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Review article

Clinical nutrition in oncology

Probiotics – when and for whom in the oncological patient population

Igor Łoniewski[1], Karolina Kaźmierczak-Siedlecka[2], Natalia Komorniak[3], Ewa Stachowska[3]

[1]*Department of Biochemical Science, Pomeranian Medical University in Szczecin, Szczecin, Poland*
[2]*Department of Medical Laboratory Diagnostics – Fahrenheit Biobank BBMRI.pl, Medical University of Gdansk, Gdansk, Poland*
[3]*Department of Human Nutrition and Metabolomics, Pomeranian Medical University, Szczecin, Poland*

The human microbiome contains trillions of microorganisms. These organisms vary from person to person like fingerprints, and their composition depends on both host and environmental factors, of which diet plays a crucial role. Knowledge of the human microbiome is possible thanks to the introduction of new DNA sequencing methods, which have been developed over the last decade (Human Microbiome Project). This is when the notion of dysbiosis, which is not quite correct, was coined, i.e. disruption of the normal human microbiota. In the absence of standards for the composition and function of the microbiome, dysbiosis is a conventional term describing the differences in the composition and function of the microbiome between a healthy population and a population affected by, for example, a disease; despite its imperfections, this definition is quite suitable for describing changes in the microbiome in the case of various diseases, including cancer.

The microbiome can influence the development and course of cancer through direct oncogenic effects, pro-inflammatory effects on mucous membranes, generation of metabolic abnormalities, modulation of the immune response and efficacy of anticancer treatment. Both tumour tissue and neighbouring tissues contain their own microbiome, and the same applies to other tissues and body fluids, which, through the microbiome and its metabolites, antigens, etc., can influence tumour development, progression and response to treatment. The gut microbiome is an important regulator of the immune response. It can also influence tumours and their treatment in distant organs. Due to the link between the microbiome and cancer, the potential of its modification in oncological treatment is of great interest to researchers and clinicians.

The aim of this paper is to present the current state of knowledge of one of the most popular methods of modifying the microbiome-probiotics, which are commonly used by oncology patients. The safety aspects of the use of probiotics and current meta-analyses on this group of products are mainly discussed.

Key words: probiotics, cancer, chemotherapy, radiotherapy, surgery

Introduction

The human microbiome contains trillions of microorganisms [1]. These organisms vary from person to person like fingerprints, and their composition depends on both host and environmental factors, of which diet plays a crucial role [2]. Knowledge of the human microbiome is possible thanks to the introduction of new DNA sequencing methods, which have been developed over the last decade (Human Microbiome Project). This is when the notion of dysbiosis, which is not quite correct, was coined, i.e. disruption

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of the normal human microbiota. In the absence of standards for the composition and function of the microbiome, dysbiosis is a conventional term describing the differences in the composition and function of the microbiome between a healthy population and a population affected by, for example, a disease; despite its imperfections, this definition is quite suitable for describing changes in the microbiome in the case of various diseases, including cancer [2]. The microbiome can influence the development and course of cancer through direct oncogenic effects, pro-inflammatory effects on mucous membranes, generation of metabolic abnormalities, modulation of the immune response and efficacy of anticancer treatment [1, 2]. Both tumour tissue and neighbouring tissues contain their own microbiome, and the same applies to other tissues and body fluids, which, through the microbiome and its metabolites, antigens, etc., can influence tumour development, progression and response to treatment. The gut microbiome is an important regulator of the immune response. It can also influence tumours and their treatment in distant organs [2]. Due to the link between the microbiome and cancer, the potential of its modification in oncological treatment is of great interest to researchers and clinicians. The aim of this paper is to present the current state of knowledge of one of the most popular methods of modifying the microbiome--probiotics, which are commonly used by oncology patients. The safety aspects of the use of probiotics and current meta--analyses on this group of products are mainly discussed.

Material and methods

This paper is a literature review. The articles for this paper were chosen based on whether they evaluate the mechanisms of probiotic action and their effects mainly on oncological patients. The keywords used in the search queries included "probiotics", "cancer", "radiation", "chemotherapy", "surgery", "tumor", "mucositis", and related articles were identified by searching PubMed, NCBI (National Center for Biotechnology Information), and Google Scholar. Boolean terms included "And, Or, Not." We focused on meta-analyses, systematic reviews and original contributions.

Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit [3]. Probiotics must contain live bacteria that, in the digestive tract, provide an appropriate physiological effect (e.g. biofilm formation, secretion of bioactive substances, antagonism against pathogens). The amount of probiotics declared by the producer in a given product should be maintained in the indicated amount throughout its shelf life. The health benefits of taking probiotic bacteria are strain-dependent (fig. 1), and should be demonstrated after analysis of the effects of the product on the target group taking it, based on the results of well-designed and conducted clinical trials preferably supported by the results of a meta-analysis [4].

