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# Yoghurts & fermented milks

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Health • Nutrition • Flora

SCIENTIFIC SURVEY . LACTIC ACID BACTERIA . PROBIOTICS

## edito New insights in the mechanisms of immunomodulation by probiotics

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The intestine is colonized by vast societies of microorganisms that promote the development of the mucosal immune system and contribute to host health. The immune cells associated with the gut develop in proximity of an enormous population of commensal bacteria in the intestinal lumen; thus, those bacteria influence the development of the innate and adaptive gut immune systems.

The intestinal epithelium is the first line of defence against attached bacteria and acts as a physical barrier to microbial penetration. The way in which the intestinal microflora contributes to the gut immunity has often been studied in germ-free animals. Bacterial colonization has been proved to favour the expression of bactericidal proteins as a way to regulate the commensal population and the initiation of the expansion of germinal center reactions between B and T cells in the Peyer's patches, with increased B, IgA+ cells and IgA antibodies as a consequence. The modulation of dendritic cells (DC) and macrophages present in the intestine is also influenced by the gut flora.

The mechanisms involved in the modulation of the gut immune system by the commensal bacteria are not completely known. The understanding of how these microorganisms communicate with the host cells and how the microbial signals drive the intestinal immune system to induce activation or oral tolerance is one of the major challenges for microbiologists, immunologists or biologists.

Although many attempts have been made to understand the gut immunostimulation by pathogenic bacteria, much less research has been done on non pathogenic microorganisms. In this complicate context of the gut microenvironment, what can be expected from the effects of exogenous probiotic bacteria on the immune system? What kind of signals do these bacteria release? Should we expect an innate or an adaptive immune response? Which one would favour intestinal homeostasis? If, by definition, probiotic bacteria, although not able to colonize the intestine, should reach the gut lumen in a viable condition: how long will they remain so in that environment? Which would be the proper dose to ensure both a sufficient quantity of microorganisms and their permanence in the gut so as to give them the possibility of initiating an immune response? Will the continuous administration of probiotic bacteria guarantee the presence of an active amount of bacteria able to exert a beneficial effect on the host? In this sense, would the use of indigenous bacteria be more advisable than the administration of exogenous strains?

On the basis of our experience, we can say that, despite the species specific criterion, the behaviour of some indigenous isolates in the gut immune system is similar to that of certain exogenous strains, both having to overcome the same physiological and immune barriers to contact the epithelial cells. Whatever the way in which probiotic bacteria arrive at the small intestine (as whole cells or as antigenic fragments), they must interact with the M cells in the Peyer's patches or with the epithelial cells of the small intestine and with the immune cells associated with it. After bacteria make contact with the epithelial cells, the latter must send activation signals for the release of cytokines that induce the up or down regulation of the immune cells. The interaction of probiotic bacteria with the epithelial cell can be achieved through Toll-like receptors that induce mainly IL-6 responsible for the terminal differentiation of IgA+ cells to plasmocytes or increasing the IgA+ population in the lamina propria of the small intestine. However, if bacteria are internalized through the M cells from the Peyer's patches and are subsequently captured by any antigen presenting cell (APC), this one will be then the responsible for sending signals to the epithelial and/or other immune cells.

The signals from the epithelial cells or from the APC must translocate to the underlying immune cells to induce cytokine release, mainly from the innate immune cells (DC or macrophages) in order to initiate the gut immune response. The important question here is what the magnitude of the stimulation should be so as to prevent an inflammatory immune response.

... (cont'd)

Is the development of a Th1 response that mediates delayed hypersensitivity important? Should a Th2 response with antibody production against the probiotic bacteria be necessary? Obviously, Th1 or Th2 activation would not be advisable. However, a minor activation of these populations would be desirable to enhance the immunological surveillance with no alteration of the intestinal homeostasis. A concomitant production of the regulatory cytokines IL-4, IL-10 or TGF $\beta$  is also desirable to upregulate the immune activation. If the interaction of probiotic bacteria with the immune cells takes place in the lamina propria through the intestinal epithelial cells, the antigenic presentation with the consequent Th1 or Th2 activation is unlikely to occur. However, if the interaction of probiotic bacteria with DC or macrophages in Peyer's patches, is not through Toll-like receptors, which are signal transducers, there is no possibility of an increase in the adaptive response.

