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Review Article

Role of Probiotics and Synbiotics in Preventing Chemoradiotherapy-Associated Toxicity in Colorectal Cancer Patients: A Systematic Review

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Abstract

Background: Previous studies found that the use of probiotics may have a protective effect on chemotherapy-associated toxicity in cancer patients. A systematic review was conducted to evaluate the effect of probiotics and synbiotics on chemoradiotherapy-associated toxicity in colorectal cancer (CRC) patients.

Methods: A systematic review of randomized controlled trials (RCTs) was performed to assess the effect of probiotics and synbiotics in CRC patients undergoing chemotherapy. All RCTs in English, up to January 2021, were included through a literature search in Scopus, Google Scholar, PubMed (PMC Central, MEDLINE), ClinicalTrials.gov, and ProQuest databases. The impact of probiotics and synbiotics on the side effects associated with chemotherapy, radiotherapy, and chemoradiotherapy in CRC patients was evaluated. The quality of the RTCs was independently assessed by two reviewers. EndNote X8 software was used to manage the search results.

Results: Of the 904 identified articles, three studies finally met the inclusion criteria and were systematically reviewed. Two studies reported that patients who received probiotics had less abdominal discomfort and required less bowel toxicity-related hospital care. Although probiotic supplementation lowered radiation-associated diarrhea, it had no significant effect when anti-diarrheal drugs were used. Another study reported that synbiotic supplementation improved quality of life and marginally reduced diarrhea and serum levels of high-sensitivity C-reactive protein (hs-CRP) and matrix metalloproteinase (MMP-2 and MMP-9).

Conclusion: Probiotics and synbiotics do not have a significant effect on reducing chemotherapy-associated toxicity and diarrhea in CRC patients. These findings should be substantiated by further RCTs with rigorous placebo-controlled studies.

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Keywords ● Probiotics ● Synbiotic ● Colorectal neoplasms ● Systematic review

What's Known

- Findings on the effect of probiotics and synbiotics in reducing chemoradiotherapy-associated toxicity in cancer patients are contradictory.
- The majority of previous systematic reviews considered patients with various types of cancer without a specific focus on colorectal cancer (CRC).

What's New

- Probiotic or synbiotic supplementation does not significantly reduce chemoradiotherapy-associated toxicity in CRC patients.
- Further randomized controlled trials with rigorous placebo-controlled studies are required to substantiate the findings.

Introduction

Colorectal cancer (CRC) is highly prevalent and one of the leading causes of cancer death worldwide.[1] Treatment modalities for CRC include chemotherapy, radiotherapy

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(with or without chemotherapy), and surgery. Despite major efforts to develop innovative approaches for CRC treatment, there is still room for improvements in terms of success rate, long-term stability, and side effects of the proposed treatment. Chemotherapy has been widely accepted as the main CRC treatment modality. However, relief from the associated gastrointestinal side effects to reduce pain and address other life-threatening complications is a necessity. Intestinal mucosal inflammation caused by chemotherapy and radiation therapies were associated with intestinal microbiota.[2] Microbiota modulates the autophagy and metabolism of the host response to such treatments.[3-6] Furthermore, studies showed that chemotherapy and radiation therapies affect the composition of intestinal flora, which is a key factor in the treatment of side effects.[7, 8] It was reported that probiotics and synbiotics might have protective effects on mucosal inflammation and diarrhea.[9-11] However, a previous study suggested that probiotics have no significant effect on chemotherapy-associated diarrhea or toxicity.[12]

Overall, improving the efficacy of chemotherapy in CRC patients remains a challenging task. Recently, researchers have focused on the modulation of gut microbiota, since its composition positively affects the efficiency, toxicity, breakdown, and absorption of chemotherapy, and radiation therapies.[13] Liu and colleagues demonstrated that probiotic supplementation reduced radiation-associated diarrhea, but had no significant effect when anti-diarrheal drugs were used.[14] In a meta-analysis study, Devaraj and colleagues found that probiotic supplementation did not reduce the incidence of chemoradiotherapy-related diarrhea in cancer patients, but it reduced its severity in patients undergoing radiation therapy for certain types of cancer.[15]

