The effect of probiotic and synbiotic consumption on the most prevalent chemotherapy-related complications: A systematic review of current literature

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ABSTRACT

Background: To date, many investigations have employed pro-/synbiotic to examine their effects on chemotherapy-related side-effects; nevertheless, their findings are inconclusive. To address this issue, we carried out a systematic review to explore the effect of pro-/synbiotic consumption on chemotherapy-related side effects, including nausea, vomiting, mucositis, diarrhea, and constipation in adults using randomized controlled trials (RCTs).

Methods: The electronic databases, including PubMed, Scopus, and ISI Web of Sciences, were searched systematically from the earliest available date to March 2021 to identify eligible studies. The quality of the enrolled studies was done based on the Cochrane Collaboration Risk of Bias tool.

Results: A total of 10 studies involving 788 individuals were included in the current systematic review with a sample size ranged from 25 to 200, and the mean age ranged from 51.04 to 66.91 years. The findings of this study imply that probiotics consumption may be more effective in terms of mucositis compared to other complications.

Conclusion: Further good-quality RCTs with better methodology are called to determine whether and how pro-/synbiotics can prevent or treat chemotherapy-induced side effects. The current systematic review findings may help investigators for future studies regarding the selection study population and probiotic strains.

KEYWORDS: cancer; probiotic; synbiotic; chemotherapy complications

INTRODUCTION

Chemotherapy is a crucial part of treatment for many cancers, while cancer patients undergoing chemotherapy often experience various related side effects. Previously, it was believed that chemotherapy drugs only kill cancer cells. However, it is well established nowadays that it also damages the non-cancerous human cells causing the chemotherapy dose-dependent side effects including nausea, vomiting, mucositis, fatigue, diarrhea and constipation (Aslam et al., 2014). These chemotherapy-related side effects affect patients' physical health and impact their mood status and quality of life (Pearce et al., 2017), sometimes leading to a reduction in the dose intensity of chemotherapy, which ultimately increases mortality (Kuo et al., 2008). Therefore, finding complementary therapies that do not reduce the therapeutic effects of chemotherapy drugs and reduce their side effects should be a priority of clinical research.

The microbiota has been suggested recently to be related to responses to immunotherapy. The exact mechanisms regarding the interaction between cancer, microbiota, and the immune system have not been fully understood (Jiang et al., 2019). The microbiota of the epithelial barrier, especially in the gut, affects adaptive immunity, local and systemic metabolic functions, and inflammation, which modulate cancer initiation, progression, and response to anticancer drugs (Roy & Trinchieri, 2017). Cancer and chemotherapy worsen the immune system, accompanied by the breaking of natural protective barriers leading to the colonization of pathogenic microorganisms. Previous preclinical and clinical studies proposed that probiotics may have a beneficial role in radiochemotherapy toxicity by strengthening homeostasis of gut microbiota, subsequently diminishing chemotherapy-related side effects (Roy & Trinchieri, 2017). Thus, it can be speculated that pro-/synbiotic administration alongside routine chemotherapy drugs may

indirectly and directly affect human response to cancer therapy in terms of chemotherapy-related side effects.

To date, many investigations have employed these dietary constituents to examine their effects on chemotherapy-related side effects (Farshi Radvar et al., 2020; Limaye et al., 2013; Mego et al., 2015; Topuz et al., 2008; Zaharuddin, Mokhtar, Nawawi, & Ali, 2019); nevertheless, their findings are inconclusive. To address this issue, we carried out a systematic review to examine the effect of pro-/synbiotic consumption on chemotherapy-related side effects, including nausea, vomiting, mucositis, diarrhea, and constipation in adults using randomized controlled trials (RCTs). Understanding this issue provides information to clinicians in diminishing the side effects and increasing the compliance of cancer therapy to improve the quality of life of patients and decrease their mortality.

METHODS

Data source and search strategy

The present systematic review was conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statements (Moher, Liberati, Tetzlaff, & Altman, 2010), and also was registered (Prospero database: CRD42021240510). The electronic databases, including PubMed, Scopus, and ISI Web of Sciences, were searched systematically from the earliest available date to March 2021 to identify eligible studies. The above databases were searched by two independent investigators (A.A and E.K) using the following keywords: (“cancer” OR “neoplasm” OR “tumor”) AND (“chemotherapy” OR “chemotherapy side-effects” OR “chemotherapy complications”) AND (“probiotics” OR “synbiotics” OR “fermented foods” OR “*Lactobacillus*” OR “*Bifidobacterium*” OR “*Lactococcus*” OR “*Saccharomyces*”). The full

electronic search strategy of each database is presented in **Table 1**. No filtering was made upon the database searching in publication time, study design, and language. The reference list of eligible studies and Google scholar were also screened to identify any possible citations that had not been captured via online database searches. Moreover, expert scientists in pro-/synbiotic and chemotherapy were also contacted to lessen the chance of missing any additional study.

