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Effect of probiotic supplementation on chemotherapy- and radiotherapy-related diarrhoea in patients with cancer: an umbrella review of systematic reviews and meta-analyses

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Abstract

To date, several systematic reviews and meta-analyses (SRMA) have investigated the effects of probiotics, but the certainty of the evidence for an effect on chemotherapy and radiotherapy-related diarrhoea has not been assessed. We conducted an overview of SRMA, searching MEDLINE, Scopus, and ISI Web of Science from inception up to February 2022. We summarised the findings of eligible SRMA. Subsequently, we included randomised clinical trials (RCT) from the SRMA in meta-analyses, using a quality effects model to calculate the OR and 95 % CI for each outcome. We used 'A Measurement Tool to Assess Systematic Reviews' and the Cochrane risk of bias tool to assess the methodological quality of the SRMA and their RCT, respectively. We used the 'Grading of Recommendations Assessment, Development, and Evaluation'.We included thirteen SRMA, which reported pooled effect sizes for chemotherapy and radiotherapy-related diarrhoea based on a total of eighteen RCT. Our meta-analyses demonstrated statistically significant beneficial effects from probiotics on all outcomes, except stool consistency; diarrhoea (any grade) OR 0·35 (95 % CI 0·22, 0·54), grade ≥ 2 diarrhoea 0·43 (0·25, 0·74), grade ≥ 3 diarrhoea 0·30 (0·15, 0·59), use of medication 0·49 (0·27, 0·88), soft stool 1·10 (0·44, 2·76) and watery stool 0·52 (0·29, 1·29). Probiotics use can reduce the incidence of diarrhoea in cancer patients in chemotherapy and radiotherapy, but the certainty of evidence for significant outcomes was very low and low.

Key words: **Diarrhoea: Chemotherapy: Radiotherapy: Probiotics: Meta-analysis**

Chemotherapy the most common therapy for cancerous tumours, and chemotherapy-induced diarrhoea, is one of the most prevalent side effects[1]. Severe diarrhoea affects around 20–45 % of all patients receiving chemotherapy[2]. Chemotherapy-induced diarrhoea can be induced by many chemotherapeutics, but mainly 5-fluorouracil and irinotecan (CPT-11), which account for up to 80 % of all cases[3]. Moreover, with more abdominal and pelvic tumours being treated with radiation, radiotherapy-induced diarrhoea is becoming more prevalent[4]. Radiotherapy-induced diarrhoea is common during the third week of therapy, with incidence rates ranging from 20 % to 70 %[5].

Diarrhoea caused by radiotherapy or chemotherapy may reduce the quality of life and sometimes cause treatment suspension or termination[6]. Radiation can change bacterial flora, intestinal motility and mucosal cell vascular permeability[7,8]. Additionally, chemotherapy alters the composition of the intestinal microflora, which generates numerous enzymes and controls intestinal angiogenesis and immunological processes to preserve the integrity of the gut barrier[9]. The gut microbiota

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomised clinical trials; RD, risk difference; SRMA, systematic reviews and meta-analyses.

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impacts human health by influencing the gut mucosal barrier, nutrient utilisation and immunological function, as well as by directly interacting with the gastrointestinal epithelium[10,11].

Probiotics are described as living microorganisms that, when administered in sufficient concentrations, provide a health benefit to the host[12,13]. Lactobacilli and bifidobacteria are two genera that may be found in a variety of consumer products, including yogurt[14]. *Lactobacillus rhamnosus* is a bacterium that has the potential to boost the healing of mucosa damaged by radiation and/or chemotherapy exposure with the mechanisms of stimulating the immune response and increasing the production of enterocytes, according to researchers at the University of Bristol in the UK[15]. Furthermore, these lactobacilli may help restore bacterial balance in the intestine, preventing bacterial translocation into tissues and boosting local and systemic immune responses to pathogens[16–18].

So far, several systematic reviews and meta-analyses (SRMA) have evaluated the effect of probiotic supplements on diarrhoea caused by radiotherapy and/or chemotherapy. Nevertheless, the certainty of the evidence for the effect has not been assessed.

For this purpose, overviews of SRMA (also called 'umbrella reviews') are useful, as they summarise the evidence from published SRMA on a particular topic[19,20]. We conducted an overview of SRMA to evaluate the evidence from published SRMAs of randomised clinical trials (RCT) that examine the effects of probiotics on diarrhoea caused by chemotherapy and radiotherapy.

Methods

For the present overview of SRMA, we used the Cochrane Handbook's methodology for conducting systematic reviews of interventional trials[21], where applicable, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework[22]. The study's protocol was registered in PROSPERO (CRD42022312083), prior to initiating the study selection process. The study was reported according to 'The Preferred Reporting Items for Overviews of Reviews' statement[23,24].

Eligibility criteria

Studies that fulfilled the following criteria were included in this overview of SRMA: SRMA that (1) included RCT conducted on adults with cancer who were receiving chemotherapy and/or radiotherapy; (2) evaluated the efficacy of probiotic supplementation for the prevention or treatment of chemotherapy and/or radiotherapy-related diarrhoea compared with a control group; (3) considered the incidence of diarrhoea (in terms of any diarrhoea, as well as diarrhoea of certain severities) during the intervention; (4) reported relative risk or OR of diarrhoea incidence with 95 % CI. Narrative reviews and systematic reviews without meta-analyses were excluded. If multiple meta-analyses were available for each outcome, the meta-analysis with the largest number of RCT was selected for each outcome[25].

