

Is there a role for modified probiotics as beneficial microbes: a systematic review of the literature

L. Zorzela, S.K. Ardestani, L.V. McFarland and S. Vohra

Methods S1. Medline search strategy.

1. Probiotics/
2. Probiotic*.mp.
3. Lactobacillus acidophilus/ or Lactobacillus brevis/ or Lactobacillus casei/ or Lactobacillus helveticus/ or Lactobacillus plantarum/ or Lactobacillus reuteri/ or Lactobacillus rhamnosus/
4. Lactobacillus/
5. Lactobacill*.mp.
6. Lactobacillus GG.mp.
7. Bifidobacterium/
8. Bifidobacterium infantis.mp.
9. Bifidobacterium bifidum.mp.
10. Bifidobacterium lactis.mp.
11. Bifidobacter*.mp.
12. Streptococcus thermophilus/
13. Streptococc*.mp.
14. Bacillus coagulans.mp.
15. Saccharomyces/
16. Saccharomyces boulardii.mp.
17. Enterococcus/
18. Enterococc*.mp.
19. exp Lactococcus/
20. Lactococc*.mp.
21. Lacteol.mp.
22. Lactobacillus LB.mp.
23. or/1-22
24. (dead or killed or nonviable or inactivated or sonicate\$).mp.
25. 23 and 24
26. randomized controlled trial.pt.
27. clinical trial.pt.
28. randomi?ed.ti,ab.
29. placebo.ti,ab.
30. randomly.ti,ab.
31. 26 or 27 or 28 or 29 or 30
32. 25 and 31
33. limit 32 to humans

Table S1. Excluded studies.

Modified probiotic or test microbe(s)	Reason excluded	Reference
<i>Lactobacillus acidophilus</i>	control strains were different: Living 'Lacidofil' (<i>Lactobacillus helveticus</i> R0052 and <i>Lactobacillus</i> <i>rhamnosus</i> R0011	Rampengan <i>et al.</i> , 2010
<i>Lactobacillus acidophilus</i>	not a RCT	Bin, 1995
<i>Mycobacterium vaccae</i>	not a RCT	Dlugovitzky <i>et al.</i> , 2010
Sweet acidophilus milk	not a RCT	McDonough <i>et al.</i> , 1987
<i>Lactobacillus acidophilus</i> LB	not a RCT	Michielutti <i>et al.</i> , 1996
<i>Pediococcus parvulus</i> and <i>Enterococcus faecium</i>	not a RCT	Otsuka <i>et al.</i> , 2007
<i>Escherichia coli</i> and <i>Enterococcus faecalis</i>	not a RCT	Penders <i>et al.</i> , 2012
<i>Lactobacillus acidophilus</i>	not a RCT	De Francesco <i>et al.</i> , 2000
<i>Lactobacillus brevis</i>	not a RCT	Takii <i>et al.</i> , 2013
<i>Lactobacillus acidophilus</i> , <i>Lactobacillus helveticus</i> , <i>Bifidobacterium species</i> nr	not a RCT	Tsuchiya <i>et al.</i> , 2004
<i>Lactobacillus casei</i>	not a RCT	Wutzke <i>et al.</i> , 2006
<i>Lactobacillus johnsonii</i>	not a RCT	Wutzke <i>et al.</i> , 2008
Living Bifido. versus acidified milk	no modified probiotic tested	Yang <i>et al.</i> , 2008
<i>Bifidobacterium [animalis] lactis</i>	no modified probiotic tested	Tabbers <i>et al.</i> , 2011
Living <i>Escherichia coli</i>	no modified probiotic tested	Kruis <i>et al.</i> , 1997
Living <i>Bifidobacterium breve</i> BBG-01	no modified probiotic tested	Matsuda <i>et al.</i> , 2011
Living <i>Lactobacillus casei</i> Shirota	no modified probiotic tested	Takeda <i>et al.</i> , 2006
<i>Lactobacillus species</i> nr	duplicated data with included study	Kecskes <i>et al.</i> , 2003
<i>Lactobacillus plantarum</i> 299v	duplicated data with included study	Rayes <i>et al.</i> , 2002
<i>Lactobacillus pentosus</i> b240	duplicated data with included study	Toba <i>et al.</i> , 2011

Abbreviations: nr = not reported; RCT = randomized controlled trial.

References of excluded studies

- Bin Li Xie, 1995. Controlled clinical trial of Lacteol Fort Sachet versus furazolidone or berberine in treatment of acute diarrhoea in children. *Annales de Pediatrie* 42: 396-401.
- De Francesco, V., Stoppino, V., Sgarro, C. and Faleo, D., 2000. *Lactobacillus acidophilus* administration added to omeprazole/amoxicillin-based double therapy in *Helicobacter pylori* eradication. *Digestive and Liver Disease* 32: 746-747.
- Dlugovitzky, D., Notario, R., Martinel-Lamas, D., Fiorenza, G., Farroni, M., Bogue, C., Stanford, C. and Stanford, J., 2010. Immunotherapy with oral, heat-killed, *Mycobacterium vaccae* in patients with moderate to advanced pulmonary tuberculosis. *Immunotherapy* 2: 159-169.

