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Probiotics for Prevention of Recurrent Urinary Tract Infections in Women

A Review of the Evidence from Microbiological and Clinical Studies

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Abstract

Recurrent urinary tract infections (UTIs) afflict a great number of women around the world. The use of probiotics, especially lactobacilli, has been considered for the prevention of UTIs. Since lactobacilli dominate the urogenital flora of healthy premenopausal women, it has been suggested that restoration of the urogenital flora, which is dominated by uropathogens, with lactobacilli may protect against UTIs. This review is based on a search of PubMed for relevant articles. Many *in vitro* studies, animal experiments, microbiological studies in healthy women, and clinical trials in women with UTIs have been carried out to assess the effectiveness and safety of probiotics for prophylaxis against uropathogens. Most of them had encouraging findings for some specific strains of lactobacilli. *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 (previously called *L. fermentum* RC-14) seemed to be the most effective among the studied lactobacilli for the prevention of UTIs. *L. casei shirota* and *L. crispatus* CTV-05 have also shown efficacy in some studies. *L. rhamnosus* GG did not appear to be quite as effective in the prevention of UTIs. The evidence from the available studies suggests that probiotics can be beneficial for preventing recurrent UTIs in women; they also have a good safety profile. However, further research is needed

to confirm these results before the widespread use of probiotics for this indication can be recommended.

Recurrent urinary tract infections (UTIs) are a common cause of morbidity, especially in postmenopausal and sexually active premenopausal women. Recurrence occurs in 25–30% of adult women who have a first episode of UTI.[1] The decrease in quality of life of these women and the high healthcare cost of treating them have made the prevention of recurrent UTIs very important. Antibacterials have been used widely for this purpose, but long-term antimicrobial prophylaxis is associated with increased drug resistance and adverse effects. Thus, efforts have been made to discover and develop alternative preventive strategies.

Probiotics are one of these promising alternatives. They are defined as "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host".[2] There is strong evidence that they are effective for the treatment of rotavirus diarrhoea and the prevention of antibacterial-associated diarrhoea in children.[3] Their usefulness for the prevention of *Helicobacter pylori* infections, inflammatory bowel diseases, allergy, cancer,[3] respiratory tract infections and other diseases[4] is still under investigation. Prevention of recurrent UTIs is a further possible clinical use for probiotics. It should be emphasised that there have been changes to the nomenclature of the various lactobacilli recently. More specifically, *Lactobacillus acidophilus* RC-14 and *L. fermentum* RC-14 studied in The Netherlands and Canada have been renamed *L. reuteri* RC-14 and *L. casei* GR-1, respectively, and *L. casei* var *rhamnosus* has been renamed *L. rhamnosus* GR-1. However, in our review, we use the terms of lactobacillus species as specified in the publications from which we derived our data.

1. Literature Search

We searched PubMed (1950–2005) for publications and relevant references from the initially identified articles. The key words we used included 'probiotics', 'lactobacillus', 'urinary', 'urogenic' and 'infections'. We focused on articles regarding *in vitro* studies of the effect of probiotics on colonisation and infection of the urogenital epithelium; experiments on probiotics in animals; and studies investigating the *in vivo* effect of intravesical, intravaginal and oral probiotics on female vaginal flora and recurrence of UTI.

2. Pathophysiology of Recurrent Urinary Tract Infections (UTIs) in Women

The healthy female urogenital flora consists of many species of micro-organisms, among which lactobacilli (especially *L. crispatus,*[5,6] *L. jensenii*[5] and *L. iners*[6,7]) are dominant in healthy premenopausal women. Bruce et al.[8] were the first to show that there is a high prevalence of vaginal lactobacilli in women without any history of UTIs. Lactobacilli and the other microorganisms that dominate the vaginal flora of some healthy women, such as *Atopobium* spp., *Megasphaera* spp. and *Leptotrichia* spp.,[6] produce lactic acid and other substances which keep the vaginal pH low and prevent the overgrowth of pathogens. Estrogens seem to promote the colonisation of the vagina with lactobacilli and reduce the vaginal pH, thus controlling the growth of pathogens.[9] This is thought to be one of the main reasons why postmenopausal women are more susceptible to urogenital infections than premenopausal women. Moreover, vaginal microflora often changes considerably during the menstrual cycle, even in women without any episodes of UTI.[10]

