Original Article

Probiotics in preventing and treating chemotherapy-induced diarrhea: A meta-analysis

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Background and Objectives: To systematically assess the safety and effectiveness of probiotics in preventing and treating chemotherapy-induced diarrhea (CID), so as to provide the evidence-based evidence for clinical practice. **Methods and Study Design:** Electronic databases, including EMbase, Cochrane Library, pubMed, CNKI, VIP, CBM, and Wanfang databases, were retrieved to search for the randomized controlled trials (RCTs) of CIDs among patients with malignant tumors treated with probiotics as of March 2019. Later, the Rev Man 5.3 statistical software was employed to extract data and assess the quality of the identified literature for meta-analysis. **Results:** Finally, 13 RCTs involving a total of 1024 patients were included into the current meta-analysis. Results of this meta-analysis showed that the addition of probiotics to conventional symptomatic treatment could evidently reduce the total diarrhea rate in patients with cancer [RR=0.47, 95% CI (0.35, 0.63), p<0.00001] and grade III-IV diarrhea [RR=0.16, 95% CI (0.05, 0.42), p=0.0008], increase the total effective rate [OR=4.26, 95% CI (2.55, 7.12), p<0.00001], and shorten the duration of diarrhea [MD=-1.92, 95% CI (-1.96, -1.88), p<0.00001]; meanwhile, the difference was statistically significant. But in patients with grade I-II diarrhea [RR=0.81, 95% CI (0.53, 1.24), p=0.34], the difference was not statistically significant. Besides, none of the enrolled study had reported adverse reactions. **Conclusions:** The application of probiotics before or during chemotherapy can effectively prevent the occurrence of CID among cancer patients. Moreover, the combination of probiotics in treating CID can also improve the therapeutic effect on CID, with less adverse events.

Key Words: probiotic preparation, chemotherapy, diarrhea, chemotherapy-induced diarrhea, randomized controlled trial

INTRODUCTION

Chemotherapy is one of the major treatments for malignant tumors, and chemotherapy-induced diarrhea (CID) is one of the most common adverse reactions during chemotherapy.[1] CID can be caused by a variety of chemotherapeutics, among which, 5-fluorouracil (5-FU) as well as irinotecan (CPT-11) has accounted for the greatest proportion of up to 50% to 80%.[2] CID will not only reduce the quality of life and extend the length of hospital stay, but also lead to serious circulatory failure, such as electrolyte imbalance and chemotherapy-related death; as a result, it may interrupt cancer treatment, lower the cure rate, increase the treatment cost, and thus worsen the disease prognosis.

Given the complexity of primary disease and the diversity of chemotherapeutics, no uniform treatment for CID is available currently. The guidelines for preventing and treating cancer chemotherapy-induced diarrhea in 2014 recommends that loperamide,[3] which can inhibit the intestinal peristalsis, can be used as a first-line drug for CID; while octreotide, which can inhibit the intestinal secretion, can not only be used as a first-line drug for CID at grade III or higher, but can also be used for patients with persistent diarrhea after grade I and II CID or for those with high risk factors for loperamide. However, the

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clinical efficacy remains unsatisfactory.[4]

Studies have shown that most CID patients are associated with dysbacteriosis, increased intestinal mucosal permeability, and destroyed intestinal mucosal barrier. Glutamine, celecoxib, probiotics, and activated carbon are recommended in the guidelines to prevent and treat CID, nonetheless, the evidence-based medical support is lacking so far. Probiotics include lactobacilli, bifidobacteria and yeast, which can maintain the hemostasis of the intestinal microenvironment by regulating the intestinal flora,[5,6] but the findings on its use to control CID are still controversial.

Therefore, this meta-analysis aimed to systematically evaluate the safety as well as effectiveness of probiotics in preventing and treating CID, so as to provide the evidence-based medical support for clinical practice.

METHODS

Inclusion criteria

Study types

All randomized controlled trials (RCTs, published in peer-reviewed journals at home and abroad) regarding the single or combined use of probiotics for CID, together with cross-study and parallel studies meeting the requirements would be included in the review, with no requirement for language or blindness.

Subjects

Tumor patients diagnosed histopathologically or cytologically, with no history of diarrhea before chemotherapy, or other diarrhea susceptibility factors; there was no requirement for gender, age, race or nationality.

Interventions

CID prevention: The control group was only given conventional supportive treatment, such as pre-treatment and rehydration before chemotherapy. The experimental group was given probiotics based on the conventional treatment. CID treatment: The control group was given conventional symptomatic treatment like drug therapy and placebo alone. The experimental group was given probiotic preparation coupled with conventional symptomatic treatment.