Various systematic reviews were conducted to establish the beneficial effects of probiotic or synbiotic dietary supplementation in cancer patients. We found that most of these studies did not primarily focus on CRC patients.[16] However, those that addressed the effect of probiotics on CRC patients only dealt with a specific aspect of CRC treatment, such as postoperative complications,[17] prevention of surgical site infections,[18] and chemotherapy-associated diarrhea.[19] To overcome the limitation of previous studies, the present systematic review aimed to include a comprehensive set of outcomes to gain a better insight into the effect of probiotics and synbiotics in CRC patients undergoing chemotherapy.

Materials and Methods

Search Strategy

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020),[20] a systematic review of randomized controlled trials (RCTs) was performed to assess the effect of probiotics and synbiotics in CRC patients undergoing chemotherapy. All RCTs in English, up to January 2021, were included through a literature search in databases such as Scopus, Google Scholar, PubMed (PMC Central, MEDLINE), ClinicalTrials.gov, and ProQuest. The search strategy included a combination of MeSH (medical subject headings) terms and text words using boolean operators: ("probiotic" OR "lactobacillus" OR "bifid bacterium" OR "lactic acid bacteria" OR "synbiotic") AND ("chemotherapy" OR "chemoradiotherapy" OR "pelvic radiotherapy") AND ("colorectal cancer"). The search was independently performed by two of the authors (E.F and F.F.R). Reference manager software EndNote X8, version 18.0.0.10063 (Clarivate Analytics, London, UK) was used to manage the search results.

Inclusion and Exclusion Criteria

The PICO (population, intervention, comparison, outcomes) elements were colorectal cancer, probiotic, synbiotic, placebo, and chemotherapy-associated toxicity, respectively. The inclusion criteria were RCTs written in English on the effect of probiotics and synbiotics on the side effects associated with chemotherapy, radiotherapy, and chemoradiotherapy in the treatment of CRC patients. The exclusion criteria were articles written in other languages, review articles, books, case reports, congress letters, and personal opinions.

Data Extraction

The abstract and reference list of all articles from the initial search were independently reviewed for eligibility criteria by two of the authors (E.F and F.F.R). Disagreements were resolved by the first author (R.M). The information extracted from the eligible articles was the year of publication, study design, characteristics of participants (sex, age, number, and comparison group), intervention (supplement type, intervention dose, and duration), primary outcome, and trial outcomes.

Risk of Bias

The assessment was independently performed by two authors (E.F and F.F.R) using Cochrane Collaboration's tool for assessing the

risk of bias in RCTs,[21] using parameters such as participant, personnel, and assessor blinding, allocation sequence concealment, selective reporting bias, and incomplete outcome data.

Results

Study Design and Participants

A total of 904 articles were identified through the initial search, of which 24 articles were removed due to duplication. Of the remaining 880 articles, 864 articles did not meet the inclusion criteria and were disregarded. The full text of these last 16 articles was assessed for eligibility of which 13 articles were found to contain insufficient data. Finally, three articles with a total sample size of 234 patients were included in the qualitative analysis phase. The PRISMA flow diagram of the study selection process is presented in figure 1. A descriptive summary of the included studies and the risk of bias assessment are presented in tables 1 and 2, respectively.

