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Microbiome-Modifiers for Cancer-Related Fatigue Management: A Systematic Review

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ABSTRACT

Objectives: This study systematically investigates the evidence regarding the use of probiotics in managing cancer-related fatigue (CRF).
Study Design: We conducted a systematic review of randomized controlled trials.
Data Sources: The systematic search encompassed six databases: PubMed, CINHAL, Cochrane Database of Systematic Reviews, Web of Science, Scopus, and EMBASE, covering the period from inception to December 2023. The assessment of risk of bias employed the Cochrane risk of bias tool (RoB 2). A narrative synthesis and an exploratory meta-analysis were conducted to summarize the evidence.
Results: Among 460 records, three studies met the eligibility criteria and were included in the review. These studies involved a total of 284 participants with colorectal and breast cancer. One study demonstrated a marginal improvement in CRF postchemotherapy in colorectal cancer patients using probiotics. Another study, also using probiotics, reported a significant reduction in CRF among colorectal cancer patients undergoing chemotherapy. Additionally, a study employing synbiotics showed a substantial decrease in CRF severity in breast cancer patients receiving chemotherapy.
Conclusion: The study presents initial but varied evidence suggesting the potential of probiotics and synbiotics as adjunctive therapies in managing CRF alongside anticancer treatments.
Implications for Nursing Practice: In nursing practice, large-scale clinical trials are urgently needed to evaluate the effectiveness of probiotics in treating cancer-related fatigue during cancer therapy. Insights from this review could guide nurses in selecting appropriate probiotic strains and integrating microbiome modifiers into comprehensive care plans, potentially enhancing the quality of life for cancer patients.

Cancer-related fatigue (CRF) is a widespread symptom affecting approximately 52% of adult cancer patients, although its prevalence varies widely from 14% to 100%.[1] The National Comprehensive Cancer Network (NCCN) defines CRF as a distressing, persistent feeling of physical, emotional, and cognitive tiredness or exhaustion related to cancer or its treatment, which is not in proportion to recent activity and hampers daily functioning. CRF stands as one of the most common side effects of cancer,[2] presenting a range of symptoms, including cognitive impairments, persistent fatigue, hot flashes, functional decline, insomnia, and depression.[3] These symptoms vary depending on cancer type, treatment, and the patient's pretreatment health and nutritional status.[4] Importantly, these symptoms profoundly affect employment opportunities, social relationships, and daily life, significantly reducing the quality of life for cancer patients.[5]

Various biological mechanisms contribute to the etiology of CRF, encompassing a complex interplay of physiological and biochemical processes.[6] While dysregulation of the hypothalamic-pituitary-adrenal axis, inflammatory cytokine dysregulation, and anemia are significant factors, these represent only a part of the broader spectrum of mechanisms involved.[7] Among these, the dysregulation of the proinflammatory cytokine network, leading to increased inflammation, is one of the most extensively studied areas.[6] In addition to these factors, recent research highlights the role of central nervous system dysfunction in the onset and persistence of CRF. For instance, studies

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have found that peripheral leukocytes, which concentrate in the brain in the context of specific diseases, significantly influence the neuroinflammatory response.[8] Furthermore, growing evidence points to the hypothalamus as a crucial component in the pathophysiology of both acute and chronic disease responses.[8] The hypothalamus, when activated by inflammatory cytokines, could induce skeletal muscle catabolism and lipolysis through modulating neurotransmitters, systemic circulation, and autocrine and paracrine signaling. However, it is essential to recognize that the etiology of CRF is multifactorial and not limited to these mechanisms.[7] Other factors such as oxidative stress, mitochondrial dysfunction, alterations in muscle and ATP metabolism, neuroendocrine and circadian rhythm disturbances, and psychological factors also play a critical role in the development and maintenance of CRF.[7] These aspects underscore the complexity of CRF, where multiple interconnected pathways are involved. The exact mechanism of CRF remains to be fully elucidated, and it is still unclear whether its origin is peripheral, central, or a combination of both. This complexity necessitates a comprehensive approach to understanding and addressing CRF, taking into account the multitude of contributing factors.

Cancer treatments and tumors can activate this network, leading to fatigue-related symptoms through cytokine signaling in the central nervous system.[6] Additionally, cancer treatments have been shown to disrupt the balance of the gut microbiota.[9,10] Gut microbiota dysbiosis, characterized by changes in composition and function due to various environmental and host-related factors,[11] contributes to the development of neuropsychological disorders, including chronic fatigue syndrome.[12,13] While cancer and its treatment can trigger inflammation, resulting in CRF, other factors may also contribute to inflammation and fatigue in cancer patients, suggesting that the link between inflammation and CRF is not solely treatment-dependent.[14] Overall, the processes behind the gut microbiome's impact on human health remain mainly unidentified, making developing a safe and beneficial microbiome-based intervention increasingly difficult.

Recent research has unveiled a new avenue for investigating potential CRF pathways through the connections between the gut microbiota and the brain.[15] Data have established the gut-brain axis, illustrating how gut microorganisms influence the human brain, particularly through immunological and inflammatory responses.[16] Specifically, the gut microbiota influences the human brain in various ways, most notably through immunological[17] and inflammatory responses.[15] For example, structural bacterial elements like lipopolysaccharides can trigger the innate immune system, leading to systemic and central nervous system inflammation.[18] In contrast, butyrate, a microbiota-produced short-chain fatty acid, boosts inflammation.[19]

In recent decades, nutritional metabolomics, which focuses on the study of diet-related small molecules, has gained traction in cancer care, aiming to identify correlations between dietary patterns and health.[20-22] Microbiota-modulating dietary interventions include fermented foods, fiber-rich dietary regimens, probiotics, prebiotics, and synbiotics.[23] Probiotics are living microorganisms, often found in fermented foods, that provide health benefits when consumed in adequate amounts. Prebiotics are nondigestible food components that promote the growth of beneficial gut bacteria, essentially serving as "nourishment" for probiotics. Synbiotics refer to a combination of probiotics and prebiotics designed to improve the survival and effectiveness of beneficial micro-organisms in the gut. Postbiotics refer to the byproducts or waste left behind after the body digests both prebiotics and probiotics.

Current strategies for managing CRF in cancer patients include pharmaceutical agents, such as psychostimulant drugs. However, these treatments can result in toxicities and potential adverse interactions with cancer therapies.[24] Several national scientific societies and organizations have recommended nonpharmacological approaches as the first option to treat CRF,[25-27] such as psychological interventions (e.g., cognitive behavioral therapy),[28] structured programs of physical activity (aerobic, anaerobic, and resistance exercises),[29] complementary and integrative medicine interventions (eg, acupuncture, massage, Tai Chi and Qigong),[30] and self-management and educational strategies.[24]

Among nonpharmacological interventions, nutritional supplements represent a promising option for reducing CRF.[4] Using these interventions to treat gut microbiota dysbiosis affects inflammation processes, implying that giving microbiome modifiers to cancer patients may influence CRF syndrome.[31,32] However, the effects of these approaches are underinvestigated,[24,33] and the extent of relevant literature is unknown. Research is needed to synthesize the specific contribution of probiotics to CRF. Therefore, this study aims to systematically investigate the available evidence on the efficacy of microbiome modifiers on CRF.

Materials and Methods

Study Design

This study is a systematic review (SR) of randomized control trials (RCTs), undertaken according to Cochrane Guidelines,[34] including the Preferred Reporting Items Systematic Reviews and Meta-analysis guidelines (PRISMA).[35] The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42023394928).