We have obtained scientific evidence, using a murine model and testing different probiotic lactobacilli strains and yogurt, that: 1) the whole cell of probiotic bacteria is able to interact with the gut epithelial cells and their fragments internalize and contact immune cells; 2) the epithelial cell is able to produce mainly IL-6; 3) after probiotic bacteria contact DC or macrophages through their membrane receptors, the release of inflammatory and regulatory cytokines to maintain intestinal homeostasis is induced; 4) the increase in the number of IgA+ cells is not accompanied by an increase of T population (CD4 or CD8); 5) the viability of administered bacteria would be important for a better probiotic stimulation; 6) the continuous consumption of probiotic bacteria is the proper way to maintain immunological surveillance, especially as regards the number of IgA+ cells; 7) no specific antibodies against probiotic bacteria are produced; 8) the oral administration of probiotics also promotes immunity at mucosal distant sites such as bronchus and mammary glands.

For probiotic immunomodulation, the up and down regulation of the innate response would be advisable to maintain homeostasis. Our results would confirm this hypothesis, although more intimate studies concerning the signals induced are necessary to demonstrate that probiotic bacteria stimulate the innate immune response. In our opinion, the above would be the way in which probiotics work in our murine models and all the aspects discussed should be considered for human trials.

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## *L. casei* modulates its metabolism during gastro-intestinal transit

A challenge for probiotic researchers lies in determining whether bacteria administered live, survive during their passage through the host's digestive tract. It is today accepted that some of the actions of probiotics can only occur if the bacteria are delivered live to the intestinal lumen.

In a human flora-associated murine model, Gérard Corthier's team has shown that *L. casei* DN-114 001 appears able to initiate protein synthesis during intestinal transit (1). To confirm this result and analyze the expression of different genes, the same team created recombinant strains of *L. casei* DN-114 001 in which the luciferase gene was placed under the control of 4 promoters (2). The activity of each promoter was evaluated by quantifying the luminescence and the production of luciferase mRNA.

The luciferase expression of the different promoters was assessed *in vitro* and during transit through the gastro-intestinal tract of human flora-associated mice. In the latter case, an analysis was performed on faeces collected 6 hours after the oral administration of the tested bacteria to the mice ( $5 \times 10^7$  to  $5 \times 10^8$  cfu administered).

*In vitro*, after three days of culture, no activity was detected from the target promoters. However, *in vivo*, two of the four promoters were activated during gastro-intestinal transit. This indicates that the probiotic is not metabolically active when it is administered to the mouse, but that it becomes so during transit through the digestive tract of the mouse.

This study shows that during gastro-intestinal transit in human flora-associated

mice, *L. casei* DN-114001 initiated specific protein synthesis. This proves not only that the bacterium survives in this environment but also that it adapts its metabolism to the environmental conditions of the digestive tract.

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2. Oozeer R, Furet JP, Goupil-Feuillerat N, Anba J, Mengaud J, Corthier G. (2005). Differential activities of four *Lactobacillus casei* promoters during bacterial transit through the gastrointestinal tracts of human-microbiota-associated mice. *Appl Environ Microbiol.* 71(3):1356-63.

This scientific letter "Yoghurts & fermented milks" is also available on the following website:

[www.maison-du-lait.com](http://www.maison-du-lait.com)

## Research into the laxative effect of *Lactobacillus GG* on constipated children

The administration of probiotics to remedy problems of constipation could constitute an alternative to traditionally prescribed laxatives. Studies show that this type of treatment could be beneficial to adults (3). A Polish team has tested the impact on constipated children of consuming *Lactobacillus rhamnosus GG* (LGG) at the same time as lactulose, an osmotic laxative (4).

This randomized, double-blind clinical study, involved 84 children aged between 2 and 16 all suffering from constipation (less than three defecations per week) for at least 12 weeks. For 12 weeks, each participant received an oral dose of lactulose together with either a placebo or LGG ( $2 \times 10^9$  cfu/day). During the test period,

the constipation-related symptoms were assessed either by the patients or by their parents. At 4, 8, 12 and 24 weeks after the start of the study, the children were examined by a doctor.

