

BB-12[®]

Selected summaries, January 2003



Literature on BB-12[®] Bifidobacterium from Chr. Hansen A/S

This binder provides you with a selection of publications on BB-12[®] Bifidobacterium - one of the most important probiotics from our company.

The publications are clinical studies performed in humans documenting the effects in various conditions. You will also find survey articles summarizing other publications. The publications are covering not only single dose applications but also use in functional food.

In addition to the selected publications, Chr. Hansen can provide documentation on animals and on in vitro studies of the actual bacterial strain. These publications are available on request for specific purposes.

The literature binder is recommended for use as sales material to Chr. Hansen customers.

Chr. Hansen A/S
Human Health
Business Development

Human Health Studies Probio-Tec[®]

Reference Number: 56

Health Effect On: Diarrhea / Constipation / Intestinal Health

Chr. Hansen Lactobacillus acidophilus LA-5

Probiotic Strain: Bifidobacterium BB-12

Study Design: 23 elderly geriatric patients with a history of chronic constipation consumed either unfermented or fermented milk. The study ran over 4 periods of 5 - 6 weeks.

Dosage: 500 ml of fermented milk (0.4 - 1.6 billion CFU/g) daily.

Total CFU/Day: 200 - 800 billion

Reported Results There was a significant improvement in frequency of bowel movement
Conclusions: (P<0.05). No negative side effects were observed, and the product appears unlikely to cause electrolyte disturbances that can follow chronic use of laxatives. Supplementation with Lactobacilli and Bifidobacteria can improve natural bowel transit time and elimination rate, and can diminish the need for laxatives in the elderly and severely immobilized patients.

Date: 1993

Research Facility: Karolinska Institute, Stockholm, Sweden

Published Source: Alm, L., Ryd-Kjellen, E., Setterberg, G., Blomquist, L. Effect of a new fermented milk product "CULTURA" on constipation in geriatric patients. 1993. 1st Lactic Acid Bacteria Computer Conference Proceedings. Horizon Scientific Press, Norfolk, England.

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**Human Health Studies
Probio-Tec[®]****Reference Number:** 90**Health Effect On:** Lactose Intolerance**Chr. Hansen** Bifidobacterium BB-12**Probiotic Strain:** Lactobacillus acidophilus LA-5
Lactobacillus bulgaricus LBY-27
Streptococcus thermophilus STY-31**Study Design:** Part 3: On 2 separate days, 12 lactose intolerant subjects received 50 g of lactose with or without probiotic. Lactose malabsorption was measured by the breath hydrogen test.**Dosage:** 12 capsules of 3.5 billion CFU/capsule**Total CFU/Day:** 42 billion**Reported Results** It did not appear that these organisms improved lactose tolerance in subjects with lactose malabsorption.**Conclusions:****Date:** 1994**Research Facility:** University of Copenhagen, Denmark**Published Source:** Hove, H., Nordgaard-Andersen, I., Mortensen, P.B. Effect of lactic acid bacteria on the intestinal production of lactate and short-chain fatty acids, and the absorption of lactose. 1994. Am. J. Clin. Nutr., 59:74-79.

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Human Health Studies Probio-Tec[®]

Reference Number: 91

Health Effect On: Immunity
Cancer

Chr. Hansen Lactobacillus acidophilus LA-5

Probiotic Strain: Bifidobacterium BB-12

Study Design: In a randomized, double-blind, placebo-controlled study, the prophylactic effect on infections in 30 neutropenic patients undergoing cytoreductive chemotherapy for acute leukemia was studied. Probiotic was given for 30 days, beginning at the start of chemotherapy.

Dosage: 2 capsules (4 billion CFU/capsule) thrice daily.

Total CFU/Day: 24 billion

Reported Results Fever was significantly postponed from 8 to 12 days with probiotic
Conclusions: (P=0.033). Although not statistically significant, diarrhea was slightly higher in the probiotic group. A smaller decline in serum albumin concentration was seen in the probiotic group (P=0.056), which may be a rough estimation of the severeness of constitutional symptoms. No lactobacilli were cultured from blood, indicating no risk of septicemia from the probiotic.

Date: 1992

Research Facility: Marselisborg Hospital, Denmark

Published Source: Ellegaard, J., Peterslund, N.A., Black, F.T. Infection prophylaxis in neutropenic patients by oral administration of Lactobacilli. 1992. Presented at The Seventh International Symposium on Infections in the Immunocompromised host, June 21-24, 1992, Boulder, CO.

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Human Health Studies Probio-Tec[®]

Reference Number: 92

Health Effect On: Antibiotic Side Effects

Chr. Hansen Lactobacillus acidophilus LA-5

Probiotic Strain: Bifidobacterium BB-12

Study Design: In a double-blind, placebo-controlled study, 20 healthy subjects received 500 mg of the antibiotic ampicillin, plus probiotic or placebo capsules for 7 days. Probiotic or placebo capsules were taken for another 14 days. The effect on intestinal microflora was evaluated.

Dosage: 1 capsule (4 billion CFU/capsule) daily.

Total CFU/Day: 4 billion

Reported Results The intestinal tract of those subjects receiving probiotic capsules were recolonised slightly faster than those receiving placebo. Adverse effects (diarrhea) were seen in only 1 person receiving probiotic compared to 3 persons receiving placebo (felt sick, candida vaginitis, diarrhea). Therefore, lactic acid producing bacteria may be useful in the reestablishment of the microflora during and after antibiotic treatment.

Conclusions:

Date: 1991

Research Facility: Huddinge University, Karolinska Institute, Stockholm, Sweden

Published Source: Black, F.T., Einarsson, K., Lidbeck, A., Orrhage, K., Nord, C.E. Effect of lactic acid producing bacteria on the human intestinal microflora during ampicillin treatment. 1991. Scand. J. Infect. Dis., 23: 247-254.

