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SCIENTIFIC SURVEY • LACTIC ACID BACTERIA • PROBIOTICS

edito Probiotics and Fermented Milks in the Development of Host Defense in Infants

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Species of *bifidobacteria* and *lactobacilli* are found in large quantities in the human gastrointestinal tract shortly after birth, particularly in exclusively breast-fed infants. These same bacteria exist in fermented milks, including yogurt. Our laboratory has had a longstanding interest in the mechanism of bacteria interaction in developing human intestine (Kalliomakii & Walker 2005).

Using human intestinal models (cell lines, organ cultures, and xenografts of human small intestinal transplants), we have shown that the immature human enterocyte responds inappropriately to bacterial colonization and develops an inappropriate innate immune response (Yuan & Walker 2004). Pathogens can adhere/translocate on the surface of the intestine which influences the adherence of bacteria (Nanthakumar *et al.* 2005a). We have also shown that immature enterocytes produce excessive inflammation (IL-8 response) after exposure to inflammatory stimuli (LPS, IL-1 β).

We have reported that enterocyte genes that regulate toll-like receptors signalling and transcription leading to an innate immune response may be underexpressed in immature enterocytes, accounting for the excessive inflammatory response (Claud *et al.* 2004). Since probiotics have been used to prevent/treat infectious diarrhoeas in a premature inflammatory condition or necrotizing enterocolitis, we have begun to study their effect on the pathogenesis of this disease (Nanthakumar *et al.* 2005b).

Recently, unpublished data has suggested that extracts of *lactobacilli* and *bifidobacteria* can stimulate a maturation of underexpressed, developmentally regulated genes (e.g. I κ B) and reduce the excessive IL-8 response. These exciting new observations suggest that probiotics and fermented foods may mediate maturation of innate immunity in the developing gut of newborns. Further in-depth studies are needed to specifically define the actual mechanisms of the probiotic effects in the protection of infants against age-related, gastrointestinal disorders.

Claud EC, Lu L, Anton PM, Savidge T, Walker WA, Cherayil BJ (2004). Developmentally-regulated I κ B expression in intestinal epithelium and susceptibility to flagellin-induced inflammation. *Proc Natl Acad Sci* 101(19):7404-7408.

Kalliomaki M, Walker WA (2005). Physiologic and pathologic interactions of bacteria with gastrointestinal epithelium. *Gastroenterol Clin North Am* 34(3):383-399.

Nanthakumar NN, Young C, Ko JS, Meng D, Chen J, Buie T, Walker WA (2005a). Glucocorticoid responsiveness in the developing human intestine: possible role in the prevention of necrotizing enterocolitis. *Am J Physiol Gastrointest Liver Physiol* 288(1):G85-G92.

Nanthakumar NN, Dai D, Meng D, Chaudry N, Newburg DS, Walker WA (2005b). Regulation of intestinal ontogeny: effect of glucocorticoids and luminal microbes on galactosyltransferase and terehalase induction in mice. *Glycobiology* 15(3):221-232.

Yuan Q, Walker WA (2004). Innate immunity of the gut: Mucosal defense in health and disease. *J Pediatr Gastroenterol Nutr* 38(5):463-472.

Prevention and treatment of antibiotic-induced diarrhoea:

results of a meta-analysis

The use of probiotics to prevent diarrhoea induced by antibiotics and to treat *Clostridium difficile* infections is currently a much debated subject. Antibiotic-associated diarrhoea is a frequent complication when taking a good number of antibiotics and *C. difficile* infections are considered as nosocomial infections in which the taking of antibiotics plays a role. A meta-analysis has attempted to clarify this controversy (1).

In the period 1977-2005, 180 randomised, double-blind and placebo controlled clinical studies - all published in journals with a reading committee - were identified. After eliminating pre-clinical, safety and Phase 1 studies, summary articles and studies in which probiotics were not specified, the author of this meta-analysis retained 31 useful publications: 25 concerned antibiotic-induced diarrhoea (total of 2810

patients) and 6 others *C. difficile* infections (total of 354 patients). Of the 31 useful publications, the data from 25 placebo-controlled and randomized studies was combined to carry out the meta-analysis.

