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Evaluation of the efficacy of probiotics in the chemoradiotherapy of colorectal cancer: a meta-analysis of Randomized Controlled Trials

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Abstract

Objective We undertook this study to assess the efficacy of probiotics in managing adverse reactions during chemoradiotherapy in patients with colorectal cancer.

Method A comprehensive literature search was conducted on PubMed, ClinicalTrials.gov, Embase, Cochrane library, Web of Science, and Chinese databases until July 27, 2024. Data analysis was performed using RevMan5.3 statistical software. The risk of bias was assessed using the Cochrane collaboration tool. Relative risk (RR) was employed to incorporate statistical measures and calculate 95% confidence intervals (95%CI) for bipartite data. Standardized mean difference (SMD) was utilized to incorporate statistical measures and calculate 95% confidence intervals for continuous variables.

Results A meta-analysis of 633 patients with colorectal cancer was conducted across eight studies. In comparison to the control group, probiotics demonstrated a significant reduction in the incidence of chemoradiotherapy-induced diarrhea among colorectal cancer patients ($RR = 0.51, 95\%CI: 0.38 \sim 0.68, P < 0.001$). Additionally, probiotic usage exhibited improvements in pain index ($SMD = -2.27, 95\%CI: -4.49 \sim -0.05, P = 0.04$), dyspnea ($SMD = -0.92, 95\%CI: -1.61 \sim 0.22, P = 0.01$) and insomnia ($SMD = -2.95, 95\%CI: -5.44 \sim -0.47, P = 0.02$) compared to the control group. However, there were no significant differences between two groups in abdominal distension ($RR = 0.79, 95\%CI: 0.21 \sim 3.00, P = 0.72$), stomatitis risk ($RR = 1.23, 95\%CI: 0.48 \sim 3.21, P = 0.67$), fatigue ($SMD = -7.12, 95\%CI: -14.99 \sim 0.75, P = 0.08$) and loss of appetite ($SMD = -2.86, 95\%CI: -5.83 \sim 0.11, P = 0.06$). Furthermore, the use of probiotics did not significantly improve the quality of life (QOL) ($SMD = 8.82, 95\%CI: -1.11 \sim 18.75, P = 0.08$) of colorectal cancer patients receiving chemoradiotherapy.

Conclusions This meta-analysis suggested that probiotic consumption may ameliorate certain adverse reactions in patients with colorectal cancer receiving chemoradiotherapy.

Trial registrations Prospero registration number: PROSPERO (CRD42023465966).

Keywords Probiotics, Chemoradiotherapy, Colorectal cancer, Efficacy

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Background

The global burden of colorectal cancer is a substantial menace to life and well-being, ranking third in terms of incidence and second in terms of mortality rates worldwide. Among male malignancies, it holds the third position for both incidence and mortality rates, while among female malignancies, it ranks second for incidence and third for mortality rates [1]. Chemoradiotherapy are currently the primary treatment modalities for patients with colorectal cancer; however, the adverse effects associated with chemoradiotherapy, such as nausea, vomiting, diarrhea, and decreased appetite, often result in treatment delay and ultimately disease progression. Consequently, there is a reduction in Overall Survival (OS), Objective Response Rate (ORR), Progression-Free Survival (PFS), and quality of life (QOL) for these patients. Antidiarrheal medications, such as octreotide and loperamide, are commonly employed in the management of early adverse reactions induced by chemoradiotherapy, specifically targeting diarrhea [2]. In recent years, the research and development of novel pharmaceuticals and the formulation of treatment protocols have become increasingly crucial in mitigating the adverse reactions associated with chemoradiotherapy.

The human gut harbors over 500 distinct bacterial species with approximately 100 trillion in number. These microorganisms not only play a pivotal role in the pathogenesis, progression, and prognosis of intestinal disorders, but also actively participate in immune regulation and nutrient metabolism as an essential biological barrier within the human body [3]. The dysbiosis of intestinal microbiota is a crucial factor contributing to intestinal inflammation and tumorigenesis. Certain beneficial bacteria modulate the REDOX balance, suppress ribosome biogenesis and protein translation, thereby impeding the occurrence and progression of colorectal malignancies. Moreover, probiotics hinder intestinal malignancies by generating metabolites that facilitate apoptosis in colorectal cancer cells [4, 5]. The utilization of probiotics can modulate the biological barrier of the gut microbiota and mitigate the risk of perturbation in gut microbiota induced by treatment of underlying diseases [6]. However, certain pathogenic bacteria can facilitate the development of intestinal tumors by producing relevant toxins and disrupting the metabolism of both normal and cancerous cells in the body, thereby impeding the efficacy of anti-tumor therapies [7–9]. Additionally, probiotics also play a crucial role in the management of other malignant tumors. Preliminary studies have indicated that LC9018 derived from *Lactobacillus casei* could serve as an effective adjunct immunotherapeutic agent, and when combined with radiation therapy, it can augment the anti-tumor

efficacy in the treatment of cervical cancer [10]. The combination of chemotherapy and *Lactobacillus casei* can effectively reduce the postoperative recurrence rate of bladder cancer [11]. The regulation of plasma metabolites by probiotics prevents the development of Chemotherapy-related cognitive impairment (CRCI) in breast cancer patients [12]. Probiotic intervention can effectively decrease the occurrence of complications in patients with thyroid cancer following withdrawal of thyroid hormone [13].

The existing clinical studies have demonstrated that probiotics possess the potential to mitigate the adverse reactions induced by radiotherapy and chemotherapy, thereby enhancing the quality of life for patients undergoing treatment for various malignant tumors [12, 14, 15]. The combination of *Bifidobacterium* and *Lactobacillus acidophilus* can effectively reduce the incidence of radiation-induced diarrhea in patients with cervical cancer [16]. However, relevant studies have also demonstrated that nutritional intervention using probiotic beverages containing *Lactobacillus casei* did not exhibit a reduction in the incidence of grade 2 and higher radioactive diarrhea among patients with gynecological tumors. Nevertheless, it did significantly impact fecal consistency [17]. The administration of *Bifidobacterium* can enhance the intestinal flora environment in pediatric patients with malignant tumors undergoing chemotherapy, thereby mitigating the adverse effects associated with chemotherapy [18]. Probiotic supplementation during chemotherapy can also enhance the quality of life and alleviate certain side effects in lung cancer patients [19]. Probiotics combined with enteral nutrition can enhance the diversity of intestinal microbiota and mitigate chemotherapy-induced diarrhea in patients diagnosed with esophageal cancer [20]. Similarly, probiotic intervention to colorectal cancer patients undergoing irinotecan chemotherapy may potentially mitigate the occurrence and severity of gastrointestinal toxicity induced by chemotherapy [21]. Probiotic intake has been shown to enhance gastrointestinal symptoms and improve the overall quality of life in individuals diagnosed with colorectal cancer [22]. However, some research suggested that probiotics may not yield significant improvements in the quality of life and may lead to adverse reactions among colorectal cancer patients following chemotherapy [23]. We will provide a comprehensive analysis of the role and mechanism of probiotics in managing adverse reactions during radiotherapy or chemotherapy for patients with colorectal cancer, aiming to develop an innovative treatment strategy that effectively reduces these reactions, enhances patients' quality of life, and ultimately improves their anti-tumor response.

Materials and methods

This systematic review and meta-analysis strictly adheres to the guidelines outlined in the Cochrane Manual which has been registered with PROSPERO (CRD42023465966).

The study was conducted in accordance with the PICOS model, adhering to the guidelines outlined by the Reporting Project of Systematic Review and Meta-Analysis (PRISMA) [24]. The study population comprised of patients diagnosed with histologically confirmed colorectal cancer who were undergoing radiotherapy or chemotherapy. The intervention group consisted of patients receiving oral probiotics, while the control group included patients receiving oral placebo or not receiving probiotics, encompassing both open-label and blind trials. The adverse events, including diarrhea, stomatitis, bloating, decreased appetite, constipation, and nausea were observed and documented in patients with colorectal cancer undergoing chemotherapy or chemoradiotherapy as part of their anti-tumor therapy. These events were assessed based on the National Cancer Institute General Terminology Standards for Adverse Events (CTCAE) [25]. Specific definitions of adverse reactions are provided in the supplementary information. The patients' quality of life (QOL) was also evaluated to document their subjective experiences and impacts on QOL in terms of physical, emotional, social, cognitive functioning, disease symptoms, and treatment-related side effects. Clinical studies must adhere to the principles of randomized controlled trials. Through relevant investigations, we examined whether probiotics can mitigate associated adverse reactions and minimize the impact on QOL during radiotherapy or chemotherapy in colorectal cancer patients.

Literature search strategy

A comprehensive literature search was conducted by two authors (Rong Yang and Wei Liu) on PubMed, ClinicalTrials.gov, Embase, Cochrane library, Web of Science, and Chinese databases until July 27, 2024 to determine the feasibility of this study. Any discrepancies were resolved through discussion with the third author (Shuiyan CAI). The search term is in the supplementary material. The search strategy employed for PubMed is provided below: (((("Colorectal Neoplasms"[Mesh]) OR "Colonic Neoplasms"[Mesh]) OR "Rectal Neoplasms"[Mesh]) OR (((colorect*[Title/Abstract] OR colon*[Title/Abstract] OR rect*[Title/Abstract] OR anal [Title/Abstract] OR anus[Title/Abstract] OR CRC[Title/Abstract] OR intestin*[Title/Abstract] OR bowel*[Title/Abstract] OR sigmoid*[Title/Abstract] OR anus[Title/Abstract]) OR (carcinom*[Title/Abstract] AND neoplas*[Title/Abstract] OR adenocarcinom*[Title/Abstract] OR

cancer*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR sarcom*[Title/Abstract] OR adenom*[Title/Abstract] OR lesion*[Title/Abstract])) AND (("Radiotherapy"[Mesh]) OR ((((((radiotherap*[Title/Abstract]) OR (irradiat*[Title/Abstract]) OR (radiat*[Title/Abstract]) OR (chemoradi*[Title/Abstract]) OR (radiochemo [Title/Abstract]) OR (chemotherap*[Title/Abstract])) AND (((((((((((("Probiotics"[Mesh]) OR "Synbiotics"[Mesh]) OR "Lactobacillus"[Mesh]) OR "Bifidobacterium"[Mesh]) OR "Saccharomyces"[Mesh]) OR "Streptococcus thermophilus" [Mesh]) OR "Cultured Milk Products"[Mesh]) OR "Lactococcus"[Mesh]) OR "Bacillus subtilis"[Mesh]) OR "Enterococcus faecalis"[Mesh]) OR (probiotic*[Title/Abstract] OR lactobacill*[Title/Abstract] OR Synbiotic* [Title/Abstract] OR bifidobacter*[Title/Abstract] OR lactococ*[Title/Abstract] OR saccharomyc*[Title/Abstract] OR microbiome*[Title/Abstract] OR microbiotica[Title/Abstract] OR "streptococcus thermophilus"[Title/Abstract] OR "bacillus subtilis"[Title/Abstract] OR "enterococcus faecalis"[Title/Abstract] OR "lactic acid bacteri*[Title/Abstract] OR yoghurt[Title/Abstract] OR yoghourt [Title/Abstract] OR yogourt[Title/Abstract] OR yogurt [Title/Abstract] OR gut[Title/Abstract] OR intestin* [Title/Abstract] AND (flora[Title/Abstract] OR microflora [Title/Abstract] OR microbiota[Title/Abstract])))).