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Human Health Studies Probio-Tec[®]

Reference Number: 100

Health Effect On: Diarrhea / Constipation / Intestinal Health

Chr. Hansen Probiotic Strain: Lactobacillus acidophilus LA-5
Bifidobacterium BB-12
Lactobacillus bulgaricus LBY-27
Streptococcus thermophilus STY-31

Study Design: In a double-blind, placebo controlled study, 94 healthy tourists on a 2 week trip to Egypt consumed either placebo or probiotic capsules, starting 2 days before departure and continuing throughout the trip.

Dosage: 3 capsules (3 billion CFU/capsule) daily.

Total CFU/Day: 9 billion

Reported Results Conclusions: Frequency of diarrhea was significantly reduced (P=0.019) with the probiotic. Protection rate against traveler's diarrhea was 39%.

Date: 1989

Research Facility: Egypt

Published Source: Black, F.T., Anderson, P.L., Orskov J., Orskov, F., Gaarslev, K., Laulund, S. Prophylactic efficacy of lactobacilli on traveler's diarrhea. 1989. Travel Medicine, 333-335.

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Human Health Studies Probio-Tec[®]

Reference Number: 103

Health Effect On: (Review Article)
Stability / Survival in Application

Chr. Hansen Probiotic Strain: Lactobacillus acidophilus LA-5
Bifidobacterium BB-12

Study Design: The health benefits of bifidobacteria with other probiotic strains, and their application in dairy products, as reported in various studies are reviewed.

Dosage: Varied.

Total CFU/Day: Varied.

Reported Results Conclusions: There is much potential for using bifidobacteria with other beneficial organisms as dietary adjuncts in cultured dairy products. Research has shown that in some cases bifidobacteria can be used to control enteric infections, lower serum cholesterol, improve infant formulas, and make milk products more nutritious and more easily digestible by lactose-intolerant people. However, if the organisms are to be used successfully, long-term storage effects on the viability of bifidobacteria in cultured dairy products need to be determined. Also, a bifidobacteria culture that is easily propagated and stored for convenient use is needed.

Date: 1990

Research Facility: The Ohio State University, Columbus, OH

Published Source: Laroia, S., Martin, J.H. Bifidobacteria as possible dietary adjuncts in cultured dairy products - a review. 1990. Cultured Dairy Products Journal, November: 18-22.

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Human Health Studies Probio-Tec[®]

Reference Number: 151

Health Effect On: Yeast Infection

Chr. Hansen Probiotic Strain: Lactobacillus acidophilus LA-5
Streptococcus thermophilus CH-3
Lactobacillus bulgaricus CH-3

Study Design: In a crossover trial that lasted 1 year, 33 women with recurrent candidal vaginitis consumed either no yogurt or yogurt for 6 months. Patients were examined for vaginal and rectal colonization by lactobacilli and candida, and vaginal candidal infection. Patients served as their own controls.

Dosage: 8 ounces of yogurt (>0.1 billion CFU/ml) daily.

Total CFU/Day: 23 billion

Reported Results Conclusions: A 3-fold decrease in infection was seen when patients consumed yogurt, 2.54 per 6 months vs. 0.38 (P=0.001). Candidal colonization decreased from 3.23 per 6 months during the control period to 0.84 during the yogurt phase (P=0.001). 8 patients who initially consumed the yogurt diet refused to enter the control phase of the trial because of clinical improvement. Researchers concluded that daily ingestion of 8 ounces of yogurt containing L. acidophilus decreased both candidal colonization and infection.

Date: 1992

Research Facility: Long Island Jewish Medical Center, New York

Published Source: Hiton, E., Isenburg, H.D., Alpenstein, P., France, K., Borenstein, M. Ingestion of yogurt containing Lactobacillus acidophilus as prophylaxis for candidal vaginitis. 1992. Annals of Internal Medicine, 116:353-357.

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Human Health Studies Probio-Tec[®]

Reference Number: 156

Health Effect On: (Review Article)

Chr. Hansen Probiotic Strain: Lactobacillus acidophilus LA-5
Bifidobacterium BB-12
Lactobacillus bulgaricus LBY-27
Streptococcus thermophilus STY-31

Study Design: This paper discusses the human microflora and succession, and reviews several probiotic studies.

Dosage: not applicable

Total CFU/Day: not applicable

Reported Results Conclusions: Because some studies are positive while others are neutral, there is no conclusive evidence for the therapeutic value of probiotic organisms. However, individual variability, the complexity of the intestinal ecosystem and probiotic strain variability may contribute to these inconsistent study results. Some studies show that combinations of various strains can be advantageous.

Date: 1991

Research Facility: Huddinge University, Karolinska Institute, Stockholm Sweden

Published Source: Lidbeck, A., Nord, C.E. Lactobacilli in relation to human ecology and antimicrobial therapy. 1991. *Int. J. Tiss. React.*, XIII (2): 115-122.

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Human Health Studies Probio-Tec[®]

Reference Number: 186

Health Effect On: Antibiotic Side Effects

Chr. Hansen Lactobacillus acidophilus LA-5

Probiotic Strain: Bifidobacterium BB-12
Lactobacillus bulgaricus LBY-27
Streptococcus thermophilus STY-31

Study Design: In a double-blind, placebo-controlled study, 23 healthy subjects received 150 mg of the antibiotic clindamycin 4 times daily for 7 days, plus probiotic or placebo capsules for 14 days. The effect on intestinal microflora was evaluated.

Dosage: 3 capsules (3.5 billion CFU/capsule) twice daily.

Total CFU/Day: 21 billion

Reported Results The total number of microorganisms was significantly higher in the subjects receiving probiotic (P=0.02). In the probiotic group, there was a trend towards delayed reduction and earlier increase in Bifidobacteria. Only 18% of the probiotic group was colonized with Clostridium difficile, compared to 41% of the placebo group. Recolonization was faster in the supplemented group, and may be of importance in preventing colonization with C. difficile which is a cause of diarrhea.