The overall results show that probiotics apparently have a preventive effect on antibiotic associated diarrhoea. However, disparities do exist depending on the probiotic strain or mixture of strains used. Two probiotics used alone are undoubtedly effective - *Saccharomyces boulardii* and *Lactobacillus rhamnosus* GG. For each of these two probiotics, 5 clinical studies were available that supported the drawing of firm conclusions whereas only 6 studies focused on the various other probiotic strains; the same goes for the mixtures of strains (7 available studies but different mixes).

As regards treating *C. difficile* infections, only *S. boulardii* would appear to reduce the recurrence of infections in contrast with *L. rhamnosus* GG, *L. plantarum* 299v and the *Lactobacillus acidophilus* and *Bifidobacterium bifidum* mixture.

This meta-analysis does not allow conclusions to be drawn as to the efficacy of the other strains used, but at the same time does not prove they are ineffective. Indeed, the number of analysable studies is still insufficient to be able to show a significant trend.

1• McFarland LV (2006). Meta-Analysis of Probiotics for the Prevention of Antibiotic Associated Diarrhea and the Treatment of *Clostridium difficile* Disease. *Am J Gastroenterol.* 101(4):812-822.

Preventing acute diarrhoea: results of a meta-analysis

A meta-analysis was given the goal of assessing all clinical studies that highlight the effectiveness of probiotics in fighting acute diarrhoea. This assessment was performed using different criteria - probiotic strains, probiotic formulation, age of the targets and causes of the diarrhoea (2).

The research strategy, applied to a period up until February 2006, enabled 690 potentially relevant studies to be identified. Finally, 34 publications were selected (4844 patients), that met the required inclusion criteria. They were all randomized, controlled studies that were conducted blind.

The authors divided the cases of acute diarrhoea into 3 categories - antibiotic-induced diarrhoea, "traveller's" diarrhoea and a third category that included all other cases of acute diarrhoea than

those included in the other two categories. Assessment according to the type of diarrhoea shows that probiotics reduce the global risk of antibiotic-associated diarrhoea (35%-65%) by 52%; travellers' diarrhoea (6%-21%) by 8% and acute diarrhoea in the last group (8%-53%) by 34%.

Probiotics would appear to be more effective in children than adults; reduction of the risk of acute diarrhoea is 57% (53%-71%) and 26% (7%-49%) respectively.

The protective effect exerted against diarrhoea in general does not appear to be significantly different according to the strain of probiotic. Whether for the strains most frequently used in these studies - *Lactobacillus rhamnosus* GG (n=10), *Lactobacillus acidophilus* plus *Lactobacillus bulgaricus* (n=7) and

Saccharomyces boulardii (n=5) or whether for other probiotic strains used individually or as a mixture of at least two strains.

Globally, the presumption is strong that probiotics are effective in fighting acute diarrhoea. However, this data concerns patients in industrialized countries, data for developing countries and particularly data for children in these countries is insufficient to be able to formulate a global recommendation as to the use of probiotics in an acute diarrhoea prevention strategy.

2• Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE (2006). Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. *Lancet Infect Dis.* 6(6):374-382.

The use of probiotics to fight inflammatory bowel disease (Crohn's disease and ulcerative colitis), and in particular to fight relapses, today presents an attractive and widely explored therapeutic opportunity. However, probiotics still have ground to cover.

Lactobacillus johnsonii LA1 does not prevent attacks of Crohn's disease

A French team has tested the *Lactobacillus johnsonii* LA1 probiotic on patients suffering from Crohn's disease (3). The patients recruited (n=98) had all undergone an intestinal resection during the 21 days prior to their enrolment in the study. At random and for 6 months, they each received either the probiotic (freeze-dried, 4×10^9 cfu/day) or a placebo, no other treatments were permitted.

The assessment parameters were endoscopic ones; they provide an account of recurrence of the disease 6 months on and assess the size, number, distribution

and type of any ileal and colic lesions according to a preset scale.

Six months on, recurrence was observed in 64% (30/47) of patients in the control group and 49% (21/43) of patients in the treatment group (p=0.15). The lesion distribution score was the same in both groups. From a clinical viewpoint, 4 patients who had been given the placebo suffered a relapse, against 3 who had received the probiotic.

