

BIFIDOBACTERIUM LACTIS BL-04®

B. lactis BL-04 is also known as DGCC2908 and RB 4825.

The strain has been deposited in the American Type Culture Collection ATCC safe deposit as SD5219. In Lammers et al., 2003 *B. lactis* BL-04 is named *B. longum* BL04. In Akin et al., 2005 and 2007, Bartosch et al., 2005, Nori et al., 2009 and Pedroso et al., 2012 *B. lactis* BL-04 is named *B. lactis* BL01.

In vitro trials

Safety

1. Morovic W, Roper JM, Smith AB, Mukerji P, Stahl B, Rae JC, Ouwehand AC. 2017. Safety evaluation of HOWARU® Restore (*Lactobacillus acidophilus* NCFM, *Lactobacillus paracasei* Lpc-37, *Bifidobacterium animalis* subsp. *lactis* BL-04 and *B. lactis* Bi-07) for antibiotic resistance, genomic risk factors and acute toxicity. *Food Chem Toxicol.* 110: 316-324. doi: 10.1016/j.fct.2017.10.037.

Immune system modulation

1. Martinez FA, Domínguez JM, Converti A, de Souza Oliveira RP. 2015. Production of bacteriocin-like inhibitory substance by *Bifidobacterium lactis* in skim milk supplemented with additives. *J Dairy Res.* 82(3): 350-5.

2. Foligné B, Nutten S, Grangette C, Dennin V, Goudercourt D, Poirer S, Dewulf J, Brassart D, Mercenier A, Pot B. 2007. Correlation between *in vitro* and *in vivo* immune modulatory properties of lactic acid bacteria. *World J Gastroenterol.* 13: 236-243.

3. Lammers KM, Brigidi P, Vitali B, Gionchetti P, Rizzello F, Caramelli E, Matteuzzi D, Campieri M. 2003. Immunomodulatory effects of probiotic bacteria DNA: IL-1 and IL-10 response in human peripheral blood mononuclear cells. *FEMS Immunol Med Microbiol.* 8: 165-72. [*B. longum* BL04 = *B. lactis* BL-04]

Prebiotic utilization

1. Ejby M, Fredslund F, Andersen JM, Vujičić Žagar A, Rosager Henriksen J, Andresen TL, Svensson B, Slotboom DJ, Abou Hachem M. 2016. An ATP-binding cassette transporter mediates the uptake of α -(1,6)-linked dietary oligosaccharides in *Bifidobacterium* and correlates with competitive growth on these substrates. *J Biol Chem.*

2. Ejby M, Fredslund F, Vujicic-Zagar A, Svensson B, Slotboom DJ, Abou Hachem M. 2013. Structural basis for arabinoxylo-oligosaccharide capture by the probiotic *Bifidobacterium animalis* subsp. *lactis* BL-04. *Mol Microbiol.* 90: 1100-1112.

3. Vigsnaes LK, Nakai H, Hemmingsen L, Andersen JM, Lahtinen SJ, Rasmussen LE, Hachem MA, Petersen BO, Duus JØ, Meyer AS, Licht TR, Svensson B. 2013. *In vitro* growth of four individual human gut bacteria on oligosaccharides produced by chemoenzymatic synthesis. *Food Funct.* 4: 784-793.

4. Maher AH, Fredslund F, Andersen JM, Jonsgaard Larsen R, Majumder A, Ejby M, Van Zanten G, Lahtinen SJ, Barrangou R, Klaenhammer T, Jacobsen S, Coutinho PM, Lo Leggio L and Birte Svensson. 2012. Raffinose family oligosaccharide utilisation by probiotic bacteria: insight into substrate recognition, molecular architecture and diversity of GH36 α -galactosidases. *Biocatalysis and Biotransformation*, 2012; Early Online: 1-10.

5. Mäkeläinen H, Saarinen M, Stowell J, Rautonen N and Ouwehand AC. 2010. Xylo-oligosaccharides and lactitol promote the growth of *Bifidobacterium lactis* and *Lactobacillus* species in pure cultures. *Beneficial Microbes* 1: 139-148.

