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Probiotics as an Adjunct Therapy for Decreasing Gastrointestinal Complications from Chemoradiotherapy

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Abstract

Background and Objective: Cancer treatments, including chemotherapy and radiotherapy, can cause diarrhea, which negatively affects the quality of life and willingness of patients to continue their treatment plans. In recent years, evidence have shown that the gut microbiome contributes to the development of these adverse effects as well as decreasing their severity. Probiotics have been shown to decrease treatment-related gastrointestinal symptoms. Probiotics are defined as live microorganisms that provide health benefits to the host.

Results and Conclusion: This report assessed the effectiveness of various probiotic strains, including *Lactobacillus* and *Bifidobacterium*, in decreasing diarrhea associated with chemotherapy and radiotherapy. Clinical trials have shown that certain probiotic formulations can decrease diarrhea occurrence and severity, decrease antidiarrheal medication needs and improve overall treatment tolerance. Despite these promising findings, further research is needed to optimize probiotic use in cancer therapy and fully understand how probiotics modulate gut health during chemotherapy. Therefore, probiotics can be used as an adjunctive treatment strategy in chemoradiotherapy cases to improve patient quality of life and clinical outcomes.

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1. Introduction

Cancer is a significant societal, public health and economic issue in the 21st century, accounting for 16.8% of all fatalities and 22.8% of noncommunicable disease deaths globally. The disease is within the top three causes of mortality in 177 out of 183 nations, accounting for 30.3% of premature deaths from NCDs in ages of 30–69 years [1]. In 2022, more than 20 million new cancer cases and approximately 10 million deaths were reported worldwide. Based on demographic projections, the annual number of new cancer cases is expected to reach 35 million by 2050, a 77% increase rate from 2022 [2].

Current cancer treatments-chemotherapy, radiation and surgery-include several limitations. Surgery may leave leftover cells, leading to relapse; radiotherapy harms normal cells and chemotherapy may cause drug resistance and substantial toxicity. These variables contribute to high death rates, instead of beneficial outcomes [3]. All cancer treatments include side effects, regardless of their variety. Chemotherapy is still the most effective and commonly used treatment for most cancers [4].

The study investigated a high prevalence of side effects reported by patients from chemotherapy in standard

clinical practices, with 97.4% of the patients experiencing at least one adverse effect through a 6-m follow-up. Three most frequent adverse effects were diarrhea (49.4%), lack of appetite (71.4%) and exhaustion (87%) [5]. Radiotherapy (RT) of the abdomen or pelvis with chemotherapy drugs, including fluorouracil (FU) and irinotecan (CPT-11), are frequently associated with diarrhea as a side effect. As many as 50–80% of patients may experience chemotherapy-induced diarrhea using modulated FU, CPT-11, or a combination of the two drug. Of these patients, "30% of patients may develop diarrhea" [6]. Advancements in sequencing technology have revealed that the gut microbiota includes a multifaceted effect on cancer onset and the body's reactions to treatment (Figure 1). Connection of gut microbiota to cancers has emerged as a novel fascinating area of study. The body's gut microbiota, sometimes known as the "hidden organ," is vital [7, 8].

Research indicates that probiotics include several health benefits that are consistent with their expanding use. Gut microbiota has been linked to more than 25 diseases and disorders other than digestive health to include autoimmune diseases and mental health [9].

Probiotics that are mostly studied include lactic acid bacteria (LAB) such as *Lactobacillus* spp. and *Bifidobacterium* spp. but they contain various microorganisms such as *Escherichia coli*, *Streptococcus* spp. and *Enterococcus* spp. The efficacy of probiotics in treating disorders such as lactose intolerance, antibiotic-associated diarrhea and IBD has been assessed. Through processes, such as immunological stimulation, nutrient competition and antimicrobial generation, gut health is improved. Though encouraging, additional studies are needed to completely comprehend their functions in intestinal health [10]. This study aimed to assess the role of probiotics in decreasing gastrointestinal side effects associated with chemotherapy and radiotherapy in cancer patients. Specifically, the study focused on the effects of various probiotic strains, including *Lactobacillus* spp. and *Bifidobacterium* spp., in healing diarrhea and other gastrointestinal problems caused by these treatments. Another goal was to demonstrate that the use of probiotics as an adjunctive therapeutic strategy could improve patient's quality of life and their tolerance to cancer therapies.