In patients with UTI, the flora of the urethra and the vagina are colonised mainly by uropathogens, especially *Escherichia coli* and other Enterobacteriaciae. Uropathogens produce many virulence factors, including adhesins, haemolysin and siderophores. The ability of uropathogens to cause infection is associated with their adhesion to urogenital cells, to each other (autoaggregation) and possibly

to other organisms (coaggregation).[11] Although the adhesion of the uropathogens on the urogenital epithelium has been demonstrated in many studies, it is still not yet well understood how they manage to survive passage through natural flora.

3. Mechanisms of Action of Probiotics

In vitro experimentation is useful for clarifying the ability of probiotics to inhibit the growth of uropathogens. However, the results of such experiments may or may not be clinically relevant. *In vitro* studies of interactions between micro-organisms may be simplified compared with the complexity of interactions within the human flora. Despite these limitations, there is sufficient evidence from *in vitro* studies to elucidate the mechanism of action of probiotics in preventing UTIs. Recent *in vitro* studies have shown that specific lactobacilli strains have the ability to interfere with the adherence, growth and colonisation of the urogenital human epithelium by uropathogenic bacteria. This interaction is believed to be important in the maintenance of a normal urogenital flora and in the prevention of infection in women.

According to one study, using glass and sulfonated polystyrene polymers, both of which are hydrophilic, lactobacilli can be used to coat biomaterial surfaces, thus decreasing the adhesion of uropathogens.[12] Precoating the polymers with lactobacilli significantly reduced adhesion of staphylococci and *E. coli*. Another study from The Netherlands demonstrated that the *L. acidophilus* RC-14 biosurfactant 'surlactin' inhibited the adhesion of the majority of bacteria from a urine suspension to silicone rubber, 4 hours after urine flow. Surlactin was especially effective against *Enterococcus faecalis*, *E. coli* and *Staphylococcus epidermidis*.[13] Some years later, a high anti-adhesive, surface-active protein against *E. faecalis* 1131 was purified from *L. fermentum* RC-14. The structure of this protein was identical to that of a collagen-binding protein from *L. reuteri* NCIB 11951 and was closely homologous with the basic surface protein from *L. fermentum* BR11. The experiment showed that this protein of lactobacillus could prevent the adhesion of uropathogens.[14] It has also been shown that *L. crispatus* blocks the adherence and the growth of many uropathogens.[15]

It is accepted today that there is considerable variation among lactobacillus strains regarding their adherence to uroepithelium, and inhibition of uropathogen adherence and growth. Under the conditions of an agar overlay inhibition assay, a combination score was allocated to each of 11 tested lactobacillus strains based on adherence, exclusion and inhibition of pathogen growth. *L. casei* GR-1 gained the highest score.[16] The production by *L. casei* GR-1 (and probably other lactobacilli, such as *L. acidophilus*) of inhibitors against pyelonephritogenic mutant *E. coli* strains was proved in another *in vitro* study, and this may have clinical implications regarding their role in the urogenital microflora.[17]

4. Animal Studies

Since no ideal animal models exist, where vaginal administration of a uropathogen causes UTI, pathogens are administered intra-urethrally. In 1985, Reid et al.,[18] using an animal model of female rats, concluded that *L. casei* prevented the onset of UTIs in 84% of the animals tested. First, they injected bacteria incorporated into agar beads into the animals' bladders. The uropathogens stimulated an immune and inflammatory response, thereby establishing a persistent adherence of bacteria on the uroepithelium, and causing a chronic UTI. Subsequently, *L. casei* GR-1, isolated from the urethra of a healthy woman, was incorporated into agar beads and instilled into the rat bladders. In 21 of 25 studied animals, no uropathogens were recovered from the bladder and kidney tissues up to 60 days after instillation. The lactobacilli excluded the uropathogens from colonising the uroepithelium within 48 hours.[18]

