Literature Review

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THE PROTECTIVE ROLE OF INTESTINAL MICROBIOTA IN COLORECTAL CANCER TREATMENT: A SCOPING REVIEW

Jéssica Rosa Thiesen Cunha[1]
Elissandra Maria Faiz[2]
Elizete Maria de Souza Bueno[1]
Eliana Rosa da Fonseca[3]
Thais Ortiz Hammes[1]
Adriana Serdotte Freitas Cardoso[1]
Leticia Becker Vieira[2]
Isabel Cristina Echer[2]

[1]Hospital de Clínicas de Porto Alegre. Porto Alegre, Rio Grande do Sul, Brasil.
[2]Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Enfermagem. Porto Alegre, Rio Grande do Sul, Brasil.
[3]Universidade Federal do Rio de Janeiro, Sistema de Bibliotecas e informação. Rio de Janeiro, Rio de Janeiro, Brasil.

ABSTRACT

Objective: to map protective factors related to the intestinal microbiota (IM) of patients with colorectal cancer undergoing intravenous chemotherapy treatment.
Method: this is a scoping review in accordance with the JBI recommendations and reported, according to the PRISMA-ScR checklist, to answer the research question: what are the protective factors for the IM of adult patients with colorectal cancer undergoing intravenous chemotherapy treatment? Data collection was carried out from January to June 2023, in the WPRIM, LILACS, IBECS, BINACIS from the VHL Portal, MEDLINE/PubMed, Embase and Scopus, Web of Science/Elsevier, Cochrane Library, CINAHL, Academic Search Premier, Food Science Source and Food Science and Technology Abstracts/EBSCO, Google Scholar and the CAPES Theses & Dissertations Catalog databases, without time or language filter. Selection was carried out by two reviewers, and any disagreements were assessed by a third party. Data extraction was performed using an instrument developed by the authors after a pilot test. The protocol registered in the Open Science Framework: OSF.IO/Y2U6V.
Results: a total of 3,025 documents were mapped during the study period. The analyses included 30 articles published between 2007 and 2023. The research reiterates the correlation of dysbiosis with the emergence of colorectal tumors and IM modulation by interventions with the reduction of side effects of chemotherapy and increased quality of life.
Conclusion: the use of probiotics, yogurts and omega 3 have been shown to be protective, safe and effective in altering IM composition, reducing the side effects of chemotherapy. However, further studies are needed to determine the relationship between IM and treatment effectiveness.

DESCRITORS: Colorectal Neoplasms. Antineoplastic Agents. Gastrointestinal Microbiome. Dysbiosis.

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O PAPEL PROTETIVO DA MICROBIOTA INTESTINAL NO TRATAMENTO DO CÂNCER COLORRETAL: REVISÃO DE ESCOPO

RESUMO

Objetivo: mapear os fatores protetivos relacionados à microbiota intestinal (MI) de pacientes com câncer colorretal em tratamento quimioterápico endovenoso.
Método: revisão de escopo em conformidade com as recomendações do Instituto Joanna Briggs e relatada, conforme *Checklist* PRISMA-ScR, para responder à questão de pesquisa: quais os fatores protetivos para a microbiota intestinal de pacientes adultos com câncer colorretal em tratamento quimioterápico endovenoso? A coleta de dados foi realizada de janeiro a junho/2023 nas bases: WPRIM, LILACS, IBECS, BINACIS do Portal BVS, MEDLINE/PubMed, Embase e Scopus, *Web of Science*/Elsevier, Cochrane *Library*, CINAHL, *Academic Search Premier, Food Science Source* e *Food Science and Technology Abstracts*/Ebsco, *Google Scholar* e o Catálogo de Teses & Dissertações/CAPES, sem filtro temporal e de idioma. A seleção foi realizada por dois revisores, e as divergências apreciadas por um terceiro. A extração dos dados foi realizada por meio de instrumento elaborado pelos autores após teste piloto. O protocolo registrado no *Open Science Framework*: OSF.IO/Y2U6V.
Resultados: foram mapeados 3.025 documentos no período do estudo. As análises incluíram 30 artigos publicados entre 2007 e 2023. As pesquisas reiteram a correlação da disbiose com surgimento de tumores colorretais e a modulação da MI por intervenções com a redução de efeitos colaterais da quimioterapia e aumento da qualidade de vida.
Conclusão: o uso de probióticos, iogurtes e ômega 3, mostraram-se protetores, seguros e eficazes em alterar a composição da MI, reduzindo os efeitos colaterais da quimioterapia. Porém, são necessários mais estudos para determinar a relação da MI com a eficácia do tratamento.

DESCRITORES: Câncer colorretal. Antineoplásico. Microbioma gastrointestinal. Disbiose.