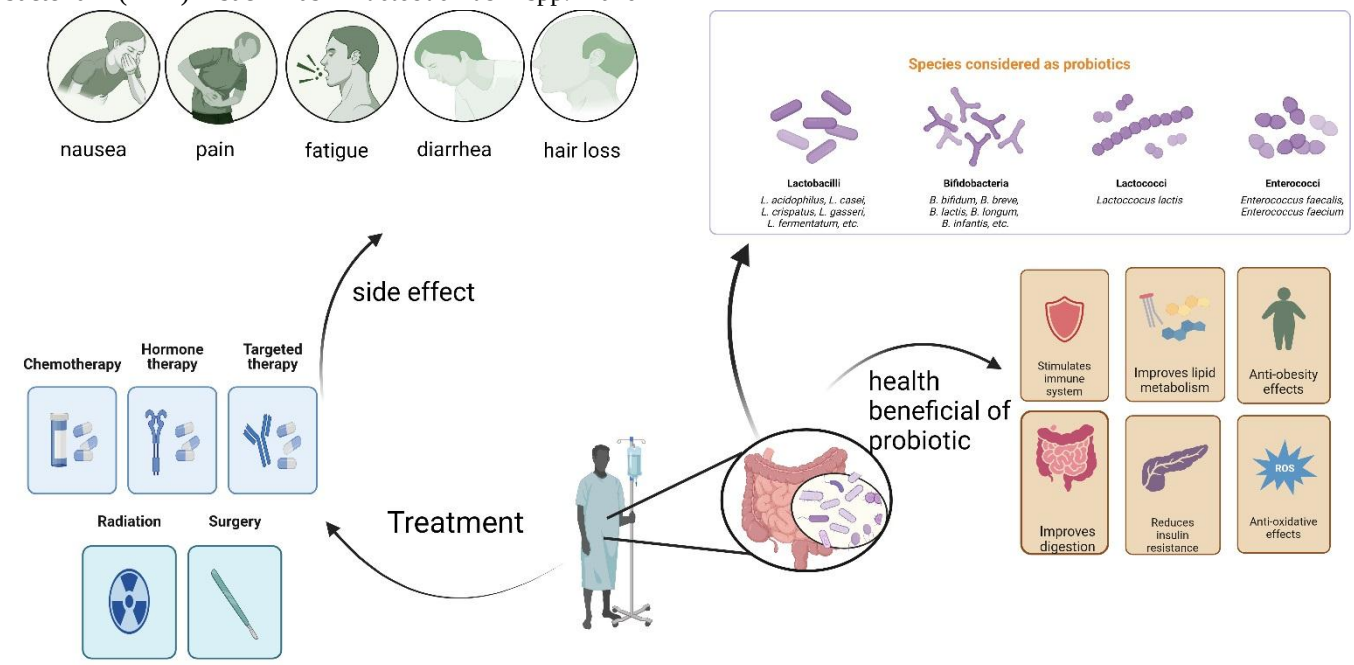

Figure 1. Illustration of the connections between cancer treatments, their side effects and potential benefits of probiotics. Cancer therapies include radiation, chemotherapy, hormone therapy, targeted therapy and surgery. The common side effects include pain, fatigue, diarrhea and hair loss. Probiotics, such as Lactobacilli and Bifidobacteria, can help digestion, boost the immune system and provide antioxidant benefits

2. Materials and Methods

This article was a commentary, synthesizing the current knowledge and perspectives on the role of probiotics in healing gastrointestinal complications associated with chemoradiotherapy. To ensure a comprehensive and evidence-based discussion, a structured literature search was carried out using PubMed, Embase and Google Scholar databases. The keywords included "gastrointestinal complications" OR "chemoradiotherapy-related diarrhea" OR "intestinal disorders" OR "gut-related side effects" AND "chemoradiation therapy" OR "radiochemotherapy" AND "probiotics" OR "gut microbiota enhancers" OR "beneficial bacteria". Studies that were unassociated to chemoradiotherapy, did not involve probiotics or lacked relevance to gastrointestinal complications were excluded. Additionally, reviews or studies with incomplete data on the use of probiotics were ignored. Titles and abstracts were screened for relevance and full texts of eligible studies were reviewed to ensure alignment with the commentary's scope.