Conclusions:

Date: 1997

Research Facility: Huddinge University, Karolinska Institute, Stockholm, Sweden

Published Source: Nord, C.E., Lidbeck, A., Orrhage, K., Sjostedt, S. Oral supplementation with lactic acid bacteria during intake of clindamycin. 1997. Clinical Microbiology and Infection, 3 (1): 124-132.

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**Human Health Studies
Probio-Tec[®]****Reference Number:** 200**Health Effect On:** Diarrhea / Constipation / Intestinal Health**Chr. Hansen** Bifidobacterium BB-12**Probiotic Strain:** Streptococcus thermophilus TH-4**Study Design:** In a double-blind, placebo-controlled trial, hospitalized infants aged 5-24 months received formula with or without probiotic. The 55 subjects were evaluated for diarrhea and rotavirus shedding for a total of 4447 patient-days during 17 months.**Dosage:** 0.2 billion CFU/g of powdered formula.**Total CFU/Day:** (child-dependent)**Reported Results** Supplementation of infant formula with the probiotic significantly reduced the incidence of diarrhea (P=0.035) and rotavirus shedding (P=0.025). In the placebo group, 31% developed diarrhea and 39% shed rotavirus, while in the probiotic group, only 7% developed diarrhea and 10% shed rotavirus. The supplemented formula was well-tolerated by the children, many of whom were initially malnourished or immunocompromised. The use of these or similar microbial preparations may provide a practical method for prevention of diarrhea in a wide range of clinical and environmental conditions.
Conclusions:**Date:** 1994**Research Facility:** Johns Hopkins Hospital, Baltimore, MD**Published Source:** Saavedra, J.M., Bauman, N.A., Oung, I., Perman, J.A., Yolken, R.H. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhea and shedding of rotavirus. 1994. The Lancet, 344: 1046-1049.

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Human Health Studies Probio-Tec[®]

Reference Number: 201

Health Effect On: (Review Article)

Chr. Hansen Lactobacillus acidophilus LA-5

Probiotic Strain: Bifidobacterium BB-12

Study Design: Possible beneficial aspects of fermented milks with selected intestinal (probiotic) bacteria, as reported in various studies, are reviewed. Criteria for selecting special microorganisms originating from the intestine of healthy humans are discussed.

Dosage: Varied.

Total CFU/Day: Varied.

Reported Results Many starter bacteria used for manufacturing fermented milk products produce substances that are directly or indirectly related to health aspects. **Conclusions:** Maldigestion of lactose may be reduced by β -galactosidase from lactic acid starter bacteria and from intestinal bacteria. Both starter and intestinal bacteria have been shown to be able to reduce the number of intestinal pathogens. Certain strains of Lactobacillus acidophilus have been shown to positively influence serum cholesterol of pigs. In vivo experiments have indicated that tumor-inhibiting effects may occur if specific tumors are induced. The immune system may be activated by specific intestinal microorganisms.

Date: 1989

Research Facility: Melkunie Holland, The Netherlands

Published Source: Driessen, F.M., de Boer, R. Fermented milks with selected intestinal bacteria: a healthy trend in new products. 1989. Netherlands Milk Dairy Journal, 43: 367-382.

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Human Health Studies Probio-Tec[®]

Reference Number: 206

Health Effect On: Immunity
Adhesion / Survival in GI Tract

Chr. Hansen Probiotic Strain: Bifidobacterium BB-12

Study Design: 28 healthy adults received milk for 3 weeks, then milk fermented with either BB-12 or Nestle's LA-1 for 3 weeks, and then milk again for 6 weeks. Blood samples were collected throughout the study to assess changes in lymphocyte subsets or leukocyte phagocytic activity.

Dosage: 120 ml of fermented milk (28 million CFU/ml) thrice daily.

Total CFU/Day: 10 billion (Nestle LA-1: 70 billion)

Reported Results Conclusions: Overall phagocytic activity of blood leukocytes was significantly increased after ingestion of fermented milks ($P < 0.0001$). Phagocytosis of *E. coli* in vitro was enhanced after administration of the BB-12 (or LA-1) fermented product. The number of Bifidobacteria in the feces increased significantly after consumption of the fermented milks ($P < 0.05$), and most corresponded to the strains present in the milks. The increment in phagocytosis coincided with fecal colonization by BB-12 (or LA-1) and persisted for 6 weeks after ingestion. No modifications of lymphocyte subpopulations were detected. Nonspecific, anti-infective mechanisms of defense can be enhanced by the ingestion of specific lactic acid bacteria strains, such as BB-12. These strains can be used as nutritional supplements to improve the immune function of particular age groups, such as the neonate or the elderly, for which these functions are diminished.

Date: 1995

Research Facility: Nestle Research Center, Switzerland

Published Source: Schiffrin, E.J., Rochat, F., Link-Amster, H., Aeschlimann, J.M., Donnet-Hughes, A. Immunomodulation of human blood cells following the ingestion of lactic acid bacteria. 1995. *Journal of Dairy Science*, 78: 491-497.

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Human Health Studies Probio-Tec[®]

Reference Number: 208

Health Effect On: Immunity
Adhesion / Survival in GI Tract

Chr. Hansen Probiotic Strain: Bifidobacterium BB-12

Study Design: In a randomized, controlled study, 30 health adults consumed either no fermented foods, or a fermented milk containing BB-12 and Nestle's LA-1 for 3 weeks, during which an attenuated *Salmonella typhi* was administered to mimic an enteropathogenic infection. Effects on intestinal flora and immune response were assessed.

Dosage: 125 g fermented milk (10 -100 million CFU/g) thrice daily.

Total CFU/Day: 4 - 40 billion

Reported Results Conclusions: The number of fecal bifidobacteria increased by 1 log during fermented milk intake (P=0.027). The specific serum IgA titre rise to *S. typhi* was significantly higher by more than four-fold (P=0.04). Total serum IgA also significantly increased (P=0.014). IgG titres in the fermented milk group remained high over a longer period than in the control group. Lactic acid bacteria which can persist in the gastrointestinal tract, such as BB-12, can act as adjuvants to the humoral immune response.