EL PAPEL PROTECTOR DE LA MICROBIOTA INTESTINAL EN EL TRATAMIENTO DEL CÁNCER COLORRECTAL: REVISIÓN DEL ALCANCE

RESUMEN

Objetivo: mapear los factores protectores relacionados con la microbiota intestinal (MI) de pacientes con cáncer colorrectal sometidos a tratamiento de quimioterapia intravenosa.
Método: esta es una revisión de alcance de acuerdo con las recomendaciones del JBI y se informa, según la lista de verificación PRISMA-ScR, para responder a la pregunta de investigación: ¿cuáles son los factores protectores para la microbiota intestinal de pacientes adultos con cáncer colorrectal sometidos a tratamiento de quimioterapia intravenosa? La recolección de datos se realizó de enero a junio de 2023 en las siguientes bases de datos: WPRIM, LILACS, IBECS, BINACIS del Portal de la BVS, MEDLINE/PubMed, Embase y Scopus, Web of Science/Elsevier, Cochrane Library, CINAHL, Academic Search Premier, Fuente de Ciencia de los Alimentos y Resúmenes de Ciencia y Tecnología de los Alimentos/EBSCO, Google Scholar y el Catálogo de Tesis y Disertaciones de la CAPES, sin filtros de tiempo ni de idioma. La selección fue realizada por dos revisores y las divergencias fueron evaluadas por un tercero. La extracción de datos se realizó mediante un instrumento desarrollado por los autores después de una prueba piloto. El protocolo registrado en Open Science Framework: OSF.IO/Y2U6V.
Resultados: durante el período de estudio se mapearon 3.025 documentos. Los análisis incluyeron 30 artículos publicados entre 2007 y 2023. La investigación reitera la correlación de la disbiosis con la aparición de tumores colorrectales y la modulación de la MI por intervenciones con reducción de los efectos secundarios de la quimioterapia y aumento de la calidad de vida.
Conclusión: el uso de probióticos, yogures y omega 3, demostró ser protector, seguro y eficaz para alterar la composición de la MI, reduciendo los efectos secundarios de la quimioterapia. Sin embargo, se necesitan más estudios para determinar la relación entre la MI y la eficacia del tratamiento.

DESCRIPTORES: Neoplasias Colorrectal. Antineoplásicos. Microbioma Gastrointestinal. Disbiosis.

INTRODUCTION

Estimates predict that by 2025 there will be 77 thousand new cases of colorectal cancer (CRC), an increase of 6.98%[1]. Research emphasizes that around 30% of new cases of CRC diagnosed will be due to preventable habits, such as diet, smoking, sedentary lifestyle, alcohol consumption, diets rich in saturated fats, and comorbidities, such as obesity and diabetes[2–3]. In this context, lifestyle, especially eating habits, can make individuals more prone to developing CRC[4–6].

The intestine is inhabited by trillions of bacteria that make up the intestinal microbiota (IM), containing microorganisms that can both help maintain health and cause disease[7–8]. For intestinal functions to occur properly, a balance between populations is necessary. Otherwise, the process of dysbiosis begins, which is associated with the development of tumors such as pancreatic, ovarian, lung, sarcomas, melanomas and especially colorectal tumors[4,9–10]. IM dysbiosis is closely related to the process of colon carcinogenesis[3,5,11] by inducing fundamental mechanisms for the proliferation of malignant cells[3].

IM dysbiosis may be related to increased adverse events of CRC chemotherapy treatment and altered effects of radiotherapy and immunotherapy[4]. Chemotherapeutic regimens used in CRC treatment can induce dysbiosis[10,12], and studies even indicate that it is involved in failure of treatment with fluorouracil and oxaliplatin[5,10,13] and in the increase in side effects [5].

Recently, studies aimed at handling IM, through the use of probiotics and nutritional strategies, have demonstrated their effectiveness in reducing side effects, increasing quality of life and the ability to enhance the activity of chemotherapy drugs[5,10]. Given the benefits obtained by reducing dysbiosis and maintaining a healthy IM, it is believed to be a relevant topic with gaps to be explored[10,14].

It is expected that mapping protective factors associated with IM during intravenous chemotherapy treatment of adult patients with CRC can provide tools for planning new strategies during chemotherapy, elucidate concepts, and encourage discussion of therapeutic interventions, especially for nursing professionals who work in health care for people with gastrointestinal oncological diseases.

Therefore, evidence-based practices and guidelines are necessary to provide patients with qualified care linked to updated and safe guidelines[15–16]. Considering the new perspectives of IM and the possible benefits in CRC treatment, the research is justified as it aims to provide professionals, especially nurses, with the knowledge the subject and to provide health guidelines, with the purpose of answering the following research question: what are the protective factors for IM in adult patients with CRC undergoing intravenous chemotherapy treatment? To answer this question, the objective was to map protective factors related to IM in adult patients with CRC undergoing intravenous chemotherapy treatment.

METHOD

This is a scoping review that followed the JBI[15,17] guidelines, with the aim of synthesizing and objectively presenting relevant results on a given topic through a rigid method and rigorous selection[18,19–20]. Recommendations[21] and amendments from other authors[22–23] were also used. The following stages[15] were used: define a research question; identify relevant studies; select studies; map data; compile, summarize and report results. Furthermore, the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist was used as a guide for preparing the report[24]. The protocol was registered on the Open Science Framework: OSF.IO/Y2U6V.