Eligibility criteria and study selection

The PICOS (Population, Intervention, Comparison, Outcome, Study design) framework was implemented in the context of study selection as follows: **P** (Adult patients diagnosed with any type of cancer who are under chemotherapy as the primary treatment), **I** (pro-/synbiotic as a supplement or food), **C** (placebo or routine care), **O** (chemotherapy-related side effects), **S** (RCTs). To identify eligible studies based on PICOS components, all search results were exported to the EndNote X7 software (Thomson Corporation, Stamford, USA). In the first step, two independent reviewers (A.A and E.K) screened the title and abstract of exported articles, and irrelevant ones were excluded. Then, the full-text of the remaining articles was also checked to identify eligible studies.

The inclusion criteria were as follows: (1) original full-text human RCTs; (2) with either cross-over or parallel design; (3) which administered pro-/synbiotic (supplement or food) in combination with chemotherapy drugs; and (4) assessed the effect of pro-/symbiotic on at least one of the chemotherapy-related complications including nausea, vomiting, diarrhea, constipation, bloating, mucositis, neutropenia, and quality of life. The exclusion criteria were as follows: (1) non-human studies; (2) recruited patients younger than 18 years or lactating/pregnant women; (3) non-original full-length articles, case reports, poster abstracts, review articles, and editorials.

Data extraction

Data extraction was done in a blinded and duplicate manner via a pre-designed word table by two independent reviewers (A.A and M.B). The following information was extracted from each of the eligible studies: name of the first author, country of origin, year of publication, sample size, type of cancer, gender, age, type of cancer therapy, chemotherapy regimen, design of the study, dose and type of the intervention in either experimental or the control group, duration of intervention, strength and limitation of studies, and reported outcomes.

Quality assessment

The quality of the enrolled studies was assessed based on the Cochrane Collaboration Risk of Bias tool (Higgins et al., 2011) by two independent reviewers (A.A and E.K). The eligible studies were examined regarding allocation concealment, sequence generation, blinding, drop-outs and incomplete outcome data, outcome assessment, selective outcome reporting, and other potential sources of bias. The risk of bias on each item was stated as high, low, or unclear risk of bias. Any discrepancies were figured out by consulting a third reviewer (M.B).

RESULTS

Search results

The initial search of the selected databases yielded a total of 3439 results. In the next step, duplicate studies were removed, and a total of 1826 studies remained for title, abstract, and full-text screening. Of 1826 studies that were assessed based on title/abstract, 37 were retrieved. Two independent investigators screened the full-text of 37 studies, and finally, ten articles were eligible to be included in the present systematic review. The PRISMA flow diagram of the study selection process is illustrated in **Figure 1**.

General characteristics of included studies in the systematic review

A total of 10 studies (Farshi Radvar et al., 2020; Jiang et al., 2019; Limaye et al., 2013; Liu & Huang, 2014; Mego et al., 2015; Österlund et al., 2007; Sharma et al., 2012; Tian, Li, Song, Jiang, & Li, 2019; Topuz et al., 2008; Zaharuddin et al., 2019) involving 788 individuals were included in the current systematic review with a sample size ranged from 25 to 200 and mean age ranged from 51.04 to 66.91 years. The enrolled studies were done between 2007 and 2020. All of the included studies were RCT, but only seven investigations administered pro-/synbiotic in a blinded approach. Among the included studies, three were from China (Jiang et al., 2019; Liu & Huang, 2014; Tian et al., 2019) and the others from India (Sharma et al., 2012), Finland (Österlund et al., 2007), the United States (Limaye et al., 2013), Slovakia (Mego et al., 2015), Turkey (Topuz et al., 2008), Iran (Farshi Radvar et al., 2020), and Malaysia (Zaharuddin et al., 2019). The effect of pro-/synbiotic administration in cancer was studied in subjects with colorectal cancer (6 studies) (Farshi Radvar et al., 2020; Liu & Huang, 2014; Mego et al., 2015; Österlund et al., 2007; Topuz et al., 2008; Zaharuddin et al., 2019), head and neck cancer (2 studies) (Limaye et al., 2013; Sharma et al., 2012), nasopharyngeal cancer (Jiang et al., 2019), and lung cancer (Tian et al., 2019). Patients consumed the pro-/synbiotic under chemotherapy in six studies (Limaye et al., 2013; Liu & Huang, 2014; Mego et al., 2015; Österlund et al., 2007; Tian et al., 2019; Zaharuddin et al., 2019) and radiochemotherapy in others (Farshi Radvar et al., 2020; Jiang et al., 2019; Sharma et al., 2012; Topuz et al., 2008). The duration of intervention was ranged from 2 to 24 weeks, while one study (Topuz et al., 2008) only administered pro-/synbiotic during the courses of chemotherapy. General characteristics of the included studies are provided in **Table 2**.

