PROBIOTICS AS FOOD SUPPLEMENTS
PROBIOTICI KAO DODACI U ISHRANI

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Summary
Many studies have shown that the use of probiotics acts positively on a disturbed intestinal ecosystem. Probiotics are defined as living, non-pathogenic microorganisms (usually bacteria), which confer a health benefit on the host when administrated in adequate amounts. Probiotics mechanisms described so far include adhesion to the surface of intestinal epithelium, competition with pathogens for receptors and nutrients, improvement of mucosal barrier function and maintenance of intestinal integrity, promotion of innate and acquired immune response, elaboration of bactericins and modulation of cellular kinetics. Dysbiosis of endogenous microbiota can lead to compromised immune responses and manifestations of various autoimmune diseases. Even some local and systemic metabolites of probiotic have been identified to have anti-inflammatory activity and may modify autoimmune diseases. The list of diseases that can benefit from the use of probiotics is long and includes acute diarrhea, urogenital infections, allergies, lactose intolerance, cystic fibrosis, carcinoma, inflammatory bowel disease, teeth and mouth disease, etc. The aim of this paper is to summarize the latest information from the currently available scientific literature on the role of probiotics in human health and disease.

Key words: probiotics, health benefits, diarrhea, allergies, obesity

Introduction
Health benefits of bacteria have been recognized throughout history. Fermented milk was consumed in the Middle East as early as 10,000 BC, followed by populations in Egypt (as evidenced by the hieroglyphs), ancient Greece and Rome. (1) During the time of Genghis Khan in the 12th century, fermented milk was considered as source of strength and health, and Mongolian women would spray horses and riders with it to protect them in the battles. Era of probiotics started with Elie Metchnikoff, a bacteriologist and Nobel Prize winner, who correlated the longevity of the Bulgarians and their high consumption of fermented milk at the beginning of the 20th century. The species Lactobacillus bulgaricus was named in his honor. At the same time, a French pediatrician HenryTissier, observed that infants presenting with diarrhea had few bifidobacteria in their stools whereas these bacteria were dominant in the stools of healthy infants.

The concept of beneficial bacteria which was forgotten during the era of antibiotics and vaccines, is again the interest of scientists, since intestinal microbiota plays a significant role in human health and disease. Dysbiosis of the intestinal ecosystem contributes to the development of many pathological conditions. Studies have shown that the use of probiotics acts positively on a disturbed intestinal ecosystem.

Probiotics are defined as living, non-pathogenic microorganisms (usually bacteria), which confer a health benefit on the host when administrated in adequate amounts. (2) Only a small number of bacteria meet this definition. Probiotics are primarily bacteria from the lactobacilli and bifidobacterium genera, however, other bacteria may also act as probiotics: Lactococcus, Streptococcus and Enterococcus species, some non-pathogenic strains of Escherichia coli, as well as certain strains of bacilli and yeasts. (3)

Nowadays, probiotic strains are applied widely due to proven health benefits in numerous randomized clinical trials. The list of diseases that can benefit from the use of probiotics is long and includes acute diarrhea,
Certain probiotic species have an effect on the function of the intestinal barrier too. The integrity of the intestinal barrier is influenced by changes in intestinal permeability, mucin composition and homeostasis between the production of new enterocytes and the rate of apoptosis of damaged enterocytes. Some probiotics have the potential to reduce the intestinal permeability by strengthening tight junctions between enterocytes and/or restoring the mucous layer. (4) The structural and functional properties of the mucin further affect the activity of bacterial adhesion.

Probiotics also affect cellular kinetics by acting on cell proliferation and apoptosis. The ability of certain probiotics to promote the propagation of normal cells and apoptosis of abnormal cells simultaneously, may have the potential to treat certain diseases such as cancer. (10)

In our intestines there is about 70% of the immune system known as GALT (gut-associated lymphoid tissue). The relationship between the intestinal microbiota and the immune system of the host was extensively examined. Dysbiosis of endogenous microbiota can lead to compromised immune responses and manifestations of various autoimmune diseases. Even some local and systemic metabolites of probiotic have been identified to have anti-inflammatory activity and may modify autoimmune diseases. These mechanisms are presented in Scheme 1.

Mechanisms of the activity of probiotics

Probiotics mechanisms described so far include adhesion to the surface of intestinal epithelium, competition with pathogens for receptors and nutrients, improvement of mucosal barrier function and maintenance of intestinal integrity, promotion of innate and acquired immune response, elaboration of bactericins and modulation of cellular kinetics. (4)

Adhesion of bacteria to mucosal surfaces and epithelial cells is one of the key features of probiotic action. (5) Factors affecting probiotic adhesion include large surface proteins and mucus-binding proteins possessing regions homologous with binding domains of proteins such as lectins (6) For example, the species Lactococcus lactis has auto-aggregation phenotype and a mucin-binding protein (MbpL) on its surface, which contributes to its adherent properties in the gut in vitro and in vivo.