Description of Included Studies

The included studies were conducted in Iran,[22] Finland,[9] and Slovakia,[12] with a sample size ranging from 38 to 150 (table 1). Two studies evaluated the effect of probiotics on the side effects of chemotherapy in CRC patients aged 20-85 years. The third study examined the effect of synbiotics on chemoradiotherapy-associated toxicity in CRC patients. The protocol for probiotic formulations in the included studies varied in terms of the type and treatment duration. Furthermore, the participants had CRC in stages II, III, Dukes B, Dukes C, or life expectancy less than three months. The intervention duration was 6, 12, or 24 weeks. The study assessments were made in accordance with the Common Toxicity Criteria of the National Cancer Institute of Canada Scale version 2,9 Common Terminology Criteria for Adverse Events version 4.1 (CTCAE),[12] and the 30-item quality of life questionnaire version 3.0 of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30).[22]

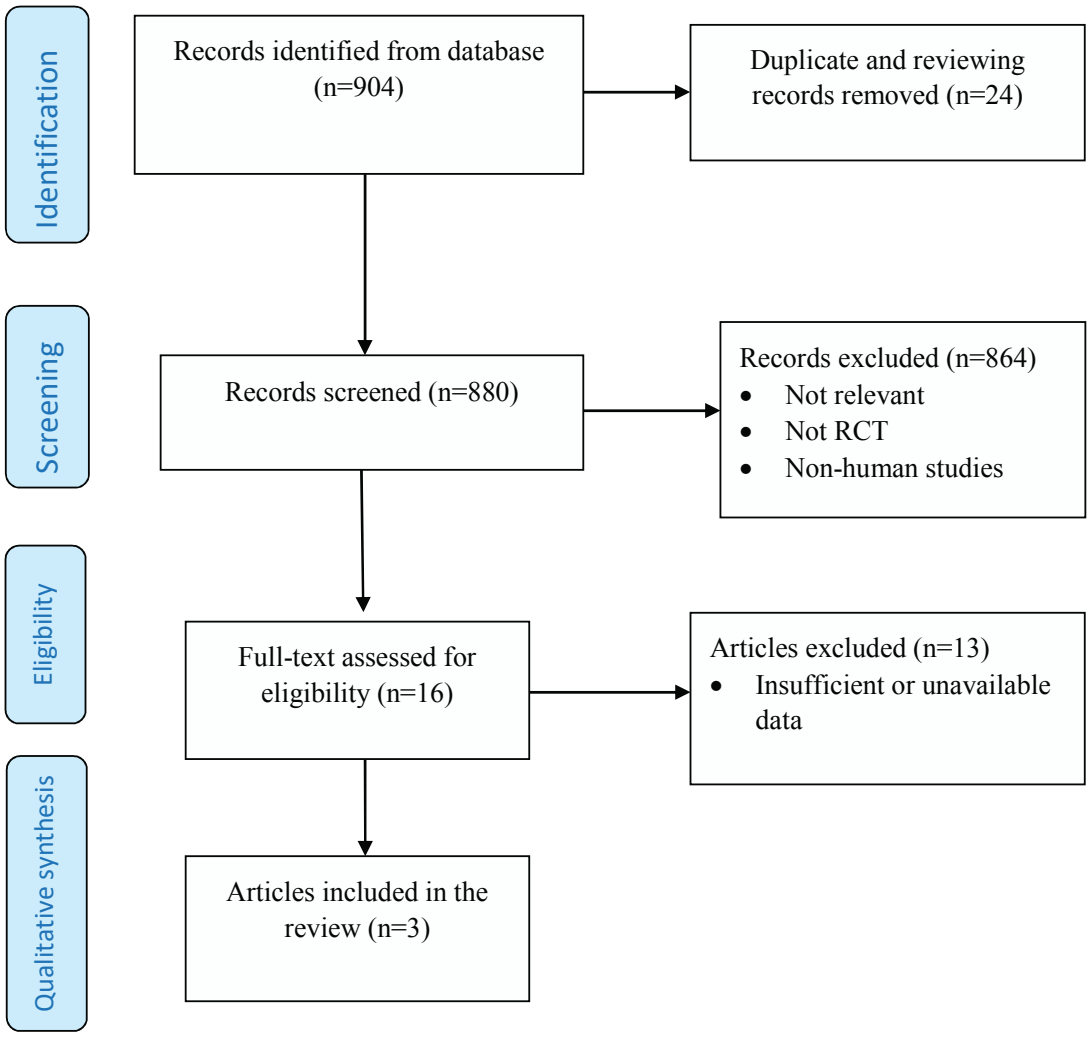

Figure 1: PRISMA flow diagram illustrates the search strategy and selection process according to the inclusion and exclusion criteria.