Operational Definitions

In this systematic review, we aim to investigate the available evidence on the efficacy of various microbiome modifiers on CRF, including probiotics, prebiotics, symbiotics, and postbiotics. To ensure clarity and consistency, we adopted the definitions provided by the International Scientific Association of Probiotics and Prebiotics (ISAPP).[23] Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host".[23] Our review primarily focuses on studies involving probiotics due to their prominent role in modulating the host's health through microbial interactions. Prebiotics are referred to as "substrates that are selectively utilized by host microorganisms conferring a health benefit".[23] These are nondigestible food components that beneficially affect the host by stimulating the growth and/or activity of beneficial micro-organisms in the gut. Symbiotics are described as "a mixture comprising live microorganisms and substrate utilized selectively by host microorganisms that confers a health benefit on the host".[23] This term encompasses combined products containing both probiotics and prebiotics. Postbiotics are defined as preparations of inanimate microorganisms and/or their components that benefit host health.[23] These include various substances like metabolic products, cellular components, or specific cell wall fragments from probiotics.

Search Strategy

The systematic search was performed up to December 2023 in the following databases to identify studies published from inception to the search date: PubMed, CINHAL, Cochrane Database of Systematic Reviews, Web Of Science, Scopus, and EMBASE. Hand Searching on Google Scholar and reference list checking were performed to identify additional studies. The WHO International Clinical Trials Registry and the Clinicaltrials.gov database were searched to identify any unpublished ongoing original clinical trials with preliminary results. The abstracts of unpublished studies from some of the leading congresses in the medical area of various associations (American Society of Clinical Oncology (ASCO), European Society of Medical Oncology

(ESMO), Multinational Association of Supportive Care in Cancer (MASCC) were also screened.

We developed a primary search strategy to explore the topic in the literature across all the databases. Given the limited number of eligible studies provided by the first search round, we built different search strategies by incorporating additional search terms to broaden our research during the search process. The search strategies were developed initially for the PubMed database utilizing MESH headings and free-text words, and then they were adapted for the other databases as appropriate. Key search terms were combined with the Boolean operators "AND" and "OR": cancer, neoplasm, tumor, probiotic, cancer-related fatigue, and RCTs. The search strategies were rerun at different times from February 2023 to August 2023. The first search strategy process and results for each database are displayed in Supplementary File 1. During the database search, no restrictions were set on the language or publication date of the articles.

Eligibility Criteria

The search query was based on the Population, Intervention, Control, Outcomes, and Study Design (PICOS) framework: (P) Adult cancer patients (≥18 years) experiencing CRF in active treatment and a post-treatment phase, (I) Probiotics (any strain), Prebiotics, Symbiotics or Postbiotics as a stand-alone therapy or as an add-on treatment, (C) Any active control or nonactive comparator group, (O) cancer-related fatigue as a primary or secondary endpoint, (S) randomized controlled trials.

No restrictions on cancer type, cancer stage, sex, or ethnicity were settled as they were not significant for the purpose of the study. All investigations that used validated scales to measure CRF were considered, including quality of life measurements. All studies undertaken in primary care settings have been included (eg, community-dwelling elderly, home-based settings, community care ambulatories) as well as ambulatory care services and cancer care pathways designed to allow clinicians to deliver cancer care in a continuum across different levels of care. This approach implies that primary, secondary, and tertiary care contexts could be included. Articles published in languages other than English were consequently excluded during the full-text selection unless they had significant content for the purpose of the study to reduce any potential misconceptions.

Screening and Data Extraction

To identify the finally included studies, two authors independently screened titles and abstracts for inclusion. Then, the articles determined as eligible after abstract screening were independently assessed by the two authors in full text to analyze the contents for the final inclusion. A third author was involved in resolving disagreements between the two authors during the screening process. We designed a piloted data extraction form for appraising and analyzing the body of evidence to guarantee that the data gathered were standardized and relevant. The following data were extracted from studies that encountered the selection criteria for inclusion: first author/year, country, study design, intervention and control, number of participants, CRF measurements, cancer type and stage of treatment, timepoint assessment, and results.

Quality Appraisal

According to recent Cochrane group suggestions, the methodological quality of each RTC selected was evaluated using the RoB 2 checklist.[34] Based on the Rob 2.0 tool guidelines, each risk of bias could be assessed as "high," "low," or "unclear."[36] The RoB 2 tool is structured into five domains: (1) "bias arising from the randomization process"; (2) "bias due to deviations from intended interventions"; (3) "bias due to missing outcome data"; (4) "bias in the measurement of the outcome"; (5) "bias in the selection of the reported result". Within each domain, signaling questions result in judgments of "low risk of bias," "some concerns," or "high risk of bias." The judgment within each area contributes to an overall risk of bias for the evaluated outcome.

Data Analysis

A peer reviewer (CG and SB) independently collected data from reports in duplicates. Controversies were either resolved by a third reviewer (RC). Data were organized into a literature table and retrieved based on the study selection framework and criteria. Extracted data was organized into a template piloted by the two authors.

Due to the limited number of studies and their relatively small sample sizes, as well as notable clinical differences in factors such as the nature of interventions (eg, how often they were administered, the specific probiotic strains used, and their combinations) and the various methods used to evaluate CRF, there exists substantial clinical heterogeneity. However, despite these challenges, the analytical summary derived from the included studies in this review provides a comprehensive overview of each study's specific contexts and findings, thereby accomplishing the primary objective of this research.

Additionally, recognizing the inherent value in exploring preliminary trends and patterns, we have conducted a meta-analysis as a supplementary analysis (see Supplementary File 2). This effort aims to synthesize the results from the two included studies to provide an initial overview of the potential impact of probiotics on CRF in adult cancer patients.[37] The decision to pursue this meta-analysis, despite its exploratory nature, is underpinned by homogeneity in crucial areas such as the cancer diagnosis (colorectal cancer), the type of intervention (probiotics), and the comparison group (placebo).[38] This commonality supports the feasibility of combining these studies for a preliminary analysis. The meta-analysis is intended as an exploratory tool rather than a definitive conclusion, serving to identify potential trends and areas for future research, acknowledging the current limitations and the need for more extensive, diverse studies in this field. Therefore, this exploratory meta-analysis, despite the acknowledged heterogeneity and limited data, serves as a preliminary step in understanding the complex relationship between probiotics and CRF. In the exploratory meta-analysis, we employed an intention-to-treat (ITT) approach for data extraction from the primary studies. The standardized mean difference (SMD) with 95% confidence intervals (95% CIs) was computed using generic inverse variance methods in a random-effects model to account for the inherent variability among the studies. Data analyses were performed using STATA 16 software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA: StataCorp LLC) and results are showed in Supplementary File 2.

Results

Initially, 410 records were identified, and 180 unique records remained after eliminating duplicates. Upon reviewing the titles and abstracts, nine papers were selected for full reading.[39–48] Three studies fulfilled the eligibility criteria and were included in the SR.[42,43,48] We have also identified two potentially eligible ongoing clinical studies, one registered under NCT05736315 on the ClinicalTrials.gov database[49] and the other under ACTRN12621000234819 on the WHO International Clinical Trials Registry.[50] It is worth noting that these studies have not yet reported any preliminary results. The selection process and the reasons for exclusion are presented in Fig. 1. Table 1 shows the characteristics of the included RCTs.