Types of outcome indicators and efficacy evaluation criteria

(1) total effective rate; (2) total incidence of diarrhea; (3) incidence of grade I-II diarrhea; (4) incidence of grade III-IV diarrhea; and (5) diarrhea duration. Diarrhea can be classified as grades I to V in accordance with the Common Terminology Criteria for Adverse Events (edition 4.0) from the National Cancer Institute (NCI-CTCAE 4.0).7Among them, grade I refers to increased frequency of bowel movement compared with baseline (<4 times/day), and slightly increased diarrhea; grade II indicates increased frequency of bowel movement (4-6 times/day), and moderately increased diarrhea; grade III suggests that the frequency of bowel movements is increased by 7 or more, with severely increased excretion that may even be lift-affecting; grade IV diarrhea is life-threatening, which requires urgent treatment; and grade V diarrhea will lead to death. Additionally, complete remission (CR) is defined as that the frequency of bowel movement and traits of stool return to normal within 72 h, and the systemic symptoms are alleviated. partial remission (PR): the bowel movement frequency and stool traits are significantly improved within 72 h after medication, and the systemic symptoms are dramatically improved. Invalid: the bowel movement frequency, or stool traits or systemic symptoms were not improved after 72 h of treatment, or were even worsened. Meanwhile, the total effective rate was calculated as follows, total effective rate = (number of PR cases + number of CR cases) / total number of cases × 100%.

Exclusion criteria

(1) studies with incomplete relevant data or with no relevant outcome indicator; (2) studies with inappropriate diagnostic criteria for CID; (3) RCTs that combined radiotherapy; (4) duplicate publication.

Literature search

The electronic databases, including PubMed, Cochrane Library, EMBASE databases, were retrieved to identify eligible studies using the key words of “probiotics” or “Yeast” or “Bifidobacterium” or “Lactococcus” or “Lactobacillus”, “chemotherapy-induced diarrhea” or “chemotherapy and diarreha”, “randomized controlled trials” or “clinical trials”. Besides, the key words of “probiotics” or “Bifidobacteria” or “Lactobacillus” or “Bacillus subtilis” or “peifeikang” or “Intestinal Health”, “Chemotherapy-associated Diarrhea” or “CID”, “Randomized Controlled trials” or “clinical research” were used to retrieve four Chinese databases, including China Knowledge Network (CNKI), Wanfang database, VIP database and China Biomedical Database (CBM), from inception to February 2019. To collect more papers, any relevant RCTs were included, with no restriction of publication language. Additionally, the bibliography of relevant research was also searched to identify other clinical trials for reference. The specific search strategy is shown in Table 1, with pubmed as an example.

Data collection and analysis

Data selection

After the initial database retrieval, the duplicated documents were deleted and the eligible studies searched from the above databases were transferred to the database created by endnotesx7. Then, the clinical literature was read, identified, and selected by two researchers independently based on the established criteria, and the detailed reasons for study elimination should be recorded. Any disagreement between them would be resolved through negotiation, or the consultation of a third party if no consensus could be reached.

Data extraction

A unified data extraction table was developed to extract the characteristics of CID-related literature based on the Cochrane systematic review criteria. In this study, the following data were extracted, including name of first author, publication year, diagnostic criteria, type of intervention, randomized method of treatment time, allocation concealment, blinded implementation, observation of the

Table 1. Pubmed retrieval strategy†

Step	Search strategy
#1	(((((chemotherapy) AND diarrhea)) OR chemotherapy-induced diarrhea) OR CID)
#2	(((((Yeast) OR Bifidobacterium) OR) OR Lactococcus) OR probiotics) OR Lactobacillus
#3	(((randomized controlled trial [pt]OR controlled clinical trial [pt]OR randomized controlled trial [mh]OR double-blind method [mh] OR single-blind method[mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial") [tw] OR singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw] AND (mask* [tw] OR blind* [tw])) OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospective* [tw] OR volunteer* [tw] NOT (animals [mh] NOT humans [mh]).)))NOT ((systematic reviews OR meta-analysis))) NOT (((Cohort studies or case reports or Letter or Historical Article or comment).pt))) NOT (((comment OR editorial OR meta-analysis OR practice-guideline OR review OR letter OR journal correspondence)))
#4	#1 and #2 and #3

CID: chemotherapy-induced diarrhea
†Table 1 shows literature screening process, Medical subject headings (Mesh) combined with free word retrieval were used.

subject, efficacy judgment indicators, research results, and adverse events.

Assessment of risk of bias

The methodological quality was assessed by two evaluators based on the biased evaluation criteria according to the Cochrane Handbook (version 5.1.0).[8] The evaluation criteria included: (1) generation of random sequence, (2) concealment of allocation, (3) blind method among the subjects as well as staff, (4) blind method regarding outcome evaluation, (5) not sufficient outcome information, (6) selectively reported results, and (7) other biases. Typically, bias is classified as low, high or unclear risk; when all seven domains of the tool are divided into the low bias risk, it can be judged that the included trial has a low bias risk.