Table 1: A descriptive summary of the included studies. In all studies, patients were randomized 1:1 to intervention or placebo and no adverse events were reported

Study	Type of RCT	Sample size	Age (years)	Intervention	Outcome	Results
Farshi Radvar et al.[22]	Parallel group, randomized, double-blind, placebo-controlled study	Synbiotic group (n=19), placebo group (n=19)	Synbiotic group: 57.58±12.78 Placebo group: 62.89±13.93	*Lactobacillus casei* PXN 37, *Lactobacillus rhamnosus* PXN 54, *Streptococcus thermophilus* PXN 66, *Bifidobacterium breve* PXN 25, *Lactobacillus acidophilus* PXN 35, *Bifidobacterium longum* PXN 30, *Lactobacillus bulgaricus* PXN 39, Fructooligosaccharide (FOS), Magnesium stearate (source: mineral and vegetable), Vegetable capsule (hydroxypropyl methyl cellulose) Dose of 1×10^8 CFU/gr twice daily for 6 weeks	Anthropometric measures, dietary intake, quality of life, biochemical factors (MMP-2, MMP-9, hs-CRP)	Synbiotic had a significant effect on carbohydrate and protein intake. Improvement in the quality of life scale, hs-CRP, MMP-2, and MMP-9 levels in the synbiotic group compared to the placebo group (not significant).
Mego et al.[12]	Randomized, double-blind, placebo-controlled pilot study	Probiotic group (n=23), placebo group (n=23)	Probiotic group: Median 62 (45-75) Placebo group: Median 64 (42-81)	*Bifidobacterium breve* HA-129 (25%), *Bifidobacterium bifidum* HA-132 HA (20%), *Bifidobacterium longum* HA-135 (14.5%), *Lactobacillus rhamnosus* HA-111 (8%), *Lactobacillus acidophilus* HA-122 (8%), *Lactobacillus casei* HA-108(8%), *Lactobacillus plantarum* HA-119 (8%), *Streptococcus thermopilus* HA-110 (6%), *Lactobacillus brevis* HA-112 (2%), *Bifidobacterium infantis* HA-116 (0.5%) Daily dose of 10×10^9 CFU for 12 weeks	Incidence of diarrhea, usage of anti-diarrheal drugs	Probiotics compared to placebo showed a reduction in the incidence of severe diarrhea of grade 3 or 4 and enterocolitis (not significant). Patients on probiotics used fewer anti-diarrheal drugs compared to placebo (not significant).
Osterlund et al.[9]	Open-label, prospective, randomized, phase III, single institution, 2×3 factorial design study	Probiotic group (n=98), placebo group (n=52)	Probiotic group: Median 61 (35-74) Placebo group: Median 57 (31-75)	*Lactobacillus rhamnosus* GG twice daily at a dose of $1\text{-}2\times10^{10}$ and 11 g of guar gum per day, both for 24 weeks	Adverse events were recorded during 5-FU-based chemotherapy. Incidence of diarrhea, neutropenia, neutropenic infection, hand-foot syndrome	Probiotics had no significant effect on diarrhea. No significant changes in stomatitis, neutropenia, neutropenic infection, and Hand-foot syndrome.

Table 2: Risk of bias in randomized controlled trial according to the Cochrane Collaboration's tool

Bias risk	Osterlund et al.[9]	Mego et al.[12]	Farshi Radvar et al.[22]
Random sequence generation (selection bias)	Y	Y	Y
Allocation concealment (selection bias)	Y	Y	Y
Blinding of participants and personnel (performance bias)	N	Y	Y
Blinding of outcome assessment (detection bias)	N	Y	Y
Incomplete outcome data (attrition bias)	Y	Y	N
Selective reporting (reporting bias)	?	Y	Y

Y: Yes; N: No

Two studies used diarrhea grades 0-4 and 1-4, expressing the results as percentages (frequencies) or means±SD (standard deviation). One study used toxicity grades 0-4.

