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Probiotic bacteria in prevention and treatment of diarrhea

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Summary

Probiotic bacteria have beneficial effects in prevention and treatment of different diseases. The results of preventive and therapeutic effect of probiotic bacteria on diarrhea during last ten years are shown in this paper. The greatest preventive and therapeutic effect of probiotic bacteria was identified for acute diarrhea in children caused by rotaviruses. Significant, but slightly lower effect of probiotic bacteria was proved for antibiotic associated diarrhea. Positive effect in prevention of traveller's diarrhea and radiation-induced diarrhea is not significant. Preventive and therapeutic effect on diarrhea is not dependent on the way of probiotic bacteria intake, by fermented milk, capsule or oral rehydration solution.

Key words: diarrhea, probiotic bacteria, prevention, treatment

Introduction

Human gastrointestinal tract is a specific ecosystem inhabited by more than 400 diverse microbial species living in perfect natural balance. These are the species that have been isolated and defined so far and they are present in the concentration higher than 10^{14} organisms/g (Šušković and Kos, 2000). The function of intestinal microbial population within gastrointestinal tract is multiple, whereas protecting organism is considered to be its most important function (Vaughan et al., 2000; Falagas et. al., 2008). During the 70's of the 20th century, scientific researches provided sufficient firm evidence that the balance among diverse microbial species within intestine population is a precondition for the preservation of human health.

Due to growing pollution of the environment, use of chemical food additives, frequent international travels, as well as antibiotic treatments and radiotherapy, intestinal population can be misbalanced. Regardless of sample, the most frequent consequence of such misbalances is diarrhea, a disease that nearly 4 billion people suffer from per year. 5 % of all people on sick-leave suffer from diarrhea. Furthermore, about 4 % of the diarrhea inflicted population die because of its consequences (Szajewska and Mrukowicz, 2005; Sazawal et al., 2006). In developing countries, diarrhea caused by pathogen strains *Shigella*, *Vibriocholera*, *Salmonella*, *Campylobacter spp.*, *Escherichia coli* and rotaviruses are major cause of infants and child mortality. However, even in developed countries, such as the USA, diarrhea is diagnosed in 21 to 37 million cases per year within the population of 16.5 million children (Nomoto, 2005). Traveller's diarrhea is found in approximately 12 million cases, and depending on destination, 5 to 50% travellers suffer from it (Cheng and Thielman, 2002; McFarland, 2007). Diarrhea often happens during or after antibiotic treatment (5-25 %) or X-ray treatment of people suffering from cancer (Bergogne-Berezin, 2000). Due to the fact that more than a half of world grown-up population have insufficient quantity of lactase enzyme, diarrhea can be caused by consuming food in which lactose share is almost 50 g. The figure of the real lactose intolerance of the population is not fully accurate when commonly consumed quantity of milk of 2.5 dcL (12 g of lactose) is taken into consideration. It is considered to be less for a half (Miller et al., 2007).

Lactic acid bacteria and bifidobacteria are characterized by ability to create diverse organic compounds and acids, hydrogen peroxide, diacethyl , CO_2, bacteriocine which they secrete into their habitat where they grow (Tamime et al., 2006). Either food or digestive tract being considered, these microrganisms have mainly inhibitory impact on the growth of undesirable microbial population for humans (Rogelj and Bogović-Matijašić, 1994; Šušković et al., 1997; Šušković

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et al., 1998; Samaržija et al., 2001, 2001a). Therefore it is no surprise that the data from numerous researches prove that, apart from their nutritional value, fermented milks have direct and/or indirect health-related value (Lukač Havranek and Samaržija, 1996). Fermented milks or preparations of lactic acid bacteria and bifidobacteria in the shape of capsule are proved to have beneficial effects in the prevention or as supplement in treatment of many different diseases (gastrointestinal, urogenital infections, tumours) (Blom and Mortvedt, 1991; Strnad and Babuš, 1996; Ouwehand et al., 1999; Betica-Radić, 2000; Sleator and Hill, 2007).

In the prevention and therapy of diarrhea caused bay misbalance within intestinal microbial population, the use of probiotic lactic acid bacteria and bifidobacteria in particular cases has also turned out to be a good choice. To a greater or less extent they are capable of re-establishing natural microbial balance in intestines (Bergogne-Berezin, 2000; Schrezenmeir and de Verse, 2001; Šušković et al., 2001).