Probiotic strains should be fully genetically characterized using molecular biology methods. It is necessary to confirm the safety of the strain based on toxicological studies [6] and to exclude the possibility of transmission of antibiotic resistance genes, as described later in this article. The efficacy of a probiotic should be confirmed in at least one randomized clinical trial. The Oxford EBM Centre describes five levels of evidence of probiotic efficacy (from highest to lowest) [7]:

1. systematic review of RCTs, 'n-of-1' studies,
2. RCT/observational study with a 'very favorable' outcome,
3. non-randomized cohort study, follow-up study,

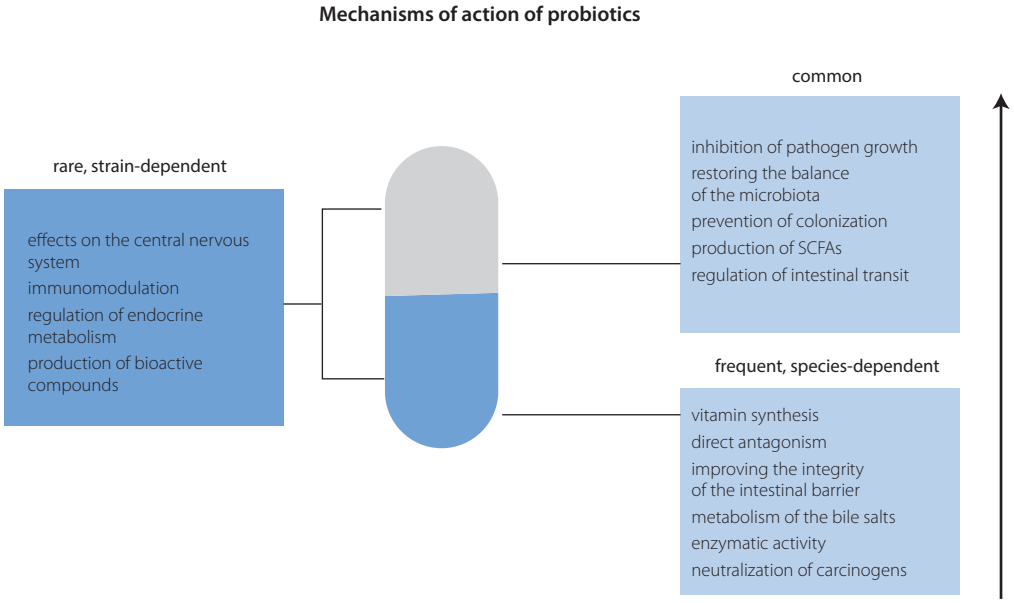

Figure 1. Overall mechanisms of probiotic action. Own elaboration based on literature (acc. Hill et al.) [5] in BioRender

4. case reports, case-control,
5. inference based on mechanism of action.

Although there are probiotics on the market with different levels of evidence, probiotics with a level 1 or 2 should be used in oncological patients. In certain cases it is acceptable to use a probiotic with a level of evidence 3, when its efficacy was tested in a large population and the adverse effects were well characterized in this study. Although there are probiotics on the market with different levels of evidence, probiotics with a level 1 or 2 should be used in oncological patients. In certain cases it is acceptable to use a probiotic with a level of evidence 3, when its efficacy was tested in a large population and the adverse effects were well characterized. Of note, that probiotics most often have the registration status of dietary supplements rather than medicines, which is due, on the one hand, to the nature of these products, which contain live bacteria, causing standardization problems from the point of view of pharmacopeial requirements and, above all, to the impossibility of patenting probiotic strains, which, occurring in nature, cannot be subject to patent restrictions, which, in turn, makes the very costly investment involved in the process of developing an innovative medicine uneconomic. The average research and development (R&D) to marketplace cost for a new medicine is nearly $4 billion, and can sometimes exceed $10 billion [8]. Due to legal requirements in the EU, manufacturers are not allowed to advertise the beneficial effects of probiotics on the body. This is a very complex issue at the intersection of medicine, law and health policy, a detailed discussion of which is beyond the scope of this paper.

To illustrate only a part of this problem, we would like to cite the assumptions of The European Food Safety Authority (EFSA) regarding health claims in accordance with the Regulation of the European Parliament and of the Council (WE) Nr 1924/2006 and (EU) nr 1169/2011 (EU) (https://www.efsa.europa.eu/sites/default/files/event/190118-ax.pdf):

1. they must not refer to a disease,
2. disease risk reduction claims must not refer to a reduction in disease risk, but to a reduction in a disease risk factor,
3. sick people must not be the target population for food claims,
4. claims should refer to the general (healthy) population or subgroups thereof.

Due to such limitations, the only sources of information on the efficacy of probiotics are scientific studies. At this point, it should be emphasized that, for example, yoghurts, pickles and other foods that contain bacterial strains with undocumented beneficial health effects are not probiotics. Unlike fermented foods, probiotic products must meet a number of quality requirements as well as those concerning the safety and efficacy of their use. These requirements are particularly important in the use of probiotics for oncological patients, who are burdened not only by the underlying disease but also by treatment with often high risks and severe side effects and complications.

The effect of probiotics is strain-dependent, so the results obtained from studies of other strains should not be extrapolated even to those that are taxonomically closely related to them. Therefore, both clinical trials and descriptions of probiotics should always give their full taxonomic names. The same problem applies to meta-analyses that describe collectively the effects of different probiotics. Such meta-analyses are, of course, of great value, especially when they contain data on their mechanism of action, but only when they include papers on a specific strain or a preparation of different strains can they be helpful to clinicians in making therapeutic decisions.