Date: 1994

Research Facility: Nestle Research Center, Switzerland

Published Source: Link-Amster, H., Rochat, F., Saudan, K.Y., Mignot, O., Aeschlimann, J.M. Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. 1994. *FEMS Immunology and Medical Microbiology*, 10: 55-64.

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Human Health Studies Probio-Tec[®]

Reference Number: 221

Health Effect On: Adhesion / Survival in GI Tract
Diarrhea / Constipation / Intestinal Health
Safety
Stability / Survival in Application

Chr. Hansen Probiotic Strain: Bifidobacterium BB-12

Study Design: In a double-blind, randomized controlled study, 54 infants were breast-fed, or fed a fermented infant formula (acidified by *Streptococcus thermophilus* and *Lactobacillus helveticus*) containing BB-12, or fed a non-acidified formula during the first 2 months of life. Growth, tolerance and fecal flora were assessed.

Dosage: 1 million CFU/g of powder.

Total CFU/Day: Varied with infant.

Reported Results Conclusions: The formula with BB-12 induced a prevalence of colonization with bifidobacteria at 1 month of age, similar to that of breast-fed infants, and significantly higher than in the group fed standard formula ($P < 0.05$). Colonization by *Streptococcus faecalis* was slower in the BB-12 fed infants compared to those fed the standard formula. The BB-12 formula was well tolerated and promoted normal growth. Viability of BB-12 in the reconstituted formula remained stable over 24 hours stored at 4Å°C.

Date: 1995

Research Facility: Children's Hospital, Rocourt, Belgium

Published Source: Langhendries, J.P., Detry, J., Van Hees, J., Lamboray, J.M., Darimont, J., Mozin, M. J., Secretin, M.C., Senterre, J. Effect of a fermented infant formula containing viable bifidobacteria on the fecal flora composition and pH of healthy full-term infants. 1995. *Journal of Pediatric Gastroenterology and Nutrition*, 21: 177-181.

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Human Health Studies Probio-Tec[®]

Reference Number: 250

Health Effect On: Diarrhea / Constipation / Intestinal Health

Chr. Hansen Lactobacillus acidophilus LA-5

Probiotic Strain: Bifidobacterium BB-12

Study Design: 24 partly or completely immobile, nursing home patients with various intestinal function problems were included in a double blind trial. Patients received placebo or probiotic capsules for 4 weeks. Observations were made by the nursing staff.

Dosage: 3 capsules (4 billion CFU/capsule) daily.

Total CFU/Day: 12 billion

Reported Results Intestinal function was improved in 56% of the group receiving probiotic
Conclusions: compared to 10% of the placebo group (P=0.019). Improvements included effect on running diarrhea and severe constipation.

Date: 1989

Research Facility: Oslo, Norway

Published Source: Sagen, O.B. Treatment of functional disturbance in the intestine by administration of lactic acid bacteria. 1989. Internal report.

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Human Health Studies Probio-Tec[®]

Reference Number: 261

Health Effect On: Adhesion / Survival in GI Tract
Immunity
(Review Article)

Chr. Hansen Probiotic Strain: Lactobacillus acidophilus LA-5
Bifidobacterium BB-12
Bifidobacterium longum BB-46
Lactobacillus paracasei ssp. paracasei LC-01

Study Design: Adhesion and immunity activation of various probiotic strains from numerous studies were reviewed and summarized. Gastrointestinal models and antimutagenicity properties were also discussed.

Dosage: Varied.

Total CFU/Day: Varied.

Reported Results Conclusions: BB-12, BB-46, LA-5 and LC-01 showed adhesion to intestinal cells and extracellular matrix, with BB-12 exhibiting good to strong adhesion. BB-12, LA-5 and LC-01 induced cytokine production from human peripheral blood leukocytes in vitro. No single in vitro test is sufficient in selecting a probiotic strain for a targeted use. In vitro results need to be validated with human clinical studies.

Date: 1996

Research Facility: University of Turku, Turku, Finland

Published Source: Salminen, S., Laine, M., von Wright, A., Vuopio-Varkila, J., Korhonen, T., Mattila-Sandholm, T. Development of selection criteria for probiotic strains to assess their potential in functional foods: A Nordic and European approach. 1996. Bioscience Microflora, 15 (2): 61-67.

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Human Health Studies Probio-Tec[®]

Reference Number: 277

Health Effect On: Cholesterol
Stability / Survival in Application

Chr. Hansen Probiotic Strain: Lactobacillus acidophilus LA-5
Bifidobacterium BB-12
Streptococcus thermophilus STY-31

Study Design: 17 non-insulin dependent diabetics consumed 200 ml of fermented milk 3 times daily for 12 weeks, and their cholesterol was periodically measured. Also, the viability of the strains in the milk product was tested over a period of 17 days.

Dosage: 200 ml of fermented milk (>1 million CFU/ml) 3 times daily.

Total CFU/Day: 0.6 billion

Reported Results Conclusions: After 4 weeks, total cholesterol decreased significantly by 20% (1.5 mmol/l). The number of viable bacteria in the refrigerated product were above 1 million CFU/ml.

Date: 1996

Research Facility: University of Belgrade

Published Source: Obradovic, D., Curic, M., Ivanovic, M., Trbojevic, B., Djordjevic, M. 1996. Probiotic function of the fermented milk Jogurt Plus. FEMS Conference (Fifthe Symposium on Lactic Acid Bacteria), Holland, Sept. 8-12.