Information sources and search strategy

We searched three electronic databases, including MEDLINE (via PubMed), Scopus and ISI Web of Science (R.A and P.S) from inception up to 2 February 2022 without any language restriction. To ensure that no relevant publications were missed, the reference lists of all relevant SRMA were screened. Details on the search strategy and keywords are given in Supplementary Table 1.

Study selection

Two independent investigators (R.A and P.S) independently screened the references based on title and abstract and subsequently assessed the full texts for eligibility. To ensure that no publication was missed, the reference lists of any pertinent meta-analysis were also searched. Disagreements were resolved by discussion and consulting a third reviewer. For the quantitative synthesis, we included RCT from the eligible SRMA.

Data extraction

Two independent investigators (R.A and S.ZM) extracted the data from the eligible SRMA and their RCT. The data items extracted from the SRMA: Last name of the first author, year of publication, number of participants, number of primary RCT in the main (largest) meta-analysis, and number of primary RCT discovered from similar meta-analyses. The data items extracted from the RCT: Study design, number of participants and events within both intervention and control groups, sex, mean age, treatment modality (chemotherapy or radiotherapy), type of cancer, follow-up length, probiotic supplementation (type, duration, route of administration, daily dose, genus, strain and species), medication usage, criteria for diarrhoea and severity of diarrhoea (grade). The arm with the higher dose was chosen in RCT with two intervention arms and the same control group.

Assessment of methodological quality

We applied 'A Measurement Tool to Assess Systematic Reviews' (AMSTAR2) tool to assess the methodological quality of the included SRMA[26]. The Cochrane tool was used to evaluate the risk of bias (RoB) of the RCT included in each SRMA[27]. Moreover, the credibility of subgroup differences was examined according to eight criteria determined by the 'Instrument to Assess the Credibility of Effect Modification Analyses' (ICEMAN)[28]. The assessments were conducted by two independent investigators (R.A and S.ZM) and disagreements were resolved by consensus.

Data synthesis and analysis

We briefly summarised the findings of the eligible SRMA Subsequently, we included RCT from the SRMA in meta-analyses. The outcomes included incidences of diarrhea (any grade), grade ≥ 2 diarrhea, grade ≥ 3 diarrhea, use of anti-diarrheal drug, soft stool consistency, and watery stool consistency. We selected OR and 95 % CI as the effect estimate for our analysis. OR and 95 % CI were calculated for each outcome using the quality effects model. Quality effects model was preferred to the random effects model because the random effects model suffers from serious overdispersion (especially when there is heterogeneity)[29], and cannot be recommended anymore, even if

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the between-studies variance estimate is not the DerSimonian-Laird method.

In meta-analyses, the risk of bias in primary studies is evaluated, but usually, the results of this evaluation are not included in the analysis. Quality effects model is one method that considers the quality of studies, and it also reduces the estimator's mean square error. Compared with the random effects model, this model maintained the correct coverage of the CI regardless of the heterogeneity level and showed lower variance[29]. Extracting quantitative data from the Cochrane RoB tool for input in the quality effects model was done using the method developed by Stone et al[30]. A score of 1 was used for a domain with a low risk of bias, a score of 0 was used for high and unclear, and finally, the total score of the domains for each study was used in the analysis

The reason why we used OR rather than RR can be due to the fact that RR changes toward its null value as the prevalence of the outcome increases. This change happens regardless of the strength of the relationship between the intervention and the outcome; RR is the ratio of the probability of the outcome in the intervention group to the probability of the outcome in the control group, and both depend on the prevalence of the outcome. Moreover, OR only measures the effect and has nothing to do with the prevalence of outcome in the study and does not overestimate. In other words, OR indicates the equal chance of the outcome from an unexposed state to an exposed state[31,32].

To calculate the absolute effect, we estimated risk difference (RD) and its 95 % CI by using logittorisk module in Stata and an estimated baseline risk[33]. The estimated baseline risk required for computing RD was the event rate of the control group of all RCT for each outcome[34]. We examined and described heterogeneity quantitatively through the I^2 statistic and conducted a chi-square test for homogeneity ($P_{\text{for heterogeneity}} > 0{\cdot}10$). For evaluating heterogeneity, we used Cochrane Handbook guidance, and I^2 was considered as follows: may not be important (0–40 %), moderate heterogeneity (30–60 %), substantial heterogeneity (50–90 %), and considerable heterogeneity (75–100)[35]. We conducted pre-defined subgroup analyses based on the type of anti-cancer therapy and outcome assessment method, as well as post hoc subgroup analyses based on the length of the intervention, probiotic genus, and singularity or combination of probiotics. To assess potential publication bias and small study effects, we used the Egger's test[36]. Stata version 16·0 was used for all analyses (StataCorp).

Grading of the evidence

The certainty of the evidence was rated with the GRADE approach[22]. High, moderate, low or very low are four possible categories for the overall quality of evidence when using the GRADE tool to judge the certainty of evidence.