Data Analysis

Statistical analysis was performed using the RevMan 5.1 statistical software (Cochrane Collaboration). Besides, the heterogeneities among all the enrolled studies would be evaluated before carrying out meta-analysis, among which, clinical as well as methodological heterogeneities would be evaluated on the basis of the recorded information in the extraction form, while statistical heterogeneity would be evaluated through the homogeneity of the Mantel-Haenszel chi-square test. Typically, Cochrane Q and I^2 can be used to assess heterogeneity, among them, Q statistic is defined as the weighted sum of the squared deviations of all study estimates, $p < 0.1$ which indicates the statistical significance of heterogeneity, whereas the I^2 statistic is defined as the observed percentage, with 0-25% suggesting no heterogeneity, 25-50% indicating moderate heterogeneity, 50-75% representing significant heterogeneity, and 75-100% denoting heterogeneity. A random effects model (DerSimonian-Laird method) would be chosen in the presence of heterogeneity among studies (Q statistic $p<0.1$ or $I^2>50\%$). Otherwise, a fixed effect model (Mantel-Haenszel method) would be used. Besides, the similar test was also combined for meta-analysis. If there were enough data, subgroup analysis might be performed based on different variables, including various interventions and outcome measures. The outcome measures for dichotomous data would be presented in the form of risk ratio (RR) and 95% CI, while those for continuous data were expressed as the standard mean difference (SMD) and 95% CI. Sensitivity analysis would be performed if there was still significant heterogeneity after subgroup analysis. Results of sensitivity analysis could be adopted if they would not result in a change in the analysis results, and the results of the meta-analysis should be interpreted with caution.[9]

RESULTS

Literature search results

980 papers were obtained from the preliminary retrieval, and 357 duplicates were excluded. Afterwards, the article titles and abstracts were read, 576 irrelevant studies were excluded, and 47 research papers were initially included. Then, the full texts of the initially enrolled studies were selected for detailed screening, among them, 17 non-RCTs and 16 animal studies were removed. Meanwhile, one article could not find the full text, and 13 (item) studies were finally included.[10-22] The literature screening process is as follows (Figure 1).

Altogether 1032 cases involving 13 studies were enrolled, among them, 520 cases were in experimental group, while 512 were in control group. The basic research information included in the study is as follows (Table 2). All experimental groups and control groups involved in the enrolled articles had been randomly grouped. The study by Mego et al had applied the double-blind method and allocation concealment, while other studies did not mention the specific blind method or allocation concealment.[22] All study data were complete and non-selective, and the baseline was comparable between the two groups. Results of the quality evaluation of the included studies are as follows (Figure 2A, Figure 2B)

Meta-analysis results

Total diarrhea rate

Six included studies, involving a total of 441 patients, had reported the total incidence of CID.[11-13,19-20,22] The heterogeneity test indicated that there was no statistical heterogeneity among the studies (p=0.80, I^2=0%), so the fixed effect model (FEM) was adopted. The results showed thatRR=0.47, 95% CI (0.35, 0.63), $p<0.00001$, which suggested that the difference between the two groups was statistically significant, indicating that probiotics could dramatically reduce the overall incidence of CID (Figure

Figure 1. Literature retrieval and screening procedure.

3).

Total efficiency

Seven studies recruiting a total of 605 patients had mentioned the total effective rate (ORR).[10,13-18] The heterogeneity test indicated that there was no statistical heterogeneity between the studies (p=1.00, I^2=0%), so the FEM was adopted. The results were as follows: OR=4.26, 95% CI (2.55, 7.12), p<0.00001, which revealed a statistically significant difference between the two groups, indicating that the combination of probiotics could remarkably increase the ORR of CID compared with conventional symptomatic treatment (Figure 4).

Grade I-II diarrhea rate

Four studies involving 186 patients had reported the grade I-II diarrhea rates.[11-12,20,22] The heterogeneity test demonstrated no statistical heterogeneity between the studies (p=0.95, I^2=0%), so the FEM was utilized. The results were RR=0.81, 95% CI (0.53, 1.24), p=0.34, which suggested no statistical difference between the two groups, indicating that probiotics had the same preventive effect on grade CID I-II as a conventional supportive care (Figure 5).

Grade III-IV diarrhea rate

Four studies including 186 patients had reported grade III-IV diarrhea.[11-12,20,22] The heterogeneity test indicated no statistical heterogeneity between the studies (p=0.69, I^2=0%), so the FEM was employed. The results were RR=0.16, 95% CI (0.05, 0.42), p=0.0008, which had indicated a statistical difference between the two groups, revealing that probiotics could dramatically reduce the rate of severe diarrhea (Figure 6).