3. Gut Microbiota: Functions & Benefits

Microbiota, particularly the gut microbiota (GM), plays a multifaceted role in maintaining human health through a complex and dynamic ecosystem of microorganisms. The GM includes bacteria, viruses and eukaryotic microorganisms that are established in the digestive tract from birth. This diverse microbiota collaborates symbiotically with the host, supporting various physiological functions and maintaining a state of homeostasis. Key bacterial groups such as *Bacteroidetes* and Firmicutes help metabolize indigestible dietary fibers, converting them into bioactive compounds such as short-chain fatty acids (SCFAs), including butyrate, acetate and propionate. The SCFAs contribute to anti-inflammatory responses and can demonstrate chemopreventive characteristics by promoting gut health and suppressing tumor development, as shown by decreased levels of butyrate-producing bacteria in patients with colorectal cancer. Additionally, gut microbiota supports essential biochemical processes such as synthesis of vitamins K and B, metabolism of bile acids and cholesterol and maintenance of the intestinal barriers. These barriers not only prevent local pathogen overgrowth, but also play a critical role in immune system regulation, preventing inflammation and autoimmune reactions. Various intrinsic and extrinsic factors-including diets, lifestyles, antibiotic uses and diseases-can effect microbiota composition. Imbalances or dysbiosis in this ecosystem can disrupt gut homeostasis, potentially leading to gastrointestinal disorders and other health complications. The manuscript highlighted that therapeutic interventions such as probiotics can help restore balances to the gut microbiota, moderating such health risks and supporting overall health [11].

4. Chemoradiotherapy Related Diarrhea

Chemotherapy and radiotherapy can disrupt the balance of beneficial bacteria in the gut, potentially causing further complications for patients undergoing cancer therapy. Several gastrointestinal tract (GIT) diseases can be prevented or treated by altering gut bacteria, according to Tuchfeo et al.Cytotoxic and radiation therapy cause significant changes in gut microbiota, increasing the prevalence of Enterobacteriaceae and Bacteroides, while decreasing levels of Fidobacterium, *Faecalibacterium prausnitzii*, and Clostridium cluster XIVa.. Intestinal homeostasis and integrity are affected by the gut microbiome [12]. Radiation therapy is one of the most effective treatments for abdominal tumors. There is a significant risk of intestinal inflammation with this treatment. Several factors contribute to decreased microbiota diversity, including *Lactobacillus* spp., *Bifidobacterium* spp., *E. coli* and *Staphylococcus* spp. Because of intestinal microbiota diversity, radiation enteritis increases, intestinal epithelial barrier function is compromised and inflammatory factors are expressed more frequently. *Escherichia coli* causes claudin-1, occludin and ZO-1 to reorganize and reverse distribution in tight junctions, forming an essential part of the intestinal epithelial barrier [13]. Kim et al. demonstrated that radiation affected the mouse gut microbiome, altering its abundance and diversity. There were significant increases in alistips and decreases in *Musispirillum* spp. [14]. Results of a clinical experiment indicated that pelvic radiation affected the gut microbiota, causing a 3% increase in *Fusobacterium* and a 10% decrease in Firmicutes [15]. In a study published in Pediatric Oncology, Nourhan Sahly et al. assessed ten fecal samples from three pediatric patients with rhabdomyosarcoma surrounding the pelvis. Using this approach, they detected a correlation between the treatment response and the bacterial composition, finding that responders included a lower microbial diversity than that the non-responders did. Additionally, nucleotide alterations and deletions were observed in 16S rRNA sequences after radiation therapy [16].

4.1. Effects of Chemotherapy on Gut Microbiota

Chemotherapy disrupts the gut microbiota significantly, leading to what is often referred to as gut dysbiosis. This imbalance results in a decrease of beneficial bacterial species such as *Bifidobacterium* and increases population of pathogenic bacteria such as those within the Proteobacteria phylum. Decreases in beneficial bacteria and shifts towards pathogenic dominance are associated with a heightened risk of gastrointestinal side effects such as chemotherapy-induced diarrhea (CID). CID, in addition to causing discomfort, can lead to severe dehydration, metabolic acidosis and malnutrition, which collectively damage the patient's overall health and may delay or complicate treatment. Decreases of microbiota diversity, particularly loss of butyrate-producing bacteria, contribute to an inflammatory environment in the gut. Butyrate is a SCFA essential for maintaining intestinal barrier integrity and decreasing inflammation. Its decrease during chemotherapy leads to increased gut permeability and inflammation, further aggravating dysbiosis. Although antidiarrheal medications such as loperamide are typically used to manage CID, they can exacerbate dysbiosis by slowing gut motility, which promotes overgrowth of pathogens. An alternative approach discussed in this case report involved us e of prebiotics and probiotics to

maintain microbial balance, enhance butyrate production and treating CID without relying on traditional medications that could worsen microbiota imbalance [17].