Results

Study selection

Figure 1 illustrates the study selection. Searching electronic databases resulted in 1938 records. After removing duplicates, there were 1543 studies left for screening based on titles and abstracts, which resulted in thirty-eight records for the full-text assessment. Finally, thirteen SRMA[25,37–48] were eligible for our qualitative and quantitative synthesis, contributing eighteen RCT[7,49–65]. Supplementary Table 2 lists the excluded studies with reasons.

Study characteristics of the systematic reviews and meta-analyses

The thirteen SRMA included in this overview were published between 2009 and 2021. Six studies evaluated the anti-diarrhoeal effects of probiotics in patients receiving radiotherapy[37–40,43,44], three studies in chemotherapy[25,42,46] and four studies in all cancer patients[41,45,47,48]. One study included other nutritional supplements in addition to probiotics[36], whereas the rest of the studies considered only probiotics.

Study characteristics of randomised controlled trial from the systematic reviews and meta-analyses

A total of eighteen RCT, with a total population of 2152 participants, could be included in our meta-analysis, and their characteristics are shown in Table 1. Three of the RCT featured a parallel design[50,52,61] and RCT[63–65], one was a parallel double-blind two-arm[58], one was a randomised phase II trial[54], one was a crossover[62] and the others were a parallel double-blind RCT[7,49,51,53,55–57,59,60]. The RCT were conducted between 1988 and 2018 in many different countries across the world. Four of the studies[7,50,53,57] included exclusively gynecological malignancies, such as uterine and cervical cancers, while the others[49,51,52,54–56,58–65] included abdominal pelvic tumours, such as sigmoid, colon, prostate and bladder cancers, as well as gynecological cancers. The participants' age ranged from 18 to 85 years. Radiotherapy with or without chemotherapy was used as an anti-cancer treatment in eleven trials[7,49,50,52–59], chemotherapy was used in six studies[51,60–62,64,65], and for one study, the type of anti-cancer treatment was not specified[63]. In one study, the control group received no intervention[51], in another, the control group received diet counseling[7], in eleven studies, placebo[49,50,52–60], and in the remaining five studies, the control treatment was unclear[61–65]. Follow-up range and probiotic dose varied between 6 and 208 weeks and 3×10^8 to $1{\cdot}35 \times 10^{12}$ CFU/g, respectively. The intervention dose was given to the participants from twice a day to four times a day. The major probiotics were Lactobacillus, Bifidobacterium, and Streptococcus. The outcomes, any grade[7,50–53,55–65], grade ≥ 2[52,56–62], grade ≥ 3 diarrhoea[51,53,55–62,64], use of anti-diarrhoeal drugs[7,49,52–54,57–59] and stool consistency[57–59] were evaluated in 16, 8, 11, 8 and 3 studies, respectively. Bristol scale was used to measure the consistency of stool[57–59]. The severity of diarrhoea was evaluated with the National Cancer Institute Common Toxicity Criteria in five studies[52,53,57,59,60] and WHO criteria were used in four studies[51,55,56,58]. In the other studies, the diarrhoea measuring instrument was not reported[7,50,61–65]. Among the eighteen RCT, diarrhoea was evaluated as any grade diarrhoea[7,50–53,55–65], grade ≥ 2 diarrhoea[52,56–62] and grade ≥ 3 diarrhoea[51,53,55–62,64].

