MicroMedicine ISSN 2449-8947

REVIEW ARTICLE

Probiotics in colon cancer prevention

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OPEN ACCESS

Citation: Wolek M, Bogacz A, Juskowiak B, Polaszewska A, Czerny B. Probiotics in colon cancer prevention. MicroMed. 2018; 6(2): 62-68.

DOI: http://dx.doi.org/10.5281/zenodo.1297660

Received: May 10, 2018

Revised: June 19, 2018

Accepted: June 25, 2018

Transparency declaration: The authors declare no conflicts of interest.

ABSTRACT

Probiotics are live, selected microbial strains that have a beneficial effect on the human body and when introduced into the body, they colonize in the digestive tract, especially in the large intestine, exerting a beneficial effect on the health of the host. The microbial strains, so that they can be included in the probiotics, must be thoroughly tested and meet several conditions. These microorganisms multiply in the gastrointestinal tract and are competitive for pathogenic microorganisms that cause infection. Probiotic bacteria are found in natural yogurts, sour milk, sauerkraut, pickled cucumbers. Many studies show a positive correlation between the consumption of probiotics and the risk of developing certain cancers. Probiotics are most likely to reduce the risk of developing colorectal cancer.

Keywords: Probiotics; Colon; Cancer; Prevention; Bacteria.

INTRODUCTION

Among the microorganisms of the natural microflora, bacteria with probiotic properties play an enormous role. These bacteria have a beneficial effect on the functioning of the human body, both local and systemic [1-3]. For a microbial species to be considered as probiotic it must be fully understood. Detailed studies of its impact on the human and animal organism last even several years. Clinical procedures, during which a given species of a microorganism is classified as probiotic, consist of three phases: strain's safety assessment, checking the effectiveness of the strain and verification of the strain's effectiveness on a large number of people and comparison of the effects of treatment with standard therapy [2, 4, 5].

Moreover, the qualified strain should meet the following criteria: it must come from the natural healthy microflora of the human intestine, it is an absolute or relative anaerobe, it should belong to a specific type and species that has been assigned to it using molecular methods, it should be resistant to acidic pH of gastric juice, bile salts and digestive enzymes, its positive effect should be scientifically confirmed and must maintain, it cannot show pathogenic or toxic properties, its all properties during processing and storage [6-8].

CHARACTERISTICS AND FUNCTION OF PROBIOTICS

The characteristics of the probiotics are strain-dependent. Positive properties of one microorganism will not necessarily occur in another, even closely related one. Probiotics activity may always refer only to one tested strain, not to the species, genus or to all lactic bacteria [2, 4, 5]. The composition of the probiotic may contain single strains of lactic acid bacteria (*Lactobacillus* spp., *Streptococcus* spp.), yeast (*Saccharomyces* spp.) or lactic acid bacteria in combination with yeast strains. Probiotic bacteria are found in fermented foods and can also be found in pharmaceutical preparations [9].

Table 1. Classification of probiotics.

Genus	Species
Lactobacillus spp.	*acidophilus, brevis, casei, delbrueckii gasseri, fermentum, johnsonii, lactis, paracasei, plantarum, reuteri, rhamnosus*
Bifidobacterium spp.	*adolescentis, animalis, bifidum, breve, infantis, lactis, longum, thermophilum*
Bacillus spp.	*coagulans*
Streptococcus spp.	*thermophilus*
Enterococcus spp.	*faecium*
Saccharomyces spp.	*cerevisiae*

The advantages of probiotics are used in many fields, e.g. they restore the natural intestinal microflora after the antibiotic treatment, they are used for the production of functional food and for the preservation of food products [10].

To notice the beneficial effect of probiotics on the body, they should be consumed for a long time so that the positive microflora persists at a high level. The composition of the intestinal microflora depends mainly on the type and composition of the food consumed and the age of the person. Intestinal flora is affected by past infections, antibiotic therapy, availability and composition of substrates for microflora growth, interactions with the immune system, intestinal pH, bacterial metabolites, intestinal status, as well as place of residence and lifestyle [10-12].