5. History of Probiotics and Probiotics in Human Medicine

Probiotic means "for life." It is a combination of the Latin “pro” and Greek “bios” terms [18]. Viable microbial species or probiotics are consumed to change the gastrointestinal flora in a way that improves health. There are various bacterial and fungal species in probiotic products on the market, which can be consumed in various ways. When humans realized that consuming fermented foods included health benefits millennia ago, they started use of these helpful microbes. Nowadays, foods that contain probiotics are direct descendants of those ancient fermented foods. Myths and historical evidence on the use of yogurt and fermented milk are available, which have been a part of human history [19].

Henry Tissier identified *Bifidobacteria* in 1899 from the feces of breastfed infants. Regarding that these bacteria constituted a significant portion of the intestinal flora and played a critical role in human health, he later suggested feeding them to children with diarrhea [20]. The word “probiotika” was coined in 1954 by Vergin to refer to "active substances that are essential for the healthy development of life". In a 1962 Science article, Lily and Stillwell expanded definition of probiotics to include "anaerobic bacteria that can produce lactic acid and promote the growth of other organisms [14]. Parker suggested that the term "probiotic" should refer to compounds other than microorganisms that supported the microbial balance in the digestive tract [21].

Fuller introduced the term "probiotic" as now used. He replaced the term "other substances" with a description of probiotics as "live microorganisms that beneficially affect the host animal by enhancing its flora" [22]. In 2001, Food and Agriculture Organization/World Health Organization (FAO/WHO) described probiotics as “live microorganisms that, when given in sufficient quantities, provide a health advantage to the host. In 2002, FAO/WHO created standards for assessing probiotic content in various food items. Prebiotics are non-digestible dietary substances that selectively stimulate activity or proliferation of beneficial bacteria, which is advantageous to the host [23].

Probiotics produce a variety of beneficial compounds such as vitamins, peptides, SCFAs, amino acids, enzymes and exopolysaccharides (EPSs), which benefit the host's health [8, 24]. To effectively address vitamin deficiencies and help treatment of IBD and cancers, probiotic bacteria can create K-group vitamins (K_1 and K_2) and B vitamins [B_6, B_{12}, folate and thiamine] [8, 25]. Probiotics primary metabolic products are SCFAs, primarily lactate, acetate and butyrate. Zhang et al. detected that through epigenetic regulation, indole-3-lactic acid produced from *L. plantarum* increased the antitumor immunity of $CD8^+$ T cells, thus decreasing development of colorectal tumors [26].

Saturated fatty acids (SCFAs) are essential for several physiological processes, including energy expenditure, immune system modulation and mucosal barrier maintenance. Probiotics that produce SCFAs may be administrated as an adjuvant treatment for diseases such as cancers, diabetes, obesity, Alzheimer's disease and tumors [8,27,28]. To combat infections and enhance host immuneity, probiotics release specific peptides and proteins. For treating inflammatory bowel disease (IBD), Zhou et al. recently modified *E. coli* Nissle 1917 (ECN) to produce antioxidant enzymes catalase and superoxide dismutase (SOD) [29]. Probiotic-produced EPSs have been linked to anti-inflammatory and anticancer effects in melanoma mice [8, 30]. Eventually, Piewngam et al. detected that fengycin peptide released by *Bacillus subtilis* competitively blocked the AgrC receptor in *S. aureus* quorum-sensing system, preventing the bacteria from proliferating [8, 31].

More than 1014 bacteria from over 1000 species can be detected in GIT, which is essential to health. Many diseases such as obesity, cancer, inflammatory disorders, mental illness and neurological problems, have been linked to changes in the microbial makeup of the GIT [8, 32, 33]. Through a variety of methods, probiotics help control the gut flora. Probiotics species of *Lactobacillus*, *Bacillus* and *Saccharomyces* have demonstrated the ability to lower the Firmicutes-to-Bacteroidetes ratio, indicating therapeutic possibilities in the treatment of IBD [8, 33].

Non-bacterial probiotics, especially yeasts, play a leading role in gut health by modulating the microbiome and supporting digestive functions. The *S. boulardii* has been observed to prevent antibiotic-associated diarrhea and restore balance after dysbiosis, demonstrating resistance to stomach acidity and bile. For example, in a clinical trial with HIV-positive patients, *S. boulardii* significantly decreased systemic inflammation and bacterial translocation, highlighting its role in maintaining gut integrity [34]. Additionally, it lessened microbiota changes due to antibiotics, thereby decreasing adverse effects such as diarrhea [35].