Consumption of lactulose improved the clinical condition of the patients in a statistically significant manner, but no significant difference was observed between the groups receiving the probiotic and those receiving the placebo.

Under these experimental conditions, administering LGG to children suffering from constipation did not provide any additional benefit to that of the laxative. However, this result does not mean that LGG cannot be effective. The study gives

no indication of the probiotic's intrinsic ability to act as a laxative, since LGG was only tested in combination with lactulose.

3• Koebrick C, Wagner I, Leitzmann P, Stern U, Zunft HJ. (2003). Probiotic beverage containing *Lactobacillus casei* Shirota improves gastrointestinal symptoms in patients with chronic constipation. *Can J Gastroenterol.* 17(11):655-9.

4• Banaszkiwicz A, Szajewska H. (2005). Ineffectiveness of *Lactobacillus GG* as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. *J Pediatr.* 146(3):364-9.

## A *Lactobacillus* incapable of preventing diarrhoea in healthy adults

Studies focusing on preventing infectious diarrhoea in adults by probiotic consumption have given contradictory results (5, 6). In its turn, an Israeli team asked the same question by testing the impact of *L. casei* DN-114 001 on diarrhoea among a homogenous population of adults - young recruits doing their military service (7).

501 healthy young males, with a mean age of 18.5 were allocated randomly to one of two groups. All consumed 100 ml of fermented milk 6 days per week for 8 weeks. The control group received fermented milk with no live bacteria; the test group was given fermented milk containing yoghurt bacteria and *L. casei* DN-114 001 ( $1 \times 10^{10}$  cfu/day). The subjects were unaware which group they had been allocated to. The frequency and duration of any diarrhoea were reported.

Despite the tendency of the tested product to reduce the incidence of diarrhoea (occurring in 12.2 % of the treated subjects against 16.1 % of the control group subjects), no statistically significant difference was observed between the two groups. In no cases did the consumption of the tested dairy products cause any side effects.

Compared to a fermented milk without live lactic bacteria, the probiotic was not seen to have any statistically significant impact on the occurrence of diarrhoea. It should be noted that, given the infrequent occurrence of diarrhoea observed in this population of young healthy males, distinguishing a significant difference between the groups would have required a very large number of subjects (1160 according to the authors, compared to the 501 studied). Furthermore, the product consumed by the control group was also a fer-

mented milk. This product could therefore contain lactic fermentation metabolites able to exert a preventive effect against diarrhoea. It would have been interesting to include another control group whose subjects did not consume any fermented milk products.

5• Oksanen PJ, Salminen S, Saxelin M, Hamalainen P, Ihanola-Vormisto A, Muurasniemi-Isoviita L, Nikkari S, Oksanen T, Porsti I, Salminen E, et al. (1990). Prevention of travellers' diarrhoea by *Lactobacillus GG*. *Ann Med.* 22(1):53-6.

6• Hilton E, Kolakowski P, Singer C, Smith M. (1997). Efficacy of *Lactobacillus GG* as a Diarrheal Preventive in Travelers. *J Travel Med.* 4(1):41-43.

7• Pereg D, Kimhi O, Tirosh A, Orr N, Kayouf R, Lishner M. (2005). The effect of fermented yogurt on the prevention of diarrhea in a healthy adult population. *Am J Infect Control.* (2):122-5.

## Probiotics treating diarrhoea in HIV positive adults

In HIV positive adults, administering anti-retroviral multitherapies generally causes gastro-intestinal side effects, in particular diarrhoea. To avoid this type of medication-induced diarrhoea, different strategies have already been used such as consuming probiotics (8) or taking glutamine\* (9). In a pilot study, an American team tested the effect of a food supplementation combining probiotics and glutamine on diarrhoea caused by antiretroviral multitherapy (10).

The sample included 35 HIV positive adults treated by multitherapy and suffering from diarrhoea. Seven subjects did not receive any additional treatment over and above the standard care. The 28 other patients benefited from a treatment combining nutritional advice, physical exercise and supplementation. The supplement given to the patients in this group was a symbiotic (1.2 g/day of a mixture of *L. acidophilus* and bifidobacteria + 11 g day of soluble fibre). If the diarrhoea continued for more than 4 weeks, 30 g/day of glutamine was added to the symbiotic. In all cases, the course of symbiotics was followed for 8 weeks. Over and above the clinical monitoring, the patients' quality of life\*\* was assessed every 4 weeks.