The ability of probiotics to inhibit pathogen growth has been widely studied, and antimicrobial properties of probiotics have been recently described. Many probiotic species from the lactobacilli genera have shown great potential in vitro studies to inhibit certain intestinal pathogens such as Escherichia coli and Salmonella spp. (7) Several studies have discovered the ability of probiotics to secrete probiotic factors, such as bactericins, which have been shown to inhibit the adhesion and viability of known intestinal pathogens. (8) The species Lactobacillus reuteri forms a biofilm that produces a potent antimicrobial compound called reuterin, which has been shown to inhibit a wide spectrum of microorganisms.

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Health benefits of probiotics

Among the first indications for the use of probiotics were diarrhea, inflammatory bowel disease and allergy, before the list of indications spread to other diseases.

Infectious diarrhea. One of the first recommendations for probiotics use was the treatment and/or prevention of infectious diarrhea. Numerous studies have revealed significant benefit of probiotics in acute infectious diarrhea, with a reduction in diarrhea duration and in the number of stools. (11) Three randomized controlled clinical trials involving more than 1000 children, have proved a decrease in nosocomial diarrhea caused by rotavirus, in children treated with Lactobacillus GG probiotic. (12) Antibiotic-associated diarrhea due to antibiotic-induced dysbiosis is also an indication for the use of probiotics. The most common cause of this diarrhea is Clostridium difficile whose spores are often resistant to antibiotics. The results of one meta-analyze showed the efficacy of probiotics in the prevention of C. difficile diarrhea, but not the reduction of its incidence. (13)

Inflammatory bowel disease. In addition to genetics, epigenetics and immune responses of the host, many authors suggest the intestinal microbiota to be one of the causes of inflammatory bowel disease (IBD) too. This possible association led to an increased interest in probiotics use in patients with IBD. The results of many studies have demonstrated the inefficiency of probiotics in patients with Crohn’s disease. (14,15) On the other hand, it has been found that some probiotics are effective in ulcerative colitis, leading to induction of remission or its prolonged duration. (16) In 2017, Derwa et al. showed that the probiotic VSL. # 3 (containing lactobacilli, bifidobacilli, and Streptococcus thermophilus) can be as effective as 5-ASAs in preventing relapse of UC. (17)
Allergies. The probiotic efficacy for prevention of some allergic diseases, most frequently in high risk families, was of interest to many researchers. (18) The influence of Lactobacillus GG probiotics in patients with atopic dermatitis was investigated most extensively. One study showed a 50% reduction in the frequency of atopic dermatitis in children during the first two years, whose mothers took Lactobacillus GG capsules 2-4 weeks before and 6 months after delivery date, compared to placebo. (19) The evidence for use of probiotics as a preventative or therapeutic agent for respiratory allergies appears low. Although earlier studies have shown that Lactobacillus GG probiotic led to suppression of hyper-reactivity of respiratory tract to methacholine and inhibition of inflammatory cell infiltration, in later studies these results could not be reproduced under similar circumstances, so current evidence does not support the use of probiotic in prevention of asthma. Furthermore, there is no strong evidence currently that probiotics influence the development of allergic rhinitis (20), as some studies indicated even increased prevalence of allergic rhino-conjunctivitis in those using probiotics perinatal and in early childhood. (21)

Obesity and diabetes mellitus type 2. The authors of some studies have reported relationship between microbiota and obesity, (22), as well as one with type 2 diabetes. (23) One of the explanations is the colic fermentation of food not digested by microbiota in the small bowel, which induced the production of metabolites such as short-chain fatty acids which are further absorbed, thus allowing recovering energy. (24,25) So far, the authors of interventional studies have not proved any beneficial effect of probiotics on BMI. However, Qin et al. in their study have revealed that faecal metagenomic markers differentiated obese from non-obese patients more easily than markers of the human genome, (23) and further investigations on modification of intestinal microbiota in the treatment of these diseases are necessary.

The authors of some studies have indicated the contribution of probiotics in the prevention of upper respiratory tract infections (26), the treatment of Helicobacter pylori infection (27), the prevention of dental caries (28), the prevention of necrotizing enterocolitis in preterm infants (29), in treatment of infant colic in neonates (30), as well as in many other indications, but with currently insufficiently solid evidence for their use.

**Conclusion**

It is currently acknowledged that the gut microbiota interacts with human health and that its modulation by probiotics is an interesting way to prevent some diseases. But the effectiveness has not been proven in too many indications, limiting the current recommendations for probiotic use. But, the rational and the encouraging results reported in some studies support further research on probiotics.
References