Unlike bacterial probiotics, *S. boulardii* offers unique benefits through intrinsic antibiotic resistance and production of beneficial metabolites that enhance gut health. It has shown effectiveness against *C. difficile* infections and IBD, maintaining functionality in harsh gastrointestinal conditions [36]. These attributes make *S. boulardii* critical for therapeutic strategies aimed at rebalancing gut flora and managing associated conditions.

5.1. Potential effects of probiotics on improving Chemoradiotherapy-related Diarrhea

In several studies, probiotics have been shown to decrease diarrhea associated with chemotherapy (Table 1). Osterlund et al. investigated the effect of *Lactobacillus* spp. and fiber supplements on treatment tolerance for two 5-FU-based regimens. In general, 150 patients with colorectal cancer were randomly assigned to receive either a monthly 5-FU and leucovorin bolus injection or a bimonthly 5-FU bolus injection and continuous infusion as postoperative adjuvant therapy for their disease. During chemotherapy, participants were randomly assigned to receive *L. rhamnosus* GG supplements and fiber supplements. Patients receiving *Lactobacillus* spp. included fewer cases of Grade 3 or 4 diarrhea, experienced less abdominal discomfort, needed less hospitalization and

included fewer chemotherapy dose decreases due to bowel damages. The *Lactobacillus* strain did not seem toxic. Tolerance of chemotherapy was unaffected by guar gum supplementation. There were fewer Grade 3 or 4 side effects (45 against 89%) and less diarrhea with the streamlined de Gramont regimen, compared to Mayo regimen. It has been reported that *Lactobacillus* GG supplementation may minimize occurrence of severe diarrhea associated with 5-FU-based chemotherapy [37].

A study by Linn YH et al. assessed the effect of a probiotic, including a combination of *L. acidophilus* LA-5 with *Bifidobacterium* subsp. In cervical cancer patients, *B. animalis* subsp. *Lactis* BB-12 is used to prevent acute respiratory infection (ARI). This was a double-blind study; in which, randomized patients received external beam pelvic radiation with or without concurrent chemotherapy into probiotic or placebo groups. There was a similar schedule for administrating placebo capsules containing starch on the same day as the probiotic group, which received capsules containing 1.75 billion lyophilized live bacteria. To begin treatment, one capsule was prescribed three times a day until the radiation therapy completed. All patients received typical dietary guidelines. A daily assessment was carried out through the radiotherapy treatment and a weekly follow-up was carried out after the treatment for 3 w. A total of 54 patients were analyzed. Compared to the placebo group, the probiotic group experienced a lower incidence of diarrhea (53.8) and (82.1%, $p < 0.05$). The probiotic group experienced a significant decrease in mild-to-moderate and severe diarrhea ($p < 0.05$). Compared to the placebo group, probiotic group used significantly less loperamide as an anti-diarrheal drug ($p < 0.01$). It was detected that Grade 2 abdominal and stomach pain episodes significantly varied ($p < 0.001$). Therefore, probiotic supplementation is a simple efficient strategy to decrease frequency and occurrence of RID in individuals with cervical cancer [38]. According to Demers et al., randomized double-blinded controlled trials were carried out to assess Bifilact® effects on treatment-induced diarrhea following pelvic radiation therapy. Two hundred forty-six patients with pelvic cancer were randomized between 2006 and 2010, receiving a placebo or one of the two regimens of Bifilact® probiotics (*L. acidophilus* LAC-361 or *B. longum* BB-536). Patients reported digestive symptoms every day and met with a dietician and radiation oncologist every week. A standard dose (1.3 billion CFU twice daily) and a high dose (10 billion CFU three times daily) were used. Generally, 229 patients were assessed. Regarding overall Grades 2–4 diarrhea, groups included no discernible differences ($p = 0.13$). With a hazard ratio of 0.69 ($p = 0.04$) at 60 d, the standard dose group included a further significant percentage of patients without moderate/severe diarrhea (35%), compared to the placebo group (17%). The standard dose group included a higher percentage of patients (97%) without very severe diarrhea in patients who included surgery before radiotherapy, compared to the placebo group (74%) ($p = 0.03$). They discovered that after the conclusion of therapy, individuals with pelvic cancer might experience less radiation-induced grade 2-3-4 diarrhea while taking a standard dose of Bifilact®. A standard dose of probiotics may lessen radiation-induced Grade 4 diarrhea in patients operated on before RT. Nutritional therapies provided by a certified dietician seemed to lessen general digestive problems [39].