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**Human Health Studies
Probio-Tec[®]****Reference Number:** 305**Health Effect On:** Lactose Intolerance**Chr. Hansen Probiotic Strain:** Lactobacillus acidophilus LA-5
Bifidobacterium BB-12
Lactobacillus bulgaricus LBY-27
Streptococcus thermophilus STY-31**Study Design:** 50 lactose intolerant adults, who had been on a lactose free diet for a substantial time, were selected. During the study, subjects ingested probiotic capsules, while gradually increasing the amount of lactose in their diet.**Dosage:** 3 capsules (4 billion CFU/capsule) daily.**Total CFU/Day:** 12 billion**Reported Results Conclusions:** During treatment and with ingestion of increasing amounts of lactose, 80% of the participants considered their well being unchanged or improved. Symptoms of lactose intolerance - stomach ache, flatulence, diarrhea and constipation - were reduced or unchanged compared to when they were on a lactose free diet.**Date:** 1993**Research Facility:** Pharmacia, Finland**Published Source:** Virta, P., Otterström, K., Niemi, L., Wieser-Aho, M.-T., Lähteenmäki, A.-L., Leppänen, T. The effect of a preparation containing freeze-dried lactic acid bacteria on lactose intolerance. 1993. External report

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Human Health Studies Probio-Tec[®]

Reference Number: 306

Health Effect On: Diarrhea / Constipation / Intestinal Health
Yeast Infection

Chr. Hansen Probiotic Strain: Lactobacillus acidophilus LA-5
Bifidobacterium BB-12
Lactobacillus bulgaricus LBY-27
Streptococcus thermophilus STY-31

Study Design: In a placebo-controlled, double-blind study, 107 tourists consumed a probiotic capsules at breakfast and dinner during a 13 day trip to Tunisia. Treatment began 2 days prior to departure and continued until 2 days after the trip.

Dosage: 2 capsules (4.5 billion CFU/capsule) daily.

Total CFU/Day: 9 billion

Reported Results Conclusions: Participants' subjective evaluation of the effect (recorded as accompanying symptoms) showed the general condition of the probiotic group was statistically significantly better during the trial. However, overall results indicate that 3 (vs. 2) capsules per day is more effective on traveler's diarrhea as seen in previous trials. Microbiological analyses of fecal samples appeared to show an effect against Candida infection (P=0.07).

Date: 1995

Research Facility: Tunisia (Marselisborg Hospital, Denmark)

Published Source: Black, F.T., Andersen, P.L., Laulund, S. Report from a double-blind placebo-controlled trial with HIP against traveler's diarrhea with a new dosage regimen. 1995. Internal report.

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Human Health Studies Probio-Tec[®]

Reference Number: 307

Health Effect On: Diarrhea / Constipation / Intestinal Health

Chr. Hansen Probiotic Strain: Lactobacillus acidophilus LA-5
Bifidobacterium BB-12
Lactobacillus bulgaricus LBY-27
Streptococcus thermophilus STY-31

Study Design: In 2 placebo-controlled, double-blind trials, a total of 195 travelers consumed a probiotic capsule at each meal during a 15 day tour of Egypt. Treatment began 2 or 7 days before departure, and continued to the end of, or 4 days after, the trip.

Dosage: 3 capsules (3 billion CFU/capsule) daily.

Total CFU/Day: 9 billion

Reported Results Conclusions: Only 46.8% of the probiotic group, compared to 73.3% of the placebo group, suffered from traveller's diarrhea ($P < 0.05$). Out of the subjects who suffered from diarrhea, only 45.9% of the probiotic group, compared to 68.3% in the placebo group, experienced a duration of diarrhea for more than one day.

Date: 1987 & 1988

Research Facility: Egypt (Marselisborg Hospital, Denmark)

Published Source: Black, F.T. Placebo-controlled double-blind trial of 4 lactobacilli strains (HIP) used as prophylactic agent against traveller's diarrhea (2 trials). 1996. Report by G. Nirnberger, Bioconsult, GmbH, Austria.

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Human Health Studies Probio-Tec[®]

Reference Number: 308

Health Effect On: Adhesion / Survival in GI Tract
Diarrhea / Constipation / Intestinal Health

Chr. Hansen Probiotic Strain: Lactobacillus acidophilus LA-5
Bifidobacterium BB-12

Study Design: 4 healthy adults consumed 1 encapsulated (with an acid-resistant matrix) probiotic capsule at each meal for 1 week. Fecal samples were collected before, during and after the week ingesting capsules. Duodenal samples were taken before and periodically after ingestion.

Dosage: 1 capsule (4 billion CFU/capsule) thrice daily.

Total CFU/Day: 12 billion

Reported Results Conclusions: Both strains were found to be in the duodenum after ingestion, indicating survival through the stomach. BB-12 appears to have a greater ability than LA-5 to persist in the upper small intestine in vivo. The number of Bifidobacteria in the feces increased significantly during treatment ($P < 0.01$), indicating adherence and colonization.

Date: 1988

Research Facility: Marselisborg Hospital, Denmark

Published Source: Black, F.T., Laulund, S. A study on the recovery of ingested, encapsulated Lactobacillus acidophilus and Bifidobacteria bifidum from duodenal fluid and faeces. 1988. Chr. Hansen Internal Report.

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Human Health Studies Probio-Tec[®]

Reference Number: 332

Health Effect On: Immunity
Adhesion / Survival in GI Tract
Stability / Survival in Application

Chr. Hansen Probiotic Strain: Bifidobacterium BB-12

Study Design: 7 healthy children aged 15-31 months received follow-up formula supplemented with BB-12 for 21 days. Effect on intestinal microflora and local immunity was evaluated.

Dosage: At least 200 ml reconstituted formula (about 1 billion CFU) daily.

Total CFU/Day: about 1 billion

Reported Results Conclusions: During formula intake, the number of bifidobacteria increased ($P=0.07$), and represented 35% of the total number of fecal bacteria, compared to 23% before intake. BB-12 was found in 71% of the subjects during intake, and accounted for 27% of the total fecal bifidobacteria. Other bacteria populations did not change greatly. Total fecal IgA significantly increased during intake, peaking on day 8 when the level was 2.9 -fold higher than on day 0 ($P<0.05$). Anti-poliovirus IgA also increased significantly ($P<0.05$). Seven days after intake stopped, BB-12 was not detected in the feces, and the levels of bifidobacteria and IgA decreased. BB-12 showed good stability in the formula; the viable number did not change for at least 18 months in the sealed formula can, and for at least 30 days after the can was opened. Weaned children cannot obtain IgA passively from breast milk, and therefore may be at risk from infectious diseases. Follow-up formula with BB-12 may have great potential for preventing infections in children during and after weaning by enhancing the mucosal resistance to infections by active stimulation of local IgA production.

