REVIEWS

Adv Clin Exp Med 2013, **22**, 5, 759–766
ISSN 1899–5276

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The Therapeutic Effect of Probiotic Bacteria on Gastrointestinal Diseases

Rola probiotyków w profilaktyce i leczeniu chorób przewodu pokarmowego

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

The cause of many gastrointestinal diseases, such as irritable bowel syndrome, chronic inflammatory bowel disease: inflammatory and necrotizing enterocolitis or diarrhea: infectious, traveler's diarrhea, and diarrhea caused by antibiotic treatment is an imbalance of intestinal microflora. Probiotics are live microorganisms, which administered in sufficient quantities, have beneficial health effects. The phenomenon of eating probiotic products started 100 years ago, when the first reports showed beneficial effects of probiotic bacteria on human health. Since then, probiotic preparations have become an essential element in the prevention and treatment of certain diseases. Currently, probiotics are of the utmost importance in supporting the treatment of gastrointestinal diseases and autoimmune disorders. Probiotic microorganisms are primarily lactic acid-producing bacteria of the general *Lactobacillus, Bifidobacterium*. Many studies have confirmed the beneficial effects of probiotics, particularly in the treatment of acute diarrhea. This applies in particular to diarrhea of viral etiology, especially in infants and young children (**Adv Clin Exp Med 2013, 22, 5, 759–766**).

Key words: probiotics, gastrointestinal diseases.

Streszczenie

Przyczyną wielu chorób przewodu pokarmowego, takich jak np.: zespół jelita nadwrażliwego, przewlekłe choroby zapalne jelit – nieswoiste i martwicze zapalenie jelit, biegunki – infekcyjna, podróżnych, poantybiotykowa, są zaburzenia równowagi mikroflory jelitowej. Probiotyki to żywe drobnoustroje, które podawane w odpowiednich ilościach wywierają korzystny efekt zdrowotny. Zjawisko probiozy zaczęto wykorzystywać już 100 lat temu, gdy pojawiły się pierwsze doniesienia o korzystnym wpływie bakterii probiotycznych na zdrowie człowieka. Od tamtego czasu preparaty probiotyczne stały się istotnym elementem w profilaktyce i leczeniu niektórych chorób. Obecnie probiotyki mają największe znaczenie we wspomaganiu leczenia chorób układu pokarmowego oraz zaburzeń autoimmunologicznych. Do drobnoustrojów o działaniu probiotycznym należą przede wszystkim bakterie produkujące kwas mlekowy z rodzaju: *Lactobacillus, Bifidobacterium.* Wiele badań potwierdziło korzystne działanie probiotyków, przede wszystkim w leczeniu ostrej biegunki. Dotyczy to przede wszystkim biegunek o etiologii wirusowej, zwłaszcza u niemowląt i małych dzieci (**Adv Clin Exp Med 2013, 22, 5, 759–766**).

Słowa kluczowe: probiotyki, choroby przewodu pokarmowego.

The word "probiotic" is derived from Greek *pro bios* meaning "for life". Already in ancient times people were aware of the positive effects of fermented foods on human health. Although they did not know the mechanism of action of this type of products, fermented dairy products were recognized as an excellent medication for ailments such as gastrointestinal, liver diseases, and even atherosclerosis [1].

In 1857, Louis Pasteur proved the existence of microorganisms responsible for the fermentation of lactic acid, and 20 years later, Lister identified the first pure culture of lactic acid bacteria. Breakthroughs in probiotics were made by Russian Nobel Prize laureate Elie Metchnikoff, who showed in his research that some groups of bacteria inhibit the growth of *Vibrio cholerae* [2]. In 1917, during an outbreak of salmonellosis, a strain of probiotic bacteria not belonging to the group of lactic acid bacteria (LAB) was first isolated – *Escherichia coli Nissle 1917* (*E. coli Nissle*) [3]. Other strains of microorganisms with confirmed health benefits were: *Lactobacillus casei Shirota*, isolated by Japanese scientist Minoru Shirota and *Bifidobacterium: Bacillus bifidus communis* which were first described by Henry Tissier from the Pasteur Institute [4].