To construct the research question[17,23] with specific criteria, the mnemonic Population, Concept, and Context (PCC) was used. Thus, Population consisted of: adult patients with CRC undergoing intravenous chemotherapy treatment; Concept consisted of: protective factors of IM during intravenous

chemotherapy treatment of CRC; Context consisted of: patients with CRC undergoing intravenous chemotherapy treatment in hospital or outpatient care in public or private health institutions. The search strategy was carried out in three stages. In the first, the terms were searched in controlled vocabularies of the Health Sciences Descriptors (DeCS), Medical Subject Heading (MeSH), Embase subject Headings (Emtree); then, the search was performed in the MEDLINE/PubMed (Chart 1), Cochrane Library, OSF, PROSPERO, and JBI Synthesis databases. From this search, terms were identified in titles, abstracts and descriptors such as ("Colorectal Neoplasms" OR "Neoplasms of the Colon" OR "Rectal Neoplasms") AND ("Gastrointestinal Microbiome" OR Dysbiosis) AND ("Pharmacological Treatment" OR "Adjuvant Chemotherapy" OR Antineoplastics), and alternative terms or synonyms were used. The other search strategies used, stratified by database, are available in full at: https://doi.org/10.6084/m9.figshare.27068272.v1.

Chart 1 – MEDLINE/PubMed search strategy applied on January 12, 2023. Porto Alegre, RS, Brazil, 2023.

Search	Consultation	Results
#1	*"colorectal neoplasms"[mh] OR colorectal neoplasm*[tiab] OR colorectal cancer*[tiab] OR colorectal carcinoma*[tiab] OR colorectal tumor*[tiab] OR "colorectal tumorigenesis"[tiab] OR "colorectal tumour"[tiab] OR "colonic neoplasms"[mh] OR colonic neoplasm*[tiab] OR colon adenocarcinoma[tiab] OR colon cancer*[tiab] OR colon neoplasm*[tiab] OR colonic cancer*[tiab] OR "rectal neoplasms"[mh] OR rectal neoplasm*[tiab] OR rectal cancer*[tiab] OR rectal neoplasm*[tiab] OR rectal tumor*[tiab] OR rectum cancer*[tiab] OR rectum neoplasm*[tiab]*	316,529
#2	*"gastrointestinal microbiome"[mh] OR gastrointestinal microbiome[tiab] OR "enteric bacteria"[tiab] OR gastric microbiome*[tiab] OR "gastrointestinal flora"[tiab] OR gastrointestinal microbial communit*[tiab] OR "gastrointestinal microbiomes"[tiab] OR gastrointestinal microbiota*[tiab] OR "gastrointestinal microflora"[tiab] OR "gut flora"[tiab] OR gut microbiome*[tiab] OR gut microbiota*[tiab] OR "gut microflora"[tiab] OR "intestinal flora"[tiab] OR intestinal microbiome*[tiab] OR intestinal microbiota*[tiab] OR "intestinal microflora"[tiab] OR "intestine flora"[tiab] OR "microbial metabolite"[tiab] OR "bowel flora"[tiab] OR "bowel microbiota"[tiab] OR "digestive tract flora"[tiab] OR "enteric flora"[tiab] OR "enteric microbiota"[tiab] OR "gastro intestinal flora"[tiab] OR "gastrointestinal flora"[tiab] OR "gastrointestinal tract flora"[tiab] OR "gut bacteria"[tiab] OR "gut microbiota"[tiab] OR intestinal bacteria*[tiab] OR "intestinal bacterium"[tiab] OR "intestinal flora"[tiab] OR intestinal microbe*[tiab] OR "intestinal microbiota"[tiab] OR "intestinal microflora"[tiab] OR "intestinal microorganism"[tiab] OR "intestinal tract flora"[tiab] OR "intestine bacteria"[tiab] OR "intestine microflora"[tiab] OR "intestine flora"[tiab] OR "microbial metabolite"[tiab] OR "bowel flora"[tiab] OR "bowel microbiota"[tiab] OR "digestive tract flora"[tiab] OR "enteric flora"[tiab] OR "enteric microbiota"[tiab] OR "gastro intestinal flora"[tiab] OR "gastrointestinal flora"[tiab] OR "gastrointestinal tract flora"[tiab] OR "gut bacteria"[tiab] OR "gut microbiota"[tiab] OR intestinal bacteria*[tiab] OR "intestinal bacterium"[tiab] OR "intestinal flora"[tiab] OR intestinal microbe*[tiab] OR "intestinal microbiota"[tiab] OR "intestinal microflora"[tiab] OR "intestinal microorganism"[tiab] OR "intestinal tract flora"[tiab] OR "intestine bacteria"[tiab] OR "intestine microflora"[tiab] OR Microbiome*[tiab] OR microbiota*[tiab] OR microflora[tiab] OR dysbiosis[mh] OR dysbios*[tiab] OR dysbacterios*[tiab] OR disbacterios*[tiab]*	173,338

Chart 1 – Cont.