The aim of this research is to emphasize the most important results obtained in about past ten years of probiotic bacteria preventive and therapeutic influence on: acute diarrhea in children, traveller's diarrhea, antibiotic associated diarrhea, radiotheraphy and lactose intolerance.

Acute diarrhea in children

The largest number of cases of acute diarrhea in children is a result of infection by rotaviruses. Because of that, it is no surprise that researches on the probiotic bacteria effect in prevention and therapy of diarrhea is connected with rotaviruses to a great extent. Thus a study, comprising children from one month to 36 months of age, showed that the usage of probiotic lactic acid bacteria and/or bifidobacteria on daily basis, not depending on whether these organisms were part of fermented milks, capsule or oral rehydration solution, decreases duration of diarrhea for 30-40 % (Saavedra, 2000).

In the group of children who were taking probiotics, diarrhea lasted for 1.4 to 2.3 days whereas in the placebo group diarrhea lasted for 2.4 to 3.2 days (Isolauri et al., 1991; Boudra et al., 1996; Shornikova, 1997; Guandalini et al., 2000; Weizman et al., 2005). The probiotic strains of bacteria *Lactobacillus rhamnosus GG, Lactobacillus reuteri, Lactobacillus delbruecki subsp. Bulgaricus, Bifidobacterium lactis and Strptococcus thermophilus* not only have therapeutic effect, but also have preventive effect on the manifestation of acute diarrhea in children. In the 17-month study, carried out in 1992 and 1993, only 7 % of the infants who were fed with infant formula enriched with *Bifidobacterium bifidum* and *Streptococcus thermophilus* bacteria had diarrhea. Tha manifestation of acute diarrhea during the same research period was 31 % with the babies fed with standard infant formula. However, the gravity of diarrhea, measured by its duration, frequency and stool quantity, has no significant difference among the test groups (Saavedra et al., 1994). Conversely, the results of the 2-year study (2000-2002) show that probiotic bacteria *Bifidobacterium lactis* and *Lactobacillus reuteri* in the concentration of 10^7 cfu/g decrease the prevalence of diarrhea in infants as well as its duration. However, more beneficial probiotic effect on the manifestation and duration of diarrhea was determined for *Lactobacillus reuteri* (Weizman et al., 2005). Shorter duration of acute diarrhea up to 48 % was determined by Rosenfeldt (2002) in the cases when the children were consuming *Lactobacillus reuteri* DSM 12246 (10^{10} cfu) along with *Lactobacillus rhamnosus* 19070-2 (10^{10} cfu/g) on a daily basis. Acute diarrhea was considerably eased in hospitalized children aged from one month to three years who were given *Lactobacillus rhamnosus* GG (10^{10} cfu/g) on a daily basis. Therefore, diarrhea was registered in 7-10 % of infants, whereas in the placebo group it was registered in even 33 % of cases (Szajewska et al., 2001; Mastretta et al., 2002).

After acute diarrhea in children caused by diverse infectious agents, the ability to colonize intestines with *Lactobacillus rhamnosus* GG bacterium was confirmed in 78.6 % (virus infection), in 75 % (bacterial infection) and in 85.7 % (unknown etiology) of cases (Szymanski et al., 2006). Therapeutic concentration (10^{10} cfu/g) contained three different strains of *Lactobacillus rhamnosus* GG in ratio 1:1:1.

Traveller's diarrhea

Due to contradictory results it is still not possible to talk for sure about the definite efficiency of probiotic bacteria usage in prophylaxis of traveller's diarrhea. The researches carried out in the 90's proved that probiotic strains *Lactobacillus acidophilus* alone or combined with *Lactobacillus fermentum* and *Lavtobacillus delbruecki* subsp. *bulgaricus* do not have considerable effect on prevention and/or ease of diarrhea (Kollaritsch et al., 1989; Katelaris et al., 1995). These results were confirmed by Briand (2006) in a double blind randomised study which has shown that *Lactobacillus acidophilus* (10^{10} cfu/g) taken two times a day before and after travelling does not prevent diarrhea. On the other hand, lyophilized mixed probiotic culture composed of *Lactobacillus acidophilus, Lactobacillus delbruecki* subsp. *bulgaricus, Bifidibacterium bifidum, Streptococcus thermophilus* in the concentration of $3x10^9$ cfu/g, which was consumed on the same way by Danish tourists during two weeks of journey through Egypt, reduced prevalence of diarrhea from 71 % to 43 % (Black et al., 1989). Meta analysis of six studies conducted by Sazawal et al. (2006) has shown that probiotic strains of bacteria *Lactobacillus acidophilus, Lactobacillus delbruecki* subsp. *bulgaricus Lactobacillus*