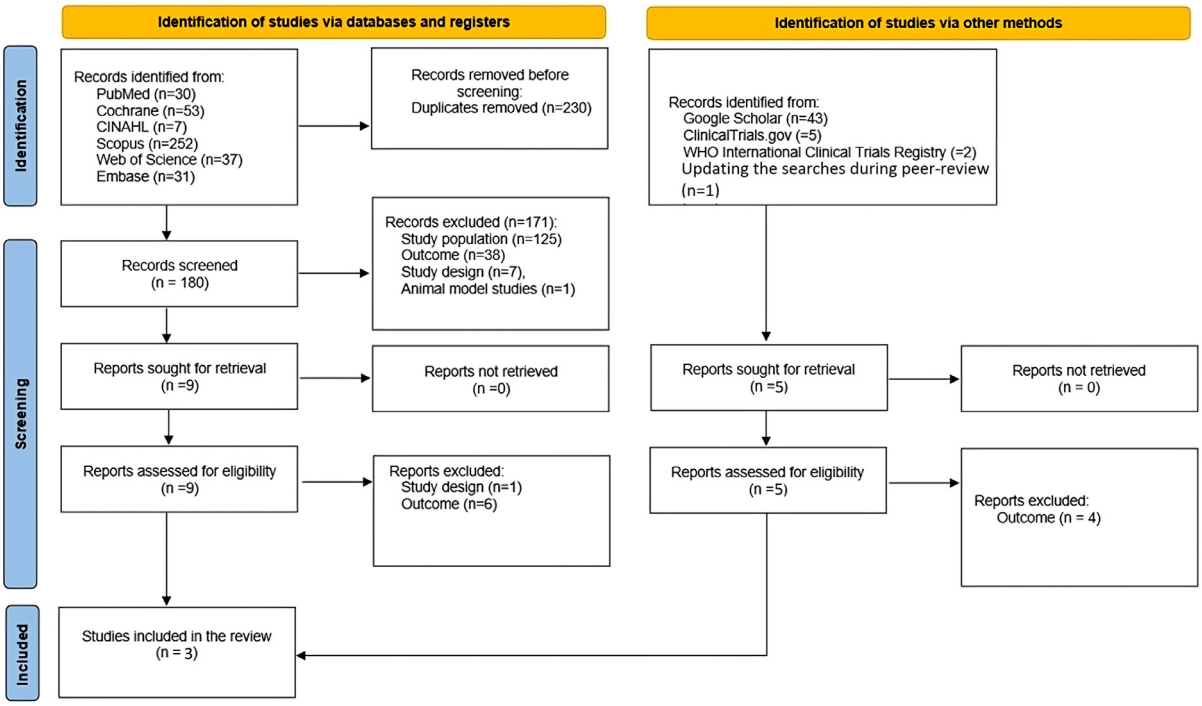

FIG. 1. PRISMA flow-diagram of the selection process.

Participants' Characteristics

The enclosed studies[42,43,48] involved male and female adult patients affected by colorectal cancer and women with breast cancer. In Lee et al.,[43] 66 participants were included as diagnosed with stage 2 or 3 colorectal cancer. Inclusion criteria included patients who completed treatments between 6 weeks and 2 years prior and had been performing well, following the Eastern Cooperative Oncology Performance scores (total score less than 1 indicating good performance). Golkhalkhali et al.[42] included 140 subjects with colorectal cancer on the XELOX chemotherapy regimen, a combination drug therapy of capecitabine and oxaliplatin. The inclusion criteria were subjects who had been newly diagnosed, had surgery, decided to receive chemotherapy ultimately, and had sufficient organ and marrow function to administer chemotherapy. The Khazaei et al.[48] study included 74 inpatient women with a definitive diagnosis of breast cancer. These participants were admitted to undergo neoadjuvant or adjuvant chemotherapy. The inclusion criteria for this study were women aged 18 years or above with a recent definitive diagnosis of breast cancer by an oncologist or pathologist, according to medical records, with no metastasis. They had to have completed at least one previous chemotherapy session to ensure they had experienced chemotherapy-induced side effects following the first session and were scheduled for at least four chemotherapy sessions with more than two future sessions planned.

All three studies implemented specific exclusion criteria to maintain the integrity of their respective research. Golkhalkhali et al. excluded patients with histories of cancer in other organs, those with signs of organ failure, HIV-positive subjects receiving combination antiretroviral therapy, and those on other investigational agents.[42] Lee et al. also excluded patients with histories of cancer in other organs and with signs of organ failure. Additionally, they excluded patients with colostomies, volunteers who consumed supplementary food containing probiotics, those with a history of chronic disease, active antibiotic use, and women who were pregnant or planning pregnancy.[43] The Khazaei et al. study's exclusion criteria were focused on a specific subset of breast cancer patients, likely excluding those with metastatic disease or treatments that could interfere with the study's objectives or outcomes.[48]

Characteristics of Interventions

In the study by Lee et al., a total of 66 participants were initially randomized, with 33 assigned to receive Lacidofil and 33 to receive a placebo for a duration of 12 weeks.[43] The Lacidofil group was administered a probiotic preparation containing L. rhamnosus R0011 and L. acidophilus R0052 bacterial cultures (at a concentration of 2×109 colony-forming units), along with maltodextrin, magnesium stearate, and ascorbic acid. The control group received placebo pills composed of maltodextrin, magnesium stearate, and ascorbic acid, designed to match the texture, taste, and color of the probiotics. Participants were instructed to take the tablets twice daily with or immediately after meals and store the bottles in refrigerators. Furthermore, participants were prohibited from consuming probiotic-containing foods, including yogurt. Data were collected after the follow-up periods for both groups, resulting in data for 60 participants. Specifically, data were obtained for the remaining 28 participants in the probiotics group and the remaining 32 participants in the control group.

Golkhalkhali et al. conducted a randomized trial with two groups.[42] The treatment group (n = 70) received a daily regimen consisting of two sachets of Hexbio microbial cell preparation. Hexbio contained a combination of beneficial bacterial strains, including L. acidophilus BCMC 12130, L. casei BCMC 12313, Lactobacillus lactis BCMC 12451, Bifidobacterium bifidum BCMC 02290, Bifidobacterium longum BCMC 02120, and Bifidobacterium infantis BCMC 02129, with each sachet containing 30 billion colony-forming units. Additionally, participants in the treatment group were administered omega-3 fatty acid supplements at a dosage of 2 g per day for 8 weeks. On the other hand, the placebo group (comprising 70 individuals) received biologically inert placebo preparations that were visually identical to the active treatment. The placebo group also received placebo omega-3 fatty acid supplements for a duration of 4 and 8 weeks, mirroring the treatment group's timeline. Follow-up assessments were conducted at two key time points: first, at the conclusion

TABLE 1
Characteristics of the Included RCTs

First author, year	Country	Study design	Sample size (intervention/control)	Type of cancer and treatment phase	Intervention	Control	Frequency	Scale	Timepoint assessment
Lee, 2014	Korea	RCT	66 (33/33)	Colorectal, stage 2 and 3 who completed treatment (between 6 weeks and 2 years prior).	L. rhamnosus R0011·L. acidophilus R0052 bacterial culture (2×10^9 colony-forming units), maltodextrin, magnesium stearate, and ascorbic.	Placebo: Maltodextrin, magnesium stearate and ascorbic acid comparable in texture, taste, and color of the probiotics.	Twice daily with or right after meals for 12 weeks.	FACT-F	After the completion of chemotherapy, at 12 weeks postintervention.
Golkhalkhali, 2017	Malaysia	RCT	140 (70/70)	Colorectal (newly diagnosed), on treatment (XELOX chemotherapy regimen: capecitabine plus oxaliplatin).	L. acidophilus + L. Casei + Lactobacillus lactis + Bifidobacterium longum+ Bifidobacterium infantis at a dose of 30 billion colony-forming units per sachet and omega-3 fatty acid at a dose of 2g daily.	Placebo: Preparations identical in Appearance.	Daily for 4 (probiotics and placebo) and 8 weeks (omega-3 fatty acid).	EORTC-QLQC30	During chemotherapy, at 8 weeks postintervention, and after the completion of chemotherapy at 6 months postintervention.
Khazaei, 2023	Iran	RCT	74 (37/37)	Women with a diagnosis of breast cancer	Each capsule had a weight of 450 mg and contained a blend of 12 safe and beneficial probiotic strains, including Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Lactobacillus helveticus, Lactobacillus lactis, Lactobacillus paraplantarum, Bifidobacterium bifidum, Streptococcus thermophilus, and Lactobacillus gasseri. These probiotics were provided at a dose of 1×109 colony-forming units per capsule, complemented with 21 grams of fructooligosaccharides serving as a prebiotic component.	Placebo: same features in terms of appearance (color, odor, shape, weight, package).	Daily, one capsule of the synbiotic supplement twice a day after their main meals.	CFS	Baseline, 4 weeks, and 8 weeks after the intervention before chemotherapy (neoadjuvant or adjuvant).