Filters: Randomized Controlled Trial.

Inclusion criteria

This study was screened based on the PICOS principle: (1) Population: patients with histologically confirmed colon or rectal cancer undergoing radiotherapy or chemotherapy; (2) Intervention: probiotics were administered to patients in the intervention group; (3) Comparison: control group patients received either placebo or no formal treatment with probiotics; (4) Outcomes: Study results encompassed adverse events such as diarrhea, stomatitis, constipation, nausea, and abdominal distension in colorectal cancer patients during radiotherapy or chemotherapy, subjective assessments of physical, emotional, social, cognitive function, disease symptoms, treatment side effects and impact on quality of life reported by the patients; (5) Study Design: This research strictly adheres to the principles of a randomized controlled trial.

Exclusion criteria

(1) Non-randomized controlled trials; (2) Articles published in languages other than English and Chinese; (3) Ongoing or unpublished experiments, studies with incomplete data; (4) Patients not diagnosed with colorectal cancer; (5) Systematic reviews, animal experiments, retrospective articles, conference abstracts, case reports, personal opinion articles, descriptive studies.

Data extraction and bias risk assessment

The data were independently extracted by the two authors (Yongjing Chen and Weiyu Ma) into a pre-designed table and subsequently collated. In cases where discrepancies arose, the third author (Xiurong Feng) conducted an independent re-extraction of the data, compared it with the findings of the first two authors, and meticulously verified each extracted data item against the original literature to ensure accuracy. Data extraction from the studies encompassed the following aspects: (1) Basic information: year of publication, first author, country, and author contact details; (2) Inclusion criteria assessment; (3) Subject characteristics: gender, disease type, age, intervention and control measures in both groups, participant countries, outcome indicators, and follow-up duration; (4) Extraction of result data; (5) Assessment of bias factors.

Literature quality evaluation

Literature quality assessment will be conducted by two researchers (Xiangyu Cheng and Junjie Ma), with a third party making a judgment if necessary in case of disagreement. The evaluation, using RevMan5.3 software and Cochrane system evaluation manual as reference, primarily focuses on the following criteria: (1) random allocation method; (2) implementation of allocation concealment; (3) implementation of blinding methods for participants and results; (4) integrity of result data; (5) selective reporting bias; (6) other biases. Each criterion is assessed as 'high risk bias', 'low risk bias', or 'unclear' based on the bias risk assessment criteria, with results presented in the form of a risk bias graph.

Statistical analysis

Statistical analysis of the extracted data was conducted using RevMan Statistical software (version 5.3). Since all included studies were randomized controlled trials, the risk ratio (RR) directly reflects the relative probability of events between the intervention and control groups, offering better clinical interpretation. RR more clearly shows the causal effect of interventions. RR was employed to incorporate statistical measures and calculate 95% confidence intervals (95%CI) for bipartite data. For continuous variables, the standardized mean difference (SMD) eliminates dimensional differences through standardization, aligning better with statistical requirements than the mean difference (MD). SMD was utilized to incorporate statistical measures and calculate 95% confidence intervals for continuous variables. A significance level of $P < 0.05$ indicated a statistically significant difference. The heterogeneity of the included studies was assessed using the I^2 value. When $I^2 \leq 50\%$, it indicated low heterogeneity among the studies, and a fixed-effect

model was applied for meta-analysis. Conversely, when $I^2 > 50\%$, a random effects model was used.

Results

Literature screening and basic characteristics

We identified a total of 694 articles from databases and relevant websites. Following the predefined inclusion and exclusion criteria, 622 articles were excluded during the initial screening process (including duplicates, studies involving non-colorectal cancer patients, non-probiotic research, animal studies, investigations unrelated to chemoradiotherapy, conference abstracts, and reviews), resulting in a final selection of 72 articles. Upon thorough examination of these remaining articles, it was found that 35 articles did not report clinical trial results, 15 articles had incomplete data, and 14 articles failed to document adverse reactions or quality of life related to chemotherapy or radiotherapy. Consequently, only 8 articles met the criteria for inclusion in the meta-analysis [21, 23, 26–31]. Figure 1 illustrates the screening process, and Table 1 presents the characteristics of the 8 studies.

The clinical trials included in our meta-analysis were conducted across multiple countries, such as Turkey, Iran, Malaysia, Slovakia, Finland, and China. All participants were adults (≥ 18 years old) diagnosed with colorectal cancer—encompassing colon cancer, rectal cancer, and rectosigmoid junction cancer—based on clinical guidelines and pathological diagnosis. Chemotherapy was administered to all participants in the 8 clinical trials; additionally, four of them received radiation therapy alongside chemotherapy [23, 26, 29, 30]. The remaining four studies exclusively underwent chemotherapy treatment [21, 27, 28, 31].

Quality assessment

Of the eight articles included in this study, randomization was mentioned; however, only three of them provided details regarding allocation concealment. Five studies described the implementation of blinding between participants and experimenters, while three studies detailed the blinding of outcome assessors. There were no instances of patient dropout or loss to follow-up. All included studies were complete, with no evidence of selective reporting bias. Each evaluation criterion was classified as either "high risk," "low risk," or "uncertain." The detailed results of the assessment are presented in Figs. 2A and 2B.

Diarrhea

Among the eight studies included, seven of them examined outcome indicators associated with diarrhea [21,

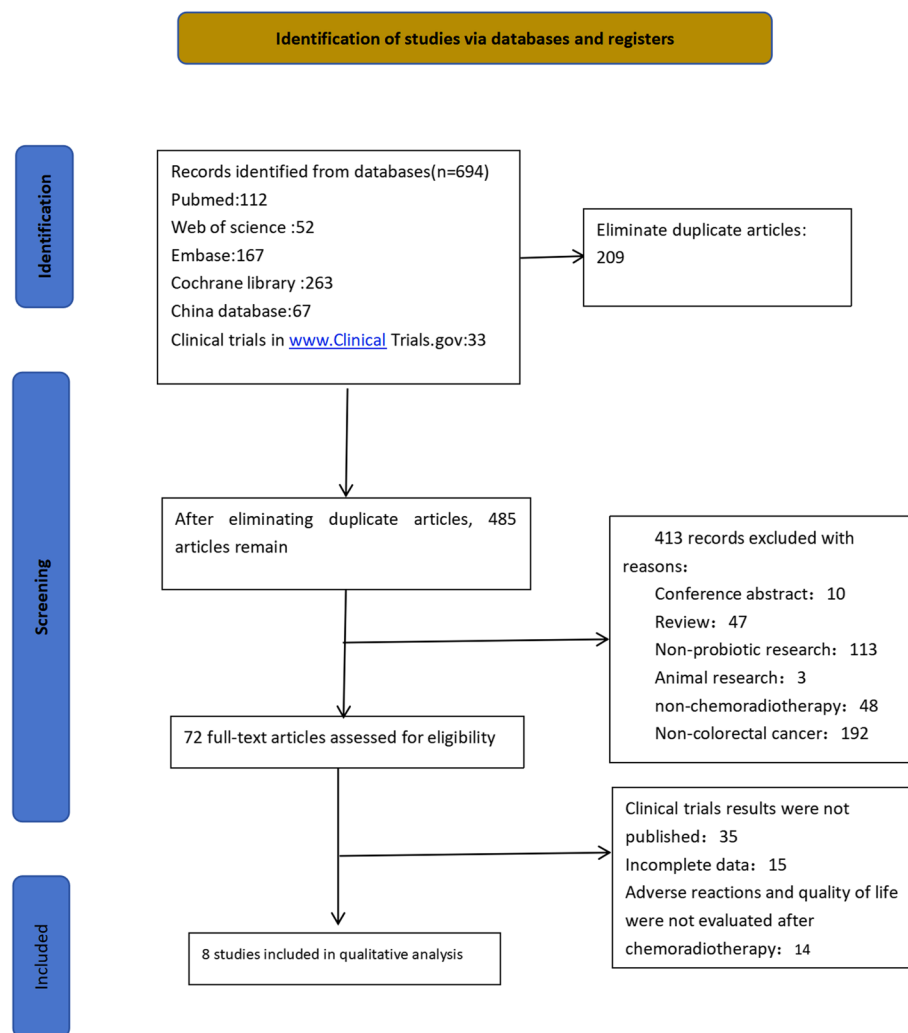


Fig. 1 Flowchart depicting the process of article screening

26–31]. A report indicates that probiotics have no statistically significant effect on the incidence of diarrhea compared to the control group [28]. Other studies have reported a significant reduction in the incidence of diarrhea with probiotics, particularly in patients classified as having grade 3–4 diarrhea, demonstrating statistical significance. Five of the studies reported outcomes that were categorized as binary variables [21, 26, 28, 29, 31], the outcomes of both studies were reported as continuous variables [27, 30]. Reveal the outcomes of meta-analyses conducted on the aggregated statistical measures. The analysis of Literature $I^2 = 40\%$ ($P = 0.15$) with a binary variable outcome was conducted using a fixed effect model, the findings depicted in Fig. 3A demonstrates a significant reduction in the risk of diarrhea through probiotic intake during radiotherapy or chemotherapy ($RR = 0.51$, $95\%CI: 0.38 \sim 0.68$, $P < 0.001$). Despite the inclusion of continuous variables in only two studies,

the analysis results did not yield statistical significance (as depicted in Fig. 3B). Nevertheless, the combined statistical trend still suggests that probiotics may offer potential improvement for chemoradiotherapy-induced diarrhea ($SMD = -6.0$, $95\%CI: -12.16 \sim 0.16$, $P = 0.06$).