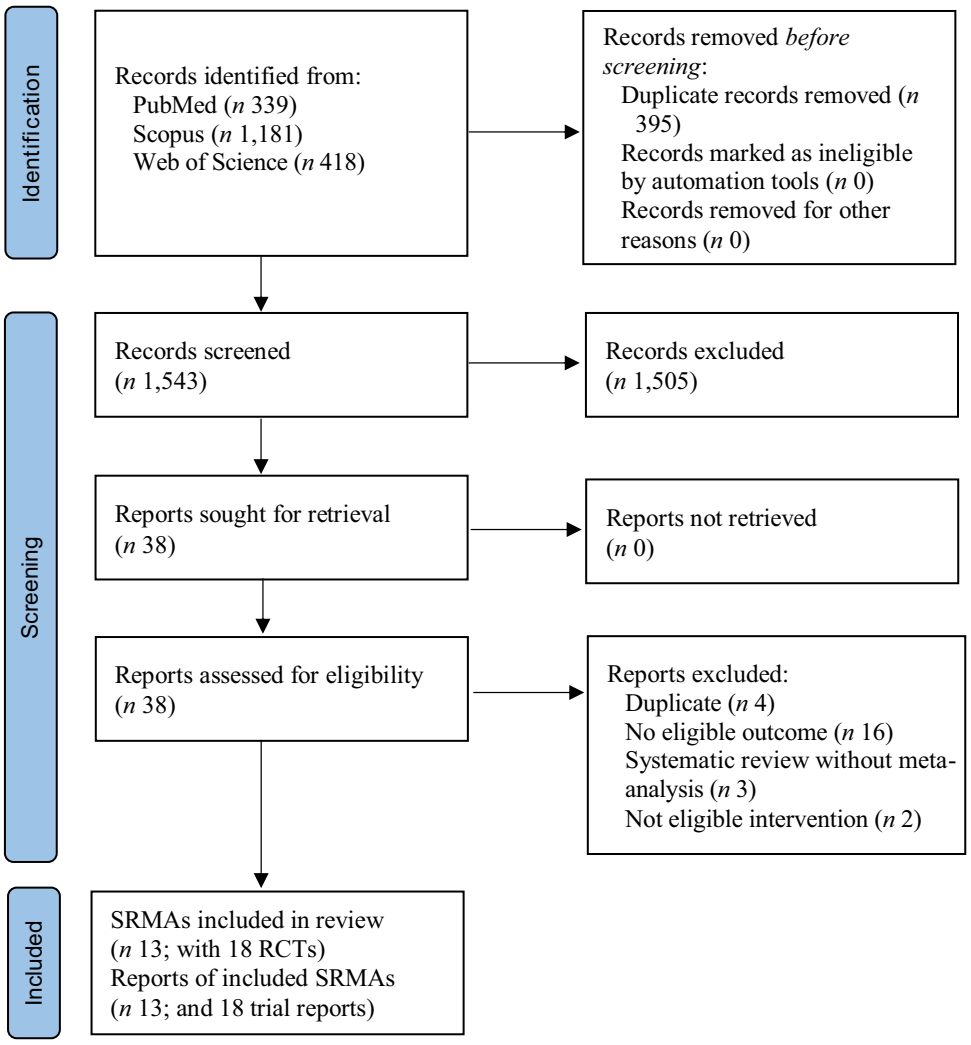

Fig. 1. Flow diagram showing the literature search and study selection process.

Methodological quality of the systematic reviews and meta-analyses

The results of the AMSTAR2 assessment for each SRMA are given in Supplementary Table 3. The main issue of the included SRMA was that the majority did not account for risk of bias when interpreting their results[37–40,42–44,47]. Using the AMSTAR2 framework, we rated the overall quality as high, low and critically low for two (15·4 %)[25,48], nine (69·2 %)[38–46] and two (15·4 %)[37,47] SRMA, respectively.

Methodological quality of the RCTs from the systematic reviews and meta-analyses

The methodological quality of the RCT included from the SRMA was determined based on the Cochrane RoB tool. According to the results, one study was of good quality[60], four were fair[53,54,57,58] and the rest were of poor quality[7,50–52,55,56,59,61–65]. The results are provided in detail in Supplementary Table 4.

Findings of the systematic reviews and meta-analyses

The results of all SRMA generally stated that probiotics can reduce the incidence of diarrhoea in patients receiving anti-cancer treatments; However, in two studies, the result was not statistically significant[39,47]. The main outcome in these studies was the occurrence of diarrhoea of any degree, but in the case of other outcomes, such as varying degrees of diarrhoea or the use of anti-diarrhoeal drugs, there was a discrepancy between the results of the studies[37,40,42]. Hence, the SRMA did not clearly indicate whether probiotics would be effective. However, SRMA of high methodological quality (i.e., a AMSTAR2 rating of high) showed beneficial effects on some outcomes.

Effect of probiotics on the incidence of diarrhoea (any grade)

Of the eighteen RCT, sixteen studies[7,50–53,55–65] from four SRMA reported incidence of diarrhea (any grade) at follow-up. The groups receiving probiotics significantly reduced the incidence

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Table 1. Study characteristics of RCT from the eligible systematic reviews and meta-analyses