Duration of diarrhea

Five studies involving 512 cases had mentioned the duration of diarrhea.11-12, 20-22 The heterogeneity test indicated no statistical heterogeneity between the studies (p=0.30, I^2=18%), so the FEM was utilized. The results were MD=-1.92, 95% CI (-1.96, -1.88), p<0.00001, which had suggested a statistically significant difference between the two groups, indicating that probiotics could outstandingly reduce the duration of diarrhea (Figure 7).

Security

None of the 13 included studies had reported obvious adverse events, which suggested that probiotics could safely and effectively assist in preventing and treating CID, and were worthy of further research and promotion

Publication bias analysis

The inverted funnel chart was used as the criterion to evaluate the publication bias, while the total diarrhea rate and total effective rate ORR were used as the research indicators. As could be seen from the results, the inverted funnel plot was basically symmetric to the left and right, suggesting a low possibility of publication bias among the enrolled studies (Figure 8A, Figure 8B).

DISCUSSION

In this review, we summarised available evidence from RCTs assessing the effects of probiotics for prevention or treatment of CID. We included 13 studies involving 1032

Table 2. Basic characteristics of the articles included in this study†

Author	Country	published date	Sample size		Chemotherapy	Intervention		Purpose of medication	Outcome indicator
			Therapy group	Control group		Therapy group	Control group		
Fangzhi Chang[10]	China	2007	21	23	GC:FAM; CRC:5-Fu+CF	Octreotide+ conventional treatment+ peficon	Octreotide + conventional treatment	Therapy	①
Huizhang Wei[11]	China	2017	30	30	CPT-11+5-Fu	Chemotherapy+Bifidobacterium	Chemotherapy	prevention	②③④⑥
Liping Fang[12]	China	2011	18	18	CPT-11	Chemotherapy+Bifidobacterium	Chemotherapy	prevention	②③④
Shaohua Le[13]	China	2011	58	58	CAM	Bacillus li- cheniformis capsul	Placebo	Prevention +Therapy	②⑥
Shuwen Liang[14]	China	2014	44	41	XELOX	Conventional treatment+ pfeiffer + Smecta	Conventional treatment + Smecta	Therapy	①⑥
Yuerong Yao[15]	China	2017	63	63	Chemotherapy	Loperamide + Bifidobacterium	Loperamide	Therapy	①⑥
Dongmei Zhang[16]	China	2013	30	30	FOLFOX4	Bacillus li- cheniformis capsule+conventional treatment	Montmorillonite + conventional treatmen	Therapy	①
Xuefeng Zhou[17]	China	2017	45	63	Chemotherapy	Montmorillonite powder + conventional treatment + bifidobacteria	Montmorillonite + conventional treatmen	Therapy	①
Yongjun He[18]	China	2014	55	53	Chemotherapy	Bacillus subtilis+ loperamide + conventional treatment	Conventional treatment + Smecta	Therapy	①
Miao Ao[19]	China	2012	74	51	HD-MTX	Bifidobacterium	Placebo	prevention	②⑥
Jiwei Liu[20]	China	2000	22	22	5-Fu+paclitaxel	Chemotherapy+Bifidobacterium	Chemotherapy	prevention	②③④
Xianxu Zhuang[21]	China	2015	37	37	Chemotherapy	Bifidobacterium+conventional treatmen	Conventional treatment	Therapy	①
Michal Mego[22]	Slovakia	2015	23	23	CPT-11+5-Fu	Bifidobacterium+Lactobacillus	Placebo	prevention	②③④

GC: Gastric Cancer; FAM: 5-Fluorouracil + Adriamycin + Mitomycin; CRC: Colorectal Cancer; 5-Fu:5-Fluorouracil; CF:citrovorum factor; CPT-11: Irinotecan; CAM: Cyclophosphamide + Cytarabine + Mercaptopurine; XELOX: Oxaliplatin + Xeloda; FOLFOX4: 5-Fluorouracil + Oxaliplatin + Folinic acid calcium salt hydrate; HD-MTX: High dose methotrexate

†Table 2 shows basic characteristics of the included studies, only one study was conducted in Slovakia and the other were all conducted in China. Five of them were prevention of CID and 8 were treatment of CID.