The characteristics of administered pro-/synbiotic

Among the included studies, one study administered probiotic drink (kefir) (Topuz et al., 2008), one study synbiotic (Farshi Radvar et al., 2020), and the others probiotic supplement (Jiang et al., 2019; Limaye et al., 2013; Liu & Huang, 2014; Mego et al., 2015; Österlund et al., 2007; Sharma et al., 2012; Tian et al., 2019; Zaharuddin et al., 2019). The total daily dose of consumed pro-/synbiotic during the study was between 2×10^8 to 12×10^{12} colony-forming units (CFU). Five studies implemented a single-strain supplement (Limaye et al., 2013; Liu & Huang, 2014; Österlund et al., 2007; Sharma et al., 2012; Tian et al., 2019), five multi-strain ones (Farshi Radvar et al., 2020; Jiang et al., 2019; Mego et al., 2015; Zaharuddin et al., 2019), and the others did not mention the characteristics of the administered supplement (Topuz et al., 2008). Among the studies which used single-strain supplement, three studies administered *Lactobacillus* genus (Limaye et al., 2013; Österlund et al., 2007; Sharma et al., 2012), and the others *Clostridium* (Tian et al., 2019) and *Bifidobacterium* (Liu & Huang, 2014). In terms of the multi-strain supplements, one study (Zaharuddin et al., 2019) used the mixture of *Lactobacillus* and *Bifidobacterium*, two studies (Farshi Radvar et al., 2020; Mego et al., 2015) *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, and one study (Jiang et al., 2019) *Lactobacillus*, *Bifidobacterium*, and *Enterococcus*. The detailed characteristics of administered pro-/synbiotic were indicated in **Table 3**.

Study quality and risk of bias findings

The risk of bias of the individual studies and the risk of bias across all studies are presented in **Table 4**. As can be seen, reporting and performance bias were the items that scored the overall highest risk of bias. Also, selection, detection, attrition, and other bias were scored the overall lowest risk of bias. One study was ranked as good (Mego et al., 2015), three as fair (Farshi Radvar et al., 2020; Jiang et al., 2019; Sharma et al., 2012), and the others as poor quality (Limaye et al.,

2013; Liu & Huang, 2014; Österlund et al., 2007; Tian et al., 2019; Topuz et al., 2008; Zaharuddin et al., 2019), respectively.

Findings from the systematic review

Pro-/synbiotic and chemotherapy-related diarrhea and constipation

Six datasets (Farshi Radvar et al., 2020; Liu & Huang, 2014; Mego et al., 2015; Österlund et al., 2007; Tian et al., 2019; Zaharuddin et al., 2019) including 427 participants, examined the effect of pro-/synbiotic consumption on chemotherapy-related diarrhea and constipation.

In 2007, Osterlund et al. explored the effect of *Lactobacillus rhamnosus* GG supplementation (1–2×10^{10} per day) for 24 weeks on 5-Fluorouracil (5-FU) related diarrhea among 150 colorectal cancer patients (mean age of 60 years). Subjects of the experimental group had less grade 3 or 4 diarrhea (22% vs 37%, P=0.027) than the control group (Österlund et al., 2007).

Later in 2014, Liu et al. investigated the efficacy of *Bifidobacterium tetragenous* in gastric and colorectal cancer patients (mean age of 61.1 years) with functional constipation during fluoropyrimidine-based chemotherapy regimen. Individuals in the intervention group (n=50) were given probiotic tablets combined with chemotherapy, while individuals in the control group (n=50) received chemotherapy alone for four weeks. Participants in the probiotic group reported less constipation compared to the control group (total effective rate was 96% vs 32%, P<0.05) (Liu & Huang, 2014).