rhamnosus GG and *Lactobacillus fermentum* decreased the risk of diarrhea development during journey by 8 %. Besides, after carrying out the meta analysis of 12 randomised studies, McFarland (2007) allege that the usage of a mixed culture containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Saccharomyces boulardii* has safe and highly effective influence on traveller's diarrhea prevention. Effectiveness of the preventive influence of *Lactobacillus rhamnosus* GG and *Lactobacillus acidophilus* was tested on a group of American tourists who were travelling to different westward civilizations risky countries. Research confirmed significantly lower prevalence of traveller's diarrhea in the group which has two days before and after the journey taken *Lactobacillus rhamnosus* GG ($2x10^9$ cfu/g) in a form of powder, or added to fermented milk. Lower preventive influence was found for *Lactobacillus acidophilus* in comparison to *Lactobacillus rhamnosus* GG (Hilton et al., 1997). The influence of taking *Lactobacillus rhamnosus* GG on diarrhea development was examined on 820 Finns travelling to two different Turkish regions. Probiotic preventive impact of *Lactobacillus rhamnosus* GG was not significant, but it was observed that preventive effect depends on travelling region. Although the study was unexplained, it is presumed that ineffectiveness in preventive effect of these probiotic strains can be ascribed to different microbiological agents and the age of placebo groups (Oksanen et al., 1990, McFarland, 2007.).

Antibiotic associated diarrhea

Very often diarrhea could be a consequence of antibiotic therapy such as clindamicin, cephalosporin and penicillin. Antibiotics cause diarrhea due to disturbance of intestinal microflora natural balance which leads to quick growth of *Clostridium difficile*. Bacteria *Clostridium difficile* normally exists at a low level in the intestine of healthy humans (Nomoto, 2005). The reason of diarrhea manifestation is increase of its number and also as its ability to produce enterotoxins - *toxin A* and/or cytotoxin - *toxin B* (Marcos and DuPont, 2007). Meta analysis of some clinical studies shows that taking probiotic strains such as *Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus* and *Lactobacillus delbruecki* subsp. *bulgaricus* during antibiotic therapy, decreases the prevalence of diarrhea by 52 % comparing to control group. However, there is no significant difference in intensity of preventive effect between strains regardless if they were used alone or in some combination (D'Souza et al., 2002; Sazawal i sur., 2006). Remarkable influence of probiotic strains in prevention of children's diarrhea as a consequence of taking antibiotics was confirmed by Johnston et al. (2006.), and Szajewska et al. (2006). Treatments with probiotics could decrease the risk of antibiotic associated diarrhea in children to 11.9 % compared with a rate of 28.5 % cases in the control group (McFarland, 2006.).

Radiation-induced diarrhea

Radiotherapy is a method used very often in a medicine for treatment of different types of tumours. Negative side of radiation is the fact that nearly 80 % of patients have acute symptoms and diarrhea. Radiotherapy induced diarrhea could be considerably minimized by consuming lyophilized mixed probiotic strains composed of four *Lactobacillus* strains, three *Bifidobacterium* strains and one *Streptococcus delbrueckii subsp. thermophilus* strain (Delia et al., 2007). Adversely, Giralt et al. (2008) through double blind randomised clinical study defined that probiotic drink containing *Lactobacillus casei* DN-114 001 in the concentration of 10^8 cfu/g does not reduce the incidence of radiation-induced diarrhea. Research was carried out on patients who were diagnosed and operated endometrial adenocarcinoma (mucous membrane of uterus). However, significant effect on stool consistency was confirmed which shows that there is still positive effect of probiotic bacteria. Similar activity in prevention of radiation-induced diarrhea was confirmed for probiotic bacteria *Lactobacillus rhamnosus* GG (Urbancsek et al., 2001).