First author year (ref.), *country*	Design	Patient population, cancer types and treatment	Intervention(s)	Comparison(s)	Follow-up, weeks	Outcomes (instruments)
Chen 2014[65] *China*	RCT	60 men and women (mean age, 60·25) with colorectal cancer with CT	*Bifidobacterium* + *Clostridium*	Placebo	NR	Diarrhoea (any grade)
Chitapanarux 2010[57] *Thailand*	Parallel, double-blind RCT	63 women (age, 18–65) with cervical cancer with RT	*Lactobacillus* + *Bifidobacterium*, 4×10^9 CFU/g for 7 weeks	Placebo	6 weeks	Diarrhoea (NCI-CTC, any grade, grade ≥ 2, grade ≥ 3) Anti-diarrhoeal drugs (self-reported) Stool consistency (Bristol scale)
Demers 2013[58] *Canada*	Parallel, double- blind RCT	246 men and women with gynaecologic, rectal or prostate cancer with RT for gynaecologic cancers without CT, gynaecologic or rectal cancers with CT	*Bifidobacterium* + *Lactobacillus acidphilus*, $2{\cdot}6 \times 10^9$ CFU/g for one arm and 3×10^9 CFU/g for another arm for 8 weeks	Placebo	10 weeks	Diarrhoea (WHO criteria, any grade, grade ≥ 2, grade ≥ 3) Anti-diarrhoeal drugs (self-reported) Stool consistency (Bristol scale)
Delia 2007[55] *Italy*	Parallel, double-blind RCT	482 men and women (age, 45–65) with sigmoid, rectal or cervical cancer with RT	VSL#3 (four strains of *Lactobacilli*, three strains of *Bifidobacteria* and one strain of *Streptococcus*), $1{\cdot}35 \times 10^{12}$ CFU/g	Placebo	weekly and 4 weeks after RT	Diarrhoea (WHO criteria, any grade, grade ≥ 3)
Delia 2002[56] *Italy*	Parallel, double-blind RCT	188 men and women (age, 45–65) with sigmoid, rectal, or cervical cancer with RT	VSL#3 (four strains of *Lactobacilli*, three strains of *Bifidobacteria* and one strain of *Streptococcus*), $1{\cdot}35 \times 10^{12}$ CFU/g for 6–7 weeks	Placebo	NR	Diarrhoea (WHO criteria, any grade, grade ≥ 2, grade ≥ 3)
Fang 2011[61] *China*	RCT	36 men and women (age, 44–69) with colorectal cancer with CT	*Bifidobacterium*	NR	NR	Diarrhoea (any grade, grade ≥ 2, grade ≥ 3)
Giralt 2008[59] *Spain*	Parallel, double-blind RCT	85 women (age ≥ 18) with endometrial adenocarcinoma or advanced cervical squamous cell carcinoma with RT and CT	*Streptococcus* and *Lactobacillus*, 3×10^8 CFU/g for 5–7 weeks	Placebo	24 weeks	Diarrhoea (NCI-CTC, any grade, grade ≥ 2, grade ≥ 3) Anti-diarrhoeal drugs (self-reported) Stool consistency (Bristol scale)
Linn 2018[53] *Myanmar*	Parallel, double-blind RCT	54 women (age > 18) with cervical cancer with RT	*Bifidobacterium*, *Lactobacillus*, $1{\cdot}75 \times 10^9$ CFU/g for 5 weeks	Placebo	8 weeks	Diarrhoea (NCI-CTC, any grade, grade ≥ 3) Anti-diarrhoeal drugs (self-reported)
Lacouture 2016[54] *USA*	Randomised phase II trial	117 men and women (age, 19–75) with non-small cell lung cancer with CT or RT	VSL#3 (four strains of *Lactobacilli*, three strains of *Bifidobacteria* and one strain of *Streptococcus*) for 4 weeks	Placebo	8 weeks	Anti-diarrhoeal drugs (self-reported)
Liu 2000[62] *China*	Crossover, RCT	44 men and women (age, 35–73) with colorectal cancer with CT	*Lactobacillus*, *Bifidobacterium*, *Streptococcus*, for 3 weeks	NR	NR	Diarrhoea (any grade, grade ≥ 2, grade ≥ 3)
Mego 2015[60] *Slovakia*	Parallel, double-blind RCT	46 men and women (age, 42–81) with colorectal cancer with CT	*Bifidobacterium*, *Lactobacillus*, *Streptococcus*, 10×10^9 CFU/g for 12 weeks	Placebo	12 weeks	Diarrhoea (NCI-CTC; any grade, grade ≥ 2 grade ≥ 3)
Mansouri-Tehrani 2015[52] *Iran*	Parallel, RCT	46 men and women (age, 20–85) with pelvic cancer with RT	*Lactobacillus casei* $1{\cdot}5 \times 10^9$ CFU/ 500 mg *Lactobacillus acidophilus* $1{\cdot}5 \times 10^{10}$ CFU/500 mg *Lactobacillus rhamnosus* $3{\cdot}5 \times 10^9$ CFU/500 mg *Lactobacillus bulgaricus* $2{\cdot}5 \times 10^8$ CFU/500 mg	Placebo	52 weeks	Diarrhoea (NCI-CTC; any grade, grade ≥ 2)

Table 1. (*Continued*)

First author year (ref.), *country*	Design	Patient population, cancer types and treatment	Intervention(s)	Comparison(s)	Follow-up, weeks	Outcomes (instruments)
			Bifidobacterium breve 1×10^{10} CFU/500 mg *Bifidobacterium longum* 5×10^{8} CFU and *Streptococcus thermophilus* $1{\cdot}5 \times 10^{8}$ CFU/500 mg for 5 weeks			Anti-diarrhoeal drugs (self-reported)
Österlund 2007[51] *Finland*	Parallel, RCT	148 men and women (age, 31–75) with colorectal cancer with CT	*Lactobacillus,* 1–2 $\times 10^{10}$ CFU/g for 24 weeks	No intervention	24 weeks	Diarrhoea (WHO criteria, any grade, grade ≥ 3)
Okawa 1993[50] *Japan*	Parallel, RCT	213 women (age, 30–75) with cervical cancer with RT	LC9018 (Yakult, prepared from *Lactobacillus casei*), 0·1 mg twice a week or 0·2 mg once a week during RT, afterward 0·1 mg/2 weeks or 0·2 mg/month for 104 weeks	Placebo	104–208 weeks	Diarrhoea (any grade)
Salminen 1988[7] *Finland*	Parallel, RCT	21 women (age, 40–75) with cervix or uterus carcinoma with CT and RT	*Lactobacillus*, 2×10^{9} CFU/g	Dietary counseling	6 weeks	Diarrhoea (any grade) Anti-diarrhoeal drugs (self-reported)
Urbancsek 2001[49] *Austria*	Parallel, double-blind RCT	205 men and women (age, 19–75) with various cancers with RT*	Antibiophilus1 sachets (*Lactobacillus*), $1{\cdot}5 \times 10^{9}$ CFU/g for 1 week	NR	104 weeks	Anti-diarrhoeal drugs (self-reported)
Wei 2017[64] *China*	RCT	60 men and women with colorectal cancer with CT	*Bifidobacterium*	No intervention	NR	Diarrhoea (any grade, grade ≥ 3)
Yi 2018[63] *China*	RCT	58 men and women (mean age, 60·25) with colon cancer	*Bifidobacterium*	NR	NR	Diarrhoea (any grade)