Interventions

Interventions included several types of probiotics and synbiotics such as *Saccharomyces*, *Propionibacterium*, *Bifidobacterium*, and

Lactobacillus rhamnosus GG. These were administered either individually or combined with other probiotics or synbiotics (e.g., Fructooligosaccharides). Placebo (standard treatment) was administered to the control group. The dosage of probiotics and synbiotics varied, ranging from two to three doses per day. The outcome measures included neutropenia, stomatitis, gastrointestinal toxicity, and diarrhea.

Risk of Bias

The reported risk of bias (e.g., incomplete outcome data and allocation sequence concealment) was low in all studies.[9, 12, 22] However, one study reported a high risk of bias due to the absence of blinding of the participants, personnel, and outcome assessors.[9]

Effect of Probiotics on Chemotherapy Toxicity

All studies reported no significant effect of probiotic or synbiotic therapy in reducing chemotherapy/chemoradiotherapy-associated toxicity. Osterlund and colleagues reported no significant effect of *Lactobacillus rhamnosus* on the overall treatment toxicity, neutropenia, stomatitis, hand-foot syndrome, and neutropenia infection. In their study, compared to the probiotic group, a larger number of participants in the placebo group required hospital care. Moreover, toxicity was significantly lower in the probiotic group than the placebo group. Additionally, they reported that *Lactobacillus rhamnosus* significantly reduced the incidence of severe diarrhea (grades 3 and 4).[9]

Mego and colleagues reported that probiotics significantly reduced the incidence of severe diarrhea (grades 3 and 4), but had a marginal effect on reducing the incidence of overall diarrhea, bloating, and enterocolitis. Furthermore, patients in the probiotic group used fewer anti-diarrheal drugs than those in the placebo group. It is worth noting that the study was prematurely terminated due to slow accrual, when only 46 of the 220 planned patients were randomized.[12]

Effect of Synbiotics on Chemoradiotherapy Toxicity

Only one study assessed the effect of synbiotic supplementation on CRC patients undergoing chemoradiotherapy.[22] Farshi Radvar and colleagues reported that the mean symptom scale score for diarrhea slightly decreased in the synbiotic group, whereas it significantly increased in the placebo group.[22]

Side Effects

Although all included studies reported various side effects caused by probiotic/synbiotic supplementation, none were considered adverse events.

Discussion

The present systematic review assessed the effect of probiotics and synbiotics on chemoradiotherapy-associated toxicity in patients with CRC. Chemoradiotherapy toxicity is common in CRC patients.[23] The findings of the present study indicate that probiotic/synbiotic supplementation may marginally reduce chemotherapy-associated toxicity in CRC patients. Depending on the severity of the side effects, a reduction in the treatment dose or even termination of chemoradiotherapy may be required, which in turn enables tumor cells to gain resistance to anti-cancer drugs. Moreover, it also affects the nutritional status and quality of life of the patients. Diarrhea is the most prevalent complication of chemoradiotherapy.[24] A previous study showed that imbalance in intestinal flora (i.e., dysbiosis) significantly contributes to the prevalence of chemotherapy-associated side effects. It is therefore recommended to use probiotic/synbiotic supplementation to correct dysbiosis in CRC patients undergoing radiotherapy, chemotherapy, or chemoradiotherapy interventions.[25]