The authors of this clinical study, conducted double-blind, concluded that

L. johnsonii LA1 is ineffective in preventing relapses in Crohn's disease. These very clear results, obtained with a strict protocol would appear to reject *L. johnsonii* as a candidate for treating Crohn's disease.

3• Marteau P, Lemann M, Seksik P, Laharie D, Colombel JF, Bouhnik Y, Cadiot G, Soule JC, Bourreille A, Metman E, Lerebours E, Carbonnel F, Dupas JL, Veyrac M, Coffin B, Moreau J, Abitbol V, Blum-Sperisen S, Mary JY (2006). Ineffectiveness of *Lactobacillus johnsonii* LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. Gut. 55(6):842-847.

Lactobacillus rhamnosus GG in ulcerative colitis relapses:

preliminary results

Adults (n=187) suffering from ulcerative colitis in quiescent phase received randomly and for one year one of the following three treatments: the probiotic *Lactobacillus rhamnosus* GG (18×10^9 cfu/day), mesalazine* or the probiotic plus mesalazine (4).

The primary end points observed concerned the number of relapses and the secondary end points were based on an evaluation of the endoscopic and histological scores and a measurement of the time lapse between two relapses (relapse before inclusion in the study and relapse during the study) as a way of

measuring the effectiveness of the treatment.

A time lapse of less than 3 months between two relapses was observed in 26% of patients given the probiotic alone and in those given the mesalazine and in 25% of those receiving a combined treatment.

The percentages of subjects still in remission 6 months or 12 months later were equal for all treatments. Variations in the histological and endoscopic scores 6 to 12 months later were also the same from one group to another.

This clinical study therefore shows that the probiotic *L. rhamnosus* GG is no more effective than mesalazine in preventing relapses of ulcerous colitis. This type of study obviously suffers from the absence of a control group given a placebo.

*Mesalazine is an intestinal anti-inflammatory derived from amino-5 salicylic acid and used to treat minor to moderate forms of ulcerative colitis.

4• Zocco MA, Dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, Novi M, Rigante D, Cazzato IA, Ojetti V, Armuzzi A, Gasbarrini G, Gasbarrini A (2006). Efficacy of *Lactobacillus* GG in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 23(11):1567-1574.

This scientific letter "Yoghurts & fermented milks" is also available on the following website:
www.maison-du-lait.com

A fermented milk as an adjuvant in eradicating *H. pylori*

To eradicate *Helicobacter pylori*, a pathogenic agent responsible for gastric ulcers, a triple therapy is today the standard recommended treatment. However, this protocol is not totally effective and, consequently, quadruple therapies are often required. Since lactobacilli and bifidobacteria have shown their ability, *in vitro*, to inhibit the development of *H. pylori*, they are today being actively tested for their ability to eradicate this pathogen in humans.

Researchers have tested the ability of fermented milk to improve the effectiveness of a quadruple therapy after the failure of a triple therapy (5).

One hundred and thirty-eight dyspeptic patients suffering from duodenal ulcers or gastritis and in whom triple therapy (amoxicillin, clarithromycin, and a proton pump inhibitor) had failed to eradicate the infection, were enrolled in the study. The patients were assigned to one of the following two groups: one was given a quadruple therapy* (control group) the other the quadruple therapy and the fermented milk (*Lactobacillus acidophilus* La5 + *Bifidobacterium lactis* Bb12 + yoghurt ferments (test group).

In both groups, the quadruple therapy was administered for one week and prior to this the tested group was also given the fermented milk for 4 weeks (total of 4×10^9 cfu/day). The patients underwent a breath ^{13}C -urea test ** before the start of the study, during the study and 6 weeks and 3 months after the end of the

study. The patients also underwent stomach biopsies in order to test the sensitivity of *H. pylori* to the antibiotics used at the start of the protocol.

The authors see the breath ^{13}C -urea test as an indicator of the *H. pylori* eradication rate. However, measuring the appearance of $^{13}\text{CO}_2$ is merely a qualitative marker of the presence of *H. pylori* and in no way enables the population to be counted. The establishment of a direct relationship between the enriched CO_2 exhaled and the quantity of *H. pylori* should consequently be seen as a relatively risky extrapolation.