Diarrhea caused by lactose intolerance

Because of the lack of the intestine enzyme β-galactosidase (lactase), some people do not have the ability to degrade lactose. Non-degraded lactose induces illness with symptoms such as convulsion, flatulence, diarrhea and nausea. After eating yoghurt or other fermented milks, lactose intolerance is considerably lower in the comparison to the reaction after eating other kinds of dairy foods. In fermented milks the concentration of lactose is much lower (30 % average), while probiotic variety of fermented milks also contains a microbial β-galactosidase (Fooks et al., 1999). Fermented milks casein, calcium-phosphate and lactate neutralized gastric acid (acting like a buffer). Therefore the microbial β-galactosidase in the active form comes to a small intestine and the symptoms of the illness absent (Pochart et al., 1989). At 80 % of lactose intolerant people, after taking 18 g of lactose by milk, diarrhea and/or flatulence will occurre. However, symptoms of the illness failed when the same content of lactose was consumed along with yoghurt. Activity of β-galactosidase contained in yoghurt is enough to digest 50-100 % of consumed lactose in amount of 20 g (Miller et al., 2007).

Conclusion

The preventive and therapeutic effect of probiotic bacteria is not the same in different types of diarrhea. The main value of proven positive results in prevention and therapy of infant's and children's acute diarrhea as in diarrhea caused by antibiotic therapy is reduction of the treatment

cost. These researches are very complex which could cause different interpretation of results about effectiveness of probiotic bacteria in diarrhea prevention and therapy.

Probiotičke bakterije u prevenciji i terapiji dijareje

Sažetak

Probiotičke bakterije pozitivno djeluju u prevenciji i terapiji različitih bolesti. U radu su prikazani rezultati istraživanja utjecaja probiotičkih bakterija u prevenciji i terapiji dijareje provedenih posljednjih desetak godina. Najveći preventivni i terapijski učinak probiotičkih bakterija utvrđen je za akutnu dijareju u djece uzrokovanu rotavirusima. Značajan, ali nešto manji učinak probiotičkih bakterija dokazan je kod dijareje kao posljedice uzimanja antibiotika. Pozitivan učinak probiotičkih bakterija u prevenciji putničke dijareje i dijareje kao posljedice terapije zračenjem nije značajan. Preventivni i terapijski učinak na dijareju neovisan je o načinu uzimanja probiotičkih bakterija, fermentiranim mlijekom, kapsulom ili oralnom rehidratacijskom otopinom.

Ključne riječi: dijareja, probiotičke bakterije, prevencija, terapija

References

Bergogne-Bérézin, E. (2000): Treatment and prevention of antibiotic associated diarrhea, *International Journal of Antimicrobial Agents* 16 (4), 521-526.

Betica-Radić, Lj. (2000): Antibiotici i probavni trakt, Medicus 9 (2), 185-191.

Blom, H., Mortved, C. (1991): Antimicrobial substances producet by food associated microorganisms, Biochemical Society Transactions 19, 694-698.

Black, F., Anderson, P., Orskov, J., Gaarslev, K., Laulund, S. (1989): Prophylactic efficacy of Lactobacilli on travelers' diarrhea, *Travel Medicine* 7, 333-335.

Boudra, G., Benboubdalla, M., Hachelaf, W. (1996): A controlled clinical trial of yoghurt vs milk in young children with acute watery diarrhea, *Journal of Pediatric Gastroenterology and Nutrition* 22, 451-455.

Briand, V., Buffet, P., Genty, S., Lacombe, K., Godineau, N. Salomon, J., Vandemelbrouck, E. (2006): Absence of efficacy of nonviable Lactobacillus acidophilus for the prevention of traveler's diarrhea: a randomized, double-blind, controlled study, Clinical Infectious disease 43 (9), 1170-1175.

Cheng, A.C., Thielman, N.M. (2002): Update on traveler's diarrhea, Current infectious disease reports 4, 70-77.

Delia, P., Sansotta, G., Donato, V., Frosina, P., Messina, G., De Renzis, C., Famularo, G. (2007): Use of probiotics for prevention of radiation-induced diarrhea, World Journal of Gastroenterology 13 (6), 912-915.

D'souza, A.L., Rajkumar, C., Cooke, J., Bulpitt, C.J. (2002): Probiotics in prevention of antibiotic-associated diarrhoea: meta analysis, British Medical Journals 324 (7350), 1361-1364.

Falagas, M.E., Petros, I.R., Makris, G.C. (2008): Bacterial interference for the prevention and treatment of infections, International Journal of Antimicrobial Agents 31 (6), 518-522.

Fooks, L.J., Fuller, R., Gibson, G.R. (1999): Prebiotics, probiotics and human gut microbiology, International Dairy Journal 9 (1), 53-61.