6. do Espírito Santo AP, Silva RC, Soares FASM, Anjos D, Gioielli LA, Oliveira MN. 2010. Açai pulp addition improves fatty acid profile and 1 probiotic viability in yoghurt. *Int Dairy J.* In press.

7. Akin MB, Akin MS, Kirmaci Z. 2007. Effects of inulin and sugar levels on the viability of yogurt and probiotic bacteria and sensory characteristics in probiotic ice-cream. *Food Chem.* 104: 93-99. [Strain BL01 = BL-04]

8. Akin MS. 2005. Effects of inulin and different sugar levels on viability of probiotic bacteria and the physical and sensory characteristics of probiotic fermented ice-cream. *Milchwissenschaft* 60: 297-301. [Strain BL01 = BI-04]

Sugar transport

1. Biczinski EP, Phillips AT, Roberts RF. 2008. Transport of Glucose by *Bifidobacterium animalis* subsp. *lactis* Occurs via Facilitated Diffusion. *Appl Environ Microbiol.* 74: 6941-6948. [Strain RB 4825 = BI-04]

Genomics

1. Korolev, Semen A, Lyzhin SA, Zverkov OA, Seliverstov AV, and Lyubetsky VA. 2015. "A Search for Genes Encoding Histidine-Containing Leader Peptides in Actinobacteria." In Proceedings of the 39th IITP RAS Interdisciplinary Conference & School "Information Technology and Systems, 53-60.

2. Milani C, Duranti S, Lugli GA, Bottacini F, Strati F, Arioli S, Foroni E, Turrone F, van Sinderen D, Ventura M. 2013. Comparative Genomics of *Bifidobacterium animalis* subsp. *lactis* Reveals a Strict Monophyletic Bifidobacterial Taxon. *Appl Environ Microbiol.* 79: 4304-4315.

3. Barrangou R, Briczinski EP, Traeger LL, Loquasto JR, Richards M, Horvath P, Coûté-Monvoisin AC, Leyer G, Rendulic S, Steele JL, Broadbent JR, Oberg T, Dudley EG, Schuster S, Romero DA, Roberts RF. 2009. Comparison of the complete genome sequences of *Bifidobacterium animalis* subsp. *lactis* DSM 10140 and BI-04. *J Bacteriol.* 191: 4144-4151.

4. Briczinski EP, Loquasto JR, Barrangou R, Dudley EG, Roberts AM, Roberts RF. 2009. Strain-specific genotyping of *Bifidobacterium animalis* subsp. *lactis* by using single-nucleotide polymorphisms, insertions and deletions. *Appl Environ Microbiol.* 75: 7501-8.

Enzyme Characterization and proteomics

1. Morrill J, Kulcinskaja E, Sulewska AM, Lahtinen S, Ståhlbrand H, Svensson B, Hachem M. 2015. The GH5 1,4- β -mannase from *Bifidobacterium animalis* subsp. *lactis* BI-04 possesses a low-affinity mannan-binding module and highlights the diversity of mannanolytic enzymes. *BMC Biochem.* 16: 26.

2. Viborg AH, Fredslund F, Katayama T, Nielsen SK, Svensson B, Kitaoka M, Lo Leggio L, Abou Hachem M. 2014. A β 1-6/ β 1-3 galactosidase from *Bifidobacterium animalis* subsp. *lactis* BI-04 gives insight into sub-specificities of β -galactoside catabolism within *Bifidobacterium*. *Mol Microbiol.* 94: 1024-1040.

Gastrointestinal ecology

3. Forssten SD & Ouwehand AC. 2017. Simulating colonic survival of probiotics in single-strain products compared to multi-strain products, *Microbial Ecology in Health and Disease*, 28: 1, 1378061.