Probiotics are primarily used to supplement microbial deficiencies that may be the cause of specific conditions. A classic example of this approach is the concept of taking probiotics prophylactically during antibiotic therapy or chemotherapy, which disrupts the patient's microbiota. However, a cause-and-effect relationship between the microbiota and the disease should always be identified. Probiotic administration often does not result in changes in the composition of the microbiota [8], and may be associated with the production of metabolites that enter the interactions with the host's metabolism and immune system. However, probiotics can affect gut microbiota gene expression, with potential anti-inflammatory effects. Moreover, probiotic intervention alters the influence of microbiota on biochemical, physiological and immunological parameters [9]. Furthermore, probiotic strains are administered to patients because of their antagonistic properties towards pathogenic bacteria. An excellent example is one of the best studied probiotic strains *Lactiplantibacillus plantarum* 299v. On the surface of this bacterium are mannose adhesins encoded by the *Msa* gene that have an affinity for receptors located on intestinal mucosal cells. *L. plantarum* 299v, by binding to these receptors, inhibits the competitive adhesion of bacteria (*Escherichia coli* – ETEC/EPEC, *Salmonella enterica serovar Enteritidis*, *Vibrio cholerae*, *Pseudomonas aeruginosa*, *Saccharomyces cerevisiae*) and *Candida albicans*. Other adhesins present on the surface *L. plantarum* 299v are glycolytic enzymes: 3-phosphoglycerate aldehyde dehydrogenase (GAPDH), enolase (ENO) and phosphoglycerate kinase (PGK). GAPDH inhibits competitively the adhesion of group A streptococci, staphylococci, *Candida albicans* and *Schistosoma mansoni*. ENO prevents adhesion of streptococci, *Streptococcus pneumoniae*, *Streptococcus aureus* and *Candida albicans*. Moreover, *L. plantarum* 299v enhances the production of mucin in intestinal epithelial cells, which explains the antagonistic effect of this bacterium towards the *Escherichia coli*. Probiotic bacteria are also recommended to increase the production of short-chain fatty acids (SCFAs) in the gut, which improve the integrity of the intestinal epithelium, reduce bacterial translocation, regulate epithelial cell proliferation and differentiation, improve nutrient absorption, are energy substrates for the liver, skeletal

muscle, heart, brain, prevent hyperinsulinemia and have anti-inflammatory effects [10–11]. According to Dogra et al. [12], probiotics can increase the resistance of the microbiome to stress factors and/or improve its ability to recover. The mechanisms of action of probiotics can be divided into rare, which are strain-dependent:

- immunomodulation,
- endocrine action,
- production of bioactive compounds,
- effects on the central nervous system;

frequent, species-dependent:

- vitamin synthesis,
- direct antagonism,
- enzymatic activity,
- metabolism of bile salts,
- neutralization of carcinogens,
- improvement of intestinal barrier integration;

and common to many probiotics: production of non-short-chain fatty acids, prevention of intestinal colonization by pathogens, regulation of intestinal transit, inhibition of pathogen growth, restoration of intestinal microbiota balance, improvement of intestinal epithelial renewal [5]. Given the complexity of cancer and the consequences of its treatment, all of these mechanisms can benefit oncological patients.

Safety

The safety of probiotic usage must be determined on the basis of established scientific principles, including the conduct of appropriate studies. A large number of species of lactic acid bacteria, bifidobacteria and yeast are available in many common dietary supplements and foods, meaning that they are safe for consumption. The EFSA has maintained and updated a list of species considered safe for human consumption since 2007. The main classifications are QPS (*qualified presumption of safety*) and novel food [13]. These qualifications are based on taxonomic identification and a comprehensive scientific data on the safety of the strain in question, which include:

1. genotypic and phenotypic identification,
2. detection of virulence-related genes by validated whole-genome sequencing (WGS), toxin production potential (toxin production potential must be considered for novel foods with respect to potentially adverse metabolic properties),
3. animal toxicity tests may be required for novel foods,
4. assessment of the risk of antimicrobial resistance is required for all; identification of intrinsic or acquired resistance and potential transferable antimicrobial resistance genes.

It seems that since the effect of probiotics is strain-dependent, the safety of their use should also be determined on a strain-by-strain basis. The only method is to conduct *in vitro* toxicological studies and clinical trials. End-product-specific studies are particularly important, especially when probiotics are used in groups of seriously ill people. Reference can be made to studies of the probiotic *L. plantarum* 299v, which, when administered to kidney transplant patients, reduced the incidence of infections caused by *Clostridium difficile* [14–15]. In addition, no risk of endocarditis was identified for this strain and the risk of use in critically ill patients [15].

In contrast, the use of *Saccharomyces boulardii* is not recommended in patients with a catheter inserted into a central vein, in critical condition or with significantly weakened immunity. Great caution is also recommended for the use of this probiotic in patients with impaired intestinal barrier integrity, which is often seen in patients treated with chemotherapy or radiotherapy [16]. Adverse reactions caused by the administration of a probiotic strain do not necessarily result in its being deprived of QPS status. For instance, cases of bacteraemia have been observed following the use of the *Lacticaseibacillus rhamnosus* GG strain and endocarditis, however, conditions predisposing to opportunistic infections were noted in all of these cases, leaving the QPS status of species previously included in the genus Lactobacillus spp. and now belonging to any of the derived genera unchanged [17].