Bacteria with beneficial effects classified as probiotics are usually heterogeneous gram-positive, catalase-negative cocci or rods of the genera *Lactobacillus*, *Lactococcus*, *Streptococcus*, *Oenococcus*, *Pediococcus*, *Leuconostoc*, *Enterococcus*, *Bifidobacterium* and rare *Weissella*, *Carnobacterium*, *Tetragenococcus*, *Vagococcus* etc. All of them are able to carry out the anaerobic fermentation of saccharides. They produce lactic acid at the level of 0.6% to 3.0%, during the fermentation process.

They produce L (+) lactic acid or D (-) lactic acid. If they only produce this acid, they are classified as homofermentative bacteria. However, when they also produce acetic acid, ethanol, carbon dioxide, succinate and formate in addition to lactic acid derivatives, they are heterofermentative bacteria. The natural habitat for the occurrence of lactic acid bacteria is: alimentary canal of humans and animals, milk, plants, mucous membranes of the oral cavity and reproductive organs [8, 13].

Numerous studies confirm the beneficial effect of probiotics on human health, which became the basis for their use both in the prevention and treatment of many diseases [1, 2].

PROBIOTICS AND COLON CANCER

Probiotics have a positive effect on intestinal epithelial cells - colonocytes. They provide them with 70% of the energy that is needed to regenerate the intestinal wall in the case of pollutants from the environment. The most important role is played by bacteria that bind to the adhesive receptors in the gastrointestinal tract using

fimbriae. Probiotic bacteria without fimbria must be delivered in larger quantities with food. An important feature of probiotics is also multiplication in the large intestine [14].

In the gastrointestinal tract of an adult, microflora constitutes over 1000 different species of microorganisms [1, 2]. Among them are lactic bacteria, which play an important role in delaying the process of colon cancer formation, most likely affecting metabolic, immune and protective functions. Their amount may increase in the large intestine after ingestion of food containing probiotics. Additional beneficial effects indicated by probiotics are alleviation of lactose intolerance, increasing the humoral immune response, biotransformation of isoflavone phytoestrogen to reduce postmenopausal symptoms, and lowering serum cholesterol [15-17].

Probiotics have an inhibitory effect on the process of carcinogenesis. This is influenced by the ability to reduce harmful bacteria such as *Clostridium*, *Peptostreptococcus* and *Staphylococcus*. Probiotic bacteria affect the inhibition of β-glucoronidase, β-glucosidase and nitroreductase produced by pathogenic bacteria.These are pro-carcinogenic faecal enzymes that are responsible for the growth of colon cancer cells. Probiotics also destroy carcinogens such as nitrosamines and their precursors, and also act destructively on nitroreductase, which is involved in the synthesis of nitrosamines. They positively affect the immune response, increase and development of harmful intestinal microflora, are responsible for the production of antimutagenic substances and the production of lactic acid, which stimulates apoptosis, inhibits the conversion of bile salts into secondary bile salts [18].

Some of the bacteriocins produced by probiotic bacteria are cytotoxic for cancer cells comparing to healthy cells. Bacteriocins, which are cationic, hydrophobic peptides, bind to a negatively charged cell membrane of tumor cells. The cause of this selective binding to the membrane of tumor cells is also due to the difference in the fluidity of their membrane and the greater number of microvilli comparing to normal cells. The bacteriocins cytotoxicity mechanisms include the induction of apoptosis and depolarization of the cell membrane leading to changes in permeability [19, 20].