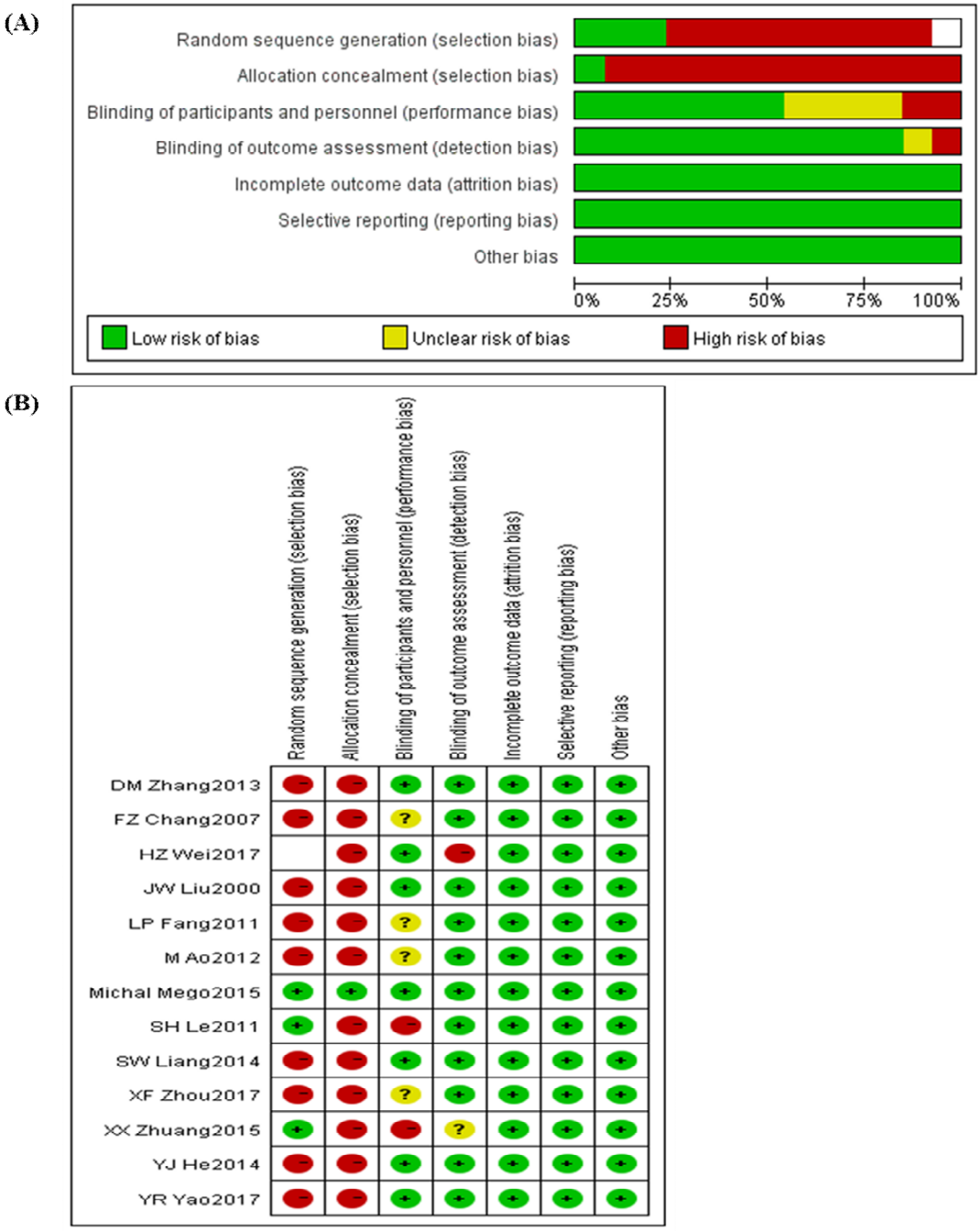

Figure 2. (A) Graph of risk of bias; (B) Summary of risk of bias.

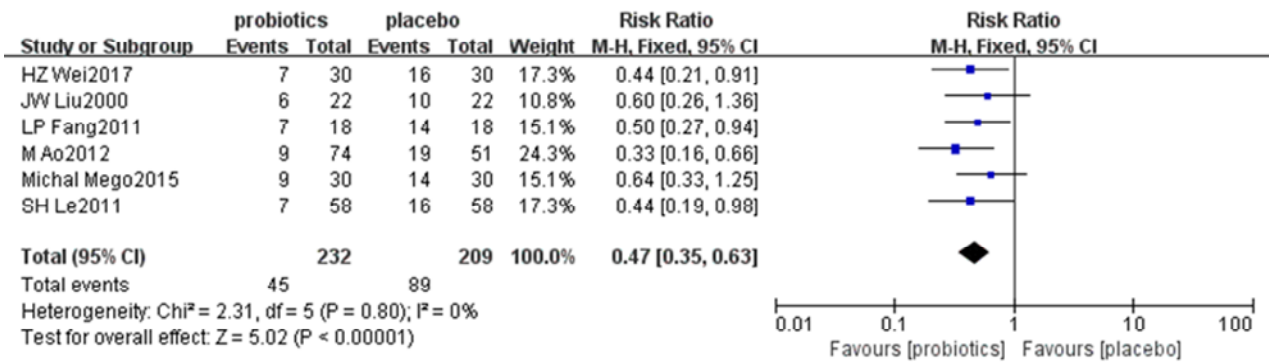

Figure 3. Forest plot of meta-analysis of total diarrhea rate in 2 groups.