Date: 1998

Research Facility: Japan

Published Source: Fukushima, Y., Kawata, Y., Hara, H., Terada, A., Mitsuoka, T. Effect of a probiotic formula on intestinal immunoglobulin A production in healthy children. 1998. International Journal of Food Microbiology, 42: 39-44.

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Human Health Studies Probio-Tec[®]

Reference Number: 341

Health Effect On: (Review Article)
Diarrhea / Constipation / Intestinal Health
Safety

Chr. Hansen Probiotic Strain: Bifidobacterium BB-12
Lactobacillus acidophilus LA-5
Lactobacillus bulgaricus LBY-27
Streptococcus thermophilus STY-31
Streptococcus thermophilus TH-4
Lactobacillus paracasei ssp paracasei CRL-431

Study Design: Present knowledge of the mode of action of probiotics, and the data from clinical trials on their use, are reviewed.

Dosage: Varied with trial.

Total CFU/Day: Varied with trial.

Reported Results Conclusions: There is considerable data on probiotics from in vitro and animal experiments, but because of the simplicity of these systems, any claims of benefit have to be tested in humans before acceptance. A significant beneficial action in preventing diarrhea due to rotavirus infection in children is seen with certain probiotics. Probiotics appear to be very safe, but caution is required before they are given to immunocompromised patients.

Date: 1998

Research Facility: University Hospital of Wales, UK

Published Source: Lewis, S.J., Freedman, A.R. Review article: The use of biotherapeutic agents in the prevention and treatment of gastrointestinal disease. 1998. Aliment Pharmacol Ther, 12: 807-822.

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Human Health Studies Probio-Tec[®]

Reference Number: 343

Health Effect On: Diarrhea / Constipation / Intestinal Health

Chr. Hansen Bifidobacterium BB-12

Probiotic Strain:

Study Design: 119 non-breast fed, healthy infants attending day care centers received formula with either high supplement of BB-12 and *Streptococcus thermophilus*, low supplement of BB-12 and *S. thermophilus*, or no supplement for a total of 24,845 subject days. Formula consumption, number of daily bowel movements, stool consistency, changes in bowel habit and diaper rash were monitored.

Dosage: 10 or 100 (low or high supplement) million CFU of BB-12/g of formula.

Total CFU/Day: Varied with child.

Reported Results Consumption of the high supplement of BB-12 and *S. thermophilus* resulted in a more desirable bowel habit characterized by higher prevalence of soft bowel movement ($P < 0.03$), lower prevalence of hard bowel movement ($P < 0.03$), decreased daily frequency of bowel movement, and lower prevalence of diaper rash ($P < 0.0001$). Consumption of the lower supplement also resulted in a higher prevalence of soft bowel movement ($P < 0.0001$), and a lower prevalence of hard bowel movement ($P < 0.0001$).

Conclusions:

Date: 1998

Research Facility: Johns Hopkins University, Baltimore, Maryland

Published Source: Saavedra, J., Abi-Hanna, A., Moore, N., Yolken, R. Effect of long term consumption of infant formulas with bifidobacteria and *S. thermophilus* on stool patterns and diaper rash in infants. 1998. *J Pediatr Gastroenterol Nutr*, 27 (4): 483.

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Human Health Studies Probio-Tec[®]

Reference Number: 344

Health Effect On: Safety

Chr. Hansen Bifidobacterium BB-12

Probiotic Strain:

Study Design: In a double-blind study, 131 infants in day care centers received standard formula with either high probiotic supplement (100 million CFU/g of BB-12 + 10 million CFU/g *Streptococcus thermophilus*), low probiotic supplement (10 million CFU/g of BB-12 + 10 million CFU/g *S. thermophilus*), or unsupplemented. Weight, length, formula intake, GI tolerance, and general health indicators were measured. Infants were followed for a total of 68.1 subject-years.

Dosage: Varied with child.

Total CFU/Day: Varied with child.

Reported Results Long term consumption of these live probiotic-containing products by infants, as their sole formula, was well tolerated, safe, and resulted in adequate growth.

Conclusions:

Date: 1998

Research Facility: Johns Hopkins University, Baltimore, Maryland

Published Source: Abi-Hanna, A., Moore, N., Yolken, R., Saavedra, J. Long term consumption of infant formulas with live probiotic bacteria: safety and tolerance. 1998. *J Pediatr Gastroenterol Nutr*, 27 (4): 484.

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Human Health Studies Probio-Tec[®]

Reference Number: 347

Health Effect On: Immunity
Skin Disorders

Chr. Hansen Probiotic Strain: Bifidobacterium BB-12

Study Design: The immunomodulatory effects of BB-12 and Lactobacillus rhamnosus L-GG was investigated in in vitro and in vivo (clinical) studies. In vitro, lymphocyte proliferation tests were performed with 5 healthy blood donors and phytohemagglutinin-induced proliferation was studied in cultures containing a probiotic extract or dexamethasone. In the clinical study, 49 atopic patients received the elimination diet supplemented with BB-12, L-GG or placebo, and the severity of skin symptoms was measured before and after supplementation.

Dosage:

Total CFU/Day:

Reported Results In vitro results indicated the suppressive effect of BB-12 on lymphocyte proliferation, the effect comparable to dexamethasone. In the clinical study, the clinical symptoms of atopic dermatitis were significantly alleviated in the group after receiving BB-12 ($P < 0.008$) compared to after receiving the placebo ($P < 0.18$). The effect of L-GG was similar to BB-12 in both studies. These findings implicate the potential use of these specific probiotics as immunomodulatory agents in the management of allergic inflammation.