Search	Consultation	Results
#3	*"drug therapy"[mh] OR drug therap*[tiab] OR chemotherap*[tiab] OR pharmacotherapies[tiab] OR pharmacotherapy[tiab] OR "chemotherapy, adjuvant"[mh] OR adjuvant chemotherap*[tiab] OR adjuvant drug therap*[tiab] OR "antineoplastic agents"[mh] OR anticancer agent*[tiab] OR antineoplastic*[tiab] OR antitumor agent*[tiab] OR antitumor drug*[tiab] OR cancer chemotherapy agent*[tiab] OR cancer chemotherapy drug*[tiab] OR chemotherapeutic anticancer agent*[tiab] OR chemotherapeutic*[tiab] OR "drug treatment"[tiab] OR "medicament therapy"[tiab] OR "medicament treatment"[tiab] OR medication[tiab] OR "medicinal therapy"[tiab] OR "medicinal treatment"[tiab] OR "pharmaceutical therapy"[tiab] OR "pharmaceutical treatment"[tiab] OR pharmaco-therapy[tiab] OR pharmaco-treatment[tiab] OR "pharmacological therapy"[tiab] OR "pharmacological treatment"[tiab] OR pharmacotreatment[tiab] OR "therapeutic uses"[tiab] OR "anti cancer drug"[tiab] OR "anti neoplastic agent"[tiab] OR "anticancer agent"[tiab] OR "anticancer drug"[tiab] OR anticancerogen[tiab] OR anticarcinogen[tiab] OR "anticarcinogenic agents"[tiab] OR "antineoplastic agents"[tiab] OR "antineoplastic drug"[tiab] OR "antitumor agent"[tiab] OR "antitumor drug"[tiab] OR "antitumour agent"[tiab] OR "antitumour drug"[tiab] OR "cancer chemotherapeutic agent"[tiab] OR "cancer inhibitor"[tiab] OR "tumor inhibitor"[tiab] OR "tumour inhibitor"[tiab]*	2,521,853
#4	Search: **#1 AND #2 AND #3**	531

In the second stage, the terms identified in the first stage were aggregated in the search strategy, applied and adapted on February 22, 2023 in the following databases and information sources: WPRIM; LILACS; IBECS; BINACIS from the Virtual Health Library (VHL) Regional Portal; MEDLINE/PubMed; Embase and Scopus; Web of Science (WoS)/Elsevier; Cochrane Library; CINAHL; Academic Search Premier; Food Science Source and Food Science and Technology Abstracts/EBSCO; Google Scholar; and CAPES Catalog of Theses & Dissertations. In the third stage, the studies selected for full reading had their reference lists consulted to identify articles that may not have been captured in the previous stages, which went through the blind peer review process.

No time or language filter was used, and all published materials, including gray literature, were accepted, as long as they answered the research question: what are the protective factors for IM in adult patients with CRC undergoing intravenous chemotherapy? Studies whose participants were adult patients with CRC who underwent intravenous chemotherapy treatment, in outpatient or inpatient settings, that addressed IM, with surgical procedures, before, concomitantly with or after treatment, were included. The sample did not include studies with pediatric patients who used monoclonal antibody therapies, molecular targeted therapy or immunotherapy.

Controlled studies (randomized and non-randomized), before-and-after studies and interrupted time series studies, analytical observational research, prospective and retrospective cohort studies, case-control and cross-sectional analytical studies, literature and systematic reviews, descriptive observational studies, case series, individual case reports and descriptive cross-sectional studies were considered. Grey literature, such as dissertations and theses, was preferably considered, with articles originating from the aforementioned research reports. Experimental and quasi-experimental studies with animals, qualitative studies, reviews, experience reports, reflections, phenomenological designs, grounded theory, ethnography and action research, abstracts and letters to the editor were excluded.

All included articles were analyzed by two independent reviewers with experience in the subject, who had access to the full search results. The selection process began with reading the titles, followed by reading the abstracts and finally reading the full text, which complied with the inclusion and exclusion criteria, followed by comparing the spreadsheets to assess agreement among reviewers. Articles that raised doubts as to their inclusion were forwarded to a third reviewer, a professor and PhD holder, who made the final decision on whether or not to include the documents. The references were stored and organized in the online Rayann software, in which duplicate articles were excluded.

To extract evidence, a data form was developed in accordance with the JBI Manual[17], which underwent a pilot test to fine-tune the extraction of documents in relation to the inclusion and exclusion criteria between the pair of reviewers, who remained blinded and worked on independent spreadsheets[25]. The test was carried out in three databases, WoS, Cochrane Library, OSF, to assess agreement for including articles. After the pilot test, the data extraction instrument was used for the other search sources (Chart 2).

Chart 2 – Data extraction tool according to the JBI[17] manual. Porto Alegre, RS, Brazil, 2023.

<table>
<tr><td colspan="6">The protective role of intestinal microbiota in colorectal cancer treatment: a scoping review</td></tr>
<tr><td>Review question</td><td colspan="5">What are the protective factors for IM* in adult patients with CRC† undergoing intravenous chemotherapy?</td></tr>
<tr><td colspan="6">Evidence</td></tr>
<tr><td>Author(s)</td><td>Study objective</td><td>Method/ design</td><td colspan="2">Population/sample</td><td>Chemotherapy</td></tr>
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<tr><td>Year</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Country</td><td rowspan="6">Results</td><td>Protective factors of IM*</td><td>IM risk factors*</td><td colspan="2">NUTRITION and IM*</td></tr>
<tr><td>Periodical</td><td></td><td></td><td>Protective factors</td><td>Risk factors</td></tr>
<tr><td>Volume</td><td></td><td></td><td></td><td></td></tr>
<tr><td>No. of pages</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Document type</td><td></td><td></td><td></td><td></td></tr>
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*Intestinal microbiota, † Colorectal cancer

The results will be presented through a flowchart with the document selection process[27] and a chart with the characteristics of mapped documents.