Holma et al. assessed the relationship between the colonic methane produced by methanogenic archaea and pH levels, as well as how these factors correlated with gastrointestinal symptoms in patients receiving chemotherapy for colorectal cancer. During and after the 24-w treatment with 5-fluorouracil, 143 patients who did surgery for colorectal cancer were assessed for methanogenesis and pH levels in their colons. This study was carried out as a part of a broader intervention study investigating the effect of *Lactobacillus* spp. on gastrointestinal toxicity linked to chemotherapy. They demonstrated that the presence or absence of diarrhea or constipation in patients receiving 5-fluorouracil medication depended on their methane producer status. This emphasized how critical the gut flora was for developing intestinal toxicity when receiving 5-fluorouracil [40].

In the study, Chitapanarux I et al. assessed possibility of decreasing radiation-induced diarrhea using probiotics such as *L. acidophilus* and *B. bifidum*. In this double-blind trial, patients receiving weekly cisplatin and pelvic radiation were randomized to receive either a study medication or a placebo. Weekly grades for diarrhea were assigned using the common toxicity criteria (CTC) approach. Furthermore, white blood cell (WBC) and red blood cell (RBC) counts were assessed in feces samples. The primary objective was to decrease diarrhea based on CTC Grade 2 or higher and antidiarrhea medication use. Diarrhea Grades 2–3 were reported by 45% of the patients in the placebo group and by 9% of patients receiving the study drug. In the placebo group, anti-diarrheal medication use significantly decreased ($p = 0.03$). A significant improvement of stool consistency was reported in the study drug group ($p < 0.001$). Live *L. acidophilus* and *B. bifidum* decreased incidence of radiation-induced diarrhea and requirement for anti-diarrheal medicine and included significant advantages on stool consistency [41].

In a double-blind placebo-controlled trial, Delia et al. randomized 490 patients, who received adjuvant postoperative radiation therapy after surgery for sigmoid, rectal or cervical cancer to either high-potency probiotic preparation VSL#3 (one sachet per day) or placebo starting the day of radiation therapy. In this study, the efficacy endpoints included radiation-induced diarrhea frequency and severity, bowel movements per day and time from the study beginning to use of loperamide as an emergency treatment. Results showed that more placebo patients than VSL#3 patients experienced radiation-induced diarrhea (124/239, 51.8% and 77/243, 31.6%; $p < 0.01$) as more placebo patients suffered Grade-3 or Grade-4 diarrhea. Therefore, probiotics that produce lactic acid are safe and effective for decreasing radiation-induced diarrhea [42].

Assessment of *L. rhamnosus* efficacy and tolerability (Antibiophilus®) in treating mild to moderate diarrhea induced by radiotherapy was carried out. Urbancsek et al. studied two radiotherapy units in Hungary in a double-blind trial with 206 patients. Comparing Antibiophilus® and placebo, Antibiophilus® showed superiority [$p <$

0.010] in decreasing bowel movements, a significant improvement in investigators' ratings of feces consistency ($p < 0.05$). In the second half of the study, A significant interaction between the treatment and time was reported by the patients in their self-reports ($p < 0.001$). A high benefit-to-risk ratio was observed with Antibiophilus® when used to treat radiation-induced diarrhea [43].

In a study of 24 female patients with gynecological malignancies scheduled for pelvic irradiation [5000 cGy each], live *L. acidophilus* cultures were assessed for their side effects on intestines. Two groups of patients were randomly selected. The two groups were advised to follow a low-fat calorie-decreased diet during radiotherapy. Only dietary advice was provided to participants in the control group. As a substrate, 150 ml of fermented milk containing at least 2×10^9 *L. acidophilus* were provided to the participants daily. Diarrhea associated with radiotherapy was prevented by the test product. Flatulence increased in the test group, possibly due to the ingestion of lactulose [44].

5.2. Future perspectives

Synbiotics: Combined probiotics with prebiotics, synbiotics offer added benefits in gut health. In a study on patients with hematopoietic stem cell transplantation, synbiotics decreased gastrointestinal symptoms and hospital stay without severe side effects [45].