CT, chemotherapy; NCI-CTC, National Cancer Institute Common Toxicity Criteria; RCT, randomised control trial; RT, radiotherapy; ref, reference; NR, not reported.
* Women (uterus or the ovaries), men (prostatic cancers), rectum cancers and miscellaneous malignancies of the lower abdomen.

of diarrhoea compared with the control group (OR of 0·35; 95 % CI: 0·22, 0·54; $P < 0·001$; RD: −25 %, 95 % CI: −34 %, −15 %; online Supplementary Fig. 1), but with a low certainty of evidence (Table 2 and online Supplementary Table 5). There was substantial heterogeneity between primary studies ($I^2 = 67·7$ %) (online Supplementary Fig. 1). When exploring potential sources of heterogeneity (type of anti-cancer treatment, duration of the intervention, outcome measurement tool, the genus of the probiotics, and the singularity or combination of the probiotics), we found no statistically significant subgroup effects (Table 3). The credibility of the subgroup analyses was all rated as low with the ICEMAN tool for this outcome, as well as for the other outcomes (online Supplementary Table 6). There was no statistically significant publication bias according to Egger's test ($P = 0·172$).

Effect of probiotics on the incidence of grade ≥ 2 diarrhoea

Eight RCT[52,56–62] reported the effect of probiotics on the incidence of diarrhoea of grade 2 or more. The use of probiotics significantly reduced the incidence (OR of 0·43; 95 % CI: 0·25, 0·74, P = 0·004; RD: −20 %, 95 % CI: −29 %, −7 %; online Supplementary Fig. 2), but with low certainty of evidence (Table 2 and online Supplementary Table 5). Egger's test revealed no statistically significant publication bias ($P = 0·999$).

Effect of probiotics on the incidence of grade ≥ 3 diarrhoea

Eleven RCT reported the effect of probiotics on the incidence of grade ≥ 3 diarrhoea. Also, for this outcome, probiotics resulted in a lower incidence of grade ≥ 3 diarrhoea compared with control (OR of 0·30; 95 % CI: 0·15, 0·29; $P = 0·004$; RD: −18 %, 95 % CI: −23 %, −9 %; online Supplementary Fig. 3). However, the certainty of the evidence was rated very low (Table 2 and online Supplementary Table 5). There was substantial heterogeneity between the studies ($I^2 = 67·6$ %). Subgroup analysis could not find the source of heterogeneity (Table 3). There was no indication of publication bias based on Egger's test ($P = 0·566$).

Effect of probiotics on the use of anti-diarrhoeal drug

The effect of probiotic usage on anti-diarrhoeal drug use was assessed in eight RCT[7,49,52–54,57–59]. Participants who received probiotics used on average less frequently anti-diarrhoea medication than those in the control group (OR of 0·49; 95 % CI: 0·27, 0·88; $P = 0·047$; RD: −17 %, 95 % CI: −28 %, −3 %; online Supplementary Fig. 4), but with a low certainty of evidence (Table 2 and online Supplementary Table 5). The heterogeneity between studies was substantial ($I^2 = 63·4$ %), and the source of the heterogeneity could not be identified from our subgroup analyses (Table 3). Based on Egger's test, there was no evidence of publication bias ($P = 0·084$).

Effect of probiotics on the incidence of soft and watery stool consistency

Three RCT evaluated the effect of probiotics on stool consistency. For the incidence of soft stools, there was no difference between the groups (OR of 1·10; 95 % CI: 0·44, 2·76,

Table 2. The effect of probiotic supplementation on diarrhea related to chemotherapy and radiotherapy

Outcomes	Comparison	Number of trials	Comparisons	Number of Participants	Intervention/ Control	Follow-up (range), wk	Dose (range)	Odds ratio*	95 % CI	Absolute effect (%)	95 % CI	*P* value	I^2 (%)	P heterogeneity†	P Egger	Certainty of evidence (GRADE)
Diarrhea																
Any grade diarrhea	Placebo/no intervention/ dietary counseling	16	17	1749	883/866	6–208	3×10^8–$1·35 \times 10^{12}$ CFU/g or 0·1 mg‡	0·35	0·22, 0·54	−25	−34 %, −15 %	< 0·001	67·7	< 0·001	0·172	Low
Diarrhea ≥ grade 2	Placebo	8	9	653	315/338	10–52	3×10^8–$1·35 \times 10^{12}$ CFU/g	0·43	0·25, 0·74	−20	−29 %, −7 %	0·004	48·9	0·048	0·999	Low
Diarrhea ≥ grade 3	Placebo/no intervention	11	12	1351	689/662	8–24	3×10^8–$1·35 \times 10^{12}$ CFU/g	0·30	0·15, 0·59	−18	−23 %, −9 %	0·004	67·6	< 0·001	0·566	Very low
Use of antidiarrheal drug																
Use of anti-diarrheal drug	Placebo/ dietary counseling	8	8	736	355/381	6–104	3×10^8–$2·94 \times 10^{10}$ CFU/g	0·49	0·27, 0·88	−17	−28 %, −3 %	0·047	63·4 %	0·008	0·084	Low
Stool consistency																
Soft stool	Placebo	3	4	291	133/158	10–24	3×10^8–4×10^9 CFU/g	1·10	0·44, 2·76	2	−20 %, −21 %	0·951	49·8	0·113	0·927	Moderate
Watery stool	Placebo	3	4	291	133/158	10–24	3×10^8–4×10^9 CFU/g	0·52	0·29, 1·29	−16	−28 %, 6 %	0·173	61·9	0·049	0·854	Very low

GRADE, Grading of Recommendations Assessment, Development, and Evaluation;wk, week.
* Calculated by quality effects model.
† Calculated by Cochran's Q test.
‡ 0·1 mg twice a week during radiotherapy, afterward 0·1 mg per two weeks.