The term "probiotics" appeared in medical terminology in 1954 because of Ferdinand Vergina, who in a paper "Anti- und Probiotika" described the adverse effects of antibiotics and other antimicrobial preparations on the intestinal microflora as compared with bacteria showing a positive effect referred to as "probiotika" [5]. A number of studies conducted on probiotics in the second half of the twentieth century affected modifications of their definition; finally scientists accepted that probiotics are "live microorganisms, which have beneficial health effects when administered in appropriate amounts (FAO/WHO)" [6]. In recent years, however, there are reports which undermine this definition, and indicate that dead probiotic microorganisms, or even bacterial DNA also show beneficial health effects [7, 8].

The purpose of this paper is to analyze the current literature on the health benefits of probiotics with special attention to their participation in the prevention and treatment of diseases of the gastrointestinal tract.

Taxonomy of Probiotic Microorganisms

Most probiotic microorganisms belong to a group of LAB (lactic acid-producing bacteria). They include Gram-positive *cocci* and rods of the genera *Lactobacillus, Lactococcus, Bifidobacterium, Streptococcus, Leuconostoc, Oenococcus, Pediococcus, Carnobacterium, Tetragenococcus, Vagococcus, Weisella* [9, 10]. A common feature of these bacteria is the ability of anaerobic digestion of saccharides and production of lactic acid. These microorganisms are characterized by a resistance to low pH and tolerance to a wide range of temperatures. The natural ecosystem of the LAB is the digestive tract, mucous membrane of the mouth and genital tract of humans and animals. Probiotic microorganisms include *Saccharomyces cerevisiae ssp boulardii* (*S. boulardii*) yeast and several species of bacteria of the genera *Escherichia* and *Bacillus.* The source of probiotics may be pharmaceutical formulations, dietary supplements or fermented products, in which mainly LAB are present [11].

Lactobacillus bacteria are a major component of the microflora of fermented food. Sauerkraut, pickled cucumbers, acidified milk, yogurt and other milk products are abundant in these bacteria. *Bifidobacteria* form primarily gastrointestinal biocenosis in humans and animals.

Mechanism of Action of Probiotics

So far, the exact mechanism of action of probiotics has not been explained, but a number of aspects of the way it affects the human body was found, including [12, 13]:

- beneficial effect on the intestinal microflora,
- prevention of intestinal infections,
- increased tolerance to lactose,
- improving the immune system,
- anti-allergic effects,
- prevention of cardiovascular disease,
- prevention of cancer.

Probiotics:

- compete for receptors or adhesion to endothelial cells, thus preventing access of pathogens to the intestinal epithelium [14],
- produce antimicrobial compounds [15],
- run competition with other microorganisms for nutrients [16],
- cause acidification of the intestinal contents, which inhibits the growth of some pathogenic bacteria [17],
- affect the enzymatic modification of the receptors for bacterial toxins [18],
- show modifying effect on cellular immune and humoral response – via lymphocyte activation, stimulation of phagocytosis, stimulation of IgA and sIgA antibody synthesis and INF cytokines production [19].

The dose of probiotics is usually given as the number of colony forming units (CFU). The optimal dosage has not been established, but the results of clinical studies show that the minimum daily therapeutic dose should be 10^6–10^9 CFU [20].

The Role of Probiotics in the Prevention and Treatment of Gastrointestinal Diseases

Phenomenon of eating probiotic products started to be used 100 years ago, when the first reports showed beneficial effects of probiotic

bacteria on human health. Since then, the probiotic preparations have become an essential element in the prevention and treatment of certain diseases. Currently, probiotics are of utmost importance in supporting the treatment of gastrointestinal diseases and autoimmune disorders. Despite the evidence for the efficacy, in many cases, still there have been no studies explicitly stating their therapeutic properties [21]. Concerns about the safety of widespread use of probiotics are associated with the risk of bacterial translocation, sepsis and the development of antibiotic resistance [22].