CFS, Cancer Fatigue Scale; EORTC QLQ C30/FA13, European Organisation for Research and Treatment of Cancer Quality-of-life/fatigue subscale); FACT-F, Functional Assessment of Cancer Therapy: Fatigue.
Significant *P* value <.05 in bold.

of the 8-week intervention period and, subsequently, at the end of the 6-month chemotherapy treatment.

In the Khazaei et al. study,[48] participants with breast cancer undergoing chemotherapy were randomized to receive a synbiotic supplement or a placebo. Each capsule in the intervention group contained 12 probiotic strains (including Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium, Lactobacillus lactis, Lactobacillus paraplantarum, Lactobacillus gasseri) at a dose of $1 \times 10\text{^}9$ colony-forming units. The placebo capsules, similar in color and appearance to the supplement, contained starch. The capsules were provided in identical packages and labeled as either A or B to maintain the double-blind study design. Participants were instructed to take one capsule twice a day after their main meals, and the capsules were stored in the refrigerator below 4°C.

Measurements and the Effect of Probiotics on CRF

In the study by Lee et al., cancer-related quality of life was assessed using the Functional Assessment of Cancer Therapy (FACT) Measurement System, version 4.[51] This assessment used the fatigue-related FACT (FACT-F), a 13-item validated tool for assessing fatigue within cancer populations. The FACT-F showed that both the control and intervention groups had the same baseline score of 43.00 (CI for the control group: 36.00-49.00, and for the intervention group: 36.50-45.50), indicating comparable levels of fatigue at the start of the study.

Golkhalkhali et al.[42] employed the fatigue subscale of the "European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" (EORTC QLQ-C30) to evaluate the quality of life of patients.[52] The fatigue subscale comprises three items, and the scoring is based on a four-point scale, ranging from "Not at All" to "Very Much." Scores for each item are averaged and then transformed to a 0 to 100 scale, with higher scores indicating greater fatigue levels. Therefore, in the context of the EORTC QLQ-C30, an increase in the score on the fatigue subscale signifies a worsening of fatigue symptoms, reflecting a decline in the patient's quality of life in this domain.

In the study by Khazaei et al.,[48] CRF was assessed using the Cancer Fatigue Scale (CFS) Questionnaire. The CFS is a concise questionnaire comprising 15 Likert-type items across three subscales assessing physical, affective, and cognitive aspects of fatigue. The ratings are assigned values from 1 (not at all) to 5 (very much), with higher scores indicating greater fatigue levels.

In the study of Lee et al.,[43] the administration of Lacidofil (a probiotic supplement) over a 12-week period showed a statistically significant improvement in CRF. The FACT-F showed that both the control and intervention groups had the same baseline score of 43.00 (CI for the control group: 36.00-49.00, and for the intervention group: 36.50-45.50), indicating comparable levels of CRF at the start of the study. The FACT-F scores in the probiotics group improved to 44.50 (CI 38.50-49.00) after 12 weeks of treatment ($P = .02$). Notably, this improvement was in contrast to the placebo group, where no substantial changes in CRF were observed (baseline FACT-F score of 43.00 [CI 36.00-49.00] compared to 44.00 [CI 39.50-48.75] after 12 weeks; $P < .05$).

The study of Golkhakhali et al.[42] examined the effect of probiotics combined with omega-3 fatty acids. The control group in this study did not receive actual omega-3 fatty acids; instead, they were given placebo preparations that visually resembled the treatment but were biologically inactive.[42] A significant aspect of this study was the initial difference in baseline fatigue scores between the intervention and control groups. The intervention group started with a higher level of reported fatigue (EORTC-QLQ30 fatigue score of 23.70 ± 2.80) compared to the control group (14.23 ± 2.90). Over time, the intervention group showed a substantial improvement in EORTC-QLQ30 fatigue scores (decreasing to 11.97 ± 1.80 at 8 weeks and further to 10.30 ± 1.90 at 6 months; $P < .05$). On the other hand, the placebo group experienced a notable increase in fatigue levels (rising to 31.10 ± 3.00 at 8 weeks and 35.40 ± 4.30 at 6 months; $P < .05$). Interpreting these findings in the context of the initial disparity in baseline fatigue levels is important. The higher baseline scores in the intervention group suggest a greater potential for observable improvement, potentially contributing to the significant changes noted. This factor must be considered when assessing the extent to which the observed improvements in the intervention group can be attributed solely to the combined probiotic and omega-3 fatty acid intervention. While the results indicate a beneficial effect, the impact of the initial higher fatigue levels in the intervention group on the study outcomes should be acknowledged.

In the study by Khazaei et al., the effects of a synbiotic intervention on CRF in breast cancer patients undergoing chemotherapy were examined. This study observed a significant reduction in CRF severity among participants in the synbiotic group, considering that the baseline levels were equal in both arms ($P = .195$). The intervention group showed a notable decrease in CFS scores, indicating an improvement in fatigue symptoms. Specifically, a significant reduction in fatigue severity was reported after 4 weeks ($P < .001$), and this reduction was maintained at the 8-week assessment ($P < .001$). In contrast, the placebo group did not demonstrate a similar improvement in fatigue symptoms over the same period.

Risk of Bias

The authors independently estimated the risk of bias of the two included RCTs using the RoB 2.0 tool.[36] In the first and second domains ("bias arising from the randomization process" and "bias due to deviations from intended interventions"), all studies[42,43,48] presented a double-blind, 1:1 randomization, and analyzed confounding variables to ensure homogeneity of the sample. Data for the outcome were available for all patients in two studies[42,48] and nearly all in the other one,[43] with a dropout rate of 9%, resulting in a low-risk bias for the third domain of bias due to missing outcome data. In all the studies, data were collected using validated fatigue scales, and all data were evaluated per a prespecified analysis plan that was completed before unblinded outcome data was available for analysis. Our analysis confirmed low risk in the fourth ("bias in the measurement of the outcome") and fifth ("bias in the selection of the reported result") domains. All the selected studies result in a low-risk bias. Fig. 2 shows the risk of bias assessment results.