Pain index

The impact of probiotic intake on pain experienced by colorectal cancer patients during chemotherapy and radiation therapy was reported in both articles [27, 30]. The observed heterogeneity is statistically significant, necessitating the utilization of a random effects model for conducting the analysis ($I^2 = 98\%$). As depicted in Fig. 4A, the utilization of probiotics demonstrates a potential to mitigate the pain index associated with chemotherapy and radiation therapy ($SMD = -2.27$, $95\%CI: -4.49 \sim -0.05$, $P = 0.04$), the observed difference exhibits statistical significance. One of the reports indicated that at eight weeks

Table 1 Basic characteristics of selected studies

Author Country	Age	Number of patients	Interventions	Control group	Chemoradiotherapy regimen
Gulbeyaz Can et al Turkey	Adult patients (≥ 18 years)	37	Took 250 ml of kefir twice daily for one week while undergoing chemotherapy treatment	YES	Adjuvant Chemoradiotherapy (XRT) with continuous 24-h infusion of 5-fluorouracil, seven days a week during XRT) FUFA FOLFOX
Fatemeh Farshi Radvar et al Iran	Synbiotic group: (57.58 $\pm$ 12.78) Placebo group: (62.89 $\pm$ 13.93)	38	Took synbiotic capsules twice daily before meals for six weeks, starting one week prior to the beginning of CRT and continuing until the end of radiotherapy	YES	Pelvic radiotherapy and intravenous administration of 5-fluorouracil
Babak Golkhalkhali et al Malaysia	Adult patients (≥ 18 years)	140	The participants were administered two sachets of microbial cell preparation (MCP) daily for a duration of four weeks, along with a dose of 2 g/day omega-3 fatty acid for eight weeks	YES	XELOX
Liyana Zaharuddin et al Malaysia	Synbiotic group: (67.33 $\pm$ 9.44) Placebo group: (66.5 $\pm$ 8.57)	52	Received a twice-daily dosage of probiotics containing six viable strains of lactobacillus and Bifidobacteria microorganisms for a duration of six months, starting four weeks after the surgery	YES	XELOX
Michal Mego et al Slovakia	Adult patients (≥ 18 years)	46	The probiotic formula was orally administered at a dosage of 10×10^9 CFU of bacteria three times daily for a duration of 12 weeks during chemotherapy	YES	Cetuximab and irinotecan
P Osterlund et al Finland	Age between 31 and 75	150	The probiotic strain Lactobacillus rhamnosus GG was orally administered in the form of gelatine capsules, twice daily at a dosage of $1-2 \times 10^{10}$ per day, throughout the 24-week period of adjuvant cancer chemotherapy	YES	Simplified de Gramont regimen or Mayo regimen Diagnosed with rectal cancer underwent locoregional radiotherapy whenever the tumor margin caudally extended below the distal peritoneal fold
Jing Han et al China	Mean age (42.82 $\pm$ 6.56)	100	Peifeikang (Bifidobacterium Triple Viable Powder) is 2 packs per administration, to be taken 3 times daily via oral route	YES	Underwent 6MV X-ray intensity modulated radiation therapy (IMRT) and received simultaneous oral administration of capecitabine
Feng Huang et al China	Age between 40 and 70	100	Took 3 tablets once daily from the third day after surgery until completion of the initial chemotherapy course	YES	XELOX

IMRT intensity modulated radiation therapy, XRT external-beam radiotherapy, FOLFOX oxaliplatin 85 mg/m² as a two-hour infusion on day 1, leucovorin 200 mg/m² as a two-hour infusion on days 1 and 2, 5-fluorouracil as a bolus infusion on days 1 and 2, followed by a fluorouracil 22-h infusion 600 mg/m², FUFA—5-fluorouracil 425 mg/m² plus leucovorin 20 mg/m² daily for five days every 28 days, XELOX oxaliplatin 130 mg/m² intravenous drip Day 1, capecitabine 1000 mg/m² is taken orally twice daily for 14 days, repeat every three weeks

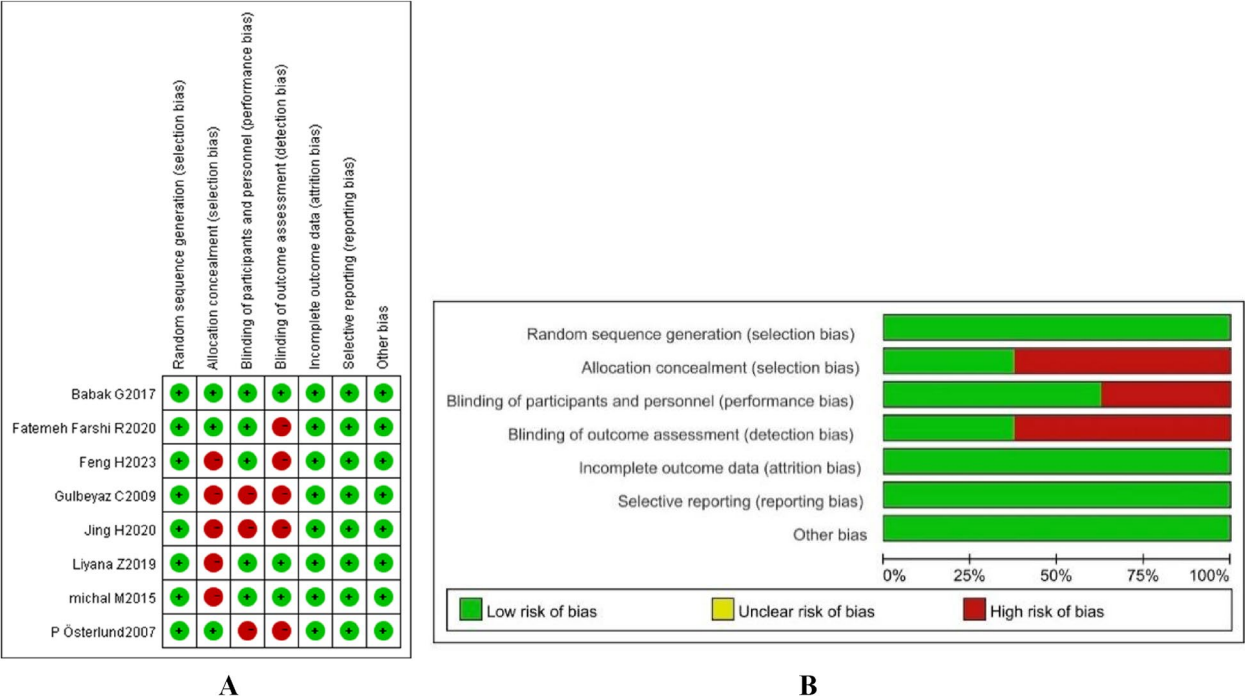


Fig. 2 **A** Risk of bias summary: review judgments about each risk of bias item for each included study. **B** Risk of bias graph: review judgments about each risk of bias item presented as percentages across all included studies

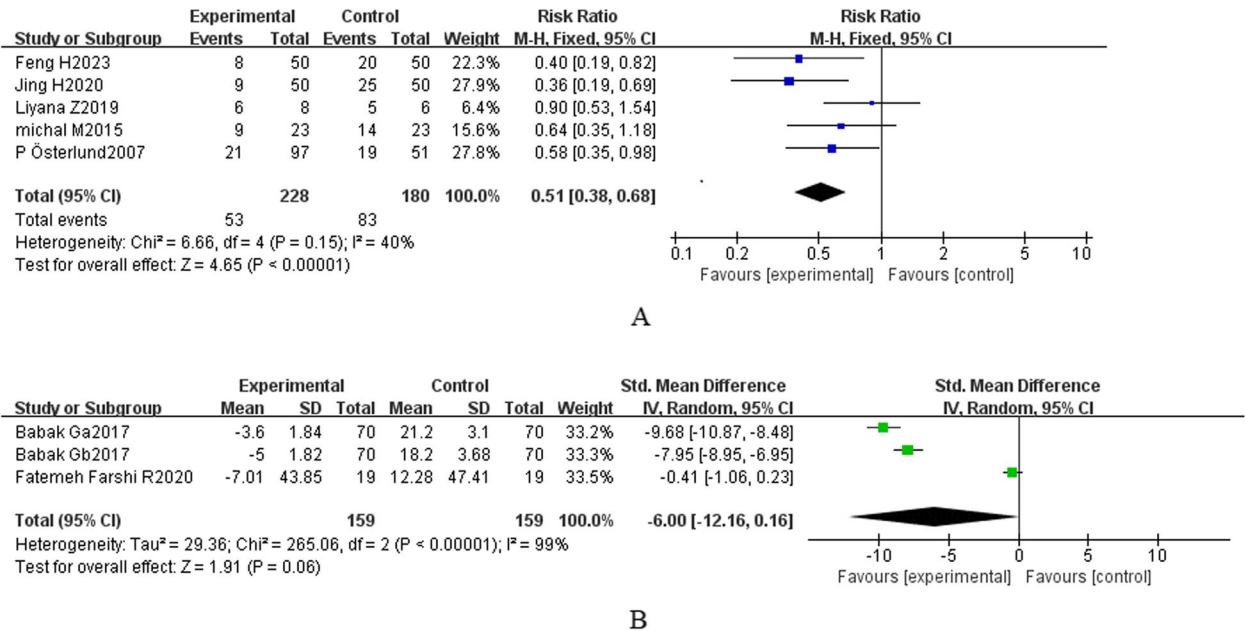


Fig. 3 **A** Forest plot of the effect of probiotics on diarrhea in colorectal cancer patients during chemoradiotherapy in binary categorical variable articles. **B** Forest plot of the effect of probiotics on diarrhea in colorectal cancer patients during chemoradiotherapy in Continuous variable articles. a: Results at the end of the probiotic intervention (include chemotherapy), 8 weeks from baseline. b: Results after completion of chemotherapy, 6 months from baseline