The next year another study was conducted by Mego et al. among 46 colorectal cancer patients (mean age of 63) who undergone irinotecan-based chemotherapy concurrent with 5-FU and capecitabine. Patients in the intervention group received a probiotic supplement containing live *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* for 12 weeks. Probiotics consumption

compared to the placebo reduced the incidence of grade 3 or 4 diarrhea (0% vs. 17.4%, P = 0.11) and the overall incidence of diarrhea (39.1% vs. 60.9%, P = 0.24). However, all of the reported differences were nonsignificant (Mego et al., 2015).

Zaharuddin and colleagues in 2019 aimed to determine the effect of a multi-strain probiotic supplement containing six live microorganisms of *Lactobacillus* and *Bifidobacteria* strains (30×10^{10} CFU) on chemotherapy-related diarrhea. Fifty-two patients with colorectal cancer (mean age of 66.91 years) were instructed to consume the probiotic product for six months. No significant difference was observed between the two groups in terms of diarrhea incidence (Zaharuddin et al., 2019).

Another investigation was conducted by Tian et al. among 41 lung cancer patients (mean age of 55.5 years) who are under chemotherapy to receive a probiotic supplement (Clostridium butyricum) or placebo for three weeks. The incidence of grade 1 and 2 of diarrhea was significantly lower among the intervention group than the control (P=0.017) (Tian et al., 2019).

The last attempt was made by Radvar et al. among the Iranian population to investigate the effect of synbiotic supplementation on diarrhea and constipation. Forty-six colorectal cancer patients (mean age of 60.23 years) undergoing chemotherapy with 5-FU and locoverin were allocated to consume two synbiotic capsules (containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* strains) or placebo for six weeks. Between-group comparisons failed to show superiority for synbiotic consumption over placebo in terms of diarrhea (P=0.20) and constipation (P=0.72) (Farshi Radvar et al., 2020).

Pro-/synbiotic and chemotherapy-related nausea and vomiting

A total of two studies (Farshi Radvar et al., 2020; Tian et al., 2019) examined the efficacy of pro-/synbiotic consumption on chemotherapy-related nausea and vomiting consisted of 79 cancer patients.

The first study was done in 2019 by Tian et al. among 41 lung cancer patients (mean age of 55.5 years) who are under chemotherapy to receive probiotic supplement (Clostridium butyricum) or placebo for three weeks. The incidence of nausea (P=0.166) and vomiting (P=0.254) was not significantly different between both groups (Tian et al., 2019).

The other investigation was conducted by Radvar et al. in 2020 to investigate the effect of synbiotic supplementation on nausea and vomiting. Forty-six colorectal cancer patients (mean age of 60.23 years) undergoing chemotherapy with 5-FU and locoverin were allocated to consume two synbiotic capsules (containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* strains) or placebo for six weeks. There was no significant difference between the two groups in nausea and vomiting (P=0.16) (Farshi Radvar et al., 2020).

Pro-/synbiotic and chemotherapy-related mucositis

The effect of pro-/synbiotic consumption on chemotherapy-related mucositis was investigated in four studies (Jiang et al., 2019; Limaye et al., 2013; Sharma et al., 2012; Topuz et al., 2008) including 361 participants.

In the first study, Topuz et al. in 2008 examined kefir administration on 5-FU induced oral mucositis among 37 patients (mean age of 54.5) diagnosed with colorectal cancer. The patients in the experimental group received 250 ml of kefir through oral lavage on the first five days of each chemotherapy cycle. The control group was given oral lavage using 0.09% NaCl twice a day.

Probiotic consumption was not beneficial in terms of the incidence of chemotherapy-related mucositis (27.3% in kefir vs 21.7% in control, P>0.05) (Topuz et al., 2008).

The other clinical trial was conducted in 2012 by Sharma et al. among 200 head and neck cancer patients (mean age of 51.22 years) to investigate *Lactobacillus* brevis CD2 lozenges on the incidence and severity of chemo-radiotherapy-related mucositis over eight weeks of anticancer treatment. Probiotic consumption compared to the placebo reduced the incidence of grade 3 and 4 of mucositis (52% vs 77%, P<0.001) (Sharma et al., 2012).

The following year, Limaye et al. conducted a multicenter study to assess the efficacy of the topically applied *Lactobacillus* against chemotherapy-induced mucositis among head and neck cancer subjects. Twenty-five patients were allocated to the control group or one of the three experimental groups to receive 2×10^{11}, 6×10^{11}, and 1.2×10^{12} CFU. The final analysis revealed a 35% reduction in days with oral mucositis of the probiotic group compared to the placebo (P<0.05) (Limaye et al., 2013).