Discussion

Managing symptoms, particularly CRF, remains a significant challenge in cancer care, adversely affecting patients' quality of life. Over recent decades, the emerging field of nutritional metabolomics has sought to understand the relationship between dietary patterns and symptom management.[53,54] Within this context, natural supplements like probiotics, prebiotics, and synbiotics have gained prominence as complementary and integrative interventions in oncology, both during and after cancer treatments. Evidence estimated that natural supplements (ie, probiotics, fish oil, flax seeds, melatonin) were the most commonly used complementary and integrative medicine interventions in oncology during and after cancer treatments (54%).[55] Despite their growing use, the efficacy of these microbiome modifiers is not well-studied, and the existing literature is limited.[56] In this scenario, to the best of our knowledge, this is the first systematic review aimed at investigating the current evidence and their directions for using probiotics in managing CRF. This study amalgamated and scrutinized the evidence from three clinical trials,[42,43,48] where two studies included patients with colorectal cancer (206 patients in total)[42,43] and one study included women with breast cancer (74 patients in total).[48] The summarized and analyzed research

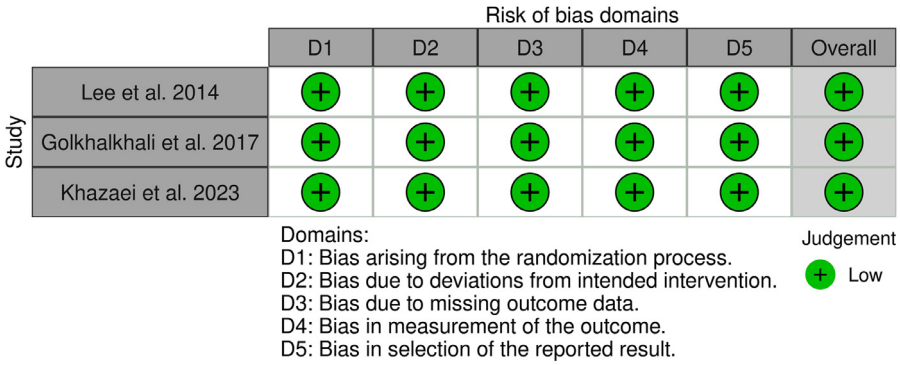

FIG. 2. RoB 2.0 assessment.

presents a groundbreaking perspective in the field, highlighting the potential of probiotics as a multifaceted intervention applicable to different cancer types and treatment scenarios.

The synthesis presented in the results was also enriched by an auxiliary analysis, which was an exploratory meta-analysis, detailed in Supplementary File 2, aimed to describe variations in the reported effect sizes across studies rather than establishing a definitive impact or estimating the precise effect size of the treatment.[57] This approach is informative, given the limited amount of evidence currently available.[58] The exploratory meta-analysis synthesized data from the three studies by extracting data from 8 weeks,[42,48] 12 weeks,[43] and 6 months,[42] using a random-effects model. The meta-analysis with an exploratory approach revealed substantial heterogeneity among the included studies, as indicated by a high I^2 value of 99.17% and a τ^2 (tau squared) of 15.31. This heterogeneity underscores the need for a cautious interpretation of the combined effect size. Overall, the heterogeneity from a statistical point of view was mainly related to the contribution of the study of Lee et al.,[43] which showed a minimal effect size, with an SMD of 0.038 at 12 weeks. In contrast, Golkhalkhali et al.[42] and Khazaei et al.[48] demonstrated substantial effect sizes at their respective follow-up points, highlighting the potential efficacy of probiotic interventions in different cancer populations and treatment stages.

The comparison of interventions between the included studies reveals distinct approaches to probiotic supplementation for managing CRF. Lee et al. employed a simpler probiotic blend of L. rhamnosus R0011 and L. acidophilus R0052, focusing on a specific combination of strains to target CRF in colorectal cancer patients post-treatment.[43] In contrast, Golkhalkhali et al. utilized a more complex multistrain probiotic blend, which included Bifidobacterium species and was combined with omega-3 fatty acids, during the chemotherapy treatment phase for colorectal cancer patients.[42] The efficacy of specific probiotic strains for CRF is still an area of active research, and both the Lactobacillus and Bifidobacterium genera have been studied for their potential benefits in alleviating gastrointestinal symptoms and improving immune function, which could indirectly affect CR.[59] Some studies have also suggested that multistrain probiotics may offer synergistic benefits that single strains do not provide.[60] Adding to this diversity, the Khazaei et al. study explored the use of a synbiotic intervention in breast cancer patients undergoing chemotherapy.[48] This study employed a combination of probiotics and prebiotics (synbiotics), including a variety of Lactobacillus and Bifidobacterium strains, highlighting a different aspect of microbiome modification. The use of synbiotics represents a novel approach in the context of CRF management, potentially offering the combined benefits of both prebiotics and probiotics.

The mechanisms by which probiotics benefit CRF remain an active research area.[7,23] This systematic review, in conjunction with insights from the recent study on CRF pathogenesis, suggests that both Lactobacillus and Bifidobacterium genera could potentially mitigate CRF.[61] These probiotics might influence the physiological dysfunctions associated with CRF, such as immune activation, inflammatory responses, and central nervous system disorders. Their potential role in normalizing disturbed intestinal microbial communities, competitively excluding pathogens, and modulating the immune system could be particularly relevant in CRF, where immune function and gut health are often compromised.[23] The complexity of CRF arises from its multifactorial nature, involving skeletal muscular and mitochondrial dysfunctions, immune and inflammation dysregulation, and central nervous system disorders.[23] Probiotics could potentially interact with these pathways by influencing gut health and immune response. However, the exact mechanisms of how probiotics modulate these varied aspects of CRF are not fully understood. Therefore, future research should focus on exploring the specific molecular and physiological interactions between probiotic strains and the diverse factors contributing to CRF. This would involve studying the role of probiotics in immune modulation, inflammation control, and possibly their effects on central nervous system function and mitochondrial health in the context of cancer and its treatment.

Choosing between simpler and more complex probiotic blends has significant clinical implications, especially in managing CRF.[60] Our study revealed that multistrain probiotics, as utilized by Golkhalkhali et al.[42] and Khazaei et al.,[48] showed a significant positive impact on CRF management in patients with colorectal cancer. While these multistrain blends may offer synergistic benefits, they could also come with a higher price tag and a different side-effect profile compared to single-strain options like those used in the study by Lee et al. For instance, multistrain probiotics may interact differently with medications or other treatments, requiring careful consideration and possibly additional monitoring. Furthermore, the complexity of multistrain probiotics could necessitate more rigorous storage conditions, affecting their feasibility for long-term use.[62] Understanding these trade-offs is crucial for clinicians when recommending probiotic supplements as a complementary treatment for CRF. For this reason, there is a need for more comprehensive studies that not only evaluate the efficacy but also the cost-effectiveness, side-effect profile, and patient compliance associated with various probiotic formulations.

The timing and context of probiotic interventions in the studies by Lee et al.,[43] Golkhalkhali et al.,[42] and Khazaei et al.[48] reveal significant differences in their approaches and potential outcomes. Lee et al. approach included patients who completed treatment between 6 months and 2 years (i.e., post-treatment probiotic supplementation),[43] Golkhalkhali et al. studied probiotics during induction chemotherapy in patients at onset,[42] and Khazaei et al.[48] included women undergoing neoadjuvant or adjuvant chemotherapy. These varying timings could influence the effectiveness of the probiotics in managing side effects and CRF. This variation in intervention timing across different cancer treatment phases indicates a need for tailored probiotic strategies depending on the treatment stage. It also

suggests that probiotics might play a role in alleviating not just gastrointestinal symptoms like mucositis but also broader aspects of CRF.[63] However, more research is needed to fully understand the efficacy of probiotics and synbiotics in different cancer treatment contexts, including their potential to manage the side effects of radiotherapy and chemotherapy.[64]

Patient compliance is a critical factor in the efficacy of any treatment regimen, and this holds particular meaning for supplementary treatments like probiotics or other microbiome modifiers. This review indicates that the feasibility of incorporating probiotics into a patient's treatment plan involves a multifaceted evaluation. Factors such as the frequency and timing of doses are crucial; for example, the study by Lee et al. and Khazaei et al. required patients to take the probiotic blend twice daily with or right after meals,[43,48] while the study by Golkhalkhali et al. involved a daily dose for 4 weeks, followed by an 8-week regimen of omega-3 fatty acids.[42] These varying dosing schedules could impact patient compliance, especially when considered alongside the already complex treatment regimens that cancer patients often undergo. Additionally, potential interactions with other medications are a significant concern:[65] cancer patients frequently take various medications for cancer treatment and symptom management, raising the possibility of drug-probiotic interactions that could either enhance or diminish the efficacy of both. The patient's lifestyle and dietary habits must also be considered in symptom management. For instance, both studies excluded patients who consumed food containing probiotics,[42,43] which could limit the applicability of these treatments to a broader patient population who may already include probiotic-rich foods in their diet. Given the complexity of cancer treatment regimens and this patient population's unique challenges, the ease of incorporating probiotics could determine their widespread adoption for managing CRF. Therefore, future studies should address these practical considerations to facilitate the seamless integration of probiotics into existing cancer care protocols.