In 1989, Herthelius and Gorbach[19] established a persistent vaginal colonisation with a pyelonephritogenic strain of *E. coli* in four adult monkeys. Repeated vaginal flushes of lactobacilli or vaginal fluid from a healthy monkey were administered for 5–9 days. Vaginal *E. coli* was eliminated in two of six experiments where lactobacilli were instilled and in

all eight experiments where vaginal fluid was administered. In the other four experiments where lactobacilli were administered, vaginal *E. coli* was only reduced. This result shows that the entire normal vaginal flora is much more effective in inhibiting the colonisation of the vagina with *E. coli* than lactobacilli alone.[19]

In 1996, Silva de Ruiz et al.[20] investigated whether *L. fermentum* CRL 1058 could control UTIs caused by uropathogenic *E. coli* in mice treated with ampicillin. Animals where inoculated intra-urethrally with agarose beads containing lactobacilli, while ampicillin was administered orally. The ampicillin dose used allowed the lactobacilli to persist in the urinary tract, leading to the elimination of pathogens.[20]

A study by Asahara et al.[21] suggested that *L. casei shirota* is a strain possibly useful for the prevention of UTIs. *E. coli* was administered intra-urethrally in female mice, causing UTI. *L. casei shirota* (10^8 colony-forming units [cfu]) was also administered intra-urethrally 1 day before and daily after the infection. The growth of *E. coli* and the inflammatory responses in the urinary tract were significantly inhibited.[21]

L. crispatus CTV-05 has also been tested in animals as a means of protection from urogenital infections, as it has been detected in the vagina of many healthy women. Patton et al.[22] inserted one capsule of *L. crispatus* CTV-05 (10^8 cfu) intravaginally into ten female animals (Macaca) and found that it had colonised the vaginas of three animals 2 days later.

5. Microbiological Studies in Healthy Women

The ability of lactobacilli to colonise the vaginal epithelium of healthy women after intravaginal or oral administration has been investigated in some studies. In 2003, Colodner et al.[23] suggested that *L. rhamnosus* GG may not be an effective probiotic agent in preventing UTIs. Forty-two postmenopausal healthy women were given one to two doses of yogurt containing *L. rhamnosus* GG (10^9 cfu) daily for 1 month. The cultures of vaginal fluid specimens showed that only 9.5% (4 of 42) of the studied women were colonised with *L. rhamnosus* GG.[23]

Cardieux et al.[24] compared the vaginal instillation (immediately after menses) of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 (10^9 cfu) with that of *Lactobacillus* GG (10^9 cfu) in 29 premenopausal healthy women without urogenital infections. No adverse effects were reported. *L. rhamnosus* GR-1/*L. fermentum* RC-14 and *Lactobacillus* GG were isolated from cultures of vaginal swabs of all women in both groups (15 and 14 women, respectively) 3 days after the instillation of probiotics. However, *L. rhamnosus* GR-1/*L. fermentum* RC-14 and *Lactobacillus* GG were isolated from 11/15 (73%) and 3/14 (21%), respectively, at day 14 ($p = 0.009$).[24] In a similar trial, Burton et al.[7] used two techniques (polymerase chain reaction denaturing gradient gel electrophoresis [PCR-DGGE] and randomly amplified polymorphic DNA [RAPD] analysis) to detect *L. rhamnosus* GR-1/*L. fermentum* RC-14 in the vagina at amounts that may not be detectable by cultures. They detected *L. rhamnosus* GR-1/*L. fermentum* RC-14 in 80% of ten healthy premenopausal women 1 week after daily vaginal instillation of 10^9 cfu. *L. rhamnosus* GR-1 was also detected in 20% of women 3 weeks after the instillation.[7]

In another clinical study, Reid et al.[25] compared the oral administration of *Lactobacillus* GG with *L. rhamnosus* GR-1 and *L. fermentum* RC-14 in 42 healthy women aged 17–50 years who were free from symptomatic urogenital infections. The women were randomly separated into four groups. Groups 1 ($n = 10$), 2 ($n = 12$) and 3 ($n = 11$) received daily oral capsules of *L. rhamnosus* GR-1/*L. fermentum* RC-14 at different dosages (8×10^8, 1.6×10^9 and 6×10^9 cfu per day, respectively), and group 4 ($n = 9$) received one capsule of *Lactobacillus* GG 10^{10} cfu daily. At the start of the study, only 40% (17/42) of women had healthy vaginal flora and 33% (14/42) had asymptomatic bacterial vaginosis. Within 28 days, the percentage of women whose vaginal flora converted from abnormal to normal was greater for groups 1, 2 and 3 compared with group 4 (the difference was statistically significant only for group 2; $p = 0.017$). This study showed that

oral administration of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 is associated with greater restoration and maintenance of normal vaginal flora than *Lactobacillus* GG, and that the required dose of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 for this effect is more than 8×10^8 cfu of viable lactobacilli.[25]