For the patients in the test group, CO_2 enrichment was significantly reduced after 4 weeks of treatment ($p < 0.0001$) in comparison with what was measured when the patients were enrolled in the study. Similar results were observed in cases where the resistance of *H. pylori* to antibiotics was measured. These observations led the authors to think that quantity of *H. pylori* had been reduced. This conclusion must nevertheless be treated with caution as regards the breath ^{13}C -urea test.

For both groups, CO_2 enrichment was also measured 6 weeks after the administration of quadruple therapy. The group that received the fermented milk showed reductions in CO_2 enrichment that were greater than in the control group (**intention to treat analysis: 85% vs. 71.1%, $p < 0.05$; per protocol analysis: 90.8% vs. 76.6%, $p < 0.05$).

This clinical study provides certain elements that lead researchers to think that consuming fermented milk may help contribute to eradicating *H. pylori* and improve the effectiveness of a quadruple therapy. Although the effectiveness of this approach still needs confirming, it does have the advantage of not adding any significant cost to the treatment. Furthermore, using a common food product to treat this disease does provide a certain guarantee of risk-free treatment.

*The quadruple therapy consists of administering amoxicillin, metronidazol, omeprazol and bismuth subcitrate.

**The breath urea ^{13}C test is a non-invasive technique used to detect the presence of the *H. pylori*. It consists of having a patient absorb a quantity of carbon-13 marked urea and 30 minutes later to measure the enrichment in ^{13}C of the exhaled carbon dioxide. $^{13}\text{CO}_2$ appears as a result of ^{13}C urea transformation through the particularly active urease of *H. pylori*.

***Intention to treat analysis: all the subjects enrolled in the study are analyzed, whether or not they follow the clinical study correctly. This is the analysis procedure that is usually used. In this case, the difference between the test and control groups is slight. Per protocol analysis: only those subjects who followed the study protocol fully and correctly are subjected to the final analysis.

5• Sheu BS, Cheng HC, Kao AW, Wang ST, Yang YJ, Yang HB, Wu JJ (2006). Pretreatment with *Lactobacillus*- and *Bifidobacterium*-containing yogurt can improve the efficacy of quadruple therapy in eradicating residual *Helicobacter pylori* infection after failed triple therapy. *Am J Clin Nutr.* 83(4):864-869.

Lactobacillus casei could prevent candida infection in premature babies

Candida species are the third cause of infection in premature babies: candida infections may result in morbidity, interference with the development of the nervous system and even mortality.

A clinical study conducted in Italy, including 80 premature babies (weight less than $\leq 1.5\text{kg}$), had as its objective to assess the effectiveness of a probiotic in preventing intestinal candida infections (6). In the first 3 days of life, the infants were either entirely breast-fed (milk from mother or other donors) or breast milk containing the *Lactobacillus rhamnosus* GG probiotic in quantities of 6×10^9 cfu/day. This protocol was applied for 6 weeks or until the infant left the care unit. Samples were taken from different sites each week: oropharynx, faeces, stomach and rectum.

The total number of positive cultures (including *Candida*), the average number of positive samples per patient and the average number of positive samples

obtained from infected patients were lower in the group given the probiotic than in the control group ($p = 0.009$, $p = 0.005$, $p = 0.005$ respectively). The percentage of infants colonized by *Candida* in the gastro-intestinal region was 23.1% in infants receiving the probiotic and 48.8% in the control group ($p = 0.01$).

These results show that the probiotic resulted in less *Candida* colonization in the digestive tract. This benefit was observed in infants whose weight was between 1001 and 1500 g but was not significant in those whose weight was less than 1000 g.

This clinical study would appear to show that consuming *L. rhamnosus* GG significantly reduces the occurrence and quantity of gastro-intestinal candida infections in premature infants. To our knowledge, very few studies have tested the benefits of using probiotics on this type of population. Since, as the present study shows, consuming the probiotic

did not have any damaging effects, it encourages the further implementation of this kind of study in order to consolidate the results. However, it should be noted that the authors do not specify whether the administered milk was fresh breast milk or whether it came from a milk bank and was therefore refrigerated. The quality of the milk used could have an impact on the occurrence of candida infections. Further information about the sources of the milk used therefore appears necessary before the probiotics can really be claimed to be responsible for the benefits shown.