RESULTS

A total of 3,025 documents were mapped during the study period in the VHL (n=30; 0.99%), CINAHL (n=329; 10.88%), Cochrane Library (n=2; 0.07%), Embase (n=354; 11.70%), PMC (n=17; 0.56%), PubMed (n=531; 17.55%), SciELO (n=2; 0.07%), Scopus (n=1,252; 41.39%) and WoS (n=508; 16.79%) databases. Of these,1,217 duplicates were suppressed, leaving 1,808 documents. After reading the title and abstracts,1,692 were excluded. A total of 116 articles remained for full-text reading; of these, 25 were included, and their 1,840 references were reviewed to include any document not mapped in previous searches. In the review of references, five studies were identified, which were included, totaling 30 articles, described in Figure 1 using the PRISMA-ScR flow diagram[26-27].

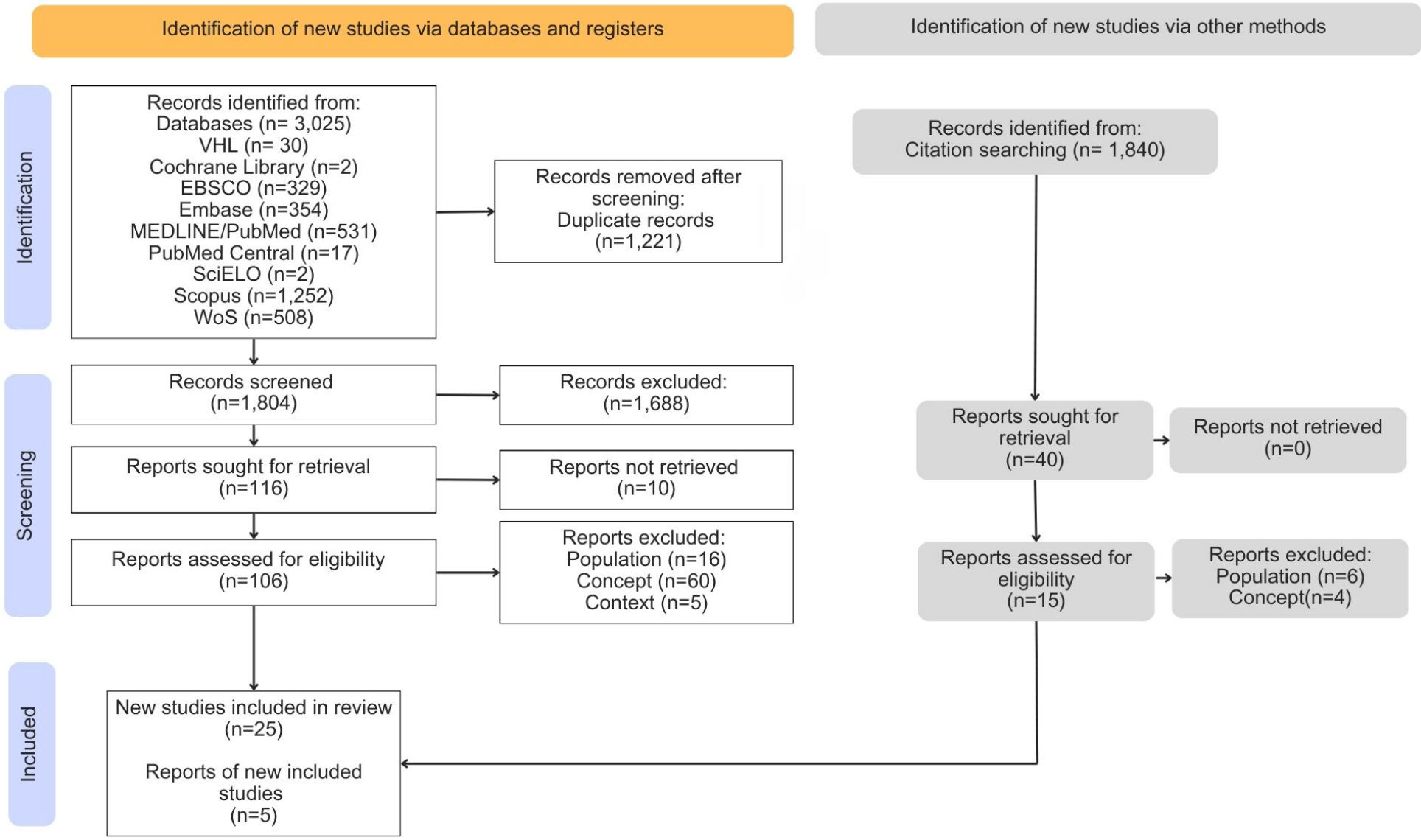

Figure 1 – Flowchart of the selection process of articles for the scoping review. Porto Alegre, RS, Brazil, 2023.