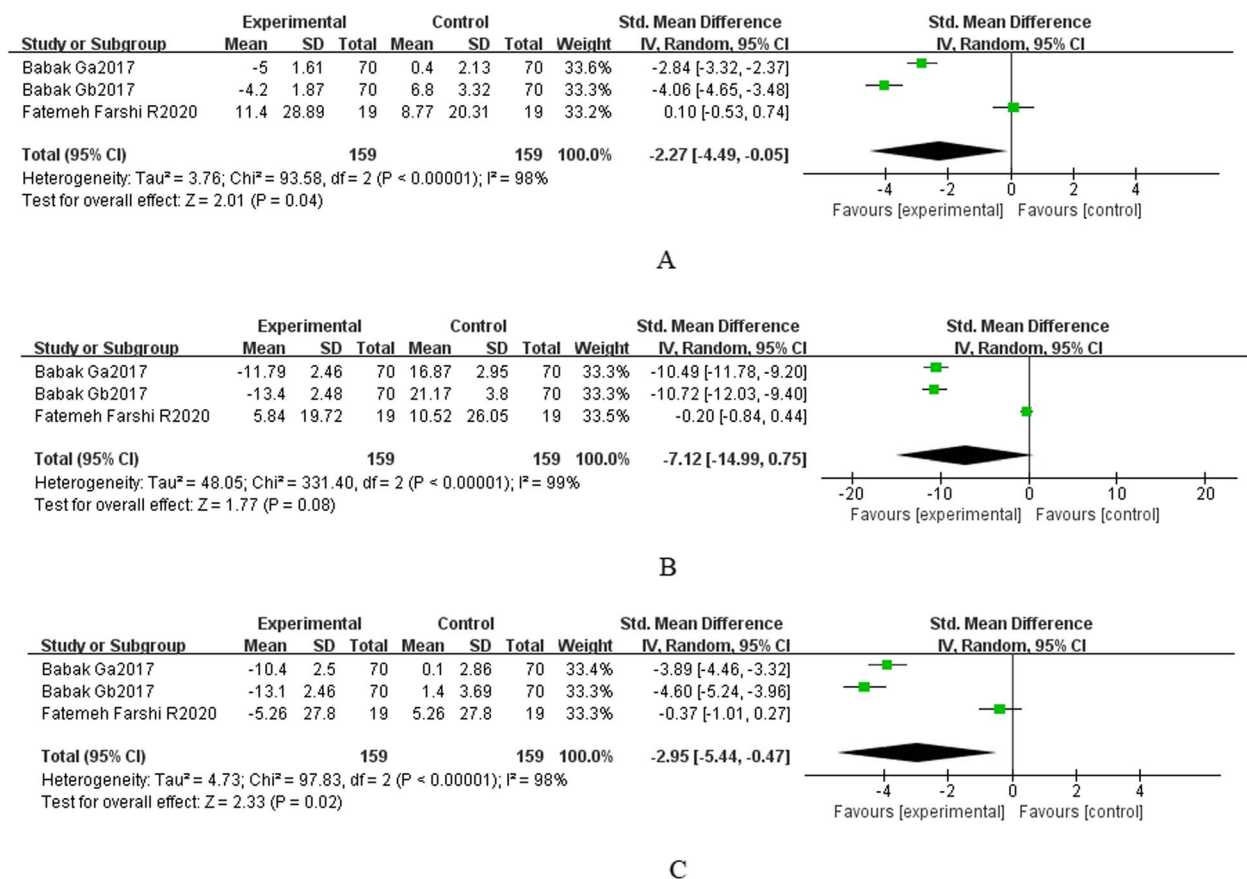


Fig. 4 **A** Forest plot of the effect of probiotics on pain index in patients with colorectal cancer during chemoradiotherapy. **B** Forest plot of the effect of probiotics on fatigue in patients with colorectal cancer during chemoradiotherapy. **C** Forest plot of the effect of probiotics on insomnia in patients with colorectal cancer during chemoradiotherapy. **a:** Results at the end of the probiotic intervention (include chemotherapy), 8 weeks from baseline. **b:** Results after completion of chemotherapy, 6 months from baseline

post-chemotherapy, the pain index in the probiotics group was comparatively lower than that in the control group [27], this difference did not reach statistical significance. However, at the conclusion of the 6-month post-chemotherapy period, the pain index in the probiotics group consistently demonstrated a statistically significant reduction compared to that of the control group ($P = 0.04$).

Fatigue

The impact of probiotics on fatigue in colorectal cancer patients during chemoradiotherapy was analyzed in both articles [27, 30]. One study indicated that the probiotic intervention group did not exhibit a statistically significant difference in alleviating fatigue symptoms compared to the control group during chemoradiotherapy. Conversely, another study demonstrated that probiotic supplementation led to a statistically significant improvement in fatigue symptoms among patients undergoing eight weeks or six months of chemotherapy, as compared to the control group ($P < 0.001$). Utilizing a random effects

model for statistical data synthesis, the analysis findings depicted in Fig. 4B demonstrate a discernible trend of diminished fatigue during chemotherapy with probiotic administration; however, no statistically significant difference was observed when compared to the control group ($SMD = -7.12$, $95\%CI: -14.99 \sim 0.75$, $P = 0.08$).

Insomnia

Both articles examined the effects of probiotic consumption during chemoradiotherapy and radiation therapy on insomnia in patients with colorectal cancer [27, 30]. The utilization of probiotics has been shown to mitigate the incidence of insomnia in patients undergoing chemoradiotherapy. Reconcile statistical measures through the utilization of a random effects model ($I^2 = 98\%$), the utilization of probiotics during chemoradiotherapy has been demonstrated to enhance sleep quality, as depicted in Fig. 4C. Moreover, the observed improvement is statistically significant when compared to the control group ($SMD = -2.95$, $95\%CI: -5.44 \sim -0.47$, $P = 0.02$).

Stomatitis and Abdominal distension

The impact of probiotics on abdominal distension in colorectal cancer patients during chemotherapy and radiation therapy was investigated in three articles [21, 23, 31]. As depicted in Fig. 5A, there was no statistically significant disparity observed in the incidence of abdominal distension between the probiotics group and the control group during chemoradiotherapy (RR = 0.79, 95%CI: 0.21 ~ 3.00, $P = 0.72$). The impact of probiotics on oral mucositis during chemoradiotherapy was analyzed in both articles [23, 29]. The combined statistical findings, as illustrated in Fig. 5B, demonstrate that the probiotic intervention did not yield a statistically significant reduction in the incidence of oral mucositis during chemoradiotherapy when compared to the control group (RR = 1.23, 95%CI: 0.48 ~ 3.21, $P = 0.67$).

Appetite and Quality of life

The impact of probiotics on appetite suppression and quality of life (QOL) in colorectal cancer patients during chemoradiotherapy was reported in both articles [27, 30]. The probiotics group exhibited a tendency towards ameliorating appetite decline during chemoradiotherapy, as depicted in Fig. 6A, however, no statistically significant difference was observed compared to the control group (SMD = - 2.86, 95%CI: - 5.83 ~ 0.11, $P = 0.06$). Meanwhile, these two articles investigate the impact of probiotics on the quality of life among colorectal cancer patients undergoing chemotherapy and radiation

therapy. The EORTC QLQ-C30 composite score, utilized for evaluating the quality of life in cancer patients, also holds significant implications for survival and prognosis [32]. The analysis results (Fig. 6B) indicate that, in comparison to the control group, the probiotics group did not exhibit any significant improvement in the quality of life score among colorectal cancer patients undergoing chemoradiotherapy, but a consistent beneficial trend was observed in the pooled estimates. There was no statistically difference observed between these two groups (SMD = 8.82, 95%CI: - 1.11 ~ 18.75, $P = 0.08$).

Dyspnea and Constipation

The two articles examined the impact of probiotics on dyspnea and constipation among colorectal cancer patients undergoing chemoradiotherapy [27, 30]. Reconcile statistical measures through the utilization of a random effects model ($I^2 = 87\%$; $I^2 = 94\%$). The results (Fig. 7A, 7B) demonstrate a significant improvement in breathlessness and constipation among colorectal cancer patients after chemoradiotherapy with the use of probiotics, the observed difference exhibits statistical significance (SMD = - 0.92, 95%CI: - 1.61 ~ 0.22, $P = 0.01$; SMD = - 1.25, 95%CI: - 2.32 ~ - 0.17, $P = 0.02$). The forest plots (Fig. 7B) depicted in these two articles demonstrate the efficacy of probiotics in the management of chemotherapy-induced constipation. (SMD = - 1.25, 95%CI: - 2.32 ~ 0.17, $P = 0.02$). Two additional studies examined the impact of probiotics on constipation in colorectal

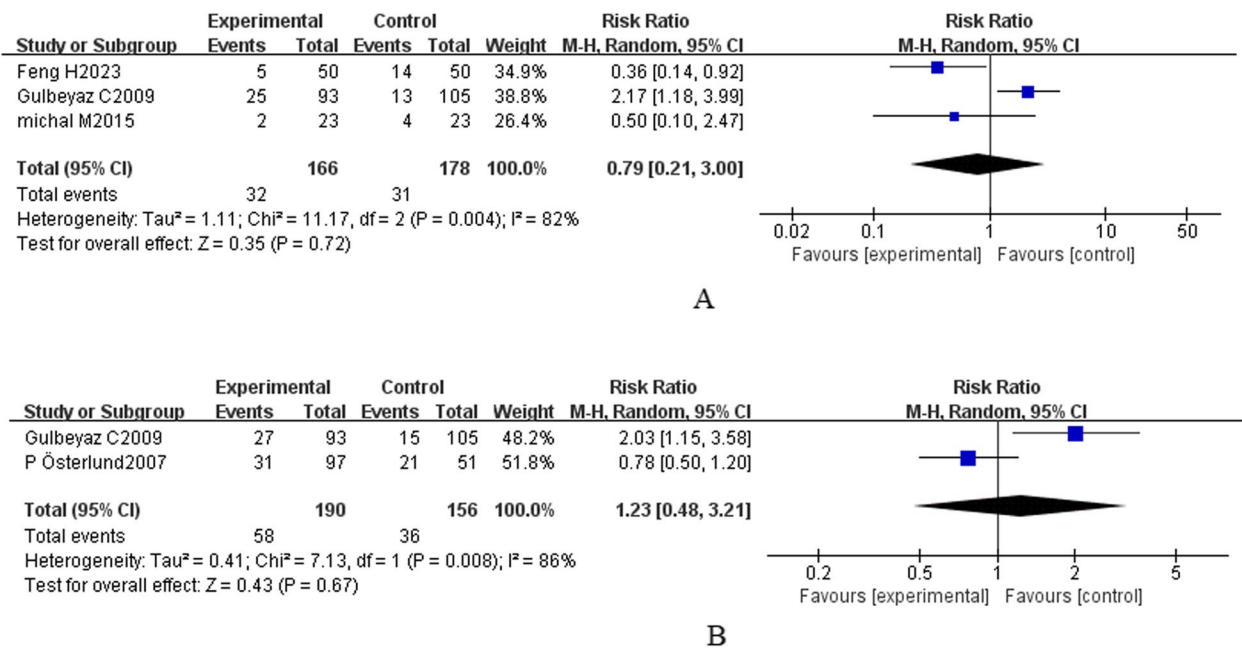


Fig. 5 **A** Forest plot of the effect of probiotics on bloating in patients with colorectal cancer during chemoradiotherapy. **B** Forest plot of the effect of probiotics on stomatitis in patients with colorectal cancer during chemoradiotherapy