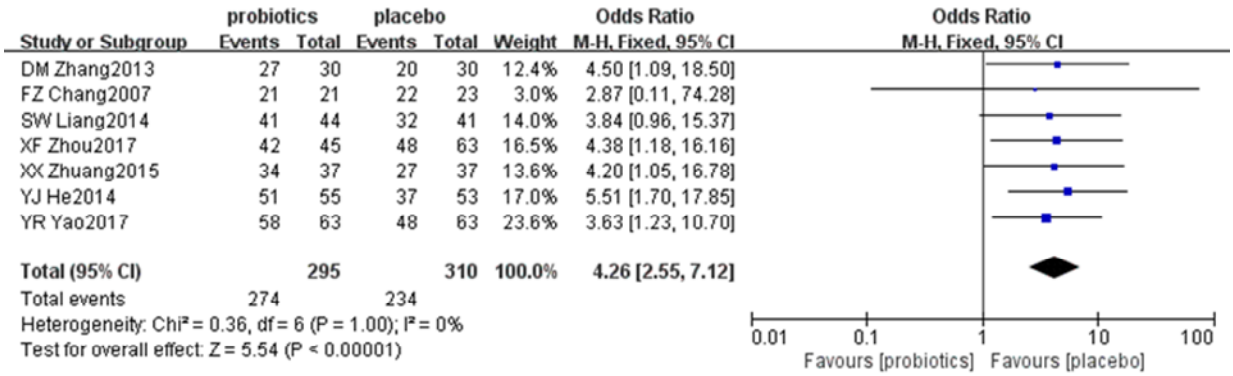

Figure 4. Forest plot of meta-analysis of overall response rate in 2 groups

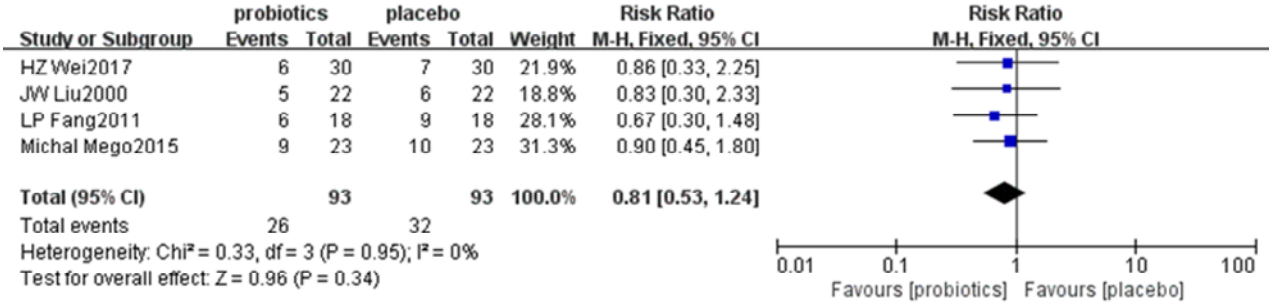

Figure 5. Forest plot of meta-analysis of grade I-II diarrhea rates in 2 groups

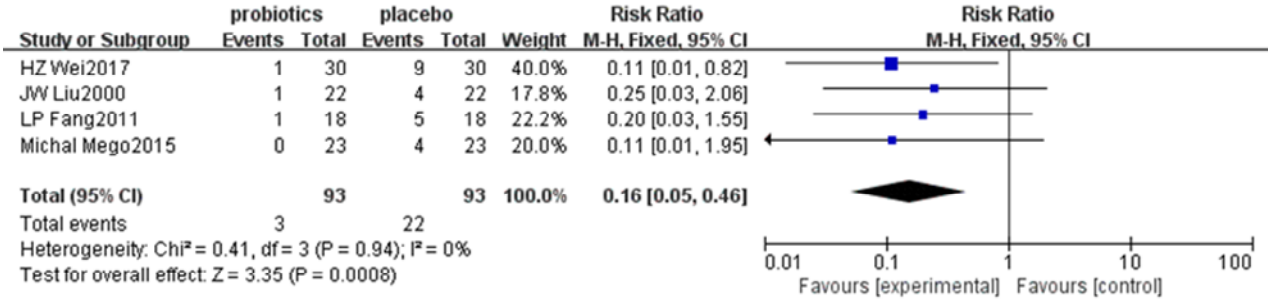

Figure 6. Forest plot of meta-analysis of grade III-IV diarrhea rates in 2 groups

participants. Six were prevention studies; three of these compared probiotics with conventional treatment (140 participants), and three compared probiotics with placebo (287 participants). Eight were treatment studies, six of these compared probiotics with another active agent (531 participants), one of these compared probiotics with conventional treatment (74 participants), the remaining study compared probiotics with placebo (116 participants) and it was also a prevention study.