Acute Infectious Diarrhea

Acute diarrhea is defined as more often than usual bowel movements lasting 10–14 days. The main causes of this ailment are viral infections (rotavirus, adenovirus, etc.), bacteria (*Salmonella* spp, some pathogenic strains of *Escherichia coli, Yersinia enterocolitica, Clostridium difficile* and other) and parasitic infections (*Giardia lamblia, Cryptosporidium parvum*) [23, 24].

Research on the beneficial effects of probiotics in various diseases, particularly diarrheal infections are carried out in many countries of the world. According to ESPGAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition)/ESPID (European Society for Paediatric Infectious Diseases) current guidelines for the treatment of acute diarrhea in children, probiotics of proven efficacy such as *Lactobacillus casei ssp. rhamnosus* (*Lactobacillus* GG) and *Saccharomyces boulardi* can be administered and one should be warned against possible antibiotic resistance, or transfer of this trait to other bacteria when given any probiotics [24, 25]. Carried out in France and Lebanon in 2010, a multicenter study of the impact of milk supplementation with the probiotic *S. boulardi* administered to children with acute diarrhea showed a significant reduction in the duration of diarrhea and body weight gain after body weight loss faster than the standard milk feeding [26].

An analysis of other studies involving a total of 1,917 patients showed that probiotics reduce the risk and average duration of diarrhea [27].

Authors of a study conducted in Brazil on 186 children aged 6 to 48 months, hospitalized for acute diarrhea, demonstrated in a double-blind trial, that the administration of the probiotic yeast *S. boulardii* to patients results in shortening of the duration of symptoms compared with the placebo group. But it is important to provide a formulation containing probiotics within 72 hours of onset of symptoms [28].

The results of clinical trials involving a group of more than 500 children, aged 3 months to 3 years indicate that, among a number of probiotic strains, the use of *Lactobacillus* GG only showed significant effect of shortening of diarrhea duration in comparison with the control group [29].

Many authors' results were also positive in terms of the efficacy of probiotics [30]. The advantages of probiotic preparation administration for acute diarrhea involve mainly shorter duration of symptoms compared to placebo as well as a reduced number of stools per day. The other author's point out, however, that the routine use of probiotics is not recommended due to the lack of clear information about the activity of a probiotic strain and dosage [31].

Taking into account the results of recent meta-analysis, it is considered that administration of probiotics in the case of infectious diarrhea offers modest benefits compared with the control group, including shortening of diarrhea duration on average by 17–30 hours. This effect depends on the type of probiotic strain administered. Documented activity is shown by *Lactobacillus* GG and *S. boulardii*. The effect of probiotics on the course of acute diarrhea was considered to be clinically relevant in the case of diarrhea of viral etiology and the best results were achieved through the use of supplements in the initial stage of the onset of symptoms. Previous observations indicate that more concentrated dose of probiotics, more than 10^9–10^{11} CFU, gives better therapeutic results. In Poland, probiotics are involved in preparations: Dicoflor 30, Dicoflor 60 and Ido-Form Kid [24, 32–34].

The results obtained by other authors have shown that the addition of *Bifdobacterium lactis* in an amount of 1.9×10^8 CFU per 1 g of powder milk for children and *Streptococcus thermophilus* in amount of 0.14×10^8 CFU per 1 g of the powder milk leads to a reduction in the frequency of nosocomial diarrhea and reduces the risk of rotavirus infection [35].

In 2009–2010 in Spain, an analysis of the impact of *Lactobacillus salivarius* as a milk supplement in 6-month-old infants demonstrated safety and tolerability of probiotics [36].

Traveler's Diarrhea

Traveler's diarrhea are symptoms manifested in an acute infection of the gastrointestinal tract, characterized by the excretion of a minimum of three unformed stools per day, associated with the change of residence, such as foreign travel.