The last study was done by Jiang et al. in 2019 to explore the effect of probiotic administration on chemoradiotherapy-induced oral mucositis among 99 patients with nasopharyngeal carcinoma. Consumption of probiotic combination (*Lactobacillus*, *Bifidobacterium*, and *Enterococcus*) for seven weeks showed a significant reduction in the severity of oral mucositis (P<0.05) (Jiang et al., 2019).

DISCUSSION

The present systematic review was done using 10 RCTs to examine the efficacy of concurrent administration of pro-/synbiotic with chemotherapy on the most prevalent chemotherapy-related complications, including diarrhea, constipation, nausea, vomiting, and mucositis. The findings of

this study imply that probiotics consumption may be more effective in terms of mucositis rather than other complications; however, between-study heterogeneity should be taken into account during the interpretation of the findings. The studies were heterogeneous in dose, strain, and duration of probiotic consumption; chemotherapy drugs and cancer types; participants' ethnicity and age; and outcome measures which explain to some extent the potential between-study heterogeneity. Considering the existing heterogeneity, the difference in reported data, and a low number of studies for each chemotherapy-related complication, it was impossible to analyze included datasets quantitatively (meta-analysis).

Out of five studies (Farshi Radvar et al., 2020; Mego et al., 2015; Österlund et al., 2007; Tian et al., 2019; Zaharuddin et al., 2019) reported on the effect of pro-/synbiotic consumption on diarrhea, three studies failed to show any significant result. Osterlund et al. (Österlund et al., 2007) and Tian et al. (Tian et al., 2019) which reported significant results for probiotics against diarrhea, both were of poor quality. However, Osterlund et al. (Österlund et al., 2007) had the largest sample size among these studies, explaining the significant findings. On the other hand, Mego et al. (Mego et al., 2015) reported a clinically significant reduction in diarrhoea incidence, but it was not statistically significant, which might be related to the small sample size (n=46). It seems that there is no superiority for synbiotic vs probiotic, multi-strain vs single strain probiotic, and duration of the intervention; however, further studies are called to establish a firm conclusion in this specific population. Moreover, two investigations (Farshi Radvar et al., 2020; Liu & Huang, 2014) were reported on constipation. The study of Liu et al. (Liu & Huang, 2014) provided evidence of probiotic efficacy in cancer patients; however, this study was of poor quality with evidence of selection and performance bias, questioning the validity of findings. A previous meta-analysis of Redman et al. on the efficacy of probiotics in patients with cancer reported that probiotic

administration might reduce the incidence and severity of diarrhea; although, the recent study enrolled all patients with chemotherapy, radiotherapy, and surgery (Redman, Ward, & Phillips, 2014). Another review also suggested that the beneficial effects of probiotic administration on preventing diarrhea related to radiochemotherapy were more prominent among patients receiving radiotherapy compared to the chemotherapy (Thomsen, Clarke, & Vitetta, 2018). Moreover, a Cochrane systematic review concluded that there is limited evidence in probiotic administration among patients receiving radiotherapy with or without chemotherapy or chemotherapy alone (Wei et al., 2018). In agreement with these studies, we believe that probiotic consumption has shown promising results in chemotherapy-induced diarrhea and constipation. However, limited evidence precludes us from reaching a firm and practical conclusion. Chemotherapy-induced diarrhea can be prevented or reduced through various mechanisms, including a reduction in the excessive activation of NF-ƙB and inflammatory mediators (van Vliet, Harmsen, de Bont, & Tissing, 2010), increasing the production of mucus in goblet cells (Caballero-Franco, Keller, De Simone, & Chadee, 2007), amelioration of intestinal dysbiosis (Vitetta, Briskey, Alford, Hall, & Coulson, 2014), and regulation of tight junctions (Qin et al., 2005). Moreover, probiotics may improve chemotherapy constipation by modulating the fecal and mucosal microbiota composition, increasing the metabolic byproducts of microbiota, including short-chain fatty acids (SCFA), and regulating mucus secretion (Dimidi, Christodoulides, Scott, & Whelan, 2017).

A total of two studies (Farshi Radvar et al., 2020; Tian et al., 2019) reported on the effect of pro-/synbiotic consumption on chemotherapy-induced nausea and vomiting. Additionally, it seems that there are no differences in terms of synbiotic/probiotic, multi-strain/single-strain probiotic, and duration of the intervention. However, a practical recommendation is not possible due to limited evidence. A pilot study among children with acute leukemia under chemotherapy demonstrated

beneficial effects for probiotic supplementation regarding chemotherapy-related nausea and vomiting (Reyna-Figueroa et al., 2019). Moreover, a meta-analysis by Lau et al. suggested that concurrent administration of probiotics with eradication treatment of Helicobacter pylori can reduce the risk of nausea and vomiting, which was independent of types of probiotics (Lau, Ward, & Chamberlain, 2016). Finally, more studies are called to investigate the effects of pro-/synbiotic on nausea and vomiting and underlying mechanisms.