As a result of the increasing interest in exploring the potential benefits of microbiome modifiers in mitigating cancer-related fatigue, several ongoing clinical have been initiated to investigate the effects of this mechanism.[66-68] These trials elucidate the mechanisms underlying the interaction between the gut microbiota and the immune system and how such interactions may influence fatigue levels. In particular, what is being investigated in these RTCs is the use of symbiotics[66,67] and fermented foods[68] in managing the symptoms related to chemotherapy administration. As per the literature we have reviewed, these studies employ established rating scales to evaluate fatigue levels in cancer patients, including the FACT, EORTC-Q30. It is interesting to underline how these studies research the effects of microbiome modifiers in pathologies other than those directly affecting the intestinal system, contrary to what is already in the literature.[42,43] However, these ongoing trials explore those effects in other solid tumors, such as breast and advanced cervical cancer.

As the nursing field continues to evolve, ongoing clinical trials in this area promise to provide us with a more comprehensive understanding of microbiome modifiers in cancer care. This knowledge is not just academic: it has profound implications for cancer nursing practice. Nurses are at the forefront of patient care, playing a vital role in symptom management and supporting patients through their cancer journey. Therefore, the findings of this review are directly relevant to nursing practice, as they can inform decisions about how to best incorporate probiotics into the holistic care of cancer patients experiencing CRF. This review equips cancer nurses with the knowledge needed to make informed decisions about the inclusion of probiotics in patient care plans by shedding light on the potential benefits, challenges, and considerations associated with probiotic interventions in managing CRF.

Limitations

While this systematic review provides valuable insights into the potential benefits of microbiome-modifiers like probiotics in managing CRF, several limitations must be acknowledged. First, the review included limited studies, with only three meeting the eligibility criteria. This small sample size limits the generalizability of this systematic review. Second, two studies included studies focused exclusively on patients with colorectal cancer, and only one study included patients with breast cancer; therefore, the available evidence may not represent the broader cancer patient population. Third, the studies employed different probiotic strains and dosing regimens, making it challenging to draw definitive conclusions about the most effective approach. Fourth, the studies used different scales to measure CRF, which could introduce variability in the results. Fifth, the included studies need to address these probiotic interventions' long-term effects and safety profiles adequately. In addition, the review did not account for potential publication bias or the quality of the studies included, which could affect the validity of our conclusions. Lastly, while Golkhalkhali et al.[42] demonstrated an adequate randomization plan with a low risk of bias, it is worth noting that it failed to achieve comparable levels of CRF between the two study groups. This disparity in baseline CRF levels could potentially introduce a confounding factor that might influence the study's outcomes, making it challenging to isolate the precise effects of the probiotic intervention on CRF. Therefore, it is crucial to interpret the study's results while considering this baseline difference, as it may impact the observed improvements in CRF. Future research should address these limitations by including a more diverse patient population, standardizing measurement scales, investigating long-term outcomes, and exploring the efficacy of other microbiome modifiers.

Conclusions

This systematic review and exploratory meta-analysis represents a pioneering effort to understand the potential role of microbiome modifiers, specifically probiotics, in managing CRF. The results suggest that multistrain probiotics may positively impact CRF management in patients with colorectal cancer. However, the limited number of studies and their focus on a specific cancer type call for caution in generalizing these results. The review also highlights significant gaps in the existing literature, including the need for more research on other microbiome modifiers and their efficacy in treating CRF. As nutritional metabolomics continues to evolve, targeted studies are essential to clarify the specific mechanisms of action, the selection of the most efficient and safe probiotic strains and their combinations, clinical implications, and the feasibility of incorporating microbiome modifiers into comprehensive cancer care plans. Additional research should focus on using microbiome modifiers in various types of cancer by exploring which combinations result in greater efficacy and greater impact on the quality of life of patients with CRF to offer novel insights and potential therapeutic strategies. Future research should aim to address these gaps and limitations to provide more robust evidence to guide clinical practice in this emerging area of cancer care.

Author Contributions

SB, CG, CA, and RC conceptualized the study. RC and SB performed the statistical analysis. IB, GC, and AM significantly contributed to data collection. SB and CG drafted the original manuscript, and all authors assisted in writing and reviewing it. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Silvia Belloni: Writing – original draft, Formal analysis, Conceptualization. **Rosario Caruso:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Chiara Giacon:** Writing – original draft, Methodology, Investigation, Conceptualization. **Irene Baroni:** Writing – review & editing, Validation, Investigation. **Gianluca Conte:** Writing – review & editing, Validation, Investigation. **Arianna Magon:** Writing – review & editing, Supervision, Investigation. **Cristina Arrigoni:** Writing – review & editing, Project administration, Conceptualization.