- Kecskes, G., Tibor, B. and Oláh, A., 2003. Early enteral nutrition with specific *Lactobacillus* and fibre reduces sepsis in patients with severe acute pancreatitis. *Magyar Sebeszet* 56: 3-8.
- Kruis, W., Schütz, E., Fric, P., Fixa, B., Judmaier, G. and Stolte, M., 1997. Double-blind comparison of an oral *Escherichia coli* preparation and mesalazine in maintaining remission of ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 11: 853-858.
- Matsuda, F., Chowdhury, M.I., Saha, A., Asahara, T., Nomoto, K., Tarique, A.A., Ahmed, T., Nishibuchi, M., Cravioto, A. and Qadri, F., 2011. Evaluation of a probiotics, *Bifidobacterium breve* BBG-01, for enhancement of immunogenicity of an oral inactivated cholera vaccine and safety: a randomized, double-blind, placebo controlled trial in Bangladeshi children under 5 years of age. *Vaccine* 29: 1855-1858.
- McDonough, F.E., Hitchins, A.D., Wong, N.P., Wells, P. and Bodwell, C.E., 1987. Modification of sweet *acidophilus* milk to improve utilization by lactose-intolerant persons. *American Journal of Clinical Nutrition* 45: 570-574.
- Michielutti, F., Bertini, M., Presciuttini, B. and Andreotti, G., 1996. Valutazione Clinica di un nuovo batteriotherapico orale in pazienti di eta pediatrica con diarreha acuta. *Minerva Medica* 87: 545-550.
- Otsuka, Y. and Pan, W., 2007. Effects of the novel symbiotic 'Immubalance' as a food supplement in relieving clinical symptoms of Japanese cedar pollinosis: a pilot study. *Clinical and Experimental Pharmacology and Physiology* 34: S73-75.
- Penders, J., Gerhold, K., Rossberg, S., Witt, I., Zimmermann, K., Wahn, U., Lau, S. and Hamerlmann, E., 2012. Establishment and role of the gastrointestinal microbiota and its role for atopic dermatitis in early childhood. *Journal of Allergy Clinical Immunology* 132: 601-607.
- Rampengan, N.H., Manoppo, J. and Warouw, S.M., 2010. Comparison of efficacies between live and killed probiotics in children with lactose malabsorption. *Southeast Asian Journal of Tropical Medicine and Public Health* 41: 474-481.
- Rayes, N., Seehofer, D., Müller, A.R., Hansen, S., Bengmark, S. and Neuhaus, P., 2002. Einfluss von Probiotika und Ballaststoffen auf die Inzidenz bakterieller Infektionen nach viszeralkirurgischen Eingriffen-Ergebnisse einer prospektiven Studie. *Zeitschrift für Gastroenterologie* 40: 869-876.
- Tabbers, M.M., Chmielewska, A., Roseboom, M.G., Crastes, N., Perrin, C., Reitsma, J.B., Norbruis, O., Szajewska, H. and Benninga, M.A., 2011. Fermented milk containing *Bifidobacterium [animalis] lactis* DN-173010 in childhood constipation: a randomized, double-blind, controlled trial. *Pediatrics* 127: e1392-e1399.
- Takeda, K., Suzuki, T., Shimada, S.I., Shida, K., Nanno, M. and Okumura, K., 2006. Interleukin-12 is involved in the enhancement of human natural killer cell activity by *Lactobacillus casei* Shirota. *Clinical and Experimental Immunology* 146: 109-115.
- Takii, Y., Nishimura, S., Yoshida-Yamamoto, S., Kobayashi, Y. and Nagayoshi, E., 2013. Effects of intake of pickles containing *Lactobacillus brevis* on immune activity and bowel symptoms in female students. *Journal of Nutritional Science and Vitaminology* 59: 402-411.
- Toba, M., Shinkai, S., Saito, T., Sato, I., Tsubouchi, M., Taira, K., Inamatsu, T., Yoshida, H., Amano, H., Fujiwara, Y. and Kohda, N., 2011. Oral intake of heat-killed *Lactobacillus pentosus* strain b240 reduces incidence of acute upper respiratory tract infection in the elderly: a randomised, double-blind, placebo-controlled trial. *Clinical Microbiology and Infection* 17: S403-S404.