6• Manzoni P, Mostert M, Leonessa ML, Priolo C, Farina D, Monetti C, Latino MA, Gomirato G (2006). Oral supplementation with *Lactobacillus casei* sub-species *rhamnosus* prevents enteric colonization by *Candida* species in preterm neonates: a randomized study. *Clin Infect Dis.* 42(12):1735-1742.

Use of probiotics to treat gynaecological infections

A study conducted by Professor Gregor Reid tested the ability of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 strains to cure a type of vaginitis (bacterial vaginosis) in women in Niger (7).

One hundred and twenty-five women (aged 18-44) suffering from this type of vaginitis were treated with metronidazole from day one to day seven and then split into two groups, one given the probiotics *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (2×10^9 cfu/day of each bacterium) and the other group a placebo from day 1 to day 30. The patients were declared "cured" on day 30 of the treatment if the clinical symptoms had disappeared, if the Nugent test was normal and the sialidase test was negative.

Only 106 femmes came for the monitoring test on day 30, 88% of those who had been given the probiotic were cured as opposed to 40% of those who had only been given the antibiotic ($p < 0.001$). Among the women in the probiotic group who were not declared cured (12%) none were suffering from vaginitis but all were in an intermediate state towards being cured (presence of irritations and intermediate scores for the Nugent and sialidase tests). However, for the women in the control group who were not cured (60%) half were still suffering from vaginitis and the other half were in an intermediate state.

The results of this double blind, placebo controlled, randomized clinical study open up the prospect of using probiotics

as an adjuvant to treatment via antibiotics of certain types of vaginitis (bacterial vaginosis). According to the authors, including *L. rhamnosus* GR-1 and *L. reuteri* RC-14 probiotics in the treatment strategy is relevant to the target group studied since the low cost and possibility of freeze-drying the probiotics should help overcome some of the difficulties experienced accessing medicines in some parts of Africa.

7• Anukam K, Osazuwa E, Ahonkhai I, Ngwu M, Osemene G, Bruce AW, Reid G (2006). Augmentation of antimicrobial metronidazole therapy of bacterial vaginosis with oral probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14: randomized, double-blind, placebo controlled trial. *Microbes Infect.* 8(6):1450-1454.

A recombinant probiotic to treat and prevent cholera

Cholera is a diarrhoeal disease caused by the *Vibrio cholerae* bacillus. According to the WHO, the earth is currently enduring its 7th cholera pandemic. The disease is therefore still a threat today and the lack of a vaccine providing long term protection against cholera makes the discovery of vaccines or prophylactic methods essential.

As a result, an Australian team has developed a new strategy based on the construction of probiotics that carry molecules on their surface that imitate the host's natural receptors of cholera toxins (8). The idea being that the toxins, by binding to the recombinant probiotics, do not reach their natural targets (the host's cells) and consequently have no damaging effects.

The cholera vibrio colonizes the small intestine and releases toxins that bind to the cells of the intestine by binding to

the GM1 gangliosides present on the cell surface. In the next step, the toxin is internalized in the host cell where it triggers a cascade of reactions causing the ionic transport to be disturbed and resulting in acute diarrhoea and electrolyte imbalance - the fatal signs of cholera.

Preventing internalization of the cholera toxin in the cells could stop the disease developing and/or assist recovery. Researchers have therefore created a strain of *E. coli* CWG308 that is non-pathogenic and recombinant. This bacterium expresses chimera cells that imitate GM1 gangliosides.

Tests conducted *in vitro* show that the recombinant bacterium is able to bind large quantities of cholera toxins. In fact, the bacterium is able to absorb more than 5% of its weight in toxins. Tests conducted *in vivo* show that the

recombinant bacterium protects young mice from cholera vibrio infection, even when administered (via the orogastric route) after the infection has developed. One hundred per cent of the mice survive when the treatment with the recombinant bacterium is conducted one hour after infection with the vibrio, without treatment, the survival rate is only 1% ($p < 10^{-5}$).

This study shows that the strategy of constructing a recombinant probiotic is effective in prophylactic terms to treat cholera. It opens up a new way of using probiotics, not for their direct effects on health but as vectors for promoting good health.