The same investigators have also studied the effect of the oral administration of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 on the vaginal flora, in a randomised, double-blind, placebo-controlled trial in 64 healthy women (19–46 years old).[26] Thirty-two women received oral freeze-dried capsules of *L. rhamnosus* GR-1/*L. fermentum* RC-14 (>10^9 cfu per strain) once daily for 60 days and the other 32 received placebo for the same duration. Cultures of vaginal fluid showed a significant increase in lactobacilli ($p = 0.01$), a decrease in yeast ($p = 0.01$) and a reduction of coliforms ($p = 0.001$) at day 28 in the group receiving the lactobacilli compared with placebo-treated women. Significantly fewer coliforms remained in the lactobacilli-treated group at day 90 ($p < 0.01$). Moreover, more women in the lactobacillus group reported improvement in vaginal health (vaginal itchiness or odour) compared with placebo-treated women, although the difference was not statistically significant ($p = 0.17$). There were no adverse effects in the probiotic-treated group.[26]

Another smaller, randomised, double-blind, placebo-controlled clinical trial demonstrating the ability of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 to colonise the vagina when received orally was conducted by Morelli et al.[27] Ten healthy women received orally either *L. rhamnosus* GR-1/*L. fermentum* RC-14 ($n = 8$) or lactose placebo ($n = 2$) once daily for 14 days. The number of lactobacilli increased in the vaginas of eight of the ten studied women 14 days later, although the increase was very small in three of eight. Genetic typing identified *L. rhamnosus* GR-1 and *L. fermentum* RC-14, respectively, in five and two of the studied women. *L. rhamnosus* GR-1 was also recovered from faecal samples of all eight women who received the lactobacilli and L. *fermentum* RC-14 was recovered from four.[27]

The ability of *L. crispatus* CTV-05 to colonise the vagina after vaginal administration has been tested clinically. The subjects in this study had just been treated for bacterial vaginosis, and received intravaginal *L. crispatus* CTV-05 or placebo. Thirty days later, *L. crispatus* CTV-05 colonised the vagina of 62% of the patients who received it and only 2% of those who received placebo ($p < 0.001$).[28]

6. Clinical and Microbiological Studies in Women with UTIs

In the first clinical trial of probiotics in women with UTIs, lactobacilli were given intravesically. Newman[29] was the first who used intravesical lactobacilli in a small number of women for the treatment of bladder infections and claimed that this approach was effective. Hagberg et al.[30] instilled *L. casei* GR-1 into the bladder of postmenopausal patients with recurrent UTIs and found that lactobacilli did not adhere to the bladder. They also implanted avirulent *E. coli* strains (6mL of 10^9 bacilli/mL) from the patients' own faecal flora intravesically and found that they colonised the mucosa.

Intravaginal administration of lactobacilli met with more success than intravesical administration. During a small, uncontrolled study conducted by Bruce and Reid[31] in 1988, five women (two of whom were postmenopausal) with recurrent UTIs were given intravaginal *L. casei* GR-1 twice weekly. *L. casei* GR-1 colonised the vaginal epithelium and prevented the colonisation of coliform bacteria in most women, without affecting enterococcal colonisation, which occurred in two women. No adverse effects were mentioned. All studied women had significantly more extended infection-free periods (4 weeks to 6 months) than before treatment (<1 month). One patient received a combination of *L. fermentum* B-54 and *L. casei* GR-1 after the second enterococcal infection that occurred during the study period. This combination treatment resulted in an increase in the coloinisation of vaginal epithelium by lactobacilli.[31]