Several studies evaluated the efficacy of probiotics and synbiotics in reducing the side effects of anti-cancer treatments. However, the reported results are contradictory due to the difference in supplementation dose, intervention duration, treatment type, and sample size. We found that probiotics did not significantly affect diarrhea in grades 3 and 4 in CRC patients undergoing chemotherapy. Similarly, Devaraj and colleagues reported that probiotics did not significantly affect the incidence of chemoradiotherapy-associated diarrhea in cancer patients compared to the placebo group.[15] Wang and colleagues also reported that probiotics did not reduce the risk of diarrhea in patients with abdominal and pelvic cancer undergoing chemotherapy.[26] In contrast, Lin and colleagues reported that probiotics significantly reduced the incidence of diarrhea in the same groups of cancer patients.[27] Nonetheless, both studies confirmed that probiotics significantly reduced the incidence of radiation-associated diarrhea.[15, 26] Moreover, Redman and colleagues demonstrated that probiotic supplementation reduced the overall rate of radiation-associated diarrhea in cancer patients.[28]

The lack of significant effects of probiotics in cancer patients undergoing chemotherapy

could be attributed to the limited number of research studies on this topic. To the best of our knowledge, our systematic review of RCTs is the first such study. Although some of the previous systematic reviews assessed the effect of probiotics in RCTs, they included all types of cancer patients undergoing radiotherapy, chemotherapy, or chemoradiotherapy. Inclusion of all types of patients and heterogeneity of RCTs could be the main reason behind the difference between our findings and those of previous systematic reviews. Moreover, the diversity index between the studies (i.e., different types of intervention, duration, dose, and strains) did not allow a one-to-one comparison between the results. The included studies reported additional results, such as the quality of life, hospital care for bowel toxicity, neutropenia, stomatitis, and the use of anti-diarrheal drugs. However, we could not assess these due to the heterogeneous data. Nonetheless, the main strength of our study is the specific focus and selection of RCTs that investigated the incidence of diarrhea in different grades.

Osterlund and colleagues found that patients who received probiotics had less abdominal discomfort and required less hospital care due to bowel toxicity.[9] However, probiotics had no significant effect on the overall chemotherapy-associated toxicity or the frequency of stomatitis/neutropenia.[12] Moreover, compared to placebo, probiotic supplementation had no effect on reducing the incidence of bloating, enterocolitis, or when anti-diarrheal drugs were used. In line with our results, Redman and colleagues also reported no significant effect of probiotics on anti-diarrheal drug use.[28] Farshi Radvar and colleagues reported that synbiotic supplementation reduced the mean symptom scale score for diarrhea in CRC patients undergoing chemoradiotherapy.[22]

The main strength of the present systematic review is a comprehensive assessment of all RCTs on the effect of probiotics and synbiotics on CRC patients undergoing radiotherapy, chemotherapy, and chemoradiotherapy. The limitation of the study is related to the high risk of bias due to different types of supplementation dose, intervention duration, probiotic strains, cancer treatment modality, and the dose/frequency of chemotherapy treatment. In addition, different scales/criteria were used to evaluate chemotherapy-associated toxicity.

Conclusion

There is limited evidence to confidently conclude a significant effect of probiotics and synbiotics on reducing chemotherapy-associated toxicity and diarrhea in CRC patients. In fact, some minor side effects were associated with probiotic and synbiotic supplementation. Nonetheless, these findings are based on a very limited number of studies. Therefore, it is strongly recommended to substantiate the findings by conducting further RCTs with rigorous placebo-controlled studies.

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Authors' Contribution

R.M, E.F, Z.N and F.F.R: conception and design; acquisition, analysis and interpretation of data for the work, drafting and revising. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424. doi: 10.3322/caac.21492. PubMed PMID: 30207593.

2 Touchefeu Y, Montassier E, Nieman K, Gastinne T, Potel G, Bruley des Varannes S, et al. Systematic review: the role of the gut microbiota in chemotherapy- or radiation-induced gastrointestinal mucositis - current evidence and potential clinical applications. Aliment Pharmacol Ther. 2014;40:409-21. doi: 10.1111/apt.12878. PubMed PMID: 25040088.

3 Yu T, Guo F, Yu Y, Sun T, Ma D, Han J, et al. Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy. Cell. 2017;170:548-63. doi: 10.1016/j.cell.2017.07.008. PubMed PMID: 28753429; PubMed Central PMCID: PMCPMC5767127.