Summary of main results

For prevention of chemotherapy-induced diarrhoea, we identified five studies including 427 participants. Researchers could demonstrate a beneficial effect of probiotics on occurrence of total diarrhoea rate (RR 0.47, 95% CI 0.35, 0.63), severity of diarrhoea and revealed a beneficial effect for the occurrence of grade 3 or higher diarrhoea (RR 0.16, 95% CI 0.05, 0.42) but showed no effect on the occurrence of grade I-II diarrhea rate (95% confidence interval (CI) 0.53 to 1.24). No studies reported serious adverse events or diarrhoea-related adverse events (low certainty of evidence).

Eight studies examined treatment for CID. These studies compared probiotics versus placebo or another active agent or conventional treatment in 721 participants. Seven of these could demonstrate a beneficial effect of probiotics on total efficiency, (OR 4.26, 95% CI 2.55, 7.12) and five of them showed a beneficial effect of probiotics on duration of diarrhea (MD-1.92, 95% CI -1.96, -1.88). They reported no difference in the occurrence of serious adverse events.

Significance of the study

CID, a common gastrointestinal adverse reaction following radiotherapy and chemotherapy, has caused problems in tumor patient's quality of life. Numerous animal and clinical studies show that, the gut microbiota in patients receiving chemotherapy are markedly changed; for instance, significant reductions in bifidobacteria, Clostridium group XIVa, and Clostridium genus, and increases

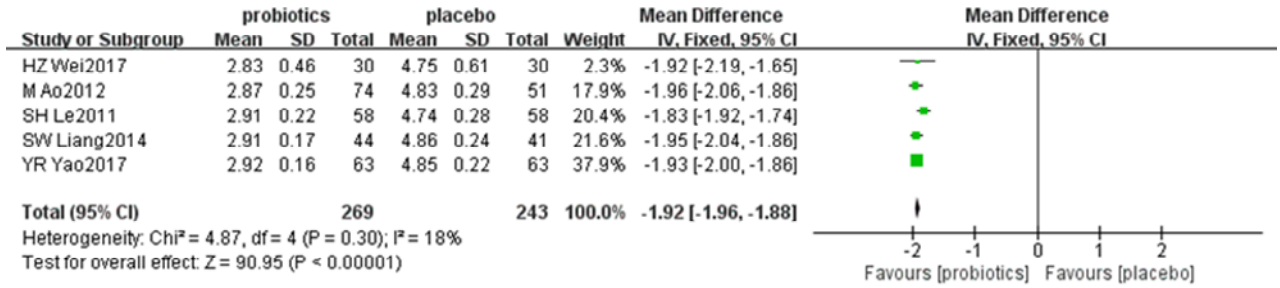

Figure 7. Forest plot of meta-analysis of grade III-IV diarrhea rates in 2 groups

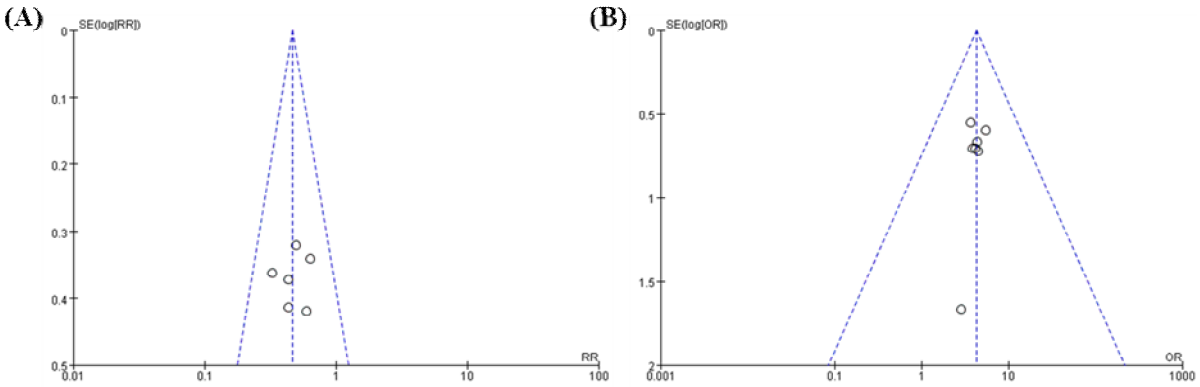

Figure 8. (A) Inverted funnel plot of total rate of diarrhea; (B) Inverted funnel plot of overall response rate

in Enterobacter and Bacteroides, which can result in intestinal mucositis, finally leading to diarrhea.[23]