A trial comparing the risk of recurrence of UTI before and after receiving lactobacilli was carried out by Reid et al.[32] in 1992. They treated 41 adult women with acute lower UTI with norfloxacin or co-trimoxazole (trimethoprim/sulfamethoxazole) for 3 days. UTI recurred in 29% of the norfloxacin-treated group and in 41% of the co-trimoxazole-treated group. Women with recurrent UTI then received vaginal suppositories of either *L. casei* var *rhamnosus* GR-1 and *L. fermentum* B-54 or sterilised skimmed milk twice weekly for 2 weeks and at the end of each of the next 2 months. The recurrence of UTIs over 6 months decreased to 21% for those receiving lactobacillus compared with 47% for the skimmed milk-treated group.[32]

A case report by Reid et al.[33] further supports the effectiveness of intravaginal lactobacilli as protection against UTIs. The vagina of a 33-year-old woman with a history of recurrent bladder and vaginal infections was implanted with one gelatin pessary of 0.5g freeze-dried *L. casei* var *rhamnosus* GR-1 ($>10^9$ viable cells). Although *E. faecalis* (and no lactobacilli) was the dominant organism in her vagina at the time of the implantation, 7 weeks after the pessary insertion, both viable *L. casei* and *L. rhamnosus* GR-1 were recovered from her vaginal swabs. She remained free from vaginal and bladder symptoms for the 7 weeks of the study and for the following 6 months (during which she had two more pessaries inserted).[33]

A randomised, double-blind clinical trial, showing a significant impact of intravaginal lactobacilli on recurrence of UTIs, was conducted in 55 premenopausal women by Reid et al.[34] Twenty-five of these women received one vaginal suppository of *L. rhamnosus* GR-1 and *L. fermentum* B-54 10^9 cfu per week and the rest received one vaginal suppository of a lactobacillus growth factor weekly for 1 year. No adverse effects were reported. The UTI rate decreased by 73% (from 6 to 1.6 episodes/year; $p < 0.001$) in the first group and 79% (from 6 to 1.3 episodes/ year; $p < 0.001$) in the second.[34]

It should be emphasised that not all clinical studies showed a beneficial effect of intravaginal probiotics in preventing the recurrence of UTIs. Baerheim et al.[35] concluded that it is uncertain whether vaginal instillation of lactobacilli decreases the incidence of cystitis in women. In a randomised, double-blind trial, 47 women (aged 18–50 years), with three or more episodes of distal urinary symptoms in the previous year (at least one confirmed as UTI) received vaginally *L. casei* var *rhamnosus* of placebo twice weekly. During the next 6 months, the incidence rate ratio of lower UTIs between the treated patients and the placebo group was 1.41 (95% CI 0.88, 1.98), a non-statistically significant result.[35]

Besides the intravesical and the intravaginal route of administration of probiotics, the effectiveness of the oral administration of these agents in reducing the recurrence of UTIs has also been assessed. Tomoda et al.[36] tested *Bifidobacterium longum* for this purpose and showed that lower UTIs due to *Candida* infections were reduced by 70% in women receiving oral *B. longum*.

Various lactobacilli administered orally have been also studied. *Lactobacillus* GG was used in some studies to test its effect on UTIs, but without much success. Kontiokari et al.[37] performed a randomised clinical trial in 150 women (mean age 30.3 years) who had a UTI caused by *E. coli.* After being treated with antibacterials for the UTI episode, they were randomly separated into three groups. The first group received cranberry-lingonberry juice 50mL per day for 6 months, the second group took a *Lactobacillus* GG 100mL (4×10^{10} cfu) drink 5 days per week for 1 year, and the third control group received no further treatment. No adverse effects were reported. During 6 months of observation, 8 women (16%) in the cranberry group, 19 (39%) in the lactobacillus group and 18 (36%) in the control group had at least one episode of UTI. Consequently, recurrence in 6 months was significantly less common ($p = 0.014$) in the cranberry than in the control group, while lactobacillus had no impact on recurrence.[37]