Conclusions:

Date: 1998

Research Facility: University of Turku, Turku, Finland

Published Source: Kankaanpaa, P., Sutas, Y., Salminen, S., Isolauri, E. Results on clinical demonstraion of probiotics on children. Presented at Functional Food Research in Europe, Third Workshop, PROBDEMO, Finland, October 1-2, 1998.

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Human Health Studies Probio-Tec[®]

Reference Number: 348

Health Effect On: Safety
(Review Article)

Chr. Hansen Bifidobacterium BB-12
Probiotic Strain: Lactobacillus acidophilus LA-5
Bifidobacterium longum BB-46
Lactobacillus paracasei ssp. paracasei LC-01

Study Design: Existing literature relating to the safety of probiotics is reviewed.

Dosage: Varied with study.

Total CFU/Day: Varied with study.

Reported Results Lactic acid bacteria have a long history of safe use. Members of the genera Lactobacillus and Lactococcus are GRAS (generally recognized as safe), while some Streptococcus, Enterococcus and some other genera contain some opportunistic pathogens. Lactic acid bacteria are intrinsically resistant to many antibiotics; however, resistances are rarely transmissible, and are sensitive to many clinically used antibiotics even in the case of a lactic acid bacteria-associated opportunistic infection. Thus, there is no particular safety concern with intrinsic resistance. Plasmid-associated antibiotic resistance occasionally occurs, and there is the possibility of the resistance spreading to other, more harmful species.

Conclusions:

Date: 1998

Research Facility: University of Turku, Turku, Finland

Published Source: Salminen, S., von Wright, A., Morelli, L., Marteau, P., Brassart, D., de Vos, W., Fonden, R., Saxelin, M., Collins, K., Mogensen, G., Birkeland, S., Mattila-Sandholm, T. Demonstration of safety of probiotics - a review. 1998. International Journal of Food Microbiology, 44: 93-106.

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Human Health Studies Probio-Tec[®]

Reference Number: 354

Health Effect On: Adhesion / Survival in GI Tract
Diarrhea / Constipation / Intestinal Health
Safety
(Review Article)

Chr. Hansen Probiotic Strain: Bifidobacterium BB-12

Study Design: Clinical trials to prove the safety and efficacy of follow-up formulas and growing-up milks fortified with BB-12 are summarized. BB-12 was selected because of its excellent survival during intestinal transit and adhesion to enterocytes.

Dosage: 1-100 million CFU/g formula powder.

Total CFU/Day: Varied with child.

Reported Results Conclusions: Studies with BB-12 in milk-based formulas show BB-12 survives through the GI tract and is present in the feces. Children fed formula with BB-12 experience less diarrhea, rotavirus infection, hard bowel movements and diaper rash. Using follow-up formulas and growing-up milk with BB-12 is safe, and can prevent diseases and discomforts frequently seen in industrialized and developing countries.

Date: 1998

Research Facility: (various)

Published Source: Haschke, F., Wang, W., Ping, G., Varavithya, W., Podhipak, A., Rochat, F., Link-Amster, H., Pfeifer, A., Diallo-Ginstl, E., Steenhout, P. Clinical trials prove the safety and efficacy of the probiotic strain Bifidobacterium Bb12 in follow-up formula and growing-up milks. 1998. Monatsschr Kinderheilkd (Suppl 1), 146: S26-S30.

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Human Health Studies Probio-Tec[®]

Reference Number: 383

Health Effect On: Diarrhea / Constipation / Intestinal Health
Adhesion / Survival in GI Tract

Chr. Hansen Lactobacillus acidophilus LA-5
Probiotic Strain: Bifidobacterium BB-12

Study Design: A double-blind study was conducted with 16 patients with restorative proctocolectomy for ulcerative colitis. Eight patients ingested 500 ml of fermented milk product containing LA-5 and BB-12 (Cultura) (treated group) and 8 patients ingested 500 ml of heat-treated Cultura (control group) once daily for one week. Effects on stool frequency, stool cultures and 6 different microflora associated characteristics (MACs) were evaluated.

Dosage: 500 ml fermented milk (>100 million CFU/ml) or heat-treated fermented milk (<10 thousand CFU/ml) once daily

Total CFU/Day: >50 billion CFU or <5 million CFU (heat-treated)

Reported Results Daily stool frequency was reduced from 5.8 to 2.8 in the treated group
Conclusions: (P<0.05). The number of LA-5 and BB-12 increased significantly during intervention (P<0.004, P<0.003 respectively). The number of LA-5 furthermore remained elevated one week thereafter. In the treated group, fecal tryptic activity increased significantly during intervention compared to the control group (P<0.004). No major effects on six MACs were observed. Intake of the heat-treated product induced no significant change for any parameter.

Date: 1999

Research Facility: Rikshospitalet University Hospital, Oslo, Norway. Karolinska Institutet, Stockholm, Sweden.

Published Source: Laake, K.O., Bjorneklepp, A., Bakka, A., Midtvedt, T., Norin, K.E., Eide, T.J., Jacobsen, M.B., Lingaas, E., Axelsen, A.K., Lotveit, T., Vatn, M.H. Influence of fermented milk on clinical state, fecal bacterial counts and biochemical characteristics in patients with ileal pouch-anal-anastomosis. 1999. Microbial Ecology in Health and Disease, 11: 211-217.