The documents were mapped from January to June 2023, including 30 articles in English published in 2021, with ten articles (33.3%), 2022, with six articles (20%), 2020, with four articles (13.3%), 2023, 2019 and 2018, with two each (6.6%), and 2017, 2016, 2015 and 2007, with only one each (3.4%). The studies were published in several countries, such as the United States of America, with five (16.9%), China, with four (13.6%), Malaysia and Italy, with three each (10%), Brazil and Iran, with two each (6.6%), Slovakia, Portugal, Poland, Thailand, Australia, Austria, Spain, Canada, South Korea, Finland and England, with one each (3.3%).

As for the method of mapped studies, 13 (43.3%) were review articles; nine (30%) were randomized clinical trials; four (13.4%) were systematic reviews with and without meta-analysis; three (10%) were cohort studies; and one (3.3%) was a prospective observational study. Chart 3 described the compiled summary of the main mapped findings.

Chart 3 – Characteristics of studies included in the scoping review. Porto Alegre, RS, Brazil, 2023

Reference	Method/ design	Sample	Main results
Mego M, et al[28].	Randomized clinical trial	46 patients	Use of probiotics in patients with metastatic CRC* undergoing treatment with irinotecan is safe and reduced chemotherapy-induced gastrointestinal toxicity.
Mocelin MC, et al[29].	Randomized clinical trial	45 patients, 37 with CRC*	The use of fish oil during chemotherapy reduced nausea and vomiting, loss of appetite, weight loss and depressive symptoms in patients with CRC*.
Mota JF, et al[30].	Review	113 articles	Dietary modifications, use of prebiotics and probiotics are useful in stabilizing IM† for CRC* prevention and treatment.
Zaharuddin L, et al[31].	Randomized clinical trial	60 patients	*Lactobacillus* and *Bifidobacteria* consumption 2x/day for six months was safe and reduced the level of pro-inflammatory cytokines and may prevent post-surgical complications in patients with CRC*. However, patients treated with XELOX‡ did not show a significant difference in the incidence of diarrhea.
Kaźmierczak-Siedlecka K,et al[32].	Review	76 articles	Intestinal dysbiosis has been associated with the process of colorectal carcinogenesis. The administration of probiotics and synbiotics are therapeutic methods to alter IM†.
Li J, et al[33].	Cohort	37 patients	The application of interventions in IM† before CRC* treatment provides an opportunity to obtain better results from chemotherapy with FOLFOX§.
Panebianco C, et al[34].	Review	46 articles	Handling IM† through selected probiotics may be a tool in CRC* prevention. The benefits are linked to improved immunity and inflammatory response in patients.
Sivamaruthi BS, et al[35].	Review	50 articles	Probiotic supplements improve immunity, gut barrier integrity, and reduce carcinogenic compounds in CRC* patients. However, not all probiotic interventions have shown positive health effects in CRC* patients.

Chart 3 – Cont.

Reference	Method/ design	Sample	Main results
Kalasabail S, et al[36].	Review	118 articles	Evidence of the influence of IM† on chemotherapy efficacy, toxicity and drug resistance suggests that dysbiosis has a negative correlation with chemotherapy outcomes.
Li N, et al[37].	Cohort	130 patients,44 CRC*	Alterations in the proportions of *R. faecis bacteria* in patients with gastrointestinal and CRC* may be a predictor of chemotherapy efficacy.
Mohamed AW, et al[38].	Review	80 articles	IM† plays a role that needs to be further studied in the context of cancer patients.
Mohebian F, et al[39].	Randomized clinical trial	66 patients	Yogurt and probiotic interventions may reduce and treat diarrhea. The study recommends the use of probiotics in chemotherapy-related diarrhea treatment.
Oh B, et al[40].	Review	742 patients, 154 com CRC*	Potential outcomes with gut microbiome modulation to predict chemotherapy outcomes and prevent adverse effects. However, studies that control for variables are needed before recommending microbiome therapy in oncology.
Rinninella E, et al[41].	Review	105 articles	IM† modulation through nutritional interventions is promising; however, data on the efficacy of chemotherapy are still scarce.
Rodriguez-Arrastia M, et al[42].	Systematic review	583 patients with CRC*	The use of probiotics such as *L. acidophilus*, *L. casei*, *B. longum*, *L. rhamnosus*, among others, is a therapeutic strategy to reduce adverse effects of chemotherapy in adult cancer patients, when used for at least four weeks.
Taghinezhad-S S, et al[43].	Review	83 articles	Probiotics containing *Lactobacillus* or *Bifidobacterium* have been shown to be safe and effective in reducing some side effects of chemotherapy and radiotherapy.
Golkhalkhali B, et al[44].	Randomized clinical trial	140 patients	Probiotic and omega-3 supplementation improved overall quality of life, reduced side effects of chemotherapy, and IL-6 levels in patients with CRC*.
Ue B, et al[45].	Review	145 articles	IM† management through diet, herbs, and probiotics should be part of future cancer treatment regimens. Probiotics have beneficial effects in CRC* patients, regardless of cancer stage.
Dikeocha IJ, et al[46].	Systematic review	2,457 patients	The use of probiotics in patients with CRC* reduced the risk of postoperative infection, the incidence of tumors, modulated the immune system, improved quality of life and reduced the adverse effects of treatment.
Feng J, et al[47].	Systematic review with meta-analysis	1,013 patients, 208 with CRC*	Probiotics have the potential to minimize chemotherapy-induced diarrhea and the incidence of oral mucositis.