Meta-analysis confirms the safety of probiotics in oncological patients. Wang et al. found in eleven studies of probiotics used for prevention of chemoradiotherapy-induced diarrhoea in people with abdominal and pelvic cancer, including 1612 people (873 receiving probiotics and 739 not receiving probiotics) that in seven studies no adverse events (AEs) caused by probiotics were observed. In four studies varying degrees of AEs were reported in both placebo and probiotic groups. The authors concluded that despite the rare occurrence of AEs after probiotic treatment, caution should be considered as many cancer patients are immunocompromised [18]. In a subsequent systematic review and meta-analysis involving twenty-five studies (n = 2,242) in patients with different types of cancer, 237 adverse events were observed in those consuming probiotics and 314 adverse events in those not consuming probiotics. No deaths related to probiotic intake were observed and infection events were not clearly related to the intervention [19]. It must be added, however, that the reporting of adverse effects in this group of patients is difficult, and distinguishing their cause is often impossible. Therefore, probiotics should not be used, and it is certainly necessary to assess the balance of benefits and losses before their possible use, in patients:

- with immunodeficiency,
- in a severe general condition hospitalized in an intensive care unit,
- with a central venous catheter.

Probiotic therapy in meta-analyses

Some papers on cancer prevention by probiotics have been published so far. One of the most interesting is the meta-analysis by Gheisary Z. et al. on the prevention of oral cancer [20], which showed a statistically significant reduction in lesions after probiotic therapy. Probiotic-mitigated changes included

a reduction in the number of subgingival periodontopathogens *P. gingivalis* (SMD = 0.402), *F. nucleatum* (SMD = 0.392), and *T. forsythia* (SMD = 0.341), immunological markers MMP-8 (SMD = 0.819), and IL-6 (SMD = 0.361). The results of this study suggest that probiotic supplementation improves clinical parameters and reduces the burden of periodontopathogens and proinflammatory markers in patients with periodontal disease. Among the bacteria analyzed in the meta-analysis are the following *B. bifidum*, *L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. salivarius Bifidobacterium*, *B. longum*, *L. acidophilus*, *L. bulgaricus*, *L. casei.*

Another meta-analysis [21] estimated the potential effect of probiotics on inhibiting oral carcinogenesis. Although the studies included in the meta-analysis are of moderate quality, it was possible to select bacterial species with potentially carcinogenesis-preventing effects, included *Acetobacter syzygii,* AJ2, *Lactobacillus plantarum* and *Lactobacillus salivarius* REN. Among them, the use of *L. salivarius* REN resulted in a 95% lower risk of developing oral cancer ($p < 0.05$).

Interestingly, another study showed that probiotics can be effective in the prevention and treatment of oral mucositis caused by chemotherapy, radiation therapy and chemo-radiotherapy [22]. Five studies involving 435 patients that were included in the meta-analysis indicated that the use of probiotics reduced the risk of inflammation.

Treatment – surgery, chemotherapy and radiation

One of the most common and typical side effects associated with chemotherapy or radiation therapy in cancer patients is diarrhea (up to 80% of treated patients). Diarrhea can lead to some severe consequences: loss of fluids and electrolytes, creation of nutritional deficiencies, increased risk of infections or delays in treatment, reduction of dosage or discontinuation of treatment. Probiotics have long been used in gastrointestinal guidelines to relieve diarrhea [23]. However, can probiotics be effective in the treatment of diarrhea in oncological patients?

In 2018, based on the results collected in the Cochrane database [24],evidence supporting the effectiveness of probiotics in preventing or treating diarrhea associated with cancer treatment was shown to be lacking. However, according to the authors, probiotics appear to be safe, as no studies have shown serious side effects. Three studies analyzed in this paper where probiotics were compared with other drugs in preventing diarrhea in patients treated with radiation therapy – with or without chemotherapy – found beneficial effects of probiotics. Remarkably, no study reported serious adverse events or deaths related to diarrhea.

Another interesting meta-analysis on the reduction of diarrhea induced by chemotherapy and or radiotherapy or chemo--radiotherapy among individuals with abdominal and pelvic cancer was published in 2016 [18]. The authors concluded that probiotics may have a beneficial effect in preventing chemo--radiotherapy-induced diarrhea, especially in cases of grade ≥2 diarrhea with rarely cause side effects. An interesting meta-analysis was conducted by Skonieczna-Zydecka et al. [25], who evaluated the effectiveness of probiotic use in the prevention of postoperative complications. The authors found a reduction in the incidence of postoperative complications like abdominal distress, diarrhea, pneumonia, sepsis, surgical wound infections and urinary tract infections. They also observed shorter duration of antibiotic therapy, occurrence of fever, administration of infusions, hospitalization, shorter times for introducing solid foods and also lower levels of C-reactive protein (CRP) and interleukin (IL) – 6. This meta-analysis shows that prophylactic administration of probiotics counteracts postoperative complications by modulating the intestinal immune response and production of [SCFAs]. In a study by Gan et al. [26], administration of probiotics before surgery was shown to reduce the incidence of infections after liver resection, and may reduce the duration of hospitalization and antibiotic use [26]. In the probiotic group, infection rates were 11.7%, while in the placebo group they were 30.3% respectively ($p < 0.001$). The rate of wound infection decreased the length of hospital stay (–0.57 days) and antibiotic use (mean difference: –3.89 days, 95% CI: –4.17 to –3.60; $p < 0.001$) were shortened in the group of patients using probiotics. The probiotics used are *L. Casei Shirota* and synbiotic *Pediococcus pentoseceus* 5–33:3, *Leuconostoc mesenteroides* 32–77:1 *L. paracasei* ssp paracasei 19 and *L. plantarum* 2362, as well as 2.5 g inulin, oat bran, pectin and resistant starch.