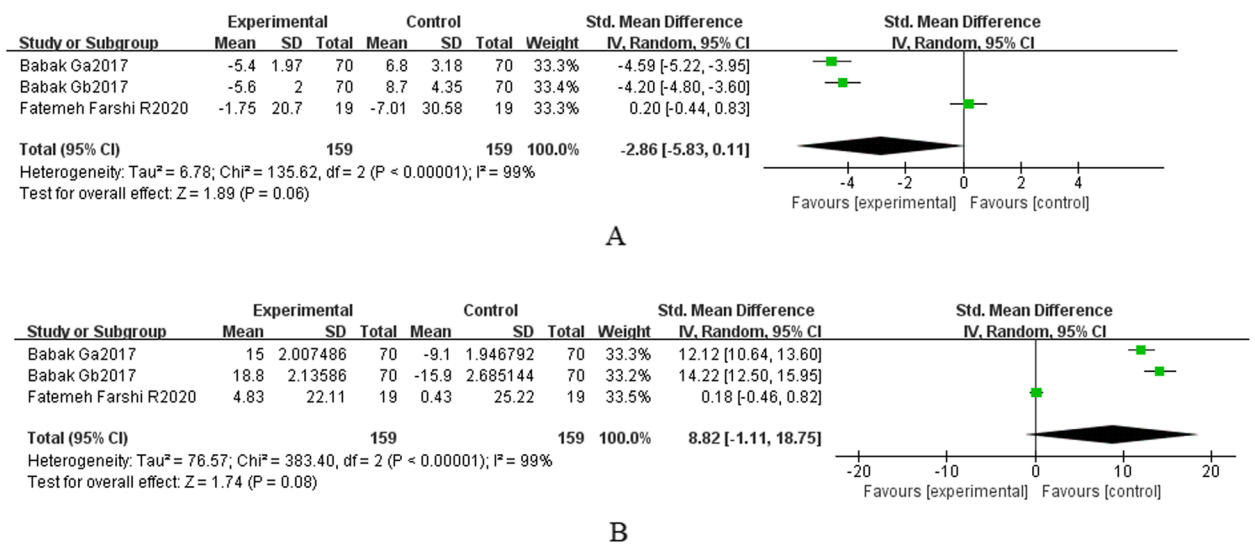


Fig. 6 **A** Forest plot of the effect of probiotics on appetite loss in patients with colorectal cancer during chemoradiotherapy. **B** Forest plot of the effect of probiotics on quality of life in patients with colorectal cancer during chemoradiotherapy. a: Results at the end of the probiotic intervention (include chemotherapy), 8 weeks from baseline. b: Results after completion of chemotherapy, 6 months from baseline

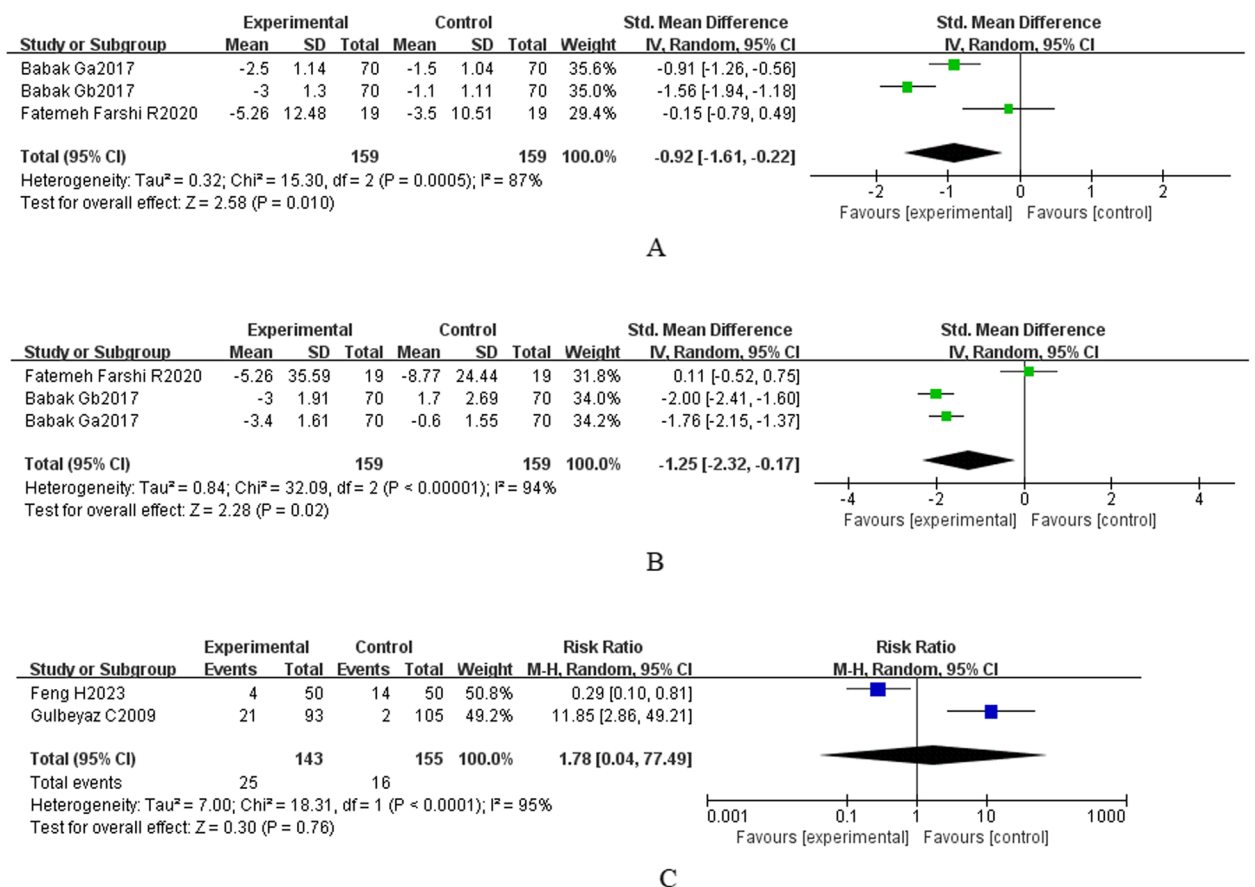


Fig. 7 **A** Forest plot of the effect of probiotics on dyspnea in patients with colorectal cancer during chemoradiotherapy. **B** Forest plot of the effect of probiotics on constipation in patients with colorectal cancer during chemoradiotherapy in the continuous variable articles a: Results at the end of the probiotic intervention (include chemotherapy), 8 weeks from baseline. b: Results after completion of chemotherapy, 6 months from baseline. **C** Forest plot of the effect of probiotics on constipation in patients with colorectal cancer during chemoradiotherapy in the binary variable articles

cancer patients undergoing chemoradiotherapy, employing dichotomous variables as outcome measures [23, 31]. However, as depicted in Fig. 7C, the probiotic intervention failed to demonstrate a significant reduction in the incidence of constipation when compared to the control group (RR = 1.78, 95% CI: 0.04 ~ 77.49, $P = 0.76$).

Subgroup analysis

In light of the potential influence of different treatment regimens on outcomes, and given that prior analyses indicated substantial heterogeneity ($I^2 > 50\%$) in some outcome measures, a stratified subgroup analysis was performed for outcome measures with ≥ 2 included studies. The effects of probiotic intervention and the source of heterogeneity were explored by distinguishing between the combined chemoradiotherapy group and the chemotherapy-alone group. The results demonstrated that: (1) Regarding diarrhea improvement, probiotic intervention exhibited significant efficacy in both the chemoradiotherapy group (RR = 0.47, 95% CI: 0.31–0.71) and the chemotherapy-alone group (RR = 0.56, 95% CI: 0.38–0.83) (Fig. 8A). (2) Concerning abdominal distension improvement, no overall effect was observed in the previous pooled analysis; however, subgroup analysis revealed that the incidence of abdominal distension was significantly reduced in the chemotherapy-alone group (RR = 0.39, 95% CI: 0.17–0.87), whereas no such effect was noted in the chemoradiotherapy group (Fig. 8B). Notably, heterogeneity decreased markedly after stratification, suggesting that differences in treatment regimens may constitute an important source of heterogeneity.

Discussion

Radiotherapy and chemotherapy are the fundamental and primary treatment modalities in the management of colorectal cancer. These interventions play a pivotal role in disease control and treatment by effectively inhibiting tumor growth and progression. Furthermore, they have demonstrated significant potential in reducing recurrence rates and mortality of patients with colorectal cancer [33]. However, the numerous deleterious effects induced by chemoradiotherapy also impose limitations on the efficacy of clinical treatment regimens and impact patients' quality of life [34]. It is very important to develop a rational treatment strategy to mitigate the deleterious effects induced by chemoradiotherapy throughout the entire course of colorectal cancer therapy. Currently, probiotics have gained extensive application in the treatment of diverse malignant tumors. Probiotics exert anti-tumor effects through various metabolic pathways. The NF- κ B signaling pathway plays a crucial role in colorectal cancer development and progression. This pathway is closely linked to mutations in key oncogenic genes such