Three out of four studies (Jiang et al., 2019; Limaye et al., 2013; Sharma et al., 2012) suggested a beneficial effect for probiotic consumption in terms of chemotherapy-related mucositis. The report of Topuz et al. (Topuz et al., 2008) failed to show any significant result which might be related to the type of probiotic (kefir probiotic drink), small sample size (n=37), and duration (first five days of each chemotherapy course). Two out of three documents (Jiang et al., 2019; Sharma et al., 2012) that provided a beneficial effect for probiotic ranked as fair quality studies. Moreover, two studies (Limaye et al., 2013; Sharma et al., 2012) used a single-strain probiotic (*Lactobacillus*) and the other one (Jiang et al., 2019) multi-strain (*Lactobacillus*, *Bifidobacterium*, and *Enterococcus*), which may highlight the role of *Lactobacillus* against mucositis. A recent systematic review also suggested a combination of *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium breve*, and *Saccharomyces boulardii* seems to be beneficial against mucositis among chemo or radiotherapy treated patients (Picó-Monllor & Mingot-Ascencao, 2019). Another meta-analysis of four studies also proposed that probiotic consumption may reduce the incidence of cancer therapy-induced oral mucositis (Shu, Li, Yu, Huang, & Chen, 2020). Although probiotics have promising results regarding oral mucositis prevention, further high-quality studies are needed to confirm these findings.

The administration of pro-/synbiotic among individuals with cancer to reduce chemotherapy-related complications or enhance chemotherapy is not part of the standard practice (Miarons, Roca, & Salvà, 2021). The main concern regarding the use of pro-/synbiotic among cancer patients is the hypothesis that subjects who are under chemotherapy are immunocompromised and at higher risk for infection (Miarons et al., 2021). Based on the reports of the included studies, consumption of pro-/synbiotic among patients with colorectal cancer, head and neck cancer, and lung cancer was generally safe and without any serious adverse events. Current recommendations for cancer patients with neutropenia are to avoid probiotic supplements, mainly based on manufacturers' recommendations and bacteremia case reports, rather than an evidence-based recommendation (Redman et al., 2014).

There are some limitations related to the current study which warrant consideration. Due to the limited evidence, we only included ten RCTs. The enrolled studies are heterogeneous in terms of chemotherapy regimens and cancer type, dose, strain, probiotic consumption duration, and general characteristics of the study population. Moreover, most of the included studies had poor quality. In addition to the limited data and poor quality of available evidence, the present heterogeneity limits our ability to conduct a meta-analysis.

CONCLUSION

The present systematic review was conducted to provide an updated literature review on the possible effect of pro-/synbiotic consumption on the most prevalent chemotherapy-related complications, including diarrhea, constipation, nausea, vomiting, and mucositis among adult patients. Based on what was discussed, it seems that probiotic consumption is more effective in reducing mucositis incidence than other chemotherapy-induced complications. However, further good-quality RCTs with better methodology are called to determine whether and how pro-

/synbiotics can prevent or treat chemotherapy-induced side effects. The findings of the current systematic review may help investigators for future studies regarding the selection of the study population and probiotic strains.

Conflict of Interests: None of the authors have any conflict of interests to declare.