The frequency of the stools and the use of anti-diarrhoea medication were both significantly reduced in the treated group ( $p < 0.001$ ), compared to the control group that received no treatment. As a whole, the supplementation (with or without glutamine) reduced the severity of the diarrhoea by at least 50 % in 86 % of the subjects. Of the 28 subjects treated, the symbiotic alone, administered over 4 weeks, cured the diarrhoea in 13 patients. Adding glutamine to the treatment caused an improvement in 11 additional patients.

Unlike the control patients, almost all the quality of life criteria were significantly improved in the group receiving the symbiotic with or without the glutamine.

This pilot study conducted in HIV positive adults treated with a multitherapy and suffering from diarrhoea showed that consumption of a symbiotic, including *L. acidophilus*, bifidobacteria and fibre, reduced the severity of the diarrhoea and improved quality of life. Adding glutamine to the treatment gave added benefits to patients that had not responded to the symbiotic. If these results are confirmed, the consumption of probiotics could cons-

tribute a simple and inexpensive solution to contribute to improving the quality of life of these patients.

\* Glutamine is an essential amino acid that helps to preserve the structure of the gut mucous membrane, hence its beneficial role in treating diarrhoea caused by water loss through the gut mucosa.

\*\* Patients' quality of life was determined using a test specific to this population - FAHI 4 (Functional Assessment of Human Immunodeficiency Virus Infection quality of life instrument).

8• Cremonini F, Di Caro S, Nista EC, Bartolozzi F, Capelli G, Gasbarrini G, Gasbarrini A. (2002). Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. *Aliment Pharmacol Ther.* 16(8):1461-7.

9• Savarese D, Al-Zoubi A, Boucher J. (2000). Glutamine for irinotecan diarrhea. *J Clin Oncol.* 18(2):450-1.

10• Heiser CR, Ernst JA, Barrett JT, French N, Schutz M, Dube MP. (2004). Probiotics, soluble fiber, and L-Glutamine (GLN) reduce nelfinavir (NFV)- or lopinavir/ritonavir (LPV/r)-related diarrhea. *J Int Assoc Physicians AIDS Care (Chic Ill).* 3(4):121-9.

## Lactobacillus GG reduces the severity of atopic eczema in children

Controlling allergies in children is a promising area of action for probiotics. The most effective bacterium in this field is *Lactobacillus rhamnosus GG* (LGG). Several studies have shown that consumption of LGG by children at risk prevents the onset of atopic diseases (11). As a pilot study involving 27 atopic children has shown, LGG modulates the immunity of the patients and reduces the severity of the symptoms (12). A recent, larger-scale study has presented new data (13).

A Finnish team analyzed the impact of LGG, a mixture of 4 probiotics or a placebo, each administered together with a skin treatment to 230 infants suffering from atopic eczema (average age: 6.4 months). The infants were allocated at random to one of the three groups; the study was conducted double blind. The daily doses consumed for 4 weeks were: LGG alone  $1 \times 10^{10}$  cfu; probiotic mixture: LGG and *L. rhamnosus LC705*  $1 \times 10^{10}$  cfu, *B. breve Bbi99*  $4 \times 10^8$  cfu, *Propionibacterium freudenreichii JS*  $4 \times 10^9$  cfu. A doctor evaluated the severity of the

eczema (SCORAD\*) at the start and end of the test period.

In all the children in the test groups, the mean score was reduced by 65 %, but there were no differences between the three groups. However, different responses to LGG were observed depending whether the infants were IgE positive or not\*\*. Between the beginning of the study and 4 weeks after the end of the treatment, in IgE positive infants more improvement in the symptoms was observed (evaluated by SCORAD) in the group receiving LGG than in the patients receiving the placebo (-26.1 vs -19.8;  $p=0.036$ ). No difference was reported in the infants that were not IgE positive or in those receiving the probiotic mixture.