as APC, P53, and BRAF, which are known to contribute to the onset of colorectal cancer [35]. Furthermore, oxidative stress can trigger pro-inflammatory signaling pathways, including NF- κ B, leading to intestinal barrier dysfunction and an increase in harmful intestinal susceptibility factors that indirectly promote colorectal cancer development [36]. Activation of the NF- κ B signaling pathway induces the production of various cytokines, such as tumor necrosis factor- α and interleukin-1 [37]. Inhibiting the NF- κ B pathway can arrest the cell cycle at the G0/G1 phase and prevent the progression of colorectal tumors [38]. *Lactobacillus plantarum* inhibits the NF- κ B pathway by producing conjugated linoleic acid (CLA), thereby promoting tumor cell apoptosis and reducing the incidence of colorectal cancer [39]. First-generation probiotics may modulate the oxidation state to influence NF- κ B signaling, thereby exerting anticancer and anti-inflammatory effects on colorectal cancer [40]. Current studies have demonstrated that probiotics can potentiate the efficacy of cancer immunotherapy in colorectal cancer treatment by modulating the oxidative microenvironment [41]. Immune checkpoint inhibitors are now widely used as anti-tumor agents. *Lactobacillus reuteri* can modulate the oxidation state of the tumor microenvironment, thereby inhibiting the proliferation and survival of colorectal cancer cells [8]. Relevant studies have demonstrated that in mouse models, the concentration of *Fusobacterium nucleatum* can regulate cancer immunotherapy targeting immune checkpoint inhibitors. Moreover, there is a direct correlation between the relative abundance of this bacterium and the efficacy of PD-L1 blockade [42]. Dietary intake of *Lactobacillus*-derived exopolysaccharides promotes the induction of CCR6 + CD8 + T cells in Peyer's patches and modulates the tumor microenvironment, thereby augmenting the therapeutic efficacy of immune checkpoint blockade against CCL20-producing tumors [43]. When camouflaged by the erythrocyte membrane, probiotics can decrease the mitochondrial membrane potential (MMP), activate the PINK1/Parkin pathway associated with mitochondrial autophagy, and thereby induce apoptosis in tumor cells [44]. It was reported that 80% of patients developed diarrhea and colitis during the treatment of pelvic radiotherapy especially in cervical cancer, prostate cancer, colorectal cancer and ovarian cancer. Preliminary investigations have demonstrated that the administration of probiotic supplements exhibits a significant potential in mitigating both the frequency and intensity of radiation-induced diarrhea. [45–47]. Patients with gastric cancer can potentially mitigate their postoperative infection rate and inflammation markers through probiotic supplementation, thereby enhancing adherence to postoperative adjuvant chemotherapy [48].

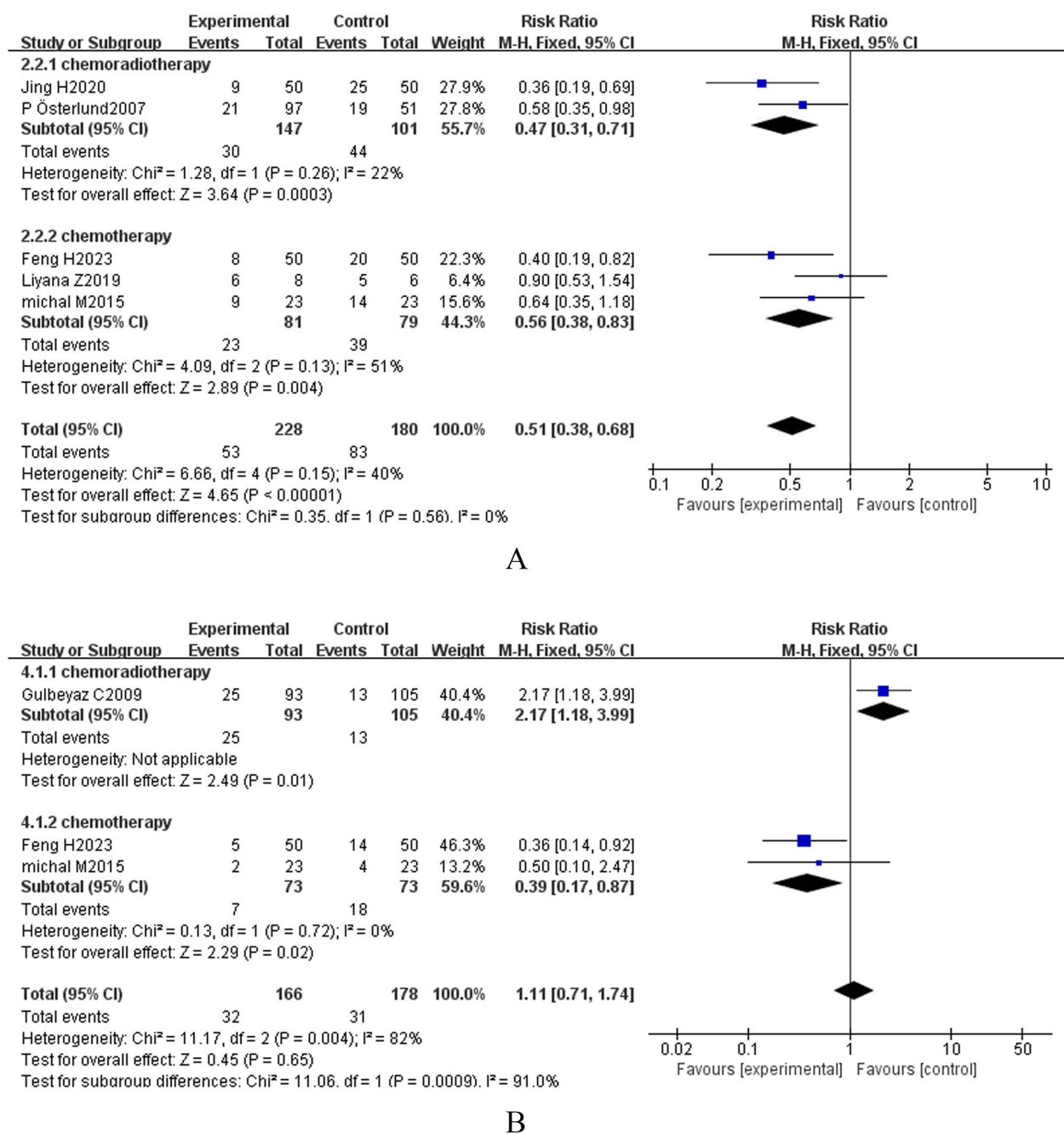


Fig. 8 **A** Diarrhea subgroup analysis. **B** Abdominal distension subgroup analysis

Probiotic intervention during neoadjuvant chemotherapy for patients with esophageal cancer can effectively mitigate the incidence of chemotherapy-related adverse events [49, 50]. Probiotic supplementation can ameliorate diarrhea and abdominal pain induced by radiotherapy during the treatment of cervical cancer [51]. Recently conducted studies have revealed that indole- 3-formaldehyde, produced by intestinal microorganisms, exhibited

an enhanced radioprotective effect on intestinal organoids. Furthermore, it has the potential to mitigate intestinal mucosal damage through modulation of probiotics to maintain the integrity of the intestinal barrier and effectively treat radiation enteritis [52]. Diarrhea, abdominal distension, pain, fatigue, oral ulceration, decreased appetite, insomnia, constipation, etc., are commonly observed adverse reactions in

patients with colorectal cancer undergoing chemoradiotherapy. These reactions can potentially contribute to or exacerbate the occurrence of malnutrition and electrolyte imbalance, finally leading to diminishing patient confidence in treatment. Consequently, they may prolong the duration of anti-tumor therapy for cancer patients and reduce treatment efficacy thereby impacting overall patient quality of life.

The meta-analysis included a total of 633 patients across the 8 articles. No evidence of publication bias was observed in these studies. Compared to the control group, probiotics demonstrate a significant reduction in the incidence of diarrhea among patients with colorectal cancer undergoing chemoradiotherapy, with a more pronounced effect observed in patients experiencing diarrhea with grade 3–4. Additionally, early probiotic intervention during chemoradiotherapy may ameliorate long-term chemoradiotherapy-induced diarrhea. This is consistent with some published meta-analyses of probiotics for alleviating diarrhea during chemoradiotherapy for pelvic tumors [53–55]. Chemoradiotherapy can induce aberrations in the crypt cells of the intestinal mucosa, trigger cellular apoptosis, disrupt the homeostasis of the intestinal microbiota, and impede nutrient absorption, consequently precipitating diarrhea [56–58]. Historically, the conventional approach to managing chemotherapy and radiation therapy-induced diarrhea involved the administration of one or more anti-diarrheal medications. While these drugs may provide temporary relief, they carry a risk of intestinal obstruction and gut dysbiosis subsequent to diarrhea. In contrast, probiotics offer superior safety profiles and are better received by patients compared to traditional anti-diarrheal drugs. Additionally, in comparison to the control group, the utilization of probiotics demonstrates an improvement in the pain index, dyspnea, and insomnia among colorectal cancer patients undergoing chemoradiotherapy. However, it is noteworthy that the probiotics group did not exhibit a significant reduction in the risk of abdominal distension and oral mucositis during chemoradiotherapy. This is contrary to previous meta-analyses showing that probiotics reduce stomatitis in cancer patients during chemoradiotherapy [59, 60]. This may be due to different probiotics, intake timing, cancer types, and treatment options. Subgroup analysis showed a significant reduction in abdominal distension in the chemotherapy-only group, but not in the chemoradiotherapy group, suggesting that treatment regimens might be a key source of heterogeneity. In addition, it was observed that probiotic intake did not significantly enhance the quality of life (QOL) among colorectal cancer patients undergoing chemoradiotherapy. This

differs from oral combination probiotic supplements, which have demonstrated potential in enhancing the quality of life for select non-colorectal cancer patients undergoing chemotherapy [61]. The limited sample size in this meta-analysis precludes a thorough assessment of the impact of probiotics on the diverse adverse reactions experienced by colorectal cancer patients during chemoradiotherapy. Furthermore, within the context of clinical trials, significant heterogeneity was observed in chemoradiotherapy protocols among patients. Specifically, some patients received neoadjuvant chemoradiotherapy, while others were administered adjuvant chemotherapy (without radiation therapy) for advanced disease or as postoperative adjuvant treatment. Among the 8 clinical studies, only one article employed a specific probiotic strain, while the remaining 7 articles utilized multiple probiotic strains. Notably, no fatalities or other adverse reactions associated with probiotics were documented throughout these rigorous clinical trials. However, previous meta-analyses on the use of probiotics in tumor radiotherapy and chemotherapy have reported some adverse effects. Some patients who consumed probiotics experienced mild adverse reactions, such as fever and slight lip edema, while one patient exhibited a more severe reaction attributed to lactose intolerance [53, 54]. For patients with lactose intolerance, researchers should place a high priority on evaluating the safety of probiotic selections. These findings indicate that probiotics can be administered safely in conjunction with chemotherapy and radiation therapy for colorectal cancer patients, potentially alleviating some treatment-related adverse effects. Nevertheless, researchers should proceed with caution when enrolling patients with specific conditions, such as lactose intolerance, into their studies. Inconsistencies in the type, timing, and treatment regimen of probiotics across current clinical studies may result in wide confidence intervals, thereby diminishing the reliability of clinical efficacy guidance. Moreover, given the considerable variability in probiotic strain types and corresponding treatment regimens among patients receiving therapy, there is a critical need to increase the sample size and conduct additional well-designed, rigorously controlled clinical trials. This will comprehensively investigate and assess the efficacy and safety of probiotics in this population.