In more than 80% of cases the cause of traveler's diarrhea is a bacterial infection, the most common with *E. coli enterotoxic* ETEC strain, rarely *Campylobacter, Shigella* and *Salmonella* [37]. This type of diarrhea occurs in 20–40% of the tourists

visiting Central America and South America, South Asia and Africa, and in 10–15% of tourists visiting the Middle East, China, Russia and southern Europe [38]. Currently, scientists looking for alternatives to antibiotics, which are not recommended in the prevention and treatment of traveler's diarrhea, drew their attention to the possibility of exploiting the potential of probiotic microorganisms.

McFarland [39] conducted a study on the use of probiotics in the prevention of traveler's diarrhea. Observations carried out by this author using *S. boulardii* probiotic yeast showed that 29–34% of the patients receiving 5×10^9–1×10^{10} CFU of probiotic for three weeks had symptoms of traveler's diarrhea, whereas patients in the placebo group suffering from traveler's diarrhea ranged 39–43%. In each of the four experiments, the beneficial effect of *S. boulardii* was statistically significant.

Other probiotic strains used in such studies involve *L. acidophilus, L. bulgaricus* and *Streptococcus thermophilus*. A mixture of bacteria taken for two weeks demonstrated efficacy in 57% of patients, while in the control group, no diarrhea was observed only in 29% of patients.

Prophylactic application of the preparation containing the *Lactobacillus* GG strain in a dose of 2×10^9 CFU for 2 weeks also proved its effectiveness in reducing the symptoms of traveler's diarrhea in 59% of patients in comparison with the control group, which reached a value of 53% [39].

However, not all probiotic strains are effective in preventing traveler's diarrhea. The use of both *L. acidophilus* and *L. fermentum* in very large doses of the order of 2×10^{11} CFU did not bring the expected results, because the effectiveness of these preparations was comparable to, or slightly lower than that in the control group [39].

Antibiotic-Associated Diarrhea

The side effects of antibiotics often include diarrhea. They occur in 11–40% of children and in 5–39% of adults treated with antibiotics such as ampicillin, amoxicillin, cephalosporins and clindamycin. These drugs cause changes in the composition of intestinal microflora, leading to a proliferation of bacterial strains resistant to the above formulations, such as *C. difficile, C. perfringens* type A, *S. aureus, K. oxytoca, Salmonella* spp, *Candida* spp. Other causes of antibiotic-associated diarrhea are: an impairment in fermentation processes carried out by intestinal microorganisms and dysfunction in the utilization of free fatty acids [40, 41].

The efficacy of some probiotic bacteria in the prevention of antibiotic-associated diarrhea (*L. rhamnosus*, *S. boulardi*) has been confirmed, which justifies the position of the Polish Group of Experts on the recommendations for prevention of this type of diarrhea [40].

In a study by Hickson et al. [42] patients undergoing antibiotic therapy, and 7 days after administering 100 g of Actimel yogurt twice a day. The results showed a lower risk of antibiotic-associated diarrhea and diarrhea caused by *C. difficile* infection compared with the control group, as confirmed by the experts on the justified use of probiotic supplementation in antibiotic therapy.

McFarland [43] investigated the possibility of preventing antibiotic-associated diarrhea (in particular due to *C. difficile*) through the use of probiotics. Meta-analysis covered more than 3000 patients. It has been found that probiotics significantly reduce the risk of antibiotic-associated diarrhea and prevent diarrhea caused by *C. difficile* infection. The most effective strains were *S. boulardii, Lactobacillus* GG, and probiotic mixtures.

Many studies of other authors have confirmed the effectiveness of *Lactobacillus* GG in the prevention of antibiotic-associated diarrhea [44, 45].

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is one of the complications occurring in premature infants. Among the reasons for this are the following: hypoxia, ischemia, or infection of the fetus. Undeveloped immune system increases the adverse effects caused by the factors mentioned above [46].