Consumption of *Lactobacillus GG* provided extra benefits to infants suffering from atopic eczema on top of their normal medication. The fact that this only occurred in infants where an allergy had been detected by the presence of IgE, is, according to the authors in agreement with the

preliminary studies showing that lactobacilli favour the expression of type Th1 cytokines to the detriment of type Th2.

\* SCORAD (SCORing Atopic Dermatitis): global score of the severity of atopic dermatitis based on objective (severity of the symptoms, extent) and subjective (degree of pruritus and insomnia) criteria.

\*\* A set of cutaneous tests has highlighted a typology of infants depending on whether or not they produce IgE specific to one of the allergens tested.

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12• Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. (2000). Probiotics in the management of atopic eczema. *Clin Exp Allergy*. 30(11):1604-10.

13• Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. (2005). Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. *Allergy*. 60(4):494-500.

## A probiotic improves the symptoms related to irritable bowel disease

The aetiology of irritable bowel disease is not yet clear and there is still today no effective treatment. Slight intestinal inflammation and excessive growth of the intestinal flora have been put forward as possible causes of the disease. Given that probiotics can modulate these factors, the administration of probiotics is foreseen as one of the strategies for fighting irritable bowel syndrome. In a randomized, double-blind study, an Irish team has compared the effects of two bacterial strains in patients suffering from this disease (14).

During 8 weeks, 77 adults suffering from irritable bowel syndrome consumed daily a malted milk drink containing either  $1 \times 10^{10}$  cfu of *L. salivarius UCC4331* or *B. infantis 35624*, or a placebo (with no bacteria). A global score of the symptoms was calculated from the data provided by the patients on a daily basis. At the beginning and end of the period of administration of the tested products, a clinical examination determined the quality of life, microbial composition of the faeces and the production of interleukins 10 and 12 (IL-10 and IL-12) by circulating mono-

nucleus lymphocytes. A group of healthy volunteers, similar to the study group, provided a point of comparison for the IL-10 and IL-12 concentrations.

The consumption of *L. salivarius* showed no differences compared to the consumption of the placebo for the parameters studied. However, for the group receiving *B. infantis*, the symptoms score was significantly better than that of the control group. The IL-10 and IL-12 concentrations observed in patients suffering from irritable bowel disease were significantly different to those of the healthy subjects and indicated an inflammatory condition. Of the 3 products tested, only *B. infantis* resulted in concentrations of similar levels to those of the healthy subjects.

The authors noted however that the significance of their results was limited by one parameter. The way smokers were spread between the groups was very irregular. Non-smokers accounted for 58 %, 72 % and 92 % of patients respectively in the groups receiving the placebo, the lactobacillus and bifidobacteria (statistically significant difference).

The product containing *B. infantis* improved the symptoms in the patients suffering from irritable bowel syndrome. At the same time, the levels of the patients' IL-10 et IL-12 cytokines, revealing an inflammatory condition, returned to values similar to those of healthy subjects. This result shows that the use of probiotics could be envisaged in the treatment of irritable bowel syndrome.

14• O'Mahony L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, O'Sullivan GC, Kiely B, Collins JK, Shanahan F, Quigley EM. (2005). Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 128(3):541-51.

## Adjuvant effect of lactobacillus on oral polio vaccine

Two probiotics often consumed by humans were tested in humans as an adjuvant to the oral polio vaccine (OPV) (15).

64 healthy young people, aged between 20 and 30, were allocated randomly to one of three groups. The probiotics were administered in a non-fermented clotted milk, containing either no bacteria (placebo), or  $1 \times 10^{10}$  cfu of *Lactobacillus rhamnosus GG* (LGG) or *Lactobacillus acidophilus CRL431*. The subjects consumed the tested product for 5 weeks and were given the OPV against poliovirus types 1, 2 & 3 at the start of the second

week. The study was carried out double-blind.

The protective effect of the serum against the poliovirus and the production of polio-specific IgG, IgA and IgM were evaluated before and after the test period.

The number of subjects immunised against polio was significantly higher after the test, with no notable differences between the groups receiving the probiotics or the placebo. However, the number of specific antibody titres was increased after the vaccination with probiotics, compared to

the placebo group. No difference in efficacy was observed between LGG and *L. acidophilus*.