Conclusions

This meta-analysis, based on 8 clinical trials, aims to provide valuable insights into the role of probiotics in managing adverse reactions and enhancing treatment efficacy and compliance during chemoradiotherapy for patients with colorectal cancer. In our study, probiotics were

found to significantly reduce the incidence of diarrhea. Additionally, they were observed to improve the pain index, alleviate dyspnea, and ameliorate insomnia among patients with colorectal cancer undergoing chemoradiotherapy. However, further clinical trials are necessary to evaluate the efficacy of probiotics in colorectal cancer patients undergoing chemoradiotherapy. More detailed protocols should be developed to optimize the strain, proportion, dose, administration time, and matched optimal chemoradiotherapy regimen for probiotics in such patients to achieve the best therapeutic outcomes.

Abbreviations

RR	Relative risk
SMD	Standardized mean difference
QOL	Quality of life
OS	Overall survival
ORR	Objective response rate
PFS	Progression-free survival
CRCI	Chemotherapy-related cognitive impairment
PICOS	Patients, intervention, comparison, outcome, study design
PRISMA	Project of systematic review and meta-analysis
CTCAE	Common terminology criteria for adverse events
EORTC	European organization for research and treatment of cancer quality of life questionnaire

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Institutional review board statement

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Conflicts of interest

There are no conflicts of interest.

Authors' contributions

Conception/design: WHY and RY. Provision of study material or patients: LL, SYC and RY. Data collection and/or assembly: LL, XRF and YJC. Data analysis and interpretation: WYM, ZHT, JJM and XYC. Manuscript writing: RY and ZHT. Final approval of the manuscript: WHY, RY, LL, SYC, XRF, YJC, WYM, ZHT, JJM, and XYC.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

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Competing interests

The authors declare no competing interests.

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References

1. H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, CA: a cancer journal for clinicians 2021;71(3):209–249.
2. Nikou GC, Polyzos A, Kostalas G, Avramopoulos H, Nikolopoulos A, Kitsou E, Potamitis C, Ioannidou P. Octreotide administration and gut hormone levels in patients with chemotherapy-induced diarrhea. Hellenic journal of gastroenterology. 1994;7(2):111–4.
3. Wu X, Xia Y, He F, Zhu C, Ren W. Intestinal mycobiota in health and diseases: from a disrupted equilibrium to clinical opportunities. Microbiome. 2021;9(1):60.
4. Sugimura N, Li Q, Chu E, Lau H, Fong W, Liu W, Liang C, Nakatsu G, Su A, Coker O, Wu W, Chan F, Yu JG. Lactobacillus gallinarum modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumorigenesis. 2021;71(10):2011–21.
5. Chen H, Tong T, Lu SY, Ji L, Xuan B, Zhao G, Yan Y, Song L, Zhao L, Xie Y, Leng X, Zhang X, Cui Y, Chen X, Xiong H, Yu T, Li X, Sun T, Wang Z, Chen J, Chen YX, Hong J, Fang JY. Urea cycle activation triggered by host-microbiota maladaptation driving colorectal tumorigenesis. Cell Metab. 2023;35(4):651–666.e7.
6. Maksimov IK, Kalinin AV, Rukavitsyn OA, Minushkin ON, Ardamskaia MD. The condition of intestinal microflora in patients with hematologic tumors receiving polychemotherapy. Klin Med. 2005;83(2):48–53.
7. Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA. The Influence of the Gut Microbiome on Cancer. Immunity, and Cancer Immunotherapy. Cancer cell. 2018;33(4):570–80.
8. Bell HN, Rebernick RJ, Goyert J, Singhal R, Kuljanin M, Kerk SA, Huang W, Das NK, Andren A, Solanki S, Miller SL, Todd PK, Fearon ER, Lyssiotis CA, Gygi SP, Mancias JD, Shah YM. Reuterin in the healthy gut microbiome suppresses colorectal cancer growth through altering redox balance. Cancer Cell. 2022;40(2):185–200.e6.
9. C. Pleguezuelos-Manzano, J. Puschhof, A. Rosendahl Huber, A. Hoeck, HM van. Wood, J. Nomburg, C. Gurjao, F. Manders, G. Dalmaso, PB. Stege, FL. Paganelli, MH. Geurts, J. Beumer, T. Mizutani, Y. Miao, R. Linden, S van der, Elst, KC van der. Garcia, J. Top, R.J.L. Willems, M. Giannakis, R. Bonnet, P. Quirke, M. Meyerson, E. Cuppen, R. van Bortel, H. Clevers, Mutational signature in colorectal cancer caused by genotoxic pks(+) E. Coli Nature 2020;580(7802):269–273.
10. Okawa T, Kita M, Arai T, Iida K, Dokiya T, Takegawa Y, Hirokawa Y, Yamazaki K, Hashimoto S. Phase II randomized clinical trial of LC9018 concurrently used with radiation in the treatment of carcinoma of the uterine cervix. Its effect on tumor reduction and histology. Cancer. 1989;64(9):1769–76.
11. Naito S, Koga H, Yamaguchi A, Fujimoto N, Hasui Y, Kuramoto H, Iguchi A, Kinukawa N. Prevention of recurrence with epirubicin and lactobacillus casei after transurethral resection of bladder cancer. J Urol. 2008;179(2):485–90.