Based on an analysis of 11 randomized controlled trials performed in the past 15 years, Deshpande et al. [47] found that in the group receiving probiotics (depending on the study: *B. bifidus, B. lactis, B. infantis, L. acidophilus, Lactobacillus* GG, *B. breve, S. boulardii, S. thermophilus, L. casei, B. longum*) the risk of NEC decreased, the incidence of sepsis remained unchanged, mortality for whatever reason was reduced, but mortality from NEC remained at the same level as in the control group.

The justification of the use of probiotics in NEC is not entirely clear, because the study involved the use of different strains of probiotic bacteria, and as it is known, different strains vary in effectiveness measures. Currently the use of probiotics with well-documented efficacy is allowed if there is a large probability of NEC [47].

In 2007, a review of studies on the use of probiotics in the prevention of NEC in premature infants born before 33 weeks and body weight under 1500 g was published [48]. Statistical analysis of clinical trials on prophylactic effects of probiotics in premature infants showed a significant reduction in the risk of NEC in the group of children

receiving probiotics, as well as a reduction in total mortality by 64% compared with the control group. These results were confirmed in other meta-analyses [49].

Inflammatory Bowel Disease

Inflammatory bowel diseases are a group of diseases involving specific lesions in different parts of the gastrointestinal tract. Their etiology has not been clarified, but the likely pathomechanism includes autoimmune process in people genetically predisposed. The second suggested reason is the impaired immune response to the indigenous intestinal microflora. The most common diseases known as inflammatory bowel diseases are ulcerative colitis and Crohn's disease. These disorders are more common in young people, and in recent years there has been a significant increase in the number of cases.

Ulcerative Colitis

According to the definition [50], it is a chronic inflammatory disease of the mucous membrane of the rectum or the rectum and the colon of unknown etiology, leading in some cases to necrosis, ulceration, and perforation of the intestine as a result. It mostly affects young people between 20 and 40 years of age. This disease is more common in the developed countries of North America and Europe.

A VSL#3 preparation consisting of 8 probiotic microorganisms – four strains of *Lactobacillus: L. acidophilus, L. casei, L. delrueckii subs. bulgaricus, L. plantarum*, three *Bifidobacterium* strains: *B. breve, B. longum, B. infantis*, and *Streptococcus salivarius* subs. *thermophilus* was tested. In a study in children aged 2–16 after a year of treatment (dose dependent on weight) in the probiotic-treated group, recurrence of symptoms was observed in 21% of patients, while in the placebo group, the rate was at 73%. As a result of VSL#3 administration to adult patients in the amount of 3.6×10^{12} CFU twice daily, an improvement was reported in 43% of patients after 12 weeks of treatment. In the control group, only 16% of patients had remission of the disease [51].

In children with ulcerative colitis, administration of VSL#3 resulted in the induction and maintenance of remission of the disease (92.8%), compared with the results of the placebo group [52].

Another microorganism, whose activity in the treatment of ulcerative colitis was demonstrated in clinical trials, is *E. coli Nissle* 1917. The efficacy of this strain was compared with the standard anti-inflammatory drug used in the treatment of this disease – mesalazine. The results after a year of treatment showed that the percentage of patients taking the probiotic, who had improved health status was similar to that in patients treated with mesalazine and amounted to 64% and 66% [53].

Crohn's Disease

Crohn's disease (CD) is another inflammatory bowel disease and is characterized by a chronic inflammatory process that is present in the gastrointestinal wall. The most common site affected is the terminal part of the ileum. Although the CD pathogenesis has not yet been explained, but there are suggestions that the development of inflammation determine three factors: abnormal intestinal microflora, impaired immune system response and genetic predisposition [54]. The incidence of CD in Europe is estimated at 1–11.4 per 100,000 per year.