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Table 3. Subgroup analyses of the effect of probiotics in diarrhoea-related chemotherapy and radiotherapy*

Sub-grouped by	No. of trials	Odds ratio*	95 % CI	I^2 (%)	$P_{\text{for heterogeneity}}$†	$P_{\text{for between subgroup heterogeneity}}$
Incidence of any grade diarrhoea						
Cancer treatment						0·519
Radiotherapy with or without chemotherapy	10	0·34	0·17, 0·67	80·2	< 0·001	
Chemotherapy	6	0·37	0·24, 0·58	0·0	0·884	
Not reported	1	0·17	0·05, 0·57	–	–	
Duration of intervention						0·278
< 8 weeks	8	0·29	0·14, 0·62	78·3	< 0·001	
≥ 8 weeks	5	0·60	0·36, 1·02	31·3	0·213	
Not reported	4	0·24	0·13, 0·45	0·0	0·786	
Assessment criteria						0·944
NCI-CTC	5	0·27	0·08, 0·92	75·9	0·002	
WHO	5	0·40	0·20, 0·78	71·9	0·007	
Not reported	7	0·32	0·15, 0·66	64·0	0·011	
Genus of probiotics						0·064
With bifidobacterium	13	0·29	0·29, 0·43	44·3	0·08	
Without bifidobacterium	4	0·67	0·29, 1·56	70·9	0·02	
Single *v.* Combined Strains of Probiotics						0·149
Combine	10	0·31	0·18, 0·51	55·2	0·017	
Single	7	0·41	0·20, 0·84	72·1	0·001	
Incidence of ≥ grade 3 diarrhea						
Cancer treatment						0·309
Radiotherapy with or without chemotherapy	7	0·35	0·13, 0·96	80·1	< 0·001	
Chemotherapy	5	0·32	0·17, 0·60	0·0	0·439	
Duration of intervention						0·061
< 8 weeks	5	0·34	0·09, 1·21	68·1	0·014	
≥ 8 weeks	4	0·55	0·32, 0·93	0·0	0·550	
Not reported	3	0·09	0·04, 0·17	0·0	0·882	
Assessment criteria						0·298
NCI-CTC	4	0·36	0·07, 2·00	52·8	0·95	
WHO	5	0·31	0·13, 0·74	78·1	0·001	
Not reported	3	0·14	0·04, 0·49	0·0	0·821	
Genus of probiotics						0·122
With bifidobacterium	10	0·22	0·11, 0·43	47·8	0·045	
Without bifidobacterium	2	0·80	0·26, 2·43	73·4	0·053	
Single *v.* Combined Strains of Probiotics						0·340
Combine	8	0·24	0·11, 0·53	52·7	0·03	
Single	4	0·43	0·14, 1·30	67·2	0·03	
Use of antidiarrhoeal drug						
Duration of intervention						0·234
< 8 weeks	6	0·53	0·26, 1·08	67·8	0·008	
≥ 8 weeks	1	0·52	0·25, 1·06	–	–	
Not reported	1	0·07	0·01, 0·75	–	–	
Genus of probiotics						0·710
With bifidobacterium	6	0·40	0·17, 0·93	67·9	0·014	
Without bifidobacterium	2	0·61	0·21, 1·74	67·0	0·048	
Single *v.* Combined strains of probiotics						0·710
Combine	6	0·40	0·17, 0·93	67·9	0·014	
Single	3	0·61	0·21, 1·74	67·0	0·048	

NCI-CTC, National cancer institute Common Toxicity Criteria.
* Calculated by quality-effects model.
† $P_{\text{heterogeneity within subgroup}}$.

$P = 0{\cdot}951$; RD: 2 %, 95 % CI: −20 %, 21 %; moderate certainty of evidence; online Supplementary Fig. 5; Table 2 and online Supplementary Table 5). The incidence of watery stool was lower in the intervention group compared with the comparator group (OR of 0·52; 95 % CI: 0·29, 1·29; $P = 0{\cdot}173$; RD: −16 %, 95 % CI: −28 %, 6 %; very low certainty of evidence online Supplementary Fig. 6; Table 2 and online Supplementary Table 5), but it was not statistically significant. Based on Egger's test, there was no evidence of publication bias for any of the two outcomes ($P_{\text{for soft stool}} = 0{\cdot}927$; $P_{\text{for watery stool}} = 0{\cdot}854$).