Table 1. Search terms

PubMed
Search hits: 2042 ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields] OR ("neoplasm s"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields])) AND ("chemotherapy s"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapies"[All Fields] OR "drug therapy"[MeSH Subheading] OR "chemotherapy"[All Fields] OR "chemotherapy side-effects"[All Fields] OR "chemotherapy complications"[All Fields]) AND ("probiotic s"[All Fields] OR "probiotical"[All Fields] OR "probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields] OR ("synbiotics"[MeSH Terms] OR "synbiotics"[All Fields] OR "synbiotic"[All Fields]) OR "fermented foods"[All Fields] OR ("lactobacillus"[MeSH Terms] OR "lactobacillus"[All Fields]) OR ("bifidobacterium"[MeSH Terms] OR "bifidobacterium"[All Fields]) OR ("lactococcus"[MeSH Terms] OR "lactococcus"[All Fields]) OR ("saccharomyces"[MeSH Terms] OR "saccharomyces"[All Fields] OR "saccharomyce"[All Fields]))
Scopus
Search hits: 906 ((TITLE-ABS-KEY("cancer") OR TITLE-ABS-KEY("neoplasm") OR TITLE-ABS-KEY("tumor")) AND ((TITLE-ABS-KEY("chemotherapy") OR TITLE-ABS-KEY("chemotherapy side-effects") OR TITLE-ABS-KEY("chemotherapy complications ")) AND ((TITLE-ABS-KEY("probiotics") OR TITLE-ABS-KEY("synbiotics") OR TITLE-ABS-KEY("fermented foods") OR TITLE-ABS-KEY("Lactobacillus") OR TITLE-ABS-KEY("Bifidobacterium") OR TITLE-ABS-KEY("Lactococcus ") OR TITLE-ABS-KEY("Saccharomyces "))
Web of Science
Search hits: 491 (TS=(cancer) OR TS=(neoplasm) OR TS=(tumor)) AND (TS=(chemotherapy) OR TS=("chemotherapy side-effects") OR TS=("chemotherapy complications")) AND (TS=(probiotics) OR TS=(synbiotics) OR TS=("fermented foods") OR TS=(Lactobacillus) OR TS=(Bifidobacterium) OR TS=(Lactococcus) OR TS=(Saccharomyces))

Table 2. General characteristics of the included studies

Author; Year; Country	RCT Design (Blinding)	Sample size (F/M)	Mean age	Type of cancer	Type of cancer therapy	Chemotherapy Regimen	Duration	Strength	Limitation	Outcomes
Radvar et al., 2020; Iran (Farshi Radvar et al., 2020)	Parallel (Yes)	38 (F/M)	60.23	Rectal cancer	RCHT	5-FU, Locoverin	6 weeks	Use of synbiotic supplementation	Small sample size	Nausea Vomiting Diarrhea Constipation
Jiang et al., 2019; China (Jiang et al., 2019)	Parallel (Yes)	99 (F/M)	51.04	Nasopharyngeal cancer	RCHT	Cisplatin	7 weeks	-	-	Mucositis
Tian et al., 2019; China (Tian et al., 2019)	Parallel (Yes)	41 (F/M)	55.5	Lung cancer	CT	NM	3 weeks	-	1. Small sample size 2. Low dose 3. No adjustment for confounding including diet and drugs	Nausea Vomiting Diarrhea
Zaharuddin et al., 2019; Malaysia (Zaharuddin et al., 2019)	Parallel (Yes)	52 (F/M)	66.91	Colorectal cancer	CT	NM	24 weeks	Long follow up	Small sample size	Diarrhea
Mego et al., 2015; Slovakia (Mego et al., 2015)	Parallel (No)	46 (F/M)	63	Colorectal cancer	CT	Irinotecan, 5-FU, Capecitabine	12 weeks	Multicenter	Low statistical power (26%)	Diarrhea
Liu et al., 2014; China (Liu & Huang, 2014)	Parallel (No)	100 (F/M)	61.1	Gastric and Colorectal cancer	CT	Fluoropyrimidine-based regimens chemotherapy	4 weeks	-	1. Non placebo-controlled 2. Not blinded	Constipation
Limaye et al., 2013; USA (Limaye et al., 2013)	Parallel (Yes)	25 (F/M)	54	Head and Neck cancer	CT	Docetaxel, Cisplatin, 5-FU or Cisplatin, 5-FU	2 weeks	Multicenter	1.The nonhomogeneous induction chemotherapy regimens 2. Small sample size 3. Single blind	Mucositis
Sharma et al., 2012; India (Sharma et al., 2012)	Parallel (Yes)	200 (F/M)	51.22	Head and Neck cancer	RCHT	Cisplatin	8 weeks	Large sample size	-	Mucositis

Topuz et al., 2008; Turkey (Topuz et al., 2008)	Parallel (No)	37 (F/M)	54.5	Colorectal cancer	RCHT	Oxaliplatin, 5-FU And Leucovorin	The first 5 days of each CT cycle	-	1. Small sample size 2. No information about kefir drink	Mucositis
Osterlund et al., 2007; Finland (Österlund et al., 2007)	Parallel (No)	150 (F/M)	60	Colorectal cancer	CT	5-FU and Leucovorin	24 weeks	Relatively large sample size	1. Non placebo-controlled 2. Not blinded 3. An out dated chemotherapy regimen	Diarrhea

F: Female, M: Male, RCHT: Radio-chemotherapy, CT: Chemotherapy, 5-FU: 5-Fluorouracil, NM: Not mentioned