Chart 3 – Cont.

Reference	Method/ design	Sample	Main results
Kim AJ, et al[48].	Review	115 articles	There is considerable preclinical data and limited clinical evidence that dietary factors may act in cancer prevention and/ or treatment and cancer treatment-related symptoms and toxicities.
Kim SH, et al[49].	Review	85 articles	Probiotics such as *B. infantis*, LGG, *L. acidophilus* and *L. casei* may play a role in immunomodulation of cancer cells and chemoprotective effects.
Lin DW, et al[50].	Prospective cohort	22 patients	Patients with squamous anal cancer receiving chemotherapy had a higher level of toxicity associated with an increased presence of *Clostridium* and *Actinobacteria* bacteria in IM†.
Ojo OA, et al[51].	Review	67 articles	Curcumin is a plant-derived chemical that may help prevent CRC*, as demonstrated in *in vitro* and *in vivo* studies. Randomized clinical trials with humans are currently underway with promising results.
Xu B, et al[52].	Systematic review with meta-analysis	4,478 patients	Herbal formulas can regulate the composition of IM, have beneficial effects on preoperative, postoperative and advanced stages of gastric cancer and CRC*.
Huang F, et al[53].	Randomized clinical trial	100 patients	Probiotics such as *B. infants*, *L. acidophilus*, *E. faecalis* and *B. cereus* reduced XELOX‡ chemotherapy-induced IM† dysbiosis, adverse effects and promoted short-chain fatty acid production.
Esfahani A, et al [54].	Randomized clinical trial	71 patients	Supplementation with n-3 PUFAs, omega 3, reduced the incidence and severity of oxaliplatin-induced peripheral neuropathy in colon cancer patients.
Osterlund P, et al[55].	Randomized clinical trial	150 patients	Supplementation with *L. rhamnosus GG* reduced 5-fluorouracil-related diarrhea.
Howells LM, et al[56].	Randomized clinical trial	28 patients	The combination of curcumin with FOLFOX§ chemotherapy was safe and had beneficial effects.
Ghidini M, et al[57].	Prospective observational study	51 patients	Supplementation with *Lactobacillus kefiri LKF01* (Kefibios®) was safe and effective in preventing diarrhea during treatment with 5-fluorouracil or capecitabine.

***** Colorectal cancer, † Intestinal Microbiota, ‡ XELOX – capecitabine, oxaliplatin, dexamethasone -, § FOLFOX– oxaliplatin, folinic acid, 5-fluorouracil.

DISCUSSION

All mapped articles were in English, confirming the current scenario of internationalization of publications[58]. Evidence points to the influence of IM and dysbiosis on the efficacy and response of patients not only to chemotherapy, but also to radiotherapy and immunotherapy, on adverse effects and some correlated with specific microorganisms[59–60].

Studies on probiotics for modulating IM show their protective potential during chemotherapy treatment, as exemplified by the nine randomized clinical trials found in this scoping review conducted with patients with CRC[28–29,31,39,44,53–56], reinforcing the capacity of probiotics in modulating IM, in search of better results in the treatment of these patients[61]. Other studies show the reduction of diarrhea in patients with CRC using fluorouracil[36] and irinotecan[28], in addition to reducing the use of loperamide, abdominal distension, intestinal colitis and toxicity[28], adding benefits during treatment due to their chemoprotective effect[49]. It is important to emphasize that the effects of probiotics also depend on individual characteristics and variables such as sex, age, eating habits, which are determinants. An example of this is the result of a study carried out in Malaysia that did not identify any difference in the side effects of the use of XELOX among groups that received probiotics[31].

The safety of administering probiotics to patients with CRC is controversial, given the possibility of inducing bacterial translocation and promoting the occurrence of sepsis, due to the fact that patients have weakened immunity associated with increased intestinal permeability[62]. To assess the safety of administering probiotics to patients with CRC undergoing chemotherapy, several studies have tested this hypothesis: randomized clinical trials[28,31,39,43] and reviews[31–32] did not identify higher infection rates in patients who received probiotics. The results obtained demonstrate not only the safety of probiotic supplementation, but also its efficacy in treating adverse events and improving patients' immunity during chemotherapy[42–43].

Gastrointestinal toxicity is a common adverse event during chemotherapy in patients with CRC, and can lead to treatment delays, suspension, drug changes, dose reductions, and hospitalizations, which exposes patients to greater risks[63]. Several studies have sought solutions for gastrointestinal toxicity in patients with CRC using probiotics, as evidenced by studies with patients using fluorouracil who had minimized gastrointestinal symptoms – reduction of abdominal pain, nausea, vomiting, constipation, abdominal distension[42] and reduction of oral mucositis[47] – after using yogurt enriched with probiotics[39,47]. It is important to highlight the duration of the intervention, which is also relevant. In the studies, the supplementation period varied from one to 24 days, and the benefits were greater when use occurred for at least four weeks[42]. Others have demonstrated benefits such as increased quality of life, diversity of IM and reduction of pathogenic microorganisms[46]. Studies using probiotics after surgical procedures have shown safety and efficacy in reducing inflammatory cytokines, postoperative complications[31], reduction of infections[46], length of hospital stay and risk of death[46].