Probiotics are the active microorganisms, and their roles in preventing and treating gastrointestinal adverse reactions after chemotherapy has been confirmed in animal and clinical studies.[24-26] The precise mechanisms include inhibiting the adhesion and growth of harmful bacteria onto the gastrointestinal mucosa, enhancing the mucosal barrier function of the gastrointestinal mucosa, repairing the jejunal villus damage, down-regulating the mRNA expression of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6) and interleukin-1β (IL-1β), and exerting the immunomodulatory effects. In this way, probiotics can reduce the severity of diarrhea, abdominal discomfort and intestinal toxicity. However, due to the limitations of various research designs, sample sources and sample sizes, the results on using probiotics to prevent and treat CID are inconsistent, and it is impossible to draw a convincing public opinion. Therefore, our research group had investigated and analyzed the effect of probiotics on preventing and treating CID based on practical clinical needs, hoping to provide the effective evidence-based medical reference for the clinical prevention and treatment of CID.

Limitations

The current meta-analysis was inevitably associated with some limitations, as displayed below.

(1) Geographical distribution: Radiotherapy-induced diarrhea was included in the exclusion criteria, therefore, the literatures on diarrhea caused by radiotherapy or combined with radiotherapy were excluded. So, the 13 studies included in this metaanalysis were 12 conducted in China and published in the Chinese language,only one conducted in Slovakia and published in the English.

(2) Poor methodological quality: only six of the enrolled studies had employed a random number table for participant groupingand no studies had reported withdrawals and dropouts.[10,11,16,18,19,22] Additionally, only one study had mentioned random sequence generation, allocation concealment, blinding of participants and personnel, or blinding of outcome assessments.[22] Moreover, there was no multicenter trial, and a majority of the included studies had a small sample size.

(3) Evident heterogeneity: The source of heterogeneity in evidence-based medicine is related to numerous factors. In this study, the sources of heterogeneity included the treatment strategy (probiotic strain, dose and treatment time), age, tumor type and outcome index. For prevention of CID, three placebo-controlled studies with 287 participants and three conventional treatment-controlled studies with 140 participants are currently available, but the number of studies evaluating prevention of CID is too less, so the evidence was low certainty. For treatment of diarrhoea, we identified eight studies. Comparisons of probiotics versus other active treatments were performed in five studies and providing evidence of middle certainty. Although two studies compared probiotics versus placebo or conventional treatment revealed a beneficial effect of probiotics, it provided evidence of low to very low certainty. But according to the above results, the heterogeneity among the enrolled studies was low, and subgroup analysis or sensitivity analysis was not required to eliminate the heterogeneity. Firstly, only 13 articles were included in this study, English literature was lacking, only one study was conducted in Slovakia and the other were all conducted in China.[22] Secondly, the number of patients

in each RCT was quite different, which was basically low. Thirdly, the randomized method of most studies (namely, blind method or allocation concealment) were not described in detail, and there might be heterogeneity between studies. Fourthly, the results of the included studies were all positive results, for the security, some of which did not involve adverse events, and some did not show significant adverse events, which might cause publication bias and other biases, thus reducing the reliability of our meta-analysis results. Last but not least, all RCTs All did not involve the assessment of quality of life, but long-time CID will inevitably lead to a reduction in quality of life, which is a deficiency.

(4) Short-term interventions and follow-up: the treatment duration in most of the included studies was 2 weeks, and no study had mentioned follow-up for a period ranging from 2 weeks to a month. However, CID is a chronic recurrent disease, and adequate treatment duration and follow-up periods should be included in the observations of studies.

Conclusion

To the best of our knowledge, probiotics are commonly used in constipation or diarrhoea in clinically. The results indicate that the method is suggestive of an effective and safe therapy, which may serve as a promising method to treat CID in practical application. However, the included studies of this meta-analysis are associated with poor methodological quality and lack of assessment of safety data, as well as evaluation of patients' quality of life; consequently, further rigorously designed, multicenter, and large-scale clinical RCTs are required to overcome the limitations of the current study and to enhance the strength of evidence.

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AUTHOR DISCLOSURES

In the manuscript, all subjects (or their parents or guardians) have given their written informed consent and that the study protocol was approved by the institute's committee on human research.

All authors have [completed the financial and personal relationships disclosure form] and declare that: (i) we have financial support for study, that is National Natural Science Foundation of CN (81673795, 81503536); A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD); and (ii) there was no conflict of interest in the study; and (iii) there are no other relationships or activities that could appear to have influenced the submitted work.

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