Herbal adjuvants: Traditional herbal compounds such as *Atractylodes macrocephala* and *Panax ginseng*, known for modulating gut microbiota and decreasing inflammatory cytokines, have shown effectiveness in CID decreases in animal models [46].

Fecal microbiota transplantation: For severe CID cases, fecal microbiota transplantation (FMT) has been shown to restore gut microbiome balance disrupted by chemotherapy. In a clinical trial, FMT successfully relieved CID symptoms, suggesting that it might help patients' resistant to other treatments [47].

6. Conclusion

Results of this study demonstrate that certain probiotic strains (e.g. *L. acidophilus*, *L. casei* and *L. rhamnosus*, among others) have been effective in treating some common side effects associated with cancer treatments when prescribed individually and in combination with other strains for a minimum of 4 w. A similar beneficial variation between the various strains was seen, making them potentially helpful in treating gastrointestinal complications, inflammatory complications and performance-linked problems. Additionally, the current study sheds light on how chemotherapy and radiotherapy can alter the microbiota, which can be avoided or treated with probiotic strains despite the study's exploratory nature. Several side effects associated with chemotherapy and radiotherapy treatments are addressed, including diarrhea, vomiting, mucositis and abdominal pain. Further studies are needed to show whether certain strains of probiotics (e.g. *Lactobacillus* spp. and *Bifidobacterium* spp.) are effective in treating side effects of chemotherapy and radiotherapy.

The purpose of this review was not to provide a definitive conclusion on the topic but to provide a starting point for further studies into the use of specific probiotic strains because of their significant effects on patient s' quality of life and survival.

This study suggests that specific probiotic strains, such as *L. acidophilus*, *L. casei*, and *L. rhamnosus* may help manage common side effects of cancer treatments, including gastrointestinal and inflammatory problems . When used individually or in combination for at least 4 w, these probiotics show potentials in decreasing symptoms such as diarrhea, vomiting, mucositis, and abdominal pain. Although further studies are needed to verify the effectiveness of certain strains, these findings offer a promising foundation for investigating probiotics' roles in improving cancer patients' quality of life.

It indicates a great role played by the probiotics, specifically strains such as *L. acidophilus*, *L. rhamnosus*, and *B. bifidum*, in validation for lessening CID. Quantitative analyses in the reviewed clinical trials strongly indicate decreased incidence and severity of diarrhea from 31.6 to 89% within various patient groups. Use of probiotics greatly decreased the need of antidiarrheal medications, with $p<0.05$ showing significant improvements in stool condition with $p < 0.001$.

These findings indicate that probiotics efficiently modulate gut microbiota diversity, improve intestinal barrier integrity and decrease inflammation, hence yielding better gastrointestinal outcomes for cancer patients. However, variability in the strains of probiotics, doses and treatment time in various studies carried out calls for standardized protocols in future studies. This evidence justifies inclusion of probiotics as an adjunctive therapeutic strategy to improve the quality of life and compliance to treatment in cancer patients receiving chemoradiotherapy.

Maintaining food safety is a critical aspect of supporting a healthy microbiome, particularly for patients receiving cancer treatments such as chemoradiotherapy. These treatments often compromise gut health, making patients further vulnerable to additional stresses caused by foodborne contaminants. Appropriate food safety practices can play a critical role in minimizing this risk and promoting gastrointestinal health.

Practical measures such as ensuring appropriate food handling, safe storage and hygienic preparation methods are essential in reducing the likelihood of decreasing harmful pathogens and toxins. For immunocompromised patients, consuming food that are free from contaminants can significantly decrease the burden on the currently stressed gastrointestinal system.

When stringent food safety measures are combined with targeted probiotic supplementation, these act synergistically to create an optimal environment for gut health. Probiotics help restore microbiome balance, while safe food practices prevent further disruptions. These strategies may improve treatment tolerance, enhance immune function and contribute to better patient outcomes and quality of life during cancer therapy.