Similar results were obtained in Chen's 2022 meta-analysis [27] in which it was shown that the use of probiotic therapy [including synbiotic therapy] is associated with a significant reduction in the risk of postoperative infectious complications by 37% (relative risk [RR] = 0.63, 95% confidence interval [CI] 0.54–0.74, $p < 0.001$). Probiotic administration was shown to be effective in reducing the incision infection, central line infection, pneumonia infection, urinary infection and incidence of diarrhea septicemia. A meta-analysis [28] evaluated the effect of probiotic therapy on reducing postoperative infectious complications in patients who underwent colorectal cancer surgery. In these patients, probiotics may result in reducing overall postoperative complications, but may result in little to no difference in hospital length of stay (LOS) and postoperative quality of life (QOL). The authors conclude that perioperative administration of probiotics can reduce infectious complications in patients undergoing colorectal cancer surgery. In addition, compared to standard of care or placebo, probiotics may have similar effects on perioperative mortality and procedure-related complications such as anastomotic leakage, hospital length of stay, and quality of life. In contrast, the meta-analysis of Yang [3] found that probiotics (*Bifidobacterium*, *Lactobacillus* and *Streptococcus* species) can more effectively reduce inflammation associated with gastric cancer by increasing levels of cluster of differentiation 4+ and significantly reducing levels of IL-6.

Table I. Summary of the effect of probiotics in gastrointestinal cancers

Type of article	Aim of the study	Number of studies analyzed	Type of sample used	Probiotic strain (examples)	Outcomes	Conclusions	References
systematic review and meta-analysis	investigating the effect of probiotics on inhibiting oral carcinogenesis	studies included in qualitative synthesis (n = 5) studies included in quantitative synthesis (meta-analysis) (n = 2)	4-nitroquioline-1-oxide (4NQO)-induced oral carcinogenesis in male F344 rats and TCA-8113 (human tongue squamous carcinoma)	*Lactocasieibacillus salivarius* REN	inhibition of oral carcinogenesis induced by 4-nitroquioline-1-oxide	the study found that the 4 strains described here show potential therapeutic activity in oral carcinogenesis. The ability of *L. salivarius* REN to inhibit oral cancer suggests that this bacterium may be a potential inhibitor of oral carcinogenesis	[21] Wan Mohd Kamaluddin et al. 2020
			human oral KB cancer cell line	*Lactocaseibacillus plantarum*	reduction of proliferation and induction of apoptosis to the cancer cell [TCA-8113]; enhancing cytotoxicity expect		
			human oral cancer cell line (KB) and human normal epithelial cell line (KDR)	*Acetobacter syzygii*	the metabolites of *Acetobacter syzygii* induced apoptosis		
			NK cells and monocytes from healthy human donors; humanized-BLT (hu-BLT; human bone marrow/ liver/ thymus) mice; nodscid gamma mouse (immunodeficient laboratory mice)	AJ2- mix of *Streptococcus thermophiles, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaricus*	super-charged NK cells inhibit OSCSCs tumor growth and improved immune system of hu-BLT mice		
systematic review, meta-analysis, and meta-regression	verify that probiotics and/or synbiotics reduce the incidence of surgical site infections and other surgery-related complications	35 trials included 3,028 adult patients; interventions were probiotics (n = 16) and synbiotics (n = 19 trials)	adult patients with hepatopancreatobillary surgery; or colorectal surgery; or oesophagectomia	*Enterococcus faecalis* T110, *Clostridium butyricum* TOA, *Bacillus mesentericus* TOA	probiotic treatment can reduce superficial incisional SSIs in patients undergoing CRC surgery; perioperative probiotic treatment can enhance immune responses and improve the intestinal microbial environment	the study found a reduction in the incidence of postoperative complications like abdominal distress, diarrhea, pneumonia, sepsis, surgical wound infections, urinary tract infections; shorter duration of antibiotic therapy, occurrence of fever, administration of infusions, hospitalization, shorter time to introduce solid foods and also lower levels of C-reactive protein (CRP) and interleukin (IL-6)	[25] Skonieczna-Żydecka et al. 2018
				Lactobacillus casei strain Shirota, *Bifidobacterium breve* strain Yakult; prebiotic: GOS	perioperative administration of synbiotics in patients with esophagectomy is useful because they suppress excessive inflammatory response and relieve uncomfortable abdominal symptoms through the adjustment of the intestinal microfloral environment		
				Lactobacillus casei strain Shirota, *Bifidobacterium breve* strain Yakult; prebiotic: GOS	perioperative synbiotic treatment attenuated the decrease in intestinal integrity and reduced the rate of infectious complications in patients with or without liver cirrhosis who underwent hepatic surgery		