Lactobacillus GG in the dose of 1.2×10^{10} CFU was used in clinical trials to determine the efficacy of the probiotic in CD. The tested formulation was administered to patients for one year after surgery. Recurrence of symptoms occurred in 16% of patients treated with the probiotic versus 10% on placebo. Controversy about the effectiveness of probiotics in CD is associated with endoscopy, in which 60% of patients in remission had recurrent pathological changes in the intestine, whereas in the control group they were found in 35%. These results may indicate a failure of probiotic therapy in CD [55].

Observations of the influence of probiotics on CD remission time were also conducted in children after pharmacological treatment. A tested probiotic strain was *Lactobacillus* GG which was administered to patients at a dose of 1×10^{11} CFU for a period of two years. The results showed that in patients treated with the probiotic average remission time was 9.8 months, and the relapse was observed in 31% of subjects and the recurrence of symptoms occurred in 17% of patients in the placebo group after an average of 11 months after the end of drug therapy [56].

Another probiotic strain tested in clinical trials in patients treated surgically for CD was *L. johnsonii*, given in a dose of 4×10^9 CFU for a period of 6 months after surgery. In this case, a beneficial effect of a probiotic on maintenance of CD remission was confirmed in 51% of patients in comparison with the placebo group, in which the percentage was 36% [56]. Presented data suggests that the beneficial effect of probiotics for the treatment and prevention of relapse of CD is debatable.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional bowel disorder that is manifested by abdominal pain and discomfort associated with defecation or a change in bowel habits [57]. The disease is chronic and is one of the most common disorders of the digestive system. IBS occurs in over 20% of the adult population, and the women are predominant group of patients affected by IBS.

It is understood that one of the causes of this disease are impaired intestinal microflora, resulting in malabsorption of bile acids in the colon and increased fluid and mucus secretion through the mucosa, which results in diarrhea. Bacteria of the genus *Lactobacillus* and *Bifidobacterium* are involved in the conjugation of bile acids in the intestine so that lower amount of acids reach the large bowel, and this in turn reduces the severity of diarrhea and reduces the discomfort of the patient [57].

In recent clinical trials, the efficacy of probiotics in alleviating the gastrointestinal symptoms has been confirmed. Treatment with a probiotic containing *L. plantarum* 299 v (Lp 299 v) significantly reduced the main symptoms of IBS, such as abdominal pain, discomfort and bloating. Sawant et al. [58], on the basis of research conducted among 214 patients with irritable bowel syndrome, have demonstrated the efficacy and clinical utility of Lp 299 v probiotic strain administered once daily for four weeks.

A study by Kruis et al. [59] involved the application of the *E. coli Nissle* 1917 probiotic strain in patients with irritable bowel syndrome. The study showed that long-term supplementation with the probiotic caused a 20% improvement compared to the placebo group.

Results of many clinical trials which involved various probiotic strains allow to conclude that these preparations support the treatment of symptoms associated with IBS [60], and specific therapeutic effect is conditioned by a kind of applied strain. It has been found that formulations containing *L. plantarum* help reduce flatulence. Similar results were obtained for VSL#3, while *Lactobacillus* GG may potentially reduce the risk of diarrhea. The clinical effects of a *B. infantis* 35,624 strain have confirmed as beneficial. The preparation administered to patients at a dose of 10^8 CFU showed at least 20% decrease in all major IBS symptoms compared with placebo.

Conclusions

Probiotics have GRAS status (Generally Recognized As Safe) granted by the FDA (Food and Drug Administration). It is believed that the risk of infection with probiotic bacteria is negligible; however, caution is advised in their use in preterm infants, immunocompromised patients, critically ill in intensive care. The use of probiotics as a treatment is justified only in relation to specific probiotic strains and the appropriate dose [20]. Probiotics are likely to find wide application in the treatment of gastrointestinal diseases [4]. So far, the best-documented treatment seems to be the prevention of acute infectious diarrhea. Also the treatment of some diseases of the gastrointestinal tract function is promising, but this requires further studies to confirm the initial results.

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Conflict of interest: None declared

Received: 6.12.2012
Revised: 4.02.2013
Accepted: 3.10.2013