Table3. Detailed of the intervention used

First Author; Year	Probiotic/Synbiotic	Intervention of the experimental group	Daily dosage	Country of origin	Genus	Strain	Single or combination	Other components	Intervention of the control group
Radvar et al., 2020 (Farshi Radvar et al., 2020)	Synbiotic	2 capsules/day	2×10^8 CFU	Protexin, United Kingdom	Lactobacillus, Bifidobacterium, Streptococcus	L. casei PXN 37, L. rhamnosus PXN 54, L. acidophilus PXN 35, L. bulgaricus PXN 39, B. breve PXN 25, B. longum PXN 30 and S. thermophilus PXN 66	Combination	Fructooligosaccharide (FOS) and magnesium stearate	Placebo
Jiang et al., 2019 (Jiang et al., 2019)	Probiotic	6 capsules/day	-	Bifico,SHANGHAI SINE PHARMACEUTICAL CO.LTD	Lactobacillus, Bifidobacterium, Enterococcus	L. lactis, B. longum and E. faecium	Combination	-	Placebo
Tian et al., 2019 (Tian et al., 2019)	Probiotic	3 tablets/day (420mg per tablet)	-	Qingdao East China Sea Pharmaceutical Co., Ltd, China	Clostridium	C. butyricum	Single	-	Placebo
Zaharuddin et al., 2019 (Zaharuddin et al., 2019)	Probiotics	Two sachets/day	30×10^9 CFU	B-Crobes Laboratories Sdn. Bhd., Malaysia	Lactobacillus, Bifidobacterium	L. acidophilus, L. lactis, L. casei subsp, B. longum, B. bifidum and B. infantis	Combination	-	Placebo
Mego et al., 2015 (Mego et al., 2015)	Probiotic	3 Capsules /day	30×10^9 CFU	Harmoniom International, Inc., Mirabel, Canada	Lactobacillus, Bifidobacterium, Streptococcus	L. rhamnosus HA-111, L. acidophilus HA-122, L. casei HA-108, L. plantarum HA-119, L. brevis HA-112, B. breve HA-129, B. bifidum HA-132 HA, B. longum HA-135, B. infantis HA-116 and S. thermopilus HA-110	Combination	Inulin, maltodextrine, magnesium stearate and ascorbic acid	Placebo
Liu et al., 2014 (Liu & Huang, 2014)	Probiotic	3 Tablets/day	NM	Siliankang®, made by Hangzhou Longda New-Tech Bio-pharmaceutical Co., Ltd.	Bifidobacterium	B. tetragenou	Single	-	-
Limaye et al., 2013 (Limaye et al., 2013)	Probiotic	15 mL Mouthwash AG013 (1,3,6 times/day)	2×10^{11}, 6×10^{11}, and 12×10^{12} CFU	NM	Lactobacillus	L. lactis	Single	-	Placebo

Sharma et al., 2012 (Sharma et al., 2012)	Probiotic	6 Lozenges/day	12×10^9 CFU	NM	Lactobacillus	L. brevis CD2	Single	-	Placebo
Topuz et al., 2008 (Topuz et al., 2008)	Kefir	500ml/day	NM	NM	NM	NM	NM	NM	Oral lavage with % 0.09 NaCl
Osterlund et al., 2007 (Österlund et al., 2007)	Probiotic	Dietary counseling + 2 capsules/day	$1\text{-}2 \times 10^{10}$ CFU	Gefiluss, Valio Ltd, Helsinki, Finland	Lactobacillus	L. rhamnosus GG	Single	-	Dietary counseling

CFU: Colony forming units, NM: Not mentioned, L: Lactobacillus, B: Bifidobacterium, S: Streptococcus, E: Enterococcus, C: Clostridium

Table 4. Risk of bias assessment for included randomized controlled clinical trails

First author (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall quality
Radvar et al., 2020	L	L	L	L	L	U	U	Fair
Jiang et al., 2019	L	L	L	U	L	L	U	Fair
Tian et al., 2019	L	U	L	U	L	U	U	Poor
Zaharuddin et al., 2019	L	L	L	H	U	U	U	Poor
Mego et al., 2015	L	L	L	L	L	L	L	Good
Liu et al., 2014	H	H	H	U	U	U	H	Poor
Limaye et al., 2013	U	U	L	U	H	L	U	Poor
Sharma et al., 2012	L	L	L	U	L	L	U	Fair
Topuz et al., 2008	U	U	H	U	L	U	U	Poor
Osterlund et al., 2007	L	L	H	U	L	L	U	Poor

L: Low risk, H: High risk, U: Unclear

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