Giralt, J., Regadera, J.P., Verges, R., Romero, J., De la Fuente, I., Biete, A., Villoria, J., Cobo, J.M., Guarner, F. (2008): Effects of probiotic Lactobacillus casei DN-114 001 in prevention of radiation-induced diarrhea: results from multicenter, randomized, placebo-controlled nutritional trial, International Journal of Radiation Oncology* Biology* Physics 71 (4), 1213-1219.

Guandalini, S., Pensabene, L., Zikri, M.A., Dias, J.A., Casali, L.G.,Hoekstra, H., Kolacek, S., Massar, K., Miceti-Turk, D., Papadopoulou, A. (2000): Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European study, Journal of Pediatric Gastroenterology and Nutrition 30, 54-60.

Hilton, E., Kolakowski, P., Singer, C., Smith, M. (1997): Efficacy of Lactobacillus GG as a diarrheal preventive in travelers, Journal of Travel Medicine 4 (1), 41-43.

Isolauri, E., Jununen, M., Rautanen, T. (1991): A human lactobacillus strain Lactobacillus casei sp strain GG promotes recovery from acute diarrhea in children, Pediatrics 88 (1), 90-97.

Johnston, B.C., Supina, A.L., Vohra, S. (2006): Probiotics for pediatric antibiotic-associated diarrhea: a meta-analysis of randomized placebo-controlled trials, C*anadian medical Association Journal* 175 (4), 377-383.

Katelaris, P.H., Salam, I., Farthing, M.J. (1995): Lactobacilli to prevent traveler's diarrhea?, The New England Journal of Medicine **333 (20)**, 1360-1361.

Kollaritsch, H., Kremsner, P., Wiedermann, G., Scheiner, O. (1989): Prevention of traveller's diarrhea: comparison of different non-antibiotic preparations, Travel Medicine International, 9-17.

Lukač Havranek, J., Samaržija, D. (1996): Prehrambene, zdravstvene i tehnološke značajke fermentiranih proizvoda, Mljekarstvo 46 (4), 265-273.

Marcos, L.A., Dupont, H.L. (2007): Advances in defining etiology and new therapeutic approaches in acute diarrhea, Journal of Infection 55 (5), 385-393.

Mastretta, E., Longo, P., Laccisaglia, A., Balbo, L., Russo, R., Mazzaccara, A., Gianino, P. (2002): Effect of Lactobacillus GG and breast-feeding in the prevention of rotavirus nosocomial infection, The Journal of Pediatric Gastroenterology and Nutrition 35 (4), 527-31.

McFarland, L.V. (2007): Meta-analysis of probiotics for the prevention of traveler's diarrhea, Travel Medicine and Infectious Disease 5 (2), 97-105.

McFarland, L.V. (2006): Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease, The American Journal of Gastroenterology 101(4), 812-22.

Miller, G.D., Jarvis, J.K., McBean, L.D. (2007): Handbook of dairy foods and nutition, 3. izd., Taylor & Francis group, New York.

Nomoto, K. (2005): Prevention of infections by probiotics, Journal of Bioscience and Bioengineering 100 (6), 583-592.

Oksanen, P.J., Salminen, S., Saxelin, M. (1990): Prevention of travelers' diarrhea by Lactobacillus GG, Annals of Medicine **22 (1)**, 53-56.

Ouwehand, A.C., Kirjavainen, P.K., Shortt, C., Salminen, S. (1999): Probiotics. Mechanisms and established effects, International Dairy Journal 9 (1), 43-52.

Pochart, P., Dewit, O., Desjeux, J., Bourlioux, P. (1989): Viable starter culture, beta-galactosidase activity, and lactose in duodenum after yogurt ingestion in lactase-deficient humans, American Journal of Clinical Nutrition 49 (5), 828-831.

Osenfeldt, V., Michaelsen, K.F., Jakobsen, M., Larsen, C.N., Miller, P.L., Pedersen, P., Tvede, M., Weyrehter, H., Valerius, N.H., Paerregaard, A. (2002): Effect of probiotic Lactobacillus strains in young children hospitalized with acute diarrhea, The Pediatric Infectious Disease 21 (5), 411-416.

Rogelj, I., Bogović-Matijašić, B. (1994): Bacteriocins of lactic acid bacteria-properties, range of inhibitory activity and methods of detection, Prehrambeno-tehnološka i biotehnološka revija, spec. izd. 32, 171-175.