Table I cont. Summary of the effect of probiotics in gastrointestinal cancers

Type of article	Aim of the study	Number of studies analyzed	Type of sample used	Probiotic strain (examples)	Outcomes	Conclusions	References
systematic review and meta--analysis	to investigate whether the use of probiotics and synbiotics can have an impact on the prevention of infectious complications in patients with colorectal cancer	studies included in meta-analysis (n = 14) 1,566 patients	human	*Lactobacillus plantarum* (CGMCC No 1258), *Lactobacillus acidophilus* (LA-11), and *Bifidobacterium longum* (BL-88)	compared with the control group, the probiotic group had increased transepithelial resistance, reduced bacterial translocation, decreased ileal-bile acid binding protein; they had decreased blood enteropathogenic bacteria and increased fecal bacterial variety; the post-operative recovery of peristalsis, incidence of diarrhea/ infectious-related complications were improved	significant reduction in the risk of postoperative infectious complications by 37% reducing the incision infection, central line infection, pneumonia infection, urinary infection, and incidence of diarrhea septicemia	[27] Chen et al. 2022
				Bifidobacterium longum, *Lactobacillus acidophilus*, and *Enterococcus faecalis*	the use of probiotics can reduce the occurrence of infectious complications		
systematic review and meta--analysis	the primary outcome measures included perioperative mortality, postoperative infectious complications, and probiotics--related adverse events. postoperative outcomes between patients with and without perioperative probiotic administration during colorectal cancer surgery. Secondary outcome measures included overall postoperative complications, hospital length of stay, and postoperative quality of life	studies included (n = 20)	human	*Bifidobacterium animalis, lactis*, *Lactobacillus casei*, and *Lactobacillus plantarum*	changes in the microbiota (typically occur over time in CRC patients) and inflammatory responses are modified by the use of probiotics before and after surgery. It reduces postoperative bowel discomfort	perioperative probiotic administration may reduce complications, including overall infectious complications, in patients undergoing colorectal cancer surgery without any additional adverse effects; probiotics may have similar effects on perioperative mortality; procedure--related complications such as anastomotic leakage, and hospital LOS; or improve the QOL	[28] An et al. 2019
				Lactobacillus acidophilus NCFM, *Lactobacillus rhamnosus HN001*, *Lactobacillus paracasei LPC-37*, and *Bifidobacterium lactis HN019* + *oligosaccharide*	the perioperative administration of synbiotics significantly reduced postoperative infection rates in patients with colorectal cancer		
				Pediococcus pentosaceus, *Leuconostoc mesenteroides*, *Lactobacillus paracasei spp. paracasei*, and *Lactobacillus plantarum*, and 2.5 g of each of the four fermentable fibers (prebiotics)	patients who use synbiotics had a better Gastro-Intestinal Quality of Life Index compared with placebo; synbiotics administration may have a beneficial effect on the post-colectomy gastrointestinal function (mainly diarrhea)		

SSIs – surgical site infections; CRC – colorectal cancer; LOS – length of stay; QOL – quality of life

In table I, we have summarized the results of systematic review and meta-analyses focusing on the potential benefits of probiotics for cancers located in the gastrointestinal tract. As can be seen, undoubtedly further research on this topic is needed, although already the effect of probiotic therapy on improving quality of life, reducing gastrointestinal complaints or the impact on reducing the frequency of infectious complications seems promising.

Other clinical work on probiotic therapy in cancer patients

Bajramagic et al. studied the effect of probiotics in patients with colorectal adenocarcinoma [29]. This study included 78 participants divided into two groups. Patients (n = 39) from the first group received a probiotic product containing *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium lactis, Bifidobacterium bifidum, Bifidobacterium breve, Streptococcusthermophilus*. The second group (n = 39) did not consume probiotics. It was observed that the length of postoperative hospitalization was shorter in the probiotic group compared to the rest of the studied patients ($p < 0.05$). Moreover, the authors reported that probiotics are able to reduce postoperative complications, however this effect depends on the localization of the tumor (i.e. *rectum* –33.3% whereas ascending colon –16.7% and sigmoid colon –12.5%) [29]. Complex multidisciplinary anti-cancer treatment should also be focused on improvement of quality of life. In Kaźmierczak-Siedlecka et al., a double-blind, randomized and placebo-controlled trial studied the effects of the bacterial probiotic strain – *L. plantarum* 299v on nutritional status, tolerance of enteral nutrition and quality of life in cancer patients who received home enteral nutrition [30]. This study included 35 patients divided into 2 groups: first received probiotics and the second a placebo for 4 weeks. Probiotic *L. plantarum* 299v was administered in doses of 2 capsules per day (1 capsule contains 10 x ^{10} CFU). After 4 weeks of probiotic supplementation, a statistically significant increase of serum albumin concentration was observed ($p = 0.032$). Additionally, in patients who received probiotics, the frequency of gastrointestinal symptoms, such as flatulence and vomiting, was reduced at week 4 in comparison to the baseline ($p = 0.0117$). Nevertheless, quality of life was improved across both groups of participants [30]. It could be associated with the introduction of enteral nutrition, not only the administration of probiotics/placebo. The effects of enteral nutrition in combination with probiotics was also analyzed in a study by Xie et al., with regards to gastric cancer patients (n = 140; n = 70 probiotics and enteral nutrition; n = 70 received only enteral nutrition) in the postoperative period [31]. It was observed that the incidence of enteral nutrition-related diarrhea was less common in patients who received probiotics. There was no difference between groups regarding nutritional status before and after intervention ($p > 0.05$) [31]. However, this result may be associated with the fact that probiotics were administered only for 8 days.