8• Focareta A, Paton JC, Morona R, Cook J, Paton AW (2006). A recombinant probiotic for treatment and prevention of cholera. *Gastroenterology.* 130(6):1688-1695.

- 9• Blaut M, Marteau P, Miller GD, Antoine JM (2006). Probiotics and the Intestinal Microflora: What Impact on the Immune System, Infections and Aging? *Curr Nutr Food Sci.* 2(1):79-95.
- 10• Camilleri M (2006). Probiotics and irritable bowel syndrome: rationale, putative mechanisms, and evidence of clinical efficacy. *J Clin Gastroenterol.* 40(3):264-269.
- 11• Choi SS, Kim Y, Han KS, You S, Oh S, Kim SH (2006). Effects of *Lactobacillus* strains on cancer cell proliferation and oxidative stress in vitro. *Lett Appl Microbiol.* 42(5):452-458.
- 12• De Keersmaecker SC, Verhoeven TL, Desair J, Marchal K, Vanderleyden J, Nagy I (2006). Strong antimicrobial activity of *Lactobacillus rhamnosus* GG against *Salmonella typhimurium* is due to accumulation of lactic acid. *FEMS Microbiol Lett.* 259(1):89-96.
- 13• Drouault-Holowacz S, Foligne B, Dennin V, Goudercourt D, Terpend K, Burckel A, Pot B (2006). Anti-inflammatory potential of the probiotic dietary supplement Lactibiane Tolerance: In vitro and in vivo considerations. *Clin Nutr.* 2006 May 12; [Epub ahead of print].
- 14• El-Nezami HS, Polychronaki NN, Ma J, Zhu H, Ling W, Salminen EK, Juvonen RO, Salminen SJ, Poussa T, Mykkanen HM (2006). Probiotic supplementation reduces a biomarker for increased risk of liver cancer in young men from Southern China. *Am J Clin Nutr.* 83(5):1199-1203.
- 15• Ewaschuk JB, Walker JW, Diaz H, Madsen KL (2006). Bioproduction of conjugated linoleic Acid by probiotic bacteria occurs in vitro and in vivo in mice. *J Nutr.* 136(6):1483-1487.
- 16• Gilman J, Cashman KD (2006). The effect of probiotic bacteria on transepithelial calcium transport and calcium uptake in human intestinal-like Caco-2 cells. *Curr Issues Intest Microbiol.* 7(1):1-5.
- 17• Gueimonde M, Kalliomaki M, Isolauri E, Salminen S (2006). Probiotic Intervention in Neonates-Will Permanent Colonization Emerge? *J Pediatr Gastroenterol Nutr.* 42(5):604-606.
- 18• Guitard J, Menotti J, Desveaux A, Alimardani P, Porcher R, Derouin F, Kapel N (2006). Experimental study of the effects of probiotics on *Cryptosporidium parvum* infection in neonatal rats. *Parasitol Res.* 99(5):522-527.
- 19• Hutt P, Shchepetova J, Loivukene K, Kullisaar T, Mikelsaar M (2006). Antagonistic activity of probiotic lactobacilli and bifidobacteria against entero- and uropathogens. *J Appl Microbiol.* 100(6):1324-1332.
- 20• Joosten H, Bidlas E, Garofalo N (2006). Salmonella detection in probiotic products. *Int J Food Microbiol.* 110(1):104-107.
- 21• Kwak C, Jeong BC, Ku JH, Kim HH, Lee JJ, Huh CS, Baek YJ, Lee SE (2006). Prevention of nephrolithiasis by *Lactobacillus* in stone-forming rats: a preliminary study. *Urol Res.* 34(4):265-270.
- 22• Larsen CN, Nielsen S, Kaestel P, Brockmann E, Bennedsen M, Christensen HR, Eskesen DC, Jacobsen BL, Michaelsen KF (2006). Dose-response study of probiotic bacteria *Bifidobacterium animalis* subsp *lactis* BB-12 and *Lactobacillus paracasei* subsp *paracasei* CRL-341 in healthy young adults. *Eur J Clin Nutr.* 2006 May 24; [Epub ahead of print].
- 23• Leblanc JG, Rutten G, Bruinenberg P, Sesma F, de Giori GS, Smid EJ (2006). A novel dairy product fermented with *Propionibacterium freudenreichii* improves the riboflavin status of deficient rats. *Nutrition.* 22(6):645-651.