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**Human Health Studies
Probio-Tec[®]****Reference Number:** 388**Health Effect On:** Skin Disorders
Immunity**Chr. Hansen
Probiotic Strain:** Bifidobacterium BB-12**Study Design:** A randomized, double-blind, placebo controlled study was conducted with 27 young infants, mean age 4.6 month, who manifested atopic dermatitis during breast feeding. The infants were divided into three groups receiving either extensively hydrolysed whey infant formula with Bifidobacterium BB-12 or Lactobacillus strain GG or without probiotics.**Dosage:** 1 billion CFU/g infant formula**Total CFU/Day:** Varied with infant and age**Reported Results
Conclusions:** Supplementation with BB-12 was found to significantly reduce the extent, severity and subjective symptoms of atopic eczema ($P < 0.002$). Thus, the severity index SCORAD decreased to 0 (0-3.8) after treatment with BB-12 and to 1 (0.1-8.7) after treatment with Lactobacillus GG vs. unsupplemented 13.4 (4.5-18.2), median (interquartile range) after 2 month of treatment ($P < 0.001$). Alleviation of allergic inflammation was indicated by a reduction in the concentration of soluble CD4 in serum and eosinophilic protein X in urine, and a reduction in TGF-Beta1 after treatment with BB-12 but not after treatment with Lactobacillus GG.**Date:** 2000**Research Facility:** University of Turku, Tampere University Hospital, University of Tampere, Finland.**Published Source:** Isolauri, E., Arvola, T., Sutas, Y., Moilanen, E., Salminen, S. Probiotics in the management of atopic eczema. 2000. Clinical and Experimental Allergy, 30: 1604-1610.

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Human Health Studies Probio-Tec[®]

Reference Number: 398

Health Effect On: Immunity

Chr. Hansen Bifidobacterium BB-12

Probiotic Strain:

Study Design: Twenty-eight volunteers were divided into two groups. For the first 3 week of study, both groups received milk; in the following 3 week the volunteers received a fermented milk product supplemented with either BB-12 or La-1. In the final 6 week of the study both groups received milk again both no fermented products. Blood samples were taken before start of study and again at week 3 and week 6 and at end-point. Lymphocyte subsets and leucocyte phagocytic activity were studied.

Dosage: Not applicable.

Total CFU/Day: 10 billion CFU.

Reported Results No modifications were detected in lymphocyte subsets. In contrast, phagocytosis of *Escherichia coli* spp. was enhanced in both groups after 3 week intake of fermented milk ($P < 0.001$ for both) and at end-point 6 week after end of fermented milk consumption ($P < 0.001$ for both). The global enhancement in phagocytic activity was considered to be mainly due to the granulocyte population although increased phagocytic activity of monocytes was also observed after 3 week intake of fermented milk ($P < 0.001$ for both). The study results indicate that anti-infective mechanism of defense can be enhanced after ingestion of specific lactic acid strains like BB-12 and La-1.

Conclusions:

Date: 1997

Research Facility: University Paris XI, France.

Published Source: Schiffrin, E.J., Brassart, D., Servin, A.L., Rochat, F., Donnet-Hughes, A. Immune modulation of blood leucocytes in humans by lactic acid bacteria: criteria for strain selection. 1997. *Am J Clin Nutr* 66: 515S-520S.

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Human Health Studies Probio-Tec[®]

Reference Number: 400

Health Effect On: Immunity
Diarrhea / Constipation / Intestinal Health

Chr. Hansen Probiotic Strain: Bifidobacterium BB-12

Study Design: A randomised double-blind placebo controlled study comprising 21 infants with early onset atopic eczema and/or gastrointestinal symptoms, who received extensively hydrolysed whey formula with or without Bifidobacteria. Among the 21 infants 8 were intolerant (highly sensitised group - HSG) and 13 were tolerant (sensitised group- SG) to the formula. In the sensitised group 7 infants were weaned to formula with BB-12 and 6 infants to formula without BB-12. Change in composition of the microflora and total serum IgE was analysed after weaning.

Dosage: 1 billion CFU/g infant formula

Total CFU/Day: 80 billion/day/kg bodyweight.

Reported Results Conclusions: Infants in HSG had greater numbers of lactobacilli/enterococci than those in the SG. Serum total IgE correlated directly with Escherichia coli counts in all groups and with bacteroides counts in the HSG indicating that the presence of these can be correlated to atopic sensitisation. Supplementation resulted in a decrease in E. coli and a controlled level of bacteroides. Allergic symptoms were decreased in supplemented groups compared to placebo group. Bifidobacterial supplementation modulates the composition of the gut microflora in a manner that could contribute to alleviation of the symptoms of atopy by a lowered IgE level.

Date: 2002

Research Facility: University of Turku, Turku, Finland.

Published Source: Kirjavainen, PV, Arvola, T, Salminen, SJ, Isolauri, E. Aberrant composition of gut microbiota of allergic infants: a target of bifidobacterial therapy at weaning? 2002. Gut, 51: 51-55.

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Human Health Studies Probio-Tec[®]

Reference Number: 401

Health Effect On: Skin Disorders

Chr. Hansen Probiotic Strain: Bifidobacterium BB-12

Study Design: Double-blind placebo controlled study with 5 infants suffering from atopic eczema in each treatment group receiving infant formula with or without probiotic bacteria. Blood samples were collected before study start and at the control examination and analysed for plasma lipids.

Dosage: 1 billion CFU/g infant formula

Total CFU/Day: 500 billion/day

Reported Results BB-12 supplemented formula reduced the overall contents of neutral lipids in plasma, whereas the proportion of neutral phospholipids were increased. Results indicate that probiotics may be associated with physiological interactions of dietary PUFA. An association between diet and increased incidence of allergies has been proposed. Especially an increased consumption of n-6 polyunsaturated fatty acids (PUFA such as linoleic acid) has been linked to this phenomenon. Linoleic acid is indirectly influencing an enhanced IgE production and thereby allergic reaction. This study indicates that the observed alleviation of allergic disorders by probiotic strains, could partly be explained by a positive influence of probiotic bacteria at the level of dietary PUFA. The article is not very conclusive though.

Conclusions:

Date: 2002.

Research Facility: University of Turku, Turku, Finland.

Published Source: Kankaanpää, PE, Yang, B, Kallio, HP, Isolauri, E, Salminen, SJ. Influence of probiotic supplemented infant formula on composition of plasma lipids in atopic infants. 2002. Journal of Nutritional Biochemistry. 13: 364-369.

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