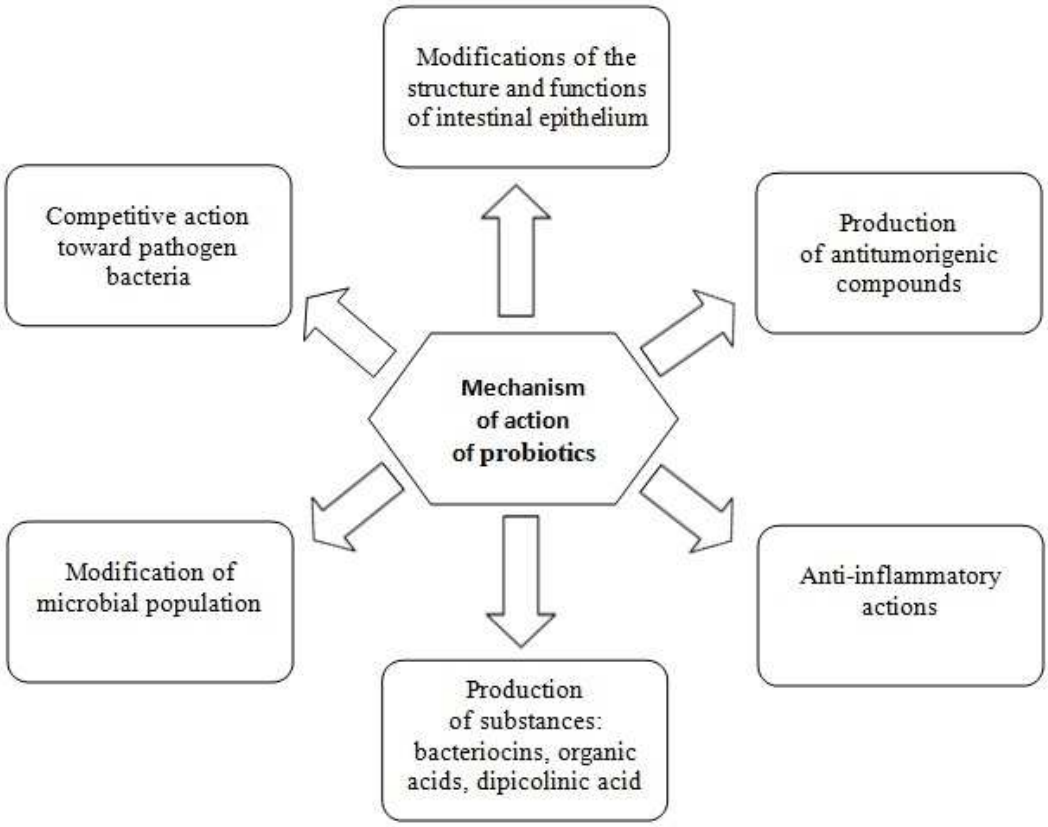

Figure 1. Ways act probiotics.

Colorectal cancer is the second cancer in Poland with the highest mortality [7, 8]. Every year, almost 16,000 new cases are diagnosed. Cancer risk factors are hereditary and environmental factors. Hereditary factors include familial polyposis, hereditary non-arterial colon cancer, Lynch I and II syndromes and ulcerative colitis. Environmental factors include pollution, exposure to certain chemicals, consumption of high-fat low-fiber diets and lack of physical activity [21, 22].

In animal and human studies on the effect of probiotics on factors predisposing to colorectal cancer, researchers investigated the increase of enzymes activity that activate carcinogens, increase the amount of proto-oncogenic chemicals in the colon, or alter populations of certain types or species of bacteria [23-31]. Many studies have shown that factors that can influence the occurrence of colorectal cancer are positively affected by the consumption of certain probiotics [23, 25, 26]. However, these studies do not show a causal relationship to the development of colorectal cancer and are circumstantial. Studies that directly examine the causal relationship are animal studies. In people with colorectal carcinomas a significant disturbance of the intestinal microflora is observed, which plays an important role in the pathogenesis of this common disease. Early studies have shown that the metabolic activity of intestinal microorganisms leads to the production of carcinogens or pro-carcinogens in the large intestine [32]. Under the influence of microflora, the activation of procarcinogens delivered to the body with the diet and biliary excreted to the large intestine, carcinogen synthesis and enzymatic modification of carcinogenic compounds detoxified in the liver are caused [32].

Animal studies show that only 20% of animals free from the microorganisms have chemically induced colon cancer. In animals with microflora, this value was 93%. Cytochrome P450 studies at the molecular level have shown that some of the P450s are also active carcinogens. Epidemiological studies show a higher risk of colorectal cancer in people with high CYP1A2 activity. The effect on this cancer in humans is mediated by the metabolic activation of food-borne heterocyclic amines that occurs via N-oxidation followed by O-acetylation with N-acetoxyarolamine formation, which binds to DNA to form carcinogenic adducts from DNA. These steps are catalyzed by the hepatic cytochrome CYP1A2 and acetyltransferase-2 (NAT-2) respectively [33]. Probiotics such as *Bifidobacterium* produce metabolites that may affect the function of P450 and cause the conversion of azoxymethane to the carcinogenic factor. These tests, along with experiments carried out by Reddy et al. suggest that the probiotic can affect the development of colon cancer. They showed in studies that stimulated growth of *Bifidobacterium* in the colon of rats may lead to inhibition of colon cancer, and suggested that the effect on the foci and the number of crypts in the large intestine has the effect of *Bifidobacterium*, which inhibit the growth of *E. coli* bacteria by lowering the pH. Reducing the amount of these microorganisms can also affect the modulation of bacterial enzymes, such as beta-glucuronidase, which can transform pro-carcinogenic factors into cancerogenic ones [23].