Adverse events

Adverse events were reported for eight RCT. In four of these, no adverse effects were observed from probiotic use[55,57,59,60]. In one trial[58], a few cases of neutropenia were seen during treatment. In another study[52], three patients complained of upper abdominal pain, and 45 patients reported bloating during treatment, of which 35 patients belonged to the intervention group and 10 to the control group. As a result of intradermally injected LC9018 (a biologic response modifier prepared from heat-killed

Lactobacillus casei YIT9018), nine cases of fever were reported; in addition, complications such as pain, tenderness, induration, swelling, necrosis, and abscess formation at the injection site were reported[50]. In the study by Urnancseka *et al.*[49], following intake of *Lactobacillus rhamnos*, three participants showed side effects. In the intervention group, one participant reported mild to moderate gastrointestinal problems, and in the control group, two patients reported moderate to severe gastrointestinal problems and one labial edema.

Discussion

In this overview of SRMA, we included thirteen SRMA contributing eighteen RCT, assessing the efficacy of probiotics on radiation and chemotherapy-related diarrhoea. The SRMA did not clearly indicate whether probiotics would be effective. However, well-performed SRMA showed a beneficial impact on some outcomes. According to our meta-analyses, probiotics markedly reduced the incidence of diarrhoea, regardless of severity, and the use of anti-diarrhoeal medications compared with the control group; however, the evidence certainty ranged from very low to low. Additionally, we did not observe any significant effects on the incidence of watery and soft stools.

Our meta-analysis findings of the RCT were generally consistent with conclusions of the included SRMA that indicated a decrease in chemotherapy or radiotherapy-related diarrhoea from intake of probiotics[37,42]. The majority of SRMA[37,38,40,43,44] were conducted on patients who received radiotherapy; however, in our analysis, individuals who had only undergone chemotherapy were also included. The SRMA conducted by Fuccio *et al.*[39] concluded that the use of probiotics did not provide beneficial effects for individuals getting chemotherapy and/or radiotherapy. This discrepancy with our results might be due to their low number of included studies (four trials in their analysis *v.* eighteen trials in our analysis) and the low sample size (793 *v.* 2152 patients), which may decrease the statistical power to detect any effects.

The SRMA by Wardill *et al.*, which analysed data from seven trials (1091 patients), found a reached a similar conclusion of no beneficial effects from probiotics[47]; however, positive results were obtained in the radiotherapy group, which might explain why the 'Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology' (MASCC/ISO) recommends *Lactobacillus* for preventing diarrhoea in pelvic cancers[66].

Systemic chemotherapy causes changes in the gut microorganisms[67]. The phenotype of the gut bacteria shifts from *Lactobacillus* to *Escherichia coli* as a result of high-dose chemotherapy[68]. As a result, probiotics containing *Lactobacillus* have shown to be effective in chemotherapy-induced diarrhoea[69,70]. Several mechanisms have been proposed for the effective action of probiotics in diarrhoea caused by cancer treatments. Probiotics exert beneficial effects by modifying dysbiosis, lowering intestinal pH, stimulating and regulating immune cell function, downmodulation apoptosis, lactase production, and aiding lactose digestion[58,71–73]. Spencer *et al.* found that mice who received probiotic supplements had more diverse microbiota than the control group in a study on mice with melanoma cancer[74]. Additionally, interferon γ, CD^+8, and the frequency of toxic T cells were significantly lower in the probiotic supplementation group[74]. However, a previous narrative review indicated that the effects of probiotics are strain specific[75]. Thus, these beneficial effects could not be attributed to all strains of probiotics. Although probiotics reduced any grade, grade ≥ 2, and grade ≥ 3 diarrhoea, the effects of probiotics on any grade and grade ≥ 3 are uncertain due to their very low and low certainty of evidence, respectively, as found in this overview of SRMA. Our subgroup analyses did not indicate any clear reason for the observed heterogeneity between studies. However, for the incidence of diarrhoea (any grade), the subgroup with the genus without *Bifidobacterium* did not reach significance, and for grade 2 and grade 3 diarrhoea, a single probiotic supplement did not reach significance. However, these subgroups include only few RCT, reducing the precision of the estimates.

This overview of SRMA has several strengths, but also some limitations. To our knowledge, this overview is presenting the most complete and comprehensive summary of the effects of probiotics on diarrhoea caused by radiation and chemotherapy. Our search strategy was comprehensive by involving many keywords applied to three electronic databases as well as screening references lists. Our study selection and data extraction were conducted by two independent investigators, increasing the methodological quality. We evaluated the methodological quality of the included SRMA and their RCT, and we evaluated the certainty of the evidence using the GRADE method. However, our study also had some limitations. Since we included RCT from SRMA, there is a risk that some newly published RCT were not identified for this study. The included RCT were heterogeneous in terms of criteria for evaluating diarrhoea, sex distributions (several RCT included women only) and chemotherapy regimens and types of radiotherapy. For some outcomes, only few RCT reported data, especially for stool consistency. Also, many SRMA and RCT were of low methodological quality, contributing to the low quality of evidence of our findings.

Conclusion

In conclusion, this overview of SRMA found evidence that probiotics can reduce the incidence of diarrhoea in cancer patients, as well as the need for anti-diarrhoeal medication. However, the certainty of evidence ranged from very low to low. There is an urgent need for high-quality RCT with a large sample size, better study design and more complete outcome assessment to provide high-quality evidence for the effects of probiotics on chemotherapy and radiotherapy-related diarrhoea as well as explore potential subgroup effects.

Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S0007114523000910

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