Oral mucositis is one of the side effects of anti-cancer therapy, which may be induced by chemotherapy and radiotherapy [32]. It is estimated that 40% of head and neck patients will develop oral mucositis 1–2 weeks after starting radiotherapy and 5–10 days after starting chemotherapy [33]. According to other data, it can occur even in 80% of patients treated with high-dose chemotherapy [32]. Oral mucositis is related to low food intake, and, as a consequence, it contributes to weight loss. Recently, in a systematic review and meta-analysis by Liu et al. (n = 708, 8 trials; finally 7 trials were included to meta-analysis) the role of probiotics as a preventive method for oral mucositis induced by anti-cancer treatment was assessed [34]. The incidence of oral mucositis in the probiotic group was significantly low (risk ratio (RR) = 0.84, 95% confidence interval (CI) = 0.77–0.93, $p = 0.0004$) in 3 trials in which Lactobacilli-based probiotics were investigated. Moreover, incidence of severe oral mucositis was significantly lower in patients who received probiotics, which was shown in 7 trials (RR = 0.65, 95% CI = 0.53–0.81, $p < 0.0001$). Therefore, the use of probiotics to limit side effects of anti-cancer treatment, such as oral mucositis, is promising.

In a meta-analysis by Lu et al. (13 trials, n = 1024), it was reported that probiotics are effective in the prevention of diarrhea induced by chemotherapy [35]. Notably, the administration of probiotics reduced both the total rate of diarrhea in these patients and diarrhea grade III–IV, however no statistically significant effect was observed in the case of diarrhea grade I–II [35]. The positive effect of probiotics on reduction of diarrhea associated with chemotherapy was also noted recently in 2023 in Huang et al., where a trial regarding colorectal cancer patients was undertaken (n = 100; n = 50 probiotics, n = 50 placebo) [36]. In this study, gut microbiota using 16S rRNA sequencing and SCFAs in the preoperative period and after the first circle of chemotherapy in the postoperative period were analyzed. Notably, chemotherapy affects gut microbiota causing dysbiotic changes observed by a reduction of microbial diversity and a decrease in the level of Firmicutes. It was noted that probiotics affect not only the composition of gut microbiota but also contribute to the production of SCFAs ($p < 0.0001$) [36]. The stimulation of SCFAs production seems to be significant in colorectal cancer patients. Recently, in 2023, in a study by Kaźmierczak-Siedlecka et al., gut microbiota-derived metabolites in 15 colorectal cancer patients in the preoperative period were analyzed [37]. Stool samples were stored in –80°C and the subsequent analysis of SCFAs was conducted by using gas chromatography. The normal proportion between SCFAs is 3:1:1 for acetate, propionate, butyrate (respectively), but in colorectal cancer patients the abnormal proportion between SCFAs was observed (based on this proportion, in 93.33% of patients the result <1 for butyrate was found) [37]. These results indicate

Table II. Use of probiotics in support of mental health

Aim of the study	Study group	Probiotic strain	Dosage	Outcomes	References
assess the effect of a psychobiotic formulation specifically on well-being	studies included 134 patients	*L. helveticus R00052* and *B. longum R0175*	3 billion CFU once a day (dissolve in a 300 ml glass of water) for 4 weeks	no significant effects of probiotic intake in whole sample outcomes; the linear mixed-effects model showed that the interaction between high scores in Healthy Behaviors and probiotic intake was the single significant predictor of positive effects on anxiety, emotional regulation and mindfulness in post-treatment outcomes	[45] Morales-Torres et. al. 2023
assess the effects of probiotic intake on symptoms of depression and metabolic status in patients with major depressive disorders	studies included 40 patients with major depressive disorder	*L. acidophilus, L. casei, B. bifidum*	6 x 10^9 CFU a day for 8 weeks (in capsules)	beneficial effects on Beck Depression Inventory, insulin, hs-CRP concentrations and glutathione concentrations	[46] Akkasheh et al. 2016
determine the effect of consumption of probiotic supplements (Winclove's Ecologic® Barrier) on depressive symptoms in a sample of participants with mild to severe depression	studies included 71 patients with depressive symptoms	*B. bifidum W23, B. lactis W51, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, L. lactis W19* and *L. lactis W58*	10^{10} CFU in powder for 8 weeks	after probiotic use participants demonstrated a significantly greater reduction in cognitive reactivity compared with the placebo group	[47] Chahwan et al. 2019
to examine whether the use of probiotic yogurt will have an impact on immune system function and mental and physical disorders caused by stress.	studies included 224 healthy adults	*L. gasseri SBT2055, B. longum SBT2928*	≥5.0 × 10^8 CFU for 12 weeks in yogurt	the NK cell activities of the test yogurt group were higher than those of the placebo yogurt group, and their serum ACTH levels were significantly decreased by the test yogurt	[48] Nishihira et al. 2014
determine the impact *of L. rhamnosus* on stress-related behaviors, physiology, inflammatory response, cognitive performance and brain activity patterns in healthy male participants.	studies included 29 healthy adults	*L. rhamnosus (JB-1)*	1 × 10^9 CFU in capsule for 8 weeks	no significant effects of probiotics on BDI scores. There was no overall effect of probiotic treatment on measures of mood, anxiety, stress or sleep quality	[49] Kelly et al. 2016
evaluate the efficacy and health benefits of the use of a tablet containing *Lactobacillus gasseri CP2305* in healthy young adults	studies included 60 medical students preparing for the exam	*L. gasseri CP2305*	1 x 10^{10} CFU per 2 tablets for 24 weeks	taking probiotics significantly reduced anxiety and sleep disturbance relative to placebo. CP2305 administration attenuated the stress-induced decline of *Bifidobacterium spp.* and the stress-induced elevation of *Streptococcus spp.*	[50] Nishida et al. 2019
determine the effects of *L. acidophilus NCFM* on irritable bowel syndrome symptoms and quality of life	studies included 340 volunteers who were diagnosed with IBS	*L. acidophilus NCFM*	*L. acidophilus NCFM* (ATCC 700,396) high dose (10^{10} CFU) and low dose (10^9 CFU) for 12 weeks	NCFM alleviates moderate to severe abdominal pain, consistent with earlier observations of this strain mitigating visceral pain through increased analgesic receptor expression	[51] Lyra et al. 2016