Saavedra, J.M., Bauman, N.A., Oung, I., Perman, J.A., Yolken, R.H. (1994): Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus, Lancet 344 , 1046-1049.

Saavedra, J. (2000): Probiotics and infectious diarrhea, The American Journal of Gastroenterology 95 (1), 16-18.

Samaržija, D., Lukač Havranek, J., Antunac, N., Sikora, S. (2001): Characteristics and role of mesophilic lactis culture, Agriculturae conspectus scientificus 66 (2), 113-120

Samaržija, D., Antunac, N., Lukač Havranek, J. (2001a): Taxonomy, physiology and growth of Lactococcus lactis: a review, Mljekarstvo 51 (1), 35-48

Sazawal, S., Hiremath, G., Dhingra, U., Malik, P., Deb, S., Black, R.E. (2006): Efficacy of probiotics in prevention of acute diarrhoea: a meta analysis of masked, randomised, placebo-controlled trials, Lancet Infectious Disease 6 (6), 374-382.

Schrezenmeir, J., **De** Vrese, M. (**2001**): **Probiotics**, prebiotics, and synbiotics-approaching a definition, American Journal of Clinical Nutrition 73 (2), 361-364.

Shornikova, A.V., Casas, I.A., Isolauri, E., Mykkanen, H., Vesikari, T. (1997): Lactobacillus reuteri as a therapeutic agent in acute diarrhea in young children, Journal of Pediatric Gastroenterology and Nutrition 24, 399-404.

Sleator, R.D., Hill, C. (2007): New frontier in probiotic research, Letters in Applied Microbiology 46 (2), 143-147

Strnad, M., Babuš, V. (1996): Antitumorsko djelovanje fermentiranih mliječnih proizvoda. U: Fermentirani mliječni proizvodi u prehrani i dijetetici, Hrvatska akademija medicinskih znanosti, Zagreb, 85-91.

Szajewska, H., Kotowska, M., Mrukowicz, J.Z., Armanska, M., Mikolajczyk, W. (2001): Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants, The Journal of Pediatrics 138 (3), 361-365.

Szajewska, H., Mrukowicz, J.Z. (2005): Use of probiotics in children with acute diarrhea, Pediatric drugs 7 (2), 111-122.

Szajewska, H., Ruszczyński, M., Radzikowski, A. (2006): Probiotics in the prevention of antibiotic-associated diarrhea in children: A meta-analysis of randomized controlled trials, The Journal of Pediatrics 149 (3), 367-367.

Szymański, H., Chmielarczyk, A., Strus, M., Pejcz, J., Jawień, M., Kochan, P., Heczko, P.B. (2006): Colonisation of the gastrointestinal tract by probiotic L. rhamnosus strains in acute diarrhoea in children, *Digestive and Liver Disease* 38 (2), 274-276.

Šušković, J., Brkić, B., Matošić, S. (1997): Mehanizam probiotičkog djelovanja bakterija mliječne kiseline, Mljekarstvo 47 (1), 57-73.

Šušković, J., Kos, B., Matošić, S. (1998): Probiotici: Znanstvena činjenica ili pomodni trend?, Mljekarstvo 48 (3), 165-176.

Šušković, J., Kos, B. (2000): Probiotici i prebiotici. Interna skripta, PBF, Zagreb.

Šušković, J., Kos, B., Goreta, J., Matošić, S. (2001): Role of Lactic acid bacteria and Bifidobacteria in synbiotic effect, Food technology and biotechnology 39 (3), 227-235.

Tamime, A.Y., Skriver, A., Nilsson, L-E. (2006): Starter Cultures. U: Fermented Milks, ed. by A.Y. Tamime, Bleckwell Publishing, 11-52.

Urbancsek, H., Kazar, T., Mezes, I., Neumann, K. (2001): Results of a double-blind, randomized study to evaluate the efficacy and safety of Antibiophilus® in patients with radiation-induced diarrhoea, European Journal of Gastroenterology and hepatology 13 (4), 391-396.

Vaughan, E.E., Schut, F., Heilig, H.G., Zoetendal, E.G., De Vos, W.M., Akkermans, A.D. (2000): A molecular view of the intestinal ecosystem, Current Issues in Intestinal Microbiology 1, 1-12.

Weizman, Z., Asli, G., Alsheikh, A. (2005): Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents, *Pediatrics* 115 (1), 174-177.