Animal trials

Safety

1. Morovic W, Roper JM, Smith AB, Mukerji P, Stahl B, Rae JC, Ouwehand AC. 2017. Safety evaluation of HOWARU® Restore (*Lactobacillus acidophilus* NCFM, *Lactobacillus paracasei* Lpc-37, *Bifidobacterium animalis* subsp. *lactis* BI-04 and *B. lactis* Bi-07) for antibiotic resistance, genomic risk factors and acute toxicity. *Food Chem Toxicol.* 110: 316-324. doi: 10.1016/j.fct.2017.10.037.

Immune system modulation

1. Foligné B, Nutten S, Grangette C, Dennin V, Goudercourt D, Poiret S, Dewulf J, Brassart D, Mercenier A, Pot B. 2007. Correlation between *in vitro* and *in vivo* immune modulatory properties of lactic acid bacteria. *World J Gastroenterol.* 13: 236-243.

Anti-pain/analgesic

1. Rousseaux C, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, Gebous K, Chamaillard M, Ouwehand A, Leyer G, Carcano D, Colombel JF, Ardid D, Desreumaux P. 2007 *Lactobacillus acidophilus* modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat Med.* 13: 35-37.

Gastrointestinal ecology

1. Pătruică S, Mot D. 2012. The effect of using prebiotic and probiotic products on intestinal micro-flora of the honeybee (*Apis mellifera carpatica*). *Bull Entomol* 102: 619-623.

Human clinical studies

Safety

1. Cox AJ, West NP, Horn PL, Lehtinen MJ, Koerbin G, Pyne DB, Lahtinen SJ, Fricker PA, Cripps AW. 2014. Effects of probiotic supplementation over 5 months on routine haematology and clinical chemistry measures in healthy active adults. *Eur J Clin Nutr.*

Antibiotic associated diarrhea

1. Barker AK, Duster M, Valentine S, Hess T, Archbald-Pannone L, Guerrant R, Safdar N. 2017. A randomized controlled trial of probiotics for *Clostridium difficile* infection in adults (PICO). *J Antimicro Chemother.* 72(11): 3177-3180. doi: 10.1093/jac/dkx254.

2. Ouwehand AC, DongLian C, Weijian X, Stewart M, Ni J, Stewart T, Miller LE. 2014. Probiotics reduce symptoms of antibiotic use in a hospital setting: a randomized dose response study. *Vaccine.* 32(4): 458-63.

Colon cancer

1. Hibberd AA, Lyra A, Ouwehand AC, et al. 2017. Intestinal microbiota is altered in patients with colon cancer and modified by probiotic intervention. *BMJ Open Gastro* 4: e000145. doi: 10.1136/bmjgast-2017-000145.

Gastrointestinal ecology

1. Engelbrektson AL, Korzenik JR, Pittler A, Sanders ME, Klaenhammer TR, Leyer G, Kitts CL. 2009. Probiotics to minimize the disruption of faecal microbiota in healthy subjects undergoing antibiotic therapy. *J Med Microbiol.* 58: 663-670.

2. Engelbrektson AL, Korzenik JR, Sanders ME, Clement B, Leyer G, Klaenhammer TR, Kitts CL. 2006. Analysis of treatment effects on the microbial ecology of the human intestine. *FEMS Microbiol Ecol.* 57: 239-250.

3. Bartosch S, Woodmansey EJ, Paterson JC, McMurdo ME, Macfarlane GT. 2005. Microbiological effects of consuming a synbiotic containing *Bifidobacterium bifidum*, *Bifidobacterium lactis* and oligofructose in elderly persons, determined by real-time polymerase chain reaction and counting of viable bacteria. *Clin Infect Dis.* 40: 28-37. [Strain BL01 = Bl-04]

Immune system enhancement

1. Paineau D, Carcano D, Leyer G, Darquy S, Alyanakian MA, Simoneau G, Bergmann JF, Brassart D, Bornet F, Ouwehand AC. 2008. Effects of seven potential probiotic strains on specific immune responses in healthy adults: a double-blind, randomized, controlled trial. *FEMS Immunol Med Microbiol.* 53: 107-13.