- 24• Ma YL, Guo T, Xu ZR, You P, Ma JF (2006). Effect of *Lactobacillus* isolates on the adhesion of pathogens to chicken intestinal mucus in vitro. *Lett Appl Microbiol.* 42(4):369-374.
- 25• Masco L, Van Hoorde K, De Brandt E, Swings J, Huys G (2006). Antimicrobial susceptibility of *Bifidobacterium* strains from humans, animals and probiotic products. *J Antimicrob Chemother.* 58(1):85-94.
- 26• Meyer AL, Micksche M, Herbacek I, Elmadfa I (2006). Daily intake of probiotic as well as conventional yogurt has a stimulating effect on cellular immunity in young healthy women. *Ann Nutr Metab.* 50(3):282-289.
- 27• Paton AW, Morona R, Paton JC (2006). Designer probiotics for prevention of enteric infections. *Nat Rev Microbiol.* 4(3):193-200.
- 28• Portugal LR, Goncalves JL, Fernandes LR, Silva HP, Arantes RM, Nicoli JR, Vieira LQ, Alvarez-Leite JI (2006). Effect of *Lactobacillus delbrueckii* on cholesterol metabolism in germ-free mice and on atherogenesis in apolipoprotein E knock-out mice. *Braz J Med Biol Res.* 39(5):629-635.
- 29• Prantera C (2006). Probiotics for Crohn's disease: what have we learned? *Gut.* 55(6):757-759.
- 30• Rioux KP, Fedorak RN (2006). Probiotics in the treatment of inflammatory bowel disease. *J Clin Gastroenterol.* 40(3):260-263.
- 31• Schroeder B, Duncker S, Barth S, Bauerfeind R, Gruber AD, Deppenmeier S, Breves G (2006). Preventive Effects of the Probiotic *Escherichia coli* Strain Nissle 1917 on Acute Secretory Diarrhea in a Pig Model of Intestinal Infection. *Dig Dis Sci.* 51(4):724-731.
- 32• Sistek D, Kelly R, Wickens K, Stanley T, Fitzharris P, Crane J (2006). Is the effect of probiotics on atopic dermatitis confined to food sensitised children? *Clin Exp Allergy.* 36(5):629-633.
- 33• Taranto MP, Perez-Martinez G, Font de Valdez G (2006). Effect of bile acid on the cell membrane functionality of lactic acid bacteria for oral administration. *Res Microbiol.* 157(8):720-725.
- 34• Tursi A, Brandimarte G, Giorgetti GM, Elisei W (2006). Mesalazine and/or *Lactobacillus casei* in Preventing Recurrence of Symptomatic Uncomplicated Diverticular Disease of the Colon: A Prospective, Randomized, Open-label Study. *J Clin Gastroenterol.* 40(4):312-316.
- 35• Wildt S, Munck LK, Vinter-Jensen L, Hanse BF, Nordgaard-Lassen I, Christensen S, Avnstroem S, Rasmussen SN, Rumessen JJ (2006). Probiotic Treatment of Collagenous Colitis: A Randomized, Double-blind, Placebo-controlled Trial With *Lactobacillus acidophilus* and *Bifidobacterium animalis* subsp. *lactis*. *Inflamm Bowel Dis.* 12(5):395-401.
- 36• Xiao JZ, Kondo S, Yanagisawa N, Takahashi N, Odamaki T, Iwabuchi N, Iwatsuki K, Kokubo S, Togashi H, Enomoto K, Enomoto T (2006). Effect of probiotic *Bifidobacterium longum* BBS36 in relieving clinical symptoms and modulating plasma cytokine levels of Japanese cedar pollinosis during the pollen season. A randomized double-blind, placebo-controlled trial. *J Invest Allergol Clin Immunol.* 2006;16(2):86-93.
- 37• Zareie M, Johnson-Henry KC, Jury J, Yang PC, Ngan BY, McKay DM, Soderholm JD, Perdue MH, Sherman PM (2006). Probiotics prevent bacterial translocation and improve intestinal barrier function in rats following chronic psychological stress. *Gut.* 2006 Apr 25; [Epub ahead of print].

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