²Black FT et al, unpublished data, 1988

QuatroCap* reduced the number of travelers experiencing loose stools after returning home from travels²



*QuatroCap is a unique formulation of the four probiotic strains BB-12[®], LA-5[®], STY-31[™]and LBY-27[™]

+140 years of know how

Strain combination	Dosage form	Shelf life	Potency at end of shelf life	
QuatroCap*	Bulk capsule	24 months at < 25°C	1 billion**	
* QuatroCap* is a unique formulation of the four probiotic strains BB-12 [®] , LA-5 [®] , STY-31 [™] and LBY-27 [™]				

** Proposed end of shelf life potency of a finished product. Provided a suitable primary packaging is selected and that the product is stored and handled correctly



SKIN HEALTH

Help maintain healthy-looking skin with a combination of probiotics and collagen in the T-Win stick

Maintaining healthy looking skin is an increasing concern among aging consumers

The skin is the body's largest organ and it is affected by urban lifestyle and stress.

The population is ageing globally and with that comes increasing demand for products to support healthy-looking skin

The T-Win stick: a unique formulation for your skin

The T-Win stick from Chr. Hansen combines ingredients targeting the skin from multiple angles; Probiotic bacteria L. paracasei F19[®] helps stimulate immune factors linked to skin health³, bioactive collagen peptides^{4,5}, and hyaluronic acid⁵ may help improve skin appearance and a micronutrient blend helps contribute to maintenance of normal skin and collagen formation⁷⁻¹²

Documented benefits

Scientific evidence suggests that ingredients in the T-Win stick may help:

our Fea

- Increase skin elasticity⁴
- Reduce skin wrinkles around the eyes⁵
- Improve skin moisture^{6*}

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Aging skin

Skin is the largest organ of the body and is constantly exposed to physical, chemical, bacterial, and fungal challenges that with time changes the structure of the skin². Aging of the skin results in multiple changes including breakdown and disorganization of collagen, a reduction of elastin and diminished ability to retain water². These changes results in wrinkles, looser and dryer skin¹³. Additionally, UV radiation results in skin barrier fragility that ultimately reduces the immune defense¹⁴⁻¹⁵

Probiotic bacteria for skin health

Human microbiome research is showing us the important role bacteria play in our daily life¹⁶. An increasing number of scientific publications are published on the topic of skin and microbiome; we now know that probiotic bacteria and especially lactobacilli are natural good bacteria that can confer systemic impacts including benefits for the skin.¹⁷ Lactobacilli have been shown to influence and help boost the immune system¹⁸, and Lactobacillus paracasei demonstrates anti-inflammatory properties in skin models¹⁹



Bioactive collagen peptides are shown to reduce wrinkle volume⁵

- Randomized placebo-controlled study with 114 women aged 45-65 randomized to consume bioactive collagen peptides or placebo for 8 weeks
- Skin wrinkle volume were measured around the eyes at baseline and after 4, 8 and 12 weeks
- Study conclusion: Bioactive collagen peptides significantly reduced eye wrinkle volume and increased the content of procollagen type I and elastin



The product

12 months shelflife

• T-Win stick double sachet

Ingredients: Hydrolyzed collagen; maltodextrin; fructo-oligosaccharide; L. Paracasei F19[®], sodium hyaluronate; ascorbic acid (Vitamin C), acidifying agent, citric acid (E 330); peach flavour; sweetening agent: sucralose (E 955); Riboflavine (vitamin B2), Niacin (Vitamin B3), zinc.

¹ LUMINA skinbiotic report | ² Krutmann et al. J Dermatol Sci. 2017 Mar;85(3):152-161 | ³ internal data on file | ⁴ Proksch et al. Skin Pharmacol Physiol 2014;27:47-55 | ⁵ Proksch et al. Skin Pharmacol Physiol 2014;27:113-119 | ⁶ Kawada et al. 2014 NutrJ.; 13: 70 | ⁷ EFSA Journal 2009; 7(9):1226. [28 pp.] | ⁸ EFSA Journal 2010; 8(10):1815. [20 pp.] | ⁹ EFSA Journal 2009; 7(9):1226. [28 pp.] | ¹⁰ EFSA Journal 2010; 7(9):1226. [28 pp.] | ¹⁰ EFSA Journal 2010; 8(10):1814. [28 pp.] | ¹¹ Naylor et al. Naturitas, 2011 Jul;69(3):249-56 | ¹⁴ Patra et al. Frontiers in Medicine 2018;5(166) | ¹⁵ Clydesdale et al. Immunol Cell Biol, 2001;79(6):547-68 | ¹⁶ Cho et al. Nature Reviws, 2012;13:260-270 | ¹⁷ Salem et al. Fromt Microbiol 2018; 9:1459 | ¹⁸ Kober et al. Int J Womens Dermatol, 2015;1(2):85-89 | ¹⁹ Benyacoub et al. Benef Microbes 2014;5:129-36 | ²⁰ internal data on file | ²¹ Ando et al. Dermatological Science, 2000;24(3):190-202 | ²² Stern et al. 2008, Clin Dermatol;26:106-122 | * Studies conducted on various doses of HA ranging from 37.5mg-240mg. F19[®] is a registered trademark of Arla Foods Amba



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