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Supplementary materials

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References

1. Ma Y, He B, Jiang M, et al. Prevalence and risk factors of cancer-related fatigue: a systematic review and meta-analysis. *Int J Nurs Stud*. 2020;111: 103707. https://doi.org/10.1016/j.ijnurstu.2020.103707.
2. Thong MSY, van Noorden CJF, Steindorf K, Arndt V. Cancer-related fatigue: causes and current treatment options. *Curr Treat Options Oncol*. 2020;21(2):17. https://doi.org/10.1007/s11864-020-0707-5.
3. Palesh O, Scheiber C, Kesler S, Mustian K, Koopman C, Schapira L. Management of side effects during and post-treatment in breast cancer survivors. *Breast J*. 2018;24 (2):167–175. https://doi.org/10.1111/tbj.12862.
4. Inglis JE, Lin PJ, Kerns SL, et al. Nutritional interventions for treating cancer-related fatigue: a qualitative review. *Nutr Cancer*. 2019;71(1):21–40. https://doi.org/10.1080/01635581.2018.1513046.
5. Muthanna FMS, Hassan BAR, Karuppannan M, Ibrahim HK, Mohammed AH, Abdulrahman E. Prevalence and impact of fatigue on quality of life (QOL) of cancer patients undergoing chemotherapy: a systematic review and meta-analysis. *Asian Pac J Cancer Prev*. 2023;24(3):769–781. https://doi.org/10.31557/APJCP.2023.24.3.769.
6. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014;11(10):597–609. https://doi.org/10.1038/nrclinonc.2014.127.
7. Yang S, Chu S, Gao Y, et al. A narrative review of cancer-related fatigue (CRF) and its possible pathogenesis. *Cells*. 2019;8(7):738. https://doi.org/10.3390/cells8070738.
8. Burfeind KG, Michaelis KA, Marks DL. The central role of hypothalamic inflammation in the acute illness response and cachexia. *Semin Cell Dev Biol*. 2016;54:42–52. https://doi.org/10.1016/j.semcdb.2015.10.038.
9. Montassier E, Gastinne T, Vangay P, et al. Chemotherapy-driven dysbiosis in the intestinal microbiome. *Aliment Pharmacol Ther*. 2015;42(5):515–528. https://doi.org/10.1111/apt.13302.
10. Li HL, Lu L, Wang XS, et al. Alteration of gut microbiota and inflammatory cytokine/chemokine profiles in 5-fluorouracil induced intestinal mucositis. *Front Cell Infect Microbiol*. 2017;7:455. https://doi.org/10.3389/fcimb.2017.00455.
11. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. *Nat Rev Immunol*. 2017;17(4):219–232. https://doi.org/10.1038/nri.2017.7.
12. Giloteaux L, Goodrich JK, Walters WA, Levine SM, Ley RE, Hanson MR. Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. *Microbiome*. 2016;4(1):30. https://doi.org/10.1186/s40168-016-0171-4.
13. Xiao C, Fedirko V, Beitler J, et al. The role of the gut microbiome in cancer-related fatigue: pilot study on epigenetic mechanisms. *Support Care Cancer*. 2021;29 (6):3173–3182. https://doi.org/10.1007/s00520-020-05820-3.
14. Xiao C, Beitler JJ, Higgins KA, et al. Fatigue is associated with inflammation in patients with head and neck cancer before and after intensity-modulated radiation therapy. *Brain Behav Immun*. 2016;52:145–152. https://doi.org/10.1016/j.bbi.2015.10.016.
15. Yoo BB, Mazmanian SK. The enteric network: interactions between the immune and nervous systems of the gut. *Immunity*. 2017;46(6):910–926. https://doi.org/10.1016/j.immuni.2017.05.011.
16. Mayer EA, Nance K, Chen S. The gut-brain axis. *Annu Rev Med*. 2022;73:439–453. https://doi.org/10.1146/annurev-med-042320-014032.
17. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res*. 2020;30(6):492–506. https://doi.org/10.1038/s41422-020-0332-7.
18. Mohajeri MH, Brummer RJM, Rastall RA, et al. The role of the microbiome for human health: from basic science to clinical applications. *Eur J Nutr*. 2018;57(suppl 1):1–14. https://doi.org/10.1007/s00394-018-1703-4.
19. Bach Knudsen KE, Lærke HN, Hedemann MS, et al. Impact of diet-modulated butyrate production on intestinal barrier function and inflammation. *Nutrients*. 2018;10(10):1499. https://doi.org/10.3390/nu10101499.
20. Kim YS, Milner JA. Bioactive food components and cancer-specific metabonomic profiles. *J Biomed Biotechnol*. 2011;2011: 721213. https://doi.org/10.1155/2011/721213.
21. Massari F, Ciccarese C, Santoni M, et al. Metabolic phenotype of bladder cancer. *Cancer Treat Rev*. 2016;45:46–57. https://doi.org/10.1016/j.ctrv.2016.03.005.
22. Ganapathy-Kanniappan S. Molecular intricacies of aerobic glycolysis in cancer: current insights into the classic metabolic phenotype. *Crit Rev Biochem Mol Biol*. 2018;53(6):667–682. https://doi.org/10.1080/10409238.2018.1556578.
23. Salminen S, Collado MC, Endo A, et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat Rev Gastroenterol Hepatol*. 2021;18(9):649–667. https://doi.org/10.1038/s41575-021-00440-6.
24. Belloni S, Arrigoni C, Baroni I, et al. Non-pharmacologic interventions for improving cancer-related fatigue (CRF): a systematic review of systematic reviews and pooled meta-analysis. *Semin Oncol*. 2023;50(1-2):49–59. https://doi.org/10.1053/j.seminoncol.2023.03.004.
25. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-related fatigue. *J Natl Compr Canc Netw*. 2015;13(8):1012–1037. https://doi.org/10.6004/jnccn.2007.0088.
26. Associazione Italiana Infermieri di Area Oncologica. Linee Guida. Gli Interventi Non Farmacologici a Supporto Della Fatigue Cancro Correlata (CRF).; 2023. https://www.iss.it/-/snlg-fatiguecancrocorrelata (last consultation on 31 Jan 2024).
27. Fabi A, Bhargava R, Fatigoni S, et al. Cancer-related fatigue: ESMO Clinical Practice Guidelines for diagnosis and treatment. *Ann Oncol*. 2020;31(6):713–723. https://doi.org/10.1016/j.annonc.2020.02.016.
28. Belloni S, Arrigoni C, Arcidiacono MA, et al. A systematic review of systematic reviews and pooled meta-analysis on psychosocial interventions for improving cancer-related fatigue. *Semin Oncol Nurs*. 2023;39(3): 151354. https://doi.org/10.1016/j.soncn.2022.151354.
29. Belloni S, Arrigoni C, Caruso R. Effects from physical exercise on reduced cancer-related fatigue: a systematic review of systematic reviews and meta-analysis. *Acta Oncol*. 2021;60(12):1678–1687. https://doi.org/10.1080/0284186X.2021.1962543.
30. Belloni S, Bonucci M, Arrigoni C, Dellafiore F, Caruso R. A systematic review of systematic reviews and a pooled meta-analysis on complementary and integrative medicine for improving cancer-related fatigue. *Clin Ther*. 2023;45(1):e54–e73. https://doi.org/10.1016/j.clinthera.2022.12.001.
31. Loman BR, Jordan KR, Haynes B, Bailey MT, Pyter LM. Chemotherapy-induced neuroinflammation is associated with disrupted colonic and bacterial homeostasis in female mice. *Sci Rep*. 2019;9(1):16490. https://doi.org/10.1038/s41598-019-52893-0.
32. Deleemans JM, Gajtani Z, Baydoun M, Reimer RA, Piedalue KA, Carlson LE. The use of prebiotic and probiotic interventions for treating gastrointestinal and psychosocial health symptoms in cancer patients and survivors: a systematic review. *Integr Cancer Ther*. 2021;20:1–15. https://doi.org/10.1177/15347354211061733.
33. Zuo S, Cheng H, Wang Z, et al. Nonpharmacological interventions for cancer-related fatigue: a comprehensive literature review. *Asia Pac J Oncol Nurs*. 2023;10 (5): 100230. https://doi.org/10.1016/j.apjon.2023.100230.
34. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ WV. Cochrane Handbook for Systematic Reviews of Interventions Version 6.0.; 2019. https://training.cochrane.org/handbook/current/chapter-25 (last consultation on 31 Jan 2024).
35. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
36. Higgins JP, Savović J, Page MJ, Sterne JAC. RoB 2 Guidance: Parallel Trial. *The Cochrane Collaboration*. 2019:(July):1–24.
37. Higgins J, Thomas J, Chandler J, et al. Chapter 10: analysing data and undertaking meta-analyses. In: Deeks JJ, Higgins JPT, Altman DG, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (Updated February 2022)*. Cochrane; 2022. www.training.cochrane.org/handbook.
38. Ryan R. Cochrane consumers and communication review group reviews: meta-analysis. *Cochrane Consumers and Communication Review Group*. 2016;2016 (December):1–6.
39. Ohigashi S, Hoshino Y, Ohde S, Onodera H. Functional outcome, quality of life, and efficacy of probiotics in postoperative patients with colorectal cancer. *Surg Today*. 2011;41(9):1200–1206. https://doi.org/10.1007/s00595-010-4450-6.
40. Limaye SA, Haddad RI, Cilli F, et al. Phase 1b, multicenter, single blinded, placebo-controlled, sequential dose escalation study to assess the safety and tolerability of topically applied AG013 in subjects with locally advanced head and neck cancer receiving induction chemotherapy. *Cancer*. 2013;119(24):4268–4276. https://doi.org/10.1002/cncr.28365.