Different studies relate IM dysbiosis to the process of colorectal carcinogenesis[32,49]. Chemotherapy and radiotherapy induce dysbiosis, leading to worse outcomes[36,42]. Research shows that probiotic administration during treatment can minimize IM dysbiosis and increase the levels of short-chain fatty acids (SCFA) in the intestine[53], causing numerous benefits during treatment, as shown by a randomized clinical trial[53,55] and a prospective study[57] with patients using capecitabine + oxaliplatin and fluorouracil, in which there was a reduction in gastrointestinal toxicity. It is important to emphasize that the efficacy of probiotics depends on an individual response. In this regard, other alternatives that are being explored, such as fecal microbiota transplantation, have limitations regarding the safety of the procedure in patients with CRC[32].

The influence of IM on drug efficacy has been studied, as evidenced by studies that showed differences in the IM of patients who presented intestinal lesions and lower response to fluorouracil and oxaliplatin depending on the bacterial species most abundant in the IM[33]. However, the toxicity of irinotecan is greater in the presence of bacteria that produce b-glucuronidase[45]. The presence of Clostridium and *Actinobacteria* worsened the side effects of cisplatin and fluorouracil[50]. *Klebsiella pneumoniae* worsened the side effects of capecitabine and oxaliplatin. Colonization by *Fusonucleatum* can reduce the response to fluorouracil so significantly that it reduced patient survival[64–65]. However,

there are still gaps that determine the results of these modifications of IM in clinical practices used on a large scale.

Evidence collected indicates that the use of prebiotics, probiotics and synbiotics can modulate IM and delay colorectal carcinogenesis[32,42]. Research reinforces that the use of probiotics improves the immune response, reduces carcinogenic compounds and damage to the intestinal mucosa, being able to alter IM composition, reduce adverse effects and improve the response to chemotherapy[34–35,42–43, 46].

In order to restore and promote a healthy balance of the microbiota, dietary interventions have been tested for their potential to restore beneficial bacterial populations in the colon[30]. Several studies with CRC patients taking omega-3 supplements have shown a reduction in the incidence and severity of oxaliplatin-induced peripheral neuropathy[54]. Fish oil supplementation reduced nausea and vomiting, loss of appetite, weight loss, loss of lean mass, and depressive symptoms[29]. And when combined with probiotics, there was an improvement in quality of life scores[44]. Studies have linked eating habits as an important factor in the development of CRC. Diets high in red meat and fats promote the growth of pro-carcinogenic bacteria in the colon, and can lead to dysbiosis, and increase inflammation. Conversely, a diet rich in fiber has a lower incidence of colorectal adenomas and subsequent development of CRC, and an increase in SCFA obtained through the digestion of fiber in the colon[38,46]. The presence of *F. prausnitzii* in IM is involved in butyrate production, which protects the intestinal mucosa; however, its populations are reduced in fecal samples from patients with CRC when compared to healthy individuals[38].

The influence of IM in CRC treatment is noticeable. As a limitation, there are still gaps regarding individual responses, geographic variables, dietary habits and exact mechanisms by which IM interacts with chemotherapeutics, requiring robust studies to determine the influence of IM in CRC.

CONCLUSION

The results of the studies analyzed showed protective factors for patients with CRC using probiotics and nutritional interventions such as yogurt, omega 3, fiber, and turmeric. These reduced the adverse effects of patients undergoing chemotherapy, culminating in an increase in quality of life as well as in the relationship between IM and dysbiosis with the process of colorectal carcinogenesis. Although the data are promising, the findings of clinical studies are inconclusive regarding greater efficacy of treatment. Drug resistance influenced by IM is better documented in preclinical studies. Therefore, probiotics and nutritional interventions should be considered as part of a complementary approach to therapy discussed among professionals. In this context, the role of the multidisciplinary team, especially nurses, in treatment planning, as well as in dissemination of knowledge, in educating patients/families about the use of concomitant therapies, which improve quality of life by reducing side effects based on updated scientific knowledge, stands out.

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NOTES

ORIGIN OF THE ARTICLE

Extracted from the dissertation "*Fatores protetivos relacionados à microbiota intestinal em pacientes com câncer colorretal em terapia antineoplásica endovenosa: uma revisão de escopo*", submitted to the Graduate Program in Nursing at the School of Nursing at UFRGS, *Universidade Federal do Rio Grande do Sul*, in 2023.

CONTRIBUTION OF AUTHORITY

Study design: Echer IC, Cunha JRTC,
Data collection: Echer IC, Hammes TO, Faiz EM, Fonseca ER.
Data analysis and interpretation: Echer IC, Cunha JRTC, Hammes TO.
Discussion of results: Echer IC, Cunha JRTC, Faiz EM.
Writing and/or critical review of content: Echer IC, Vieira LB, Cardoso ASF.
Final review and approval of the final version: Echer IC, Vieira LB, Cardoso ASF, Faiz EM, Bueno SEM.

CONFLICT OF INTEREST

There is no conflict of interest.

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CORRESPONDING AUTHOR

Jéssica Rosa Thiesen Cunha.
jr.thiesen@gmail.com