This study, conducted among humans, shows that the lactobacilli acted as an adjuvant to OPV.

15• de Vrese M, Rautenberg P, Laue C, Koopmans M, Herremans T, Schrezenmeir J. (2004). Probiotic bacteria stimulate virus-specific neutralizing antibodies following a booster polio vaccination. *Eur J Nutr*. 1:1-8.

## Fermented milk to improve mineral absorption

Milk products are an undeniable source of calcium. Could fermented milks also have a beneficial impact on the nutritional status of populations compared to other minerals? According to a study conducted on Mexicans consuming a traditional plant-based diet, the reply could

be “Yes”. After 13 days of daily consumption of milk or yoghurt in addition to the normal diet, zinc absorption had increased by more than 50 % compared to the start of the test. However, no effect was observed on iron absorption.

16• Rosado JL, Diaz M, Gonzalez K, Griffin I, Abrams SA, Preciado R. (2005). The addition of milk or yogurt to a plant-based diet increases zinc bioavailability but does not affect iron bioavailability in women. *J Nutr.* 135(3):465-8.

## Arguments suggest smokers can benefit from consuming fermented milks

In habitual smokers, the activity of natural killer (NK) immune cells is reduced. The activity level of these cells, able to kill tumoural cells or cells infected with viruses, plays a role in keeping the immune system in smooth working order. In a randomised, placebo controlled, double-blind study, a Japanese team evaluated the impact of consuming a fermented milk containing *L. casei shi-*

*rota* on the activity of NK cells in 99 smokers. The results showed that NK activity was inversely correlated to the number of cigarettes smoked. In the subjects who consumed fermented milk, NK activity was significantly greater than in the control subjects. Therefore, the consumption of this fermented milk helped to restore an immunity parameter damaged by cigarettes.

17• Morimoto K, Takeshita T, Nanno M, Tokudome S, Nakayama K. (2005). Modulation of natural killer cell activity by supplementation of fermented milk containing *Lactobacillus casei* in habitual smokers. *Prev Med.* 40(5):589-94.

## Probiotics as an oral vaccination vector

Less invasive and therefore simpler to administer, oral vaccines are an alternative to injectable ones. The use of recombinant probiotics is an oral vaccination solution currently under study. In mice, researchers have succeeded in immunising against enteropathogenic coronavirus by

administering the lactobacillus *L. casei Shirota*, a carrier of the virus antigen. The production of specific antibodies was seen at both intestinal and systemic level. This double effect could help optimize immunization against pathogens that infect humans via the digestive tract.

18• Ho PS, Kwang J, Lee YK. (2005). Intra-gastric administration of *Lactobacillus casei* expressing transmissible gastroenteritis coronavirus spike glycoprotein induced specific antibody production. *Vaccine.* 23(11):1335-42.

## Four new probiotics have proved their safety

A prerequisite to the use of probiotics in humans consists in ensuring that these micro-organisms are not a potential vector of resistance to antibiotics. For four new strains, *Lactobacillus rhamnosus HN001 (DR20™)* and *HN067*, *Lactobacillus acidophilus HN017* and *Bifido-*

*bacterium lactis HN019*, the authors have researched both the resistance of the bacterial genes and the plasmid. These four new probiotic strains showed little resistance to the 18 antibiotics tested.

19• Zhou JS, Pillidge CJ, Gopal PK, Gill HS. (2005). Antibiotic susceptibility profiles of new probiotic *Lactobacillus* and *Bifidobacterium* strains. *Int J Food Microbiol.* 98(2):211-7.

## Lactobacilli effective against intestinal inflammation

In order to study the impact of probiotics on intestinal inflammation, the authors selected murine lactobacilli able to inhibit *in vitro* the production of TNF- $\alpha$  by macrophages stimulated by the *Helicobacter hepaticus* pathogen. Two lactobacilli with this activity, *L. reuteri* and *L. paracasei*, were administered to mice. Intestinal inflammation had been experimentally

provoked in these mice by *H. hepaticus*. The consumption of the probiotic mixture reduced the intestinal inflammation without influencing the number of pathogens in the faeces. In this murine model, lactobacilli that showed anti-inflammatory properties *in vitro* also inhibited intestinal inflammation *in vivo*.

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