NK – natural killer; ACTH – adrenocorticotrophic hormone; BDI – beck depression inventory; CFU – colony-forming units

that it is reasonable to consider the administration of butyrate in the preoperative period.

Mental well being

Stress and depressive disorders accompany patients at various stages of cancer. In these cases, an important and safe option to help patients is the use of psychobiotics. Psychobiotics are probiotics that benefit mental health. Due to the high heterogeneity and limited number of studies, as well as the complex and complicated nature of the concept of using psychobiotics (effects on the brain-gut axis), their use, is not a routine procedure. In one of the first meta-analysis [38], a systematic review of existing evidence on the effect of probiotic-based interventions on depressive symptoms was conducted. The meta-analysis showed that probiotics significantly reduced depression scale scores in the study subjects. Psychobiotics had an effect on both the healthy population and patients with depression (MDD). The effect of psychobiotics was observed in the population under 60 years of age, while no effect was confirmed in the elderly. In another meta-analysis McKean et al. [39] showed that psychobiotics reduce subclinical symptoms of depression, anxiety and stress in healthy individuals.

Nikolova et al. [40] published a meta-analysis of studies involving 404 people with depression in which they confirmed that psychobiotics are effective in reducing the symptoms of this illness when administered together with antidepressants, but yet do not appear to be effective in monotherapy. Potential mechanisms of action may take place through an increase in brain-derived neurotrophic factor (BDNF) and a decrease in CRP, although the evidence currently available is quite sparse. Misera et al. [41] evaluated the effect of psychobiotics on psychometric scales in patients with MDD, showing that psychobiotics could alleviate MDD symptoms. Therapy tended to be more depending on the duration of psychobiotic supplementation. Psychobiotics have great potential in the treatment of MDD and they are also a safe form of intervention. One of the best studied bacterial strains in the psychobiotic group are *L. heleveticus* Rosell-52 and *B. longum* Rosell-175. Administration of *L. heleveticus* Rosell-52 to animals exposed to stress has been shown to reduce adhesion of pathogens to intestinal epithelial cells, preventing their translocation and reducing the synthesis of pro-inflammatory cytokines, thereby potentially having a protective effect on limbic system structures exposed to prolonged stress [42]. Clinical studies have shown that administration to healthy individuals of the bacterial strains *L. heleveticus* Rosell-52 and *B. longum* Rosell-175 reduces gastrointestinal discomfort caused by excessive stress [43]. The administration of these bacterial strains has been observed to have a positive effect on the subjects' mood, reduce the severity of anxiety and decrease cortisol excretion. In March 2016, the Canadian Directorate of Non-Prescription Natural and Health Products made the following recommendations for its use: [1] helps relieve general symptoms of anxiety; [2] relieves gastrointestinal symptoms caused by stress; and [3] promotes emotional balance.

Research indicates that psychobiotics may play an important therapeutic role in the treatment of depression and anxiety [44]. Table II summarizes studies focusing on the potential use of probiotics in supporting mental functioning.

Conclusions

There is a link between gut microbiota and the development, prognosis and treatment of cancer. Probiotics can be used in the prevention and treatment of cancer due to their clinical effectiveness and safety. When using probiotics in oncological patients, it is important to take into account the QPS status, novel foods, EFSA opinion, relevant quality, the opinions of scientific bodies and the results of clinical trials to evaluate the balance of benefits and losses. Quality aspects related to the products' manufacture should also be taken into account. This topic undoubtedly requires further research. At the moment, we do not have standards/recommendations for probiotic therapy of oncology patients.

Article information and declarations

Author contributions

Igor Łoniewski – development of the concept of the paper, drafting.
Karolina Kaźmierczak-Siedlecka – development of the concept of the paper, drafting.
Natalia Komorniak – revision of manuscript.
Ewa Stachowska – development of the concept of the paper, drafting and revision of manuscript.
Authorship requires substantial contributions to the development of the concept of the paper, the analysis and interpretation of data and the drafting and revision of manuscript submissions.

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Conflict of interest

None declared

Ewa Stachowska
Pomeranian Medical University
Department of Human Nutrition and Metabolomics
ul. Broniewskiego 24
71-460 Szczecin, Poland
e-mail: ewa.stachowska@pum.edu.pl

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