Weight management

1. Gomes AC, de Sousa RG, Botelho PB, Gomes TL, Prada PO, Mota JF. 2017. The additional effects of a probiotic mix on abdominal adiposity and antioxidant Status: A double-blind, randomized trial. *Obesity (Silver Spring).* Jan;25(1): 30-38. doi: 10.1002/oby.21671.

Allergy treatment

1. Ouwehand AC, Nermes M, Collado MC, Rautonen N, Salminen S, Isolauri E. 2009. Specific probiotics alleviate allergic rhinitis during the birch pollen season. *World J Gastroenterol.* 15: 3261-8.

General health

1. Zhang Y, Chen J, Wu J, Chalson H, Merigan L, Mitchell A. 2013. Probiotic use in preventing postoperative infection in liver transplant patients. *Hepatobiliary Surg Nutr.* Jun;2(3): 142-7.

2. West NP, Horn PL, Pyne DB, Warren HS, Asad S, Cox AJ, Lahtinen SJ, Lehtinen MJ, Fricker PA, Cripps AW, Fazekas de St Groth B. 2016. Probiotic supplementation has little effect on peripheral blood regulatory T cells. *J Allergy Clin Immunol.*

3. West NP, Horn PL, Barrett S, Warren HS, Lehtinen MJ, Koerbin G, Brun M, Pyne DB, Lahtinen SJ, Fricker PA, Cripps AW. 2014. Supplementation with a single and double strain probiotic on the innate immune system for respiratory illness. *e-SPEN Journal* 9: e178-e184.

4. West NP, Horn PL, Pyne DB, Gebiski VJ, Lahtinen SJ, Fricker PA, Cripps AW. 2014. Probiotic supplementation for respiratory and gastrointestinal illness symptoms in healthy physically active individuals. *Clin Nutr.* Aug;33(4): 581-7.