41. Ahrén IL, Bjurberg M, Steineck G, Bergmark K, Jeppsson B. Decreasing the adverse effects in pelvic radiation therapy: a randomized controlled trial evaluating the use of probiotics. *Adv Radiat Oncol*. 2023;8(1): 101089. https://doi.org/10.1016/j.adro.2022.101089.
42. Golkhalkhali B, Rajandram R, Paliany AS, et al. Strain-specific probiotic (microbial cell preparation) and omega-3 fatty acid in modulating quality of life and inflammatory markers in colorectal cancer patients: a randomized controlled trial. *Asia Pac J Clin Oncol*. 2018;14(3):179–191. https://doi.org/10.1111/ajco.12758.
43. Lee JY, Chu SH, Jeon JY, et al. Effects of 12 weeks of probiotic supplementation on quality of life in colorectal cancer survivors: a double-blind, randomized, placebo-controlled trial. *Dig Liver Dis*. 2014;46(12):1126–1132. https://doi.org/10.1016/j.dld.2014.09.004.
44. Lin B, Zhao F, Liu Y, et al. Randomized clinical trial: probiotics alleviated oral-gut microbiota dysbiosis and thyroid hormone withdrawal-related complications in thyroid cancer patients before radioiodine therapy following thyroidectomy. *Front Endocrinol (Lausanne)*. 2022;13: 834674. https://doi.org/10.3389/fendo.2022.834674.
45. Gao X, Hao C, Yan P, Zhu P, Wang J, Chen R. Effect of targeted nutritional intervention on intestinal flora, defecation function, and postoperative complications in patients who underwent radical resection of rectal carcinoma. *Anti-Tumor Pharm*. 2019;9(2):338–343.
46. Chen H, Xia Y, Shi C, Liang Y, Yang Y, Qin H. Effects of perioperative probiotics administration on patients with colorectal cancer: short-term outcomes of a randomized controlled trials. *Chin J Clin Nutr*. 2014;22(2):74–81. https://doi.org/10.3760/cma.j.issn.1674-635x.2014.02.002.
47. Zeng X, Yang S, Yang H, Chen Y, Pan QJ. Effect of bifid triple viable combined with enteral nutrition support on gastrointestinal function and nutritional indexes in patients with gastric cancer after operation. *World Chin J Digestol*. 2020;28(11):410–416.
48. Khazaei Y, Basi A, Fernandez ML, Foudazi H, Bagherzadeh R, Shidfar F. The effects of synbiotics supplementation on reducing chemotherapy-induced side effects in women with breast cancer: a randomized placebo-controlled double-blind clinical trial. *BMC Complement Med Ther*. 2023;23(1):339. https://doi.org/10.1186/s12906-023-04165-8.
49. Pérez DLC. Use of a fermented dairy beverage in cervical cancer patients undergoing concurrent chemoradiation therapy. 2023. Available at: https://clinicaltrials.gov/study/NCT05736315 Accessed January 1, 2023.
50. Raj E. The efficacy of synbiotics on gastrointestinal chemotherapy symptoms in patients with solid tumours: a randomised-crossover double-blinded placebo-controlled clinical trial (pilot study). 2023. Available at: https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12621000234819 Accessed December 27, 2023.
51. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570–579. https://doi.org/10.1200/JCO.1993.11.3.570.
52. Kaasa S, Bjordal K, Aaronson N, et al. The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. *Eur J Cancer*. 1995;31A(13-14):2260–2263. https://doi.org/10.1016/0959-8049(95)00296-0.
53. Danzi F, Pacchiana R, Mafficini A, et al. To metabolomics and beyond: a technological portfolio to investigate cancer metabolism. *Signal Transduct Target Ther*. 2023;8(1):137. https://doi.org/10.1038/s41392-023-01380-0.
54. Schmidt DR, Patel R, Kirsch DG, et al. Metabolomics in cancer research and emerging applications in clinical oncology. *CA Cancer J Clin*. 2021;71(4):333–358. https://doi.org/10.3322/caac.21670.
55. Chang KH, Brodie R, Choong MA, Sweeney KJ, Kerin MJ. Complementary and alternative medicine use in oncology: a questionnaire survey of patients and health care professionals. *BMC Cancer*. 2011;11(1):196. https://doi.org/10.1186/1471-2407-11-196.
56. Legesse Bedada T, Feto TK, Awoke KS, Garedew AD, Yifat FT, Birri DJ. Probiotics for cancer alternative prevention and treatment. *Biomed Pharmacother*. 2020;129(April): 110409. https://doi.org/10.1016/j.biopha.2020.110409.
57. Anello C, Fleiss JL. Exploratory or analytic meta-analysis: should we distinguish between them? *J Clin Epidemiol*. 1995;48(1):109–116. https://doi.org/10.1016/0895-4356(94)00084-4.
58. Chen DG, Fang D, Wilson JR. Meta-analysis of two studies with random effects? *J Minim Invasive Gynecol*. 2017;24(5):689–690. https://doi.org/10.1016/j.jmig.2017.05.008.
59. Chitapanarux I, Chitapanarux T, Traisathit P, Kudumpee S, Tharavichitkul E, Lorvidhaya V. Randomized controlled trial of live lactobacillus acidophilus plus bifidobacterium bifidum in prophylaxis of diarrhea during radiotherapy in cervical cancer patients. *Radiat Oncol*. 2010;5(1):31. https://doi.org/10.1186/1748-717X-5-31.
60. Kwoji ID, Aiyegoro OA, Okpeku M, Adeleke MA. Multi-strain probiotics: synergy among isolates enhances biological activities. *Biology (Basel)*. 2021;10(4):1–20. https://doi.org/10.3390/biology10040322.
61. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of action of probiotics. *Adv Nutr*. 2019;10:S49–S66. https://doi.org/10.1093/advances/nmy063.
62. Floch MH, Walker WA, Sanders ME, et al. Recommendations for probiotic use−2015 update: proceedings and consensus opinion. *J Clin Gastroenterol*. 2015;49(Suppl 1):S69–S73. https://doi.org/10.1097/MCG.0000000000000420.
63. Thomsen M, Vitetta L. Adjunctive treatments for the prevention of chemotherapy- and radiotherapy-induced mucositis. *Integr Cancer Ther*. 2018;17(4):1027–1047. https://doi.org/10.1177/1534735418794885.
64. Wei D, Heus P, van de Wetering FT, van Tienhoven G, Verleye L, Scholten RJPM. Probiotics for the prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer. *Cochrane Database Syst Rev*. 2018;2018(8): CD008831. https://doi.org/10.1002/14651858.CD008831.pub3.
65. Ballan R, Battistini C, Xavier-Santos D, Saad SMI. Chapter nine: interactions of probiotics and prebiotics with the gut microbiota. Sun J, ed. Chapter nine: interactions of probiotics and prebiotics with the gut microbiota. The microbiome in health and disease. *Vol 171. Progress in molecular biology and translational science*. 2020:265–300. https://doi.org/10.1016/bs.pmbts.2020.03.008.
66. International Clinical Trials Registry Platform. The effects of synbiotic supplementation in reducing of chemotherapy-induced side effects in women with breast cancer, 2023. Available at: https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20091114002709N56 Accessed September 2, 2023.
67. International Clinical Trials Registry Platform. Effect of synbiotics on gastrointestinal chemotherapy symptoms, 2023. Available at: https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12621000234819 Accessed September 2, 2023.
68. ClinicalTrials.Gov. Use of a fermented dairy beverage in cervical cancer patients undergoing concurrent chemoradiation therapy. 2023. Available at: https://clinicaltrials.gov/show/NCT05736315 Accessed September 2, 2023.