In contrast, Kontiokari et al.[38] found a positive role for fermented milk products containing probiotics, such as *L. acidopilus* or *Lactobacillus* GG. They conducted a case-controlled study in 324 women (mean age 30.5 years). The patients (n = 139) en-

tered the study 2 weeks after an acute UTI caused by *E. coli*; 109 (78%) had more than one UTI episode. The controls (n = 185) had no UTIs during the past 5 years. The questionnaire they completed showed that frequent consumption of fresh juices, especially berry juices, and fermented milk products containing probiotics were more common among controls than among patients. Specifically, consumption of fermented milk products with probiotics, such as *Lactobacillus* GG or *L. acidophilus*, more than three times per week was associated less commonly with UTIs compared with consumption of these products less than once per week (odds ratio [OR] 0.21; 95% CI 0.06, 0.66).[38]

Reid et al.[39] conducted a small, uncontrolled trial to assess the efficacy of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 in protecting women against UTIs. Ten women with a recent history of recurrent urogenital infections who were asymptomatic at the start of the study were given orally $>10^9$ cfu of various strains of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 twice daily for 14 days. Vaginal cultures, Gram-stain and ribotyping performed 1 week later revealed colonisation of the vagina with *L. rhamnosus* GR-1 and *L. fermentum* RC-14 of all patients.[39] The vaginal flora of six patients, which were considered to be intermediate or indicative of bacterial vaginosis based on the Nugent score at the beginning of the study, was restored to normal 1 week after receiving lactobacilli. In addition, all women reported relief from their symptoms of urogenital infection and had no adverse effects from the administered probiotics.

7. Adverse Effects of Probiotics

Probiotics are generally considered to be safe. However, some species of microorganisms that are also used as probiotics have recently been isolated from infection sites, causing some concerns regarding the safety of these products. Surgical operations, cancer, diabetes mellitus and long-term antimicrobial and immunosuppressive therapy are the most common underlying conditions in patients with lactobacillus infections. Lactobacillaemia usually occurs in patients with serious and fatal underlying disease.[40] During the past 30 years, 180 cases of lactobacillaemia and 69 cases of endocarditis due to lactobacilli have been reported.[41] Gasser[42] reported the isolation of *L. rhamnosus, L. acidophilus, L. casei* and other lactobacilli in patients with endocarditis. *L. rhamnosus* was also among other isolates from patients with bacteraemia.

Nevertheless, only a few cases have been reported that connect isolated lactobacilli from sites of infection with those consumed. Rautio et al.[43] reported the case of a 74-year-old woman who consumed about 500mL of dairy drinks with *L. rhamnosus* GG daily for 4 months and developed a liver abscess, an aspirate from which revealed *L. rhamnosus* indistinguishable from GG. Mackay et al.[44] reported the case of a 67-year-old man with a mild mitral valve regurgitation who consumed capsules with *L. rhamnosus* and *L. acidophilus* and developed endocarditis after a tooth extraction. *L. rhamnosus* was isolated from blood cultures of this patient. Generally, these cases are very rare compared with the increasing consumption of probiotics. An EU workshop concluded that lactic acid bacteria are of low risk, with the exception of enterococci.[45]

8. Conclusion

Conclusively, several *in vitro* and *in vivo* studies support the beneficial effect of some strains of lactobacilli on the restoration of the vaginal flora and the prevention of recurrent UTIs. Most of them show that *L. rhamnosus* GR-1 and *L. fermentum* RC-14, given either intravaginally or orally, are efficacious. However, their use for the prophylaxis of UTIs is still controversial because only a few case-controlled, double-blind clinical trials using strains carefully selected according to their laboratory-proven characteristics have been carried out so far. More randomised, controlled trials should be conducted to confirm the effectiveness of probiotics compared with placebo and antibacterials or other possible preventive agents. Moreover, although reported adverse effects are rare to date, further research on the safety of probiotics is needed.[2,3,27,46]

Probiotics are not yet approved for UTIs by several drug licensing organisations, including the US

FDA. *L. rhamnosus* GR-1 and *L. fermentum* RC-14 are currently available as Omb'e® [1] in Austria (by HSO), and are approved in Malaysia and Singapore as PRO-UTIx® by Biolife (Australia). They are also sold in Malaysia and Hong-Kong and are expected soon to be available worldwide as Urex-cap-5® by Urex Biotech Inc. (Canada) and Chr. Hansen (Denmark). It should emphasised that labelling of the commercial products should mention the strains and the viability of the probiotics they contain.

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1 The use of trade names is for product identification purposes only and does not imply endorsement.

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