4 Scott TA, Quintaneiro LM, Norvaisas P, Lui PP, Wilson MP, Leung KY, et al. Host-Microbe Co-metabolism Dictates Cancer Drug Efficacy in C. elegans. Cell. 2017;169:442-56

e18. doi: 10.1016/j.cell.2017.03.040. PubMed PMID: 28431245; PubMed Central PMCID: PMCPMC5406385.
5 Packey CD, Ciorba MA. Microbial influences on the small intestinal response to radiation injury. Curr Opin Gastroenterol. 2010;26:88-94. doi: 10.1097/MOG.0b013e3283361927. PubMed PMID: 20040865; PubMed Central PMCID: PMCPMC4063200.
6 Crawford PA, Gordon JI. Microbial regulation of intestinal radiosensitivity. Proc Natl Acad Sci U S A. 2005;102:13254-9. doi: 10.1073/pnas.0504830102. PubMed PMID: 16129828; PubMed Central PMCID: PMCPMC1193536.
7 Zwielehner J, Lassl C, Hippe B, Pointner A, Switzeny OJ, Remely M, et al. Changes in human fecal microbiota due to chemotherapy analyzed by TaqMan-PCR, 454 sequencing and PCR-DGGE fingerprinting. PLoS One. 2011;6:e28654. doi: 10.1371/journal.pone.0028654. PubMed PMID: 22194876; PubMed Central PMCID: PMCPMC3237468.
8 Stringer AM, Al-Dasooqi N, Bowen JM, Tan TH, Radzuan M, Logan RM, et al. Biomarkers of chemotherapy-induced diarrhoea: a clinical study of intestinal microbiome alterations, inflammation and circulating matrix metalloproteinases. Support Care Cancer. 2013;21:1843-52. doi: 10.1007/s00520-013-1741-7. PubMed PMID: 23397098.
9 Osterlund P, Ruotsalainen T, Korpela R, Saxelin M, Ollus A, Valta P, et al. Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. Br J Cancer. 2007;97:1028-34. doi: 10.1038/sj.bjc.6603990. PubMed PMID: 17895895; PubMed Central PMCID: PMCPMC2360429.
10 Delia P, Sansotta G, Donato V, Frosina P, Messina G, De Renzis C, et al. Use of probiotics for prevention of radiation-induced diarrhea. World J Gastroenterol. 2007;13:912-5. doi: 10.3748/wjg.v13.i6.912. PubMed PMID: 17352022; PubMed Central PMCID: PMCPMC4065928.
11 Timko J. Probiotics as prevention of radiation-induced diarrhoea. Journal of Radiotherapy in Practice. 2010;9:201-8. doi: 10.1017/S1460396910000087.
12 Mego M, Chovanec J, Vochyanova-Andrezalova I, Konkolovsky P, Mikulova M, Reckova M, et al. Prevention of irinotecan induced diarrhea by probiotics: A randomized double blind, placebo controlled pilot study. Complement Ther Med. 2015;23:356-62. doi: 10.1016/j.ctim.2015.03.008. PubMed PMID: 26051570.
13 Tonneau M, Elkrief A, Pasquier D, Paz Del Socorro T, Chamaillard M, Bahig H, et al. The role of the gut microbiome on radiation therapy efficacy and gastrointestinal complications: A systematic review. Radiother Oncol. 2021;156:1-9. doi: 10.1016/j.radonc.2020.10.033. PubMed PMID: 33137398.
14 Liu MM, Li ST, Shu Y, Zhan HQ. Probiotics for prevention of radiation-induced diarrhea: A meta-analysis of randomized controlled trials. PLoS One. 2017;12:e0178870. doi: 10.1371/journal.pone.0178870. PubMed PMID: 28575095; PubMed Central PMCID: PMCPMC5456391.
15 Devaraj NK, Suppiah S, Veettil SK, Ching SM, Lee KW, Menon RK, et al. The Effects of Probiotic Supplementation on the Incidence of Diarrhea in Cancer Patients Receiving Radiation Therapy: A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials. Nutrients. 2019;11. doi: 10.3390/nu11122886. PubMed PMID: 31783578; PubMed Central PMCID: PMCPMC6950027.
16 Lytvyn L, Quach K, Banfield L, Johnston BC, Mertz D. Probiotics and synbiotics for the prevention of postoperative infections following abdominal surgery: a systematic review and meta-analysis of randomized controlled trials. J Hosp Infect. 2016;92:130-9. doi: 10.1016/j.jhin.2015.08.028. PubMed PMID: 26601607.
17 Liu PC, Yan YK, Ma YJ, Wang XW, Geng J, Wang MC, et al. Probiotics Reduce Postoperative Infections in Patients Undergoing Colorectal Surgery: A Systematic Review and Meta-Analysis. Gastroenterol Res Pract. 2017;2017:6029075. doi: 10.1155/2017/6029075. PubMed PMID: 28484489; PubMed Central PMCID: PMCPMC5397731.
18 Skonieczna-Zydecka K, Kaczmarczyk M, Loniewski I, Lara LF, Koulaouzidis A, Misera A, et al. A Systematic Review, Meta-Analysis, and Meta-Regression Evaluating the Efficacy and Mechanisms of Action of Probiotics and Synbiotics in the Prevention of Surgical Site Infections and Surgery-Related Complications. J Clin Med. 2018;7. doi: 10.3390/jcm7120556. PubMed PMID: 30558358; PubMed Central PMCID: PMCPMC6307089.
19 Lu D, Yan J, Liu F, Ding P, Chen B, Lu Y, et al. Probiotics in preventing and treating chemotherapy-induced diarrhea: a meta-analysis. Asia Pac J Clin Nutr. 2019;28:701-10. doi: 10.6133/apjcn.201912_28(4).0005. PubMed PMID: 31826366.
20 Page MJ, McKenzie JE, Bossuyt PM,

Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71. PubMed PMID: 33782057; PubMed Central PMCID: PMCPMC8005924.

21 Higgins J. Cochrane handbook for systematic reviews of interventions. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration. 2011.

22 Farshi Radvar F, Mohammad-Zadeh M, Mahdavi R, Andersen V, Nasirimotlagh B, Faramarzi E, et al. Effect of synbiotic supplementation on matrix metalloproteinase enzymes, quality of life and dietary intake and weight changes in rectal cancer patients undergoing neoadjuvant chemoradiotherapy. Mediterranean Journal of Nutrition and Metabolism. 2020;13:225-35. doi: 10.3233/MNM-200413.

23 Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731-40. doi: 10.1056/NEJMoa040694. PubMed PMID: 15496622.

24 Bentzen AG, Balteskard L, Wanderas EH, Frykholm G, Wilsgaard T, Dahl O, et al. Impaired health-related quality of life after chemoradiotherapy for anal cancer: late effects in a national cohort of 128 survivors. Acta Oncol. 2013;52:736-44. doi: 10.3109/0284186X.2013.770599. PubMed PMID: 23438358.

25 Wong SH, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nat Rev Gastroenterol Hepatol. 2019;16:690-704. doi: 10.1038/s41575-019-0209-8. PubMed PMID: 31554963.

26 Wang YH, Yao N, Wei KK, Jiang L, Hanif S, Wang ZX, et al. The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: a systematic review and meta-analysis. Eur J Clin Nutr. 2016;70:1246-53. doi: 10.1038/ejcn.2016.102. PubMed PMID: 27329608.

27 Lin S, Shen Y. The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: A systematic review and meta-analysis based on 23 randomized studies. Int J Surg. 2020;84:69-77. doi: 10.1016/j.ijsu.2020.10.012. PubMed PMID: 33080416.

28 Redman MG, Ward EJ, Phillips RS. The efficacy and safety of probiotics in people with cancer: a systematic review. Ann Oncol. 2014;25:1919-29. doi: 10.1093/annonc/mdu106. PubMed PMID: 24618152.