Studies on the antimutagenicity of probiotics show that antimutagenic substances can be found in the cellular envelope of the bacterial cell wall [35]. During in vitro studies on colon cancer cells isolated from mice, *Bifidobacterium infantis* was found to inhibit the activity of this tumor.

These studies suggest that mutagens bind to the cell wall of probiotics and that *Bifidobacterium* binds to the final carcinogen methylazoxymethanol and the mutagen-carcinogen 3-amino-1,4-dimethyl-5H-pyrido [4,3-b] indole, thus removing it from the faeces, and then minimizing its absorption into the lumen of the intestine [24, 35].

The conducted research shows that a significant role in bacterial antimutagenicity may play the stage of their growth. In the phase of linear growth, significant antimutagenic activity is achieved, reaching the maximum level, which then decreases in the stationary growth phase [36, 37].

Baricault et al. performing an in vitro study of HT-29 colon carcinoma cells to which fermented milk was added, concluded that a protective action of probiotics is based on the change of cancer cells differentiation process. The milk was prepared to fermentation using single strains of *Lactobacillus helveticus*, *Bifidobacterium*, *L. acidophilus* or mixture of *Streptococcus thermophilus* and *L. delbrueckii* subsp. *bulgaricus*. On the basis of the research, it was shown that 10-50% of HT-29 cells under the influence of fermented milk inhibited their growth. Subsequent studies have shown that the activity of specific markers responsible for the differentiation of HT-29 cells such as dipeptidyl peptides has been increased [38].

Singh et al. performing analyzes on male F344 rats, evaluated the effect of *Bifidobacterium longumna* on the development of colorectal cancer. The obtained results showed that the administration of lyophilized *B. longum* cultures in food products inhibited the incidence of colon cancer and also reduced the tumor volume. Bacteria *B. longum* also inhibited azoxymethane induced cell proliferation by lowering ornithine decarboxylase (ODC) activity [34]. Ornithine decarboxylase participates in polyamine biosynthesis, which is responsible for the proliferation, differentiation and macromolecular synthesis of cells. The increase in ODC activity correlates with the growth of colorectal adenoma, which indicates a hyperproliferative state of the colonic mucosa [39]. In the conducted studies, it was also shown that the anti-tumor effect is affected by the reduced expression of *ras-p21* oncoprotein. Activation of *ras* proto-oncogenes may induce a malignant phenotype in colon cells [40]. The malignant potential of *ras* genes is related to the mutation in codons 12, 13 or 16 [41].

The study suggests that the administration of *Lactobacillus rhamnosus* and *Bifidobacterium animalis* ssp. *lactis* Bb12, reduces the risk of colorectal cancer as a result of the reaction with endogenous or exogenous carcinogens [42]. Research results of Witkin et al. showed a correlation between the presence of *Lactobacillus* ssp. and *Eubacterium aerofaciens* strains, and a reduced risk of colon cancer [43]. Moreover, epidemiological studies in Finland have shown that high intake of probiotic products resulted in a reduction in the incidence of colorectal cancer despite high fat intake [44].

CONCLUSIONS

Studies that have been published so far do not show clearly that probiotics can prevent colorectal cancer. Epidemiological research is contradictory. Some of them show a lower risk of colon cancer in people consuming probiotics, but there are also those that did not show a relationship the consumption of fermented milk products and the risk of developing disease. Furthermore, not all protective activities of colostoma probiotics were confirmed during in vivo tests. Inconsistent data from these studies may be related to the complexity of carcinogenesis, experimental design, variability of probiotic strains and changes in cancer stages. The onset of cancer related processes in the body occurs many years before the diagnosis, while the colonization of the digestive tract by the intestinal microflora is a very dynamic process, changing under the influence of pH, differences in the content of nutrients and oxygen. Despite the many different results obtained during probiotic studies, further studies are needed to confirm their clinical efficacy.

AUTHORS' CONTRIBUTION

MW, AB, BJ, AP: Writing of the manuscript; BC: Conception and design. All authors read and approved the final manuscript.

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