- Tsuchiya, J., Barreto, R., Okura, R., Kawakita, S., Fesce, E. and Marotta, F., 2004. Single-blind follow-up study on the effectiveness of a symbiotic preparation in irritable bowel syndrome. *Chinese Journal of Digestive Diseases* 5: 169-174.
- Wutzke, K.D. and Sattinger, V., 2006. ¹⁵N-excretion of heat-killed *Lactobacillus casei* in humans. *European Journal of Clinical Nutrition* 60: 847-852.
- Wutzke, K.D., Berg, D. and Haffner, D., 2008. The metabolic fate of doubly stable isotope labelled heat-killed *Lactobacillus johnsonii* in humans. *European Journal of Clinical Nutrition* 62: 197-202.
- Yang, Y.X., He, M., Hu, G., Wei, J., Pages, P., Yang, X.H. and Bourdu-Naturel, S., 2008. Effect of a fermented milk containing *Bifidobacterium lactis* DN-173010 on Chinese constipated women. *World Journal of Gastroenterology* 14: 6237-6243.

Table S2. Risk of bias assessment for included studies.¹

Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Study
low	unclear	low	unclear	low	low	low	Wenus <i>et al.</i> , 2008
low	unclear	low	low	low	low	low	Merenstein <i>et al.</i> , 2009
low	unclear	low	low	low	low	low	Briand <i>et al.</i> , 2006
low	unclear	low	low	low	low	low	Sharieff <i>et al.</i> , 2006
unclear	low	low	unclear	low	low	low	Rayes <i>et al.</i> , 2002a
unclear	low	low	unclear	low	low	low	Rayes <i>et al.</i> , 2002b
low	unclear	low	unclear	high	low	low	Bayona-Gonzales <i>et al.</i> , 1990
low	unclear	low	unclear	unclear	low	low	Awad <i>et al.</i> , 2010
low	unclear	low	unclear	low	low	low	Kumpu <i>et al.</i> , 2015
low	low	low	low	low	low	low	Hirose <i>et al.</i> , 2013
unclear	unclear	low	low	low	low	low	Shinkai <i>et al.</i> , 2013
unclear	unclear	low	unclear	unclear	low	low	Alberda <i>et al.</i> , 2007
low	low	low	unclear	low	low	low	Lau <i>et al.</i> , 2012
low	unclear	low	unclear	low	low	low	Morisset <i>et al.</i> , 2011
low	unclear	low	low	low	high	low	Mitra and Rabbani, 1990
unclear	unclear	low	low	low	low	low	Kaila <i>et al.</i> , 1995
unclear	low	low	unclear	low	low	low	Khanna <i>et al.</i> , 2005
unclear	unclear	low	low	low	low	low	Salazar-Lindo <i>et al.</i> , 2007
low	unclear	low	unclear	low	low	low	Simakachorn <i>et al.</i> , 2000
low	unclear	low	unclear	low	low	low	Boulloche <i>et al.</i> , 1994
low	unclear	low	unclear	low	low	low	Lievin- <i>et al.</i> , LeMoal 2007
unclear	unclear	low	unclear	low	low	low	Guyonnet <i>et al.</i> , 2007
low	unclear	low	unclear	high	low	low	Halpern <i>et al.</i> , 1996
unclear	unclear	high	unclear	low	low	low	Xiao <i>et al.</i> , 2003
unclear	unclear	low	unclear	low	low	low	Moroi <i>et al.</i> , 2011
unclear	low	low	unclear	low	low	low	Inoue <i>et al.</i> , 2014
unclear	unclear	low	unclear	low	low	low	Murosaki <i>et al.</i> , 2006
low	unclear	low	low	low	low	low	Arkwright and David, 2003
low	unclear	low	unclear	low	low	low	Brothers <i>et al.</i> , 2009
unclear	low	low	low	low	low	low	Gotoh <i>et al.</i> , 2009
unclear	unclear	low	unclear	low	low	low	Peng and Hsu <i>et al.</i> , 2005
unclear	unclear	low	unclear	high	low	low	Kirvjavainen, <i>et al.</i> , 2003
unclear	low	low	unclear	low	low	low	Canducci <i>et al.</i> , 2000
unclear	unclear	low	unclear	low	low	low	Cruchet <i>et al.</i> , 2003
unclear	unclear	low	unclear	low	low	low	Gotteland <i>et al.</i> , 2008
low	unclear	low	unclear	low	low	low	Gotteland <i>et al.</i> , 2005
unclear	unclear	low	unclear	low	low	low	Oláh <i>et al.</i> , 2002
low	unclear	low	unclear	high	low	low	Okawa <i>et al.</i> , 1989
unclear	unclear	low	unclear	high	low	low	Okawa <i>et al.</i> , 1993
low	unclear	low	low	low	low	low	Higashikawa <i>et al.</i> , 2016

¹ High risk, Low risk, unclear. [Higgins 2010 Cochrane Collaboration].