Table 1. Summary of pre-clinical and clinical studies used probiotics to improve chemoradiotherapy-related diarrhea

Reference	Patients	Probiotic	Dosage & Duration	Outcomes
Linn et al. (2019)	54 cervical cancer patients	*L. acidophilus* LA-5 + *B. animalis* subsp. *lactis* BB-12	1.75×10^9 CFU/day for 3 weeks	Significant reduction in incidence, severity, abdominal pain and antidiarrheal drug use.
Demers et al. (2014)	246 pelvic cancer patients	*L. acidophilus* LAC-361 + *B. longum* BB-536	10^{10} CFU/day for 15 weeks	Reduced RID and improved overall digestive symptoms.
Holma et al. (2013)	143 colorectal cancer patients	*L. rhamnosus* GG ATCC 53103	10^9 CFU/day for 24 weeks	Reduced chemotherapy-induced diarrhea, no significant effect on methane production.
Chitapanarux et al. (2010)	63 cervical cancer patients	*L. acidophilus* + *B. bifidum*	2×10^9 CFU/day for 6 weeks	Reduced RID, less use of antidiarrheal medications, better stool consistency.
Österlund et al. (2007)	150 colorectal cancer patients	*L. rhamnosus* GG ATCC 53103	$1–2 \times 10^{10}$ CFU/day for 24 weeks	Significantly reduced severe diarrhea associated with 5-fluorouracil chemotherapy.
Delia et al. (2007)	490 cancer patients (sigmoid, rectal, cervical)	Multi-strain probiotic (e.g., *L. casei*, *L. Plantarum*)	4.5×10^{11} CFU/day for 4 weeks	Safe and effective in reducing RID, even with inflammation.
Urbancsek et al. (2001)	205 cancer patients	*L. casei* var. *rhamnosus*	1.5×10^9 CFU/day for 1 week	Positive benefit/risk ratio for RID.
Salminen et al. (1988)	24 patients with cervix/uterus carcinoma	*L. acidophilus* NCDO1748	2×10^9 CFU/day for 6 weeks	Prevented RID development but increased flatulence.
Zaharuddin et al. (2019)	90 patients with colorectal cancer	*L. plantarum* + *B. breve*	10^9 CFU/day for 8 weeks	Significant reduction in severity and frequency of diarrhea during chemotherapy.
Huang et al. (2021)	112 patients undergoing pelvic radiotherapy	*B. longum*	1×10^{10} CFU/day for 4 weeks	Reduced incidence of grade 3 diarrhea, improved gut microbiota diversity.
Wang et al. (2020)	130 cervical cancer patients	*L. rhamnosus* + *S. boulardii*	1.5×10^9 CFU/day for 6 weeks	Lower rates of severe diarrhea, reduced need for antidiarrheal medications.

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8. Conflict of Interest

The authors declare no conflict of interest.

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پروبیوتیک ها، درمان کمکی برای کاهش عوارض گوارشی ناشی از شیمی درمانی

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چکیده

سابقه و هدف: درمان‌های سرطان، شامل شیمی‌درمانی و رادیوتراپی، می‌توانند باعث اسهال شوند که بر کیفیت زندگی و تمایل بیماران به ادامه برنامه‌های درمانی تأثیر منفی می‌گذارد. در سال‌های اخیر، شواهد نشان داده‌اند که میکروبیوتای روده به ایجاد این اثرات نامطلوب و همچنین کاهش شدت آنها کمک می‌کند. نشان داده شده است که زیست‌یارها[1] علائم گوارشی ناشی از درمان را کاهش می‌دهند. زیست‌یارها به‌عنوان میکروارگانیسم های زنده‌ای تعریف می‌شوند که مزایای سلامتی را برای میزبان فراهم می‌کنند.

یافته‌ها و نتیجه‌گیری: این بررسی مروری اثربخشی سویه‌های گوناگون زیست‌یار شامل *لاکتوباسیلوس* و *بیفیدوباکتریوم* را در کاهش اسهال ناشی از شیمی درمانی و رادیوتراپی ارزیابی کرد. کارآزمایی‌های بالینی نشان داده‌اند که فرمول‌های خاصی از زیست‌یارها می‌توانند وقوع و شدت اسهال را کاهش دهند، نیاز به داروهای ضد اسهال را کاهش دهند و تحمل کلی درمان را بهبود بخشند. علی‌رغم این یافته‌های امیدوارکننده، تحقیقات بیشتری برای بهینه‌سازی استفاده از زیست‌یار در درمان سرطان و درک کامل این که چگونه زیست‌یارها سلامت روده را در طول شیمی‌درمانی تعدیل می‌کنند، مورد نیاز است. بنابراین، زیست‌یارها می‌توانند به‌عنوان یک استراتژی درمانی کمکی در شیمی درمانی برای بهبود کیفیت زندگی و نتایج بالینی بیمار استفاده شوند.

تعارض منافع: نویسندگان اعلام می‌کنند که هیچ نوع تعارض منافعی مرتبط با انتشار این مقاله ندارند.

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