Product functionality

1. Nielsen LN, Roager HM, Casas ME, Frandsen HL, Gosewinkel U, Bester K, Licht TR, Hendriksen NB, Bahl MI. 2017. Glyphosate has limited short-term effects on commensal bacterial community composition in the gut environment due to sufficient aromatic amino acid levels. *Environ Pollut.* 233: 364-376. doi: 10.1016/j.envpol.2017.10.016.
2. dos Santos Cruzen CE, Hoffmann JF, Zandoná GP, Fiorentini AM, Rombaldi CV, Chaves FC. 2016. Probiotic butiá (*Butia odorata*) ice cream: Development, characterization, stability of bioactive compounds and viability of *Bifidobacterium lactis* during storage. *LWT - Food Science and Technology.* 75. 10.1016/j.lwt.2016.09.011.
3. Blanco-Miguez A, Gutierrez-Jacome A, Fdez-Riverola F, Lourenco A and Sanchez B. 2016. 'A peptidome-based phylogeny pipeline reveals differential peptides at the strain level within *Bifidobacterium animalis* subsp. *lactis*', *Food Microbiol.* 60: 137-41.
4. Esmerino EA, Cruz AG, Pereira EP, Rodrigues JB, Faria JA, Bolini HM. 2013. The influence of sweeteners in probiotic Petit Suisse cheese in concentrations equivalent to that of sucrose. *J Dairy Sci.* 96: 5512-521.
5. Oberg TS, Ward RE, Steele JL, Broadbent JR. 2013. Genetic and Physiological Responses of *Bifidobacterium animalis* subsp. *lactis* to Hydrogen Peroxide Stress. *J Bacteriol.* [Epub ahead of print] PubMed PMID: 23772066.
6. do Espírito Santo AP, Perego P, Converti A, Oliveira MN. 2012. Influence of milk type and addition of passion fruit peel powder on fermentation kinetics, texture profile and bacterial viability in probiotic yoghurts. *LWT - Food Science and Technology* 47: 393e399.
7. Florence ACR, Oliveira RPS, Silva RC, Soares FASM, Gioielli LA, Oliveira MN. 2012. Organic milk improves *Bifidobacterium lactis* counts and bioactive fatty acids contents in fermented milk. *LWT - Food Science and Technology* 49: 89e95.
8. Pedroso DL, Thomazini M, Heinemann RJB, Favaro-Trindade CS. 2012. Protection of *Bifidobacterium lactis* and *Lactobacillus acidophilus* by microencapsulation using spray-chilling. *International Dairy Journal* 26 127e132. [BI-01=BI-04, LAC-04=La-14]
9. do Espírito Santo AP, Cartolano NS, Silva TF, Soares FA, Gioielli LA, Perego P, Converti A, Oliveira MN. 2012. Fibers from fruit by-products enhance probiotic viability and fatty acid profile and increase CLA content in yoghurts. *Int J Food Microbiol.* 154: 135-144.
10. Oberg TS, Steele JL, Ingham SC, Smeianov VV, Briczinski EP, Abdalla A, Broadbent JR. 2011. Intrinsic and inducible resistance to hydrogen peroxide in *Bifidobacterium* species. *J Ind Microbiol Biotechnol.*
11. Ding WK, Shah NP. 2010. Enhancing the Biotransformation of Isoflavones in Soymilk Supplemented with Lactose Using Probiotic Bacteria during Extended Fermentation. *J Food Sci.* 75: M140-M149.
12. Espirito Santo AP, Silva RC, Soares FASM, Anjos D, Gioielli LA, Oliveira MN. 2010. Açai pulp addition improves fatty acid profile and probiotic viability in yoghurt. *International Dairy Journal* 20: 415-422.
13. Ding WK, Shah NP. 2009. Effect of various encapsulating materials on the stability of probiotic bacteria. *J Food Sci.* 74:M100-107.
14. Ding WK, Shah NP. 2009. An Improved Method of Microencapsulation of Probiotic Bacteria for Their Stability in Acidic and Bile Conditions during Storage. *J. Food Sci.* 74: M53-M61.
15. Ding WK, Shah NP. 2009. Effect of Homogenization Techniques on Reducing the Size of Microcapsules and the Survival of Probiotic Bacteria Therein. *J Food Sci.* 74: M231-M236.
16. Saccaro DM, Tamime AY, Pilleggi ALO, Oliveira MN. 2009. The viability of three probiotic organisms grown with yoghurt starter cultures during storage for 21 days at 4°C. *Dairy Technol.* 62: 397-404.
17. Cardarelli HR, Buriti FCA, Castro IA, Saad SMI. 2008. Inulin and oligofructose improve sensory quality and increase the probiotic viable count in potentially synbiotic petit-suisse cheese. *LWT* 41: 1037-1046.
18. Correa SBM, Castro IA, Saad AM. 2008. Probiotic potential and sensory properties of coconut flan supplemented with *Lactobacillus paracasei* and *Bifidobacterium lactis*. *International Journal of Food Science and Technology* 43, 1560-1568.

19. Ding WK, Shah NP. 2007. Acid, bile and heat tolerance of free and microencapsulated probiotic bacteria. *J Food Sci.* 72: M446-M450.
20. Oliveira AC, Moretti TS, Boschini C, Baliero JCC, Freitas LAP, Freitas O, Favaro-Trindade CS. 2007. Microencapsulation of *B. lactis* (BI 01) and *L. acidophilus* (LAC 4) by Complex Coacervation Followed by Spouted-Bed Drying. *Drying Technol.* 25: 1687-1693.
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22. Faria CP, Benedet HD, Le Guerroue J-L. 2006. Assessment of fermented buffalo milk for *Lactobacillus casei* and supply with *Bifidobacterium longum*. *Semina: Ciências Agrárias, Londrina*, 27: 407-414. [Spanish]
23. Maruyama LY, Cardarelli HR, Buriti FCA, Saad SMI. 2006. Instrumental texture of probiotic petit-suisse cheese: influence of different combinations of gums. *Ciênc Tecnol Aliment., Campinas*, 26: 386-393. [Spanish]

Reviews

1. Ouwehand AC. 2017. A review of dose-responses of probiotics in human studies. *Benef Microbes* 8(2): 143-151. doi: 10.3920/BM2016.0140.

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