12. Juan Z, Chen J, Ding B, Yongping L, Liu K, Wang L, Le Y, Liao Q, Shi J, Huang J, et al. Probiotic supplement attenuates chemotherapy-related cognitive impairment in patients with breast cancer: a randomised, double-blind, and placebo-controlled trial, *European journal of cancer* (Oxford, England. 1990;161(2022):10–22.
13. B. Lin, F. Zhao, Y. Liu, X. Wu, J. Feng, X. Jin, W. Yan, X. Guo, S. Shi, Z. Li, et al., Randomized Clinical Trial: probiotics Alleviated Oral-Gut Microbiota Dysbiosis and Thyroid Hormone Withdrawal-Related Complications in Thyroid Cancer Patients Before Radioiodine Therapy Following Thyroidectomy, *Frontiers in endocrinology*. 2022;13.
14. Mirza MA, Aruna D, Irukulla M. Efficacy of *Bacillus clausii* UBBC - 07 spores in the amelioration of oral mucositis in head and neck cancer patients undergoing radiation therapy. *Cancer treatment and research communications*. 2022;31:100523.
15. Corrao G, Latella M, Montagnese C, Ciceri S, Repetti I, Gnagnarella P, Marvaso G, Jereczek-fossa BA, De Cobelli O, Pravettoni G, et al. A RANDOMIZED CONTROLLED TRIAL ON LIFESTYLE AND INTERACTION WITH MICROBIOTA IN PROSTATE CANCER PATIENTS UNDERGOING RADIOTHERAPY: MICRO-STYLE STUDY. *Anticancer Res*. 2022;42(10):5135–6.
16. Chitapanarux I, Chitapanarux T, Traisathit P, Kudumpee S, Tharavichitkul E, Lorvidhaya V. Randomized controlled trial of live *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* in prophylaxis of diarrhea during radiotherapy in cervical cancer patients. *Radiation oncology* (London, England). 2010;5:31.
17. Giral J, Regadera JP, Verges R, Romero J, de la Fuente I, Biete A, Villoria J, Cobo JM, Guarner F. Effects of probiotic *Lactobacillus casei* DN-114 001 in prevention of radiation-induced diarrhea: results from multicenter, randomized, placebo-controlled nutritional trial. *Int J Radiat Oncol Biol Phys*. 2008;71(4):1213–9.
18. Wada M, Nagata S, Saito M, Shimizu T, Yamashiro Y, Matsuki T, Asahara T, Nomoto K. Effects of the enteral administration of *Bifidobacterium breve* on patients undergoing chemotherapy for pediatric malignancies. *Support Care Cancer*. 2010;18(6):751–9.
19. J. Zhu, J. Han, Y. Sun, M. Huang, Y. Lu, Y. Gong, X. Zhou, Y. Wang, Y. Liu, Y. Xu, et al., Oral composite probiotics supplements BP-1 can improve the quality of life in patients with lung cancer during the chemotherapy: a randomized, placebo control study, *Supportive care in cancer*. 2021;29(SUPPL 1):S202–.
20. Motoori M, Sugimura K, Tanaka K, Shiraishi O, Kimura Y, Miyata H, Yamasaki M, Makino T, Miyazaki Y, Iwama M, et al. Comparison of synbiotics combined with enteral nutrition and prophylactic antibiotics as supportive care in patients with esophageal cancer undergoing neoadjuvant chemotherapy: a multicenter randomized study. *Clinical nutrition* (Edinburgh, Scotland). 2022;41(5):1112–21.
21. Mego M, Chovanec J, Vochyanova-Andrezalova I, Konkolvsky P, Mikulova M, Reckova M, Miskovska V, Bystricky B, Beniak J, Medvecova L, Lagin A, Svetlovska D, Spanik S, Zajac V, Madiak J, Drgona L. Prevention of irinotecan induced diarrhea by probiotics: A randomized double blind, placebo controlled pilot study. *Complement Ther Med*. 2015;23(3):356–62.
22. Lee JY, Chu SH, Jeon JY, Lee MK, Park JH, Lee DC, Lee JW, Kim NK. Effects of 12 weeks of probiotic supplementation on quality of life in colorectal cancer survivors: a double-blind, randomized, placebo-controlled trial. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2014;46(12):1126–32.
23. Can G, Topuz E, Derin D, Durna Z, Aydinler A. Effect of kefir on the quality of life of patients being treated for colorectal cancer. *Oncol Nurs Forum*. 2009;36(6):E335–42.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev*. 2021;10(1):89.
25. Freitas-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. *Actas dermo-sifiliograficas*. 2011;112(1):90–2.
26. Han J, Gong C, Peng P, Zhang M, Zhang J. Application of *Bifidobacterium Triple Viable Powder* and Compound Berberine Retention Enema in Preventing Acute Radiation Proctitis. *Anti-tumor pharmacology*. 2020;10(1):103–6.
27. Golkhalkhali B, Rajandram R, Paliany AS, Ho GF, Wan Ishak WZ, Johari CS, Chin KF. Strain-specific probiotic (microbial cell preparation) and omega-3 fatty acid in modulating quality of life and inflammatory markers in colorectal cancer patients: a randomized controlled trial. *Asia-Pacific journal of clinical oncology*. 2018;14(3):179–91.
28. L. Zaharuddin, N.M. Mokhtar, K.N.M. Nawawi, R.A.R. Ali, A randomized double-blind placebo-controlled trial of probiotics in post-surgical colorectal cancer, *BMC gastroenterology*. 2019;19.
29. Österlund P, Ruotsalainen T, Korpela R, Saxelin M, Ollus A, Valta P, Kouri M, Elomaa I, Joensuu H. *Lactobacillus* supplementation for diarrhoea related to chemotherapy of colorectal cancer: A randomised study. *Br J Cancer*. 2007;97(8):1028–34.
30. Farshi Radvar F, Mohammad-Zadeh M, Mahdavi R, Andersen V, Nasirimotoagh B, Faramarzi E, Lotfi Yaghi N. 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(3):225–35.
31. F. Huang, S. Li, W. Chen, Y. Han, Y. Yao, L. Yang, Q. Li, Q. Xiao, J. Wei, Z. Liu, T. Chen, X. Deng, Postoperative Probiotics Administration Attenuates Gastrointestinal Complications and Gut Microbiota Dysbiosis Caused by Chemotherapy in Colorectal Cancer Patients, *Nutrients*. 2023;15(2).
32. Husson O, de Rooij BH, Kieffer J, Oerlemans S, Mols F, Aaronson NK, van der Graaf WTA, van de Poll-Franse LV. The EORTC QLQ-C30 Summary Score as Prognostic Factor for Survival of Patients with Cancer in the “Real-World”: Results from the Population-Based PROFILES Registry. *Oncologist*. 2020;25(4):e722–32.
33. E. Van Cutsem, M. Dico, J. Wils, D. Cunningham, E. Diaz-Rubio, B. Glime-lius, D. Haller, P. Johnston, D. Kerr, C.H. Koehne, R. Labianca, B. Minsky, B. Nordlinger, A. Roth, P. Rougier, H.J. Schmoll, Adjuvant treatment of colorectal cancer (current expert opinion derived from the Third International Conference: Perspectives in Colorectal Cancer, Dublin, 2001), *European journal of cancer* (Oxford, England : 1990). 2002;38(11):1429–36.
34. Arakawa K, Kawai K, Tanaka T, Hata K, Sugihara K, Nozawa H. Prognostic impact of interhospital variation in adjuvant chemotherapy for patients with Stage II/III colorectal cancer: a nationwide study. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland*. 2018;20(7):O162–O172.
35. Berkovich L, Gerber M, Katzav A, Kidron D, Avital S. NF-kappa B expression in resected specimen of colonic cancer is higher compared to its expression in inflammatory bowel diseases and polyps. *Sci Rep*. 2022;12(1):16645.
36. S. Keshavarz Shahbaz, K. Koushki, S.H. Ayati, A.R. Bland, E.E. Bezsonov, A. Sahebkar, Inflammation and Colorectal Cancer, *Cells*. 2021;10(9).
37. Mussbacher M, Salzmann M, Brostjan C, Hoesel B, Schoergenhofer C, Datler H, Hohensinner P, Basilio J, Petzelbauer P, Assinger A, Schmid JA. Cell Type-Specific Roles of NF-kB Linking Inflammation and Thrombosis. *Front Immunol*. 2019;10:85.
38. Rajitha B, Belalcázar A, Nagaraju GP, Shaib WL, Snyder JP, Shoji M, Pattnaik S, Alam A, El-Rayes BF. Inhibition of NF-kB translocation by curcumin analogs induces G0/G1 arrest and downregulates thymidylate synthase in colorectal cancer. *Cancer Lett*. 2016;373(2):227–33.
39. Chen Y, Ma W, Zhao J, Stanton C, Ross RP, Zhang H, Chen W, Yang B. *Lactobacillus plantarum* Ameliorates Colorectal Cancer by Ameliorating the Intestinal Barrier through the CLA-PPAR-γ Axis. *J Agric Food Chem*. 2024;72(36):19766–85.
40. Y. Kong, K.J. Olejar, S.L.W. On, V. Chelikani, The Potential of *Lactobacillus* spp. for Modulating Oxidative Stress in the Gastrointestinal Tract, *Antioxidants* (Basel, Switzerland). 2020;9(7).
41. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, Molina DA, Salcedo R, Back T, Cramer S, Dai RM, Kiu H, Cardone M, Naik S, Patri AK, Wang E, Marincola FM, Frank KM, Belkaid Y, Trinchieri G, Goldszmid RS. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science*. 2013;342(6161):967–70.
42. Gao Y, Bi D, Xie R, Li M, Guo J, Liu H, Guo X, Fang J, Ding T, Zhu H, Cao Y, Xing M, Zheng J, Xu Q, Xu Q, Wei Q, Qin H. *Fusobacterium nucleatum* enhances the efficacy of PD-L1 blockade in colorectal cancer. *Signal Transduct Target Ther*. 2021;6(1):398.
43. Kawanabe-Matsuda H, Takeda K, Nakamura M, Makino S, Karasaki T, Kakimi K, Nishimukai M, Ohno T, Omi J, Kano K, Uwamizu A, Yagita H,

- Boneca IG, Eberl G, Aoki J, Smyth MJ, Okumura K. Dietary Lactobacillus-Derived Exopolysaccharide Enhances Immune-Checkpoint Blockade Therapy. *Cancer Discov.* 2022;12(5):1336–55.
44. Y. Wang, Y. Liu, X. Su, L. Niu, N. Li, C. Xu, Z. Sun, H. Guo, S. Shen, M. Yu, Non-pathogenic Trojan horse Nissle1917 triggers mitophagy through PINK1/Parkin pathway to discourage colon cancer, *Materials Today Bio.* 2024;29.
 45. Visich KL, Yeo TP. The prophylactic use of probiotics in the prevention of radiation therapy-induced diarrhea. *Clin J Oncol Nurs.* 2010;14(4):467–73.
 46. Germain I, Desjardins J, Demers M, Dagnault A. Phase III study: impact of probiotics on diarrhea in patients treated with pelvic radiation. *Int J Radiat Oncol Biol Phys.* 2011;81(2 SUPPL. 1):S667–8.
 47. Nascimento M, Aguilar-Nascimento JE, Caporossi C, Castro-Barcellos HM, Motta RT. Efficacy of synbiotics to reduce acute radiation proctitis symptoms and improve quality of life: a randomized, double-blind, placebo-controlled pilot trial. *Int J Radiat Oncol Biol Phys.* 2014;90(2):289–95.
 48. G. Liu, S. Cao, X. Liu, Z. Li, Y. Tian, X. Zhang, H. Zhong, Y. Zhou, Effect of perioperative probiotic supplements on postoperative short-term outcomes in gastric cancer patients receiving neoadjuvant chemotherapy: a double-blind, randomized controlled trial, *Nutrition (Burbank, Los Angeles County, Calif.)* 2022;96:111574.
 49. Motoori M, Yano M, Miyata H, Sugimura K, Saito T, Omori T, Fujiwara Y, Miyoshi N, Akita H, Gotoh K, et al. Randomized study of the effect of synbiotics during neoadjuvant chemotherapy on adverse events in esophageal cancer patients. *Clinical nutrition (Edinburgh, Scotland).* 2017;36(1):93–9.
 50. Fukaya M, Yokoyama Y, Usui H, Fujieda H, Sakatoku Y, Takahashi T, Miyata K, Niihara M, Sugimoto T, Asahara T, Nagino M, Ebata T. Impact of synbiotics treatment on bacteremia induced during neoadjuvant chemotherapy for esophageal cancer: A randomised controlled trial. *Clinical nutrition (Edinburgh, Scotland).* 2021;40(12):5781–91.
 51. Linn YH, Thu KK, Win NHH. Effect of Probiotics for the Prevention of Acute Radiation-Induced Diarrhoea Among Cervical Cancer Patients: a Randomized Double-Blind Placebo-Controlled Study. *Probiotics and antimicrobial proteins.* 2019;11(2):638–47.
 52. L.W. Xie, S. Cai, H.Y. Lu, F.L. Tang, R.Q. Zhu, Y. Tian, M. Li, Microbiota-derived I3A protects the intestine against radiation injury by activating AhR/IL-10/Wnt signaling and enhancing the abundance of probiotics, *Gut Microbes.* 2024;16(1).
 53. 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. *International journal of surgery (London, England).* 2020;84:69–77.
 54. Qiu G, Yu Y, Wang Y, Wang X. The significance of probiotics in preventing radiotherapy-induced diarrhea in patients with cervical cancer: A systematic review and meta-analysis. *International journal of surgery (London, England).* 2019;65:61–9.
 55. N.K. Devaraj, S. Suppiah, S.K. Veetil, S.M. Ching, K.W. Lee, R.K. Menon, M.J. Soo, I. Deuraseh, F.K. Hoo, D. Sivarathnam, 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(12).
 56. Gibson RJ, Bowen JM, Inglis MR, Cummins AG, Keefe DM. Irinotecan causes severe small intestinal damage, as well as colonic damage, in the rat with implanted breast cancer. *J Gastroenterol Hepatol.* 2003;18(9):1095–100.
 57. Gibson RJ, Keefe DM. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies, Supportive care in cancer : official journal of the Multinational Association of Support Care Cancer. 2006;14(9):890–900.
 58. McQuade RM, Stojanovska V, Abalo R, Bornstein JC, Nurgali K. Chemotherapy-Induced Constipation and Diarrhea: Pathophysiology. Current and Emerging Treatments, *Frontiers in pharmacology.* 2016;7:414.
 59. Feng J, Gao M, Zhao C, Yang J, Gao H, Lu X, Ju R, Zhang X, Zhang Y. Oral Administration of Probiotics Reduces Chemotherapy-Induced Diarrhea and Oral Mucositis: A Systematic Review and Meta-Analysis. *Front Nutr.* 2022;9:823288.
 60. Y.C. Liu, C.R. Wu, T.W. Huang, Preventive Effect of Probiotics on Oral Mucositis Induced by Cancer Treatment: A Systematic Review and Meta-Analysis, *Int J Mol Sci.* 2022;23(21).
 61. Wei H, Yue Z, Han J, Chen P, Xie K, Sun Y, Zhu J. Oral compound probiotic supplements can improve the quality of life for patients with lung cancer during chemotherapy: A randomized placebo-controlled study. *Thoracic Cancer.* 2024;15(2):182–91.

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