



## Review article

# Probiotics for the prevention and treatment of oral mucositis in chemotherapy and radiotherapy: A meta-review

## Probióticos para la prevención y tratamiento de la mucositis oral en quimioterapia y radioterapia: una meta-revisión

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### ABSTRACT

**Introduction:** Oral mucositis is a common and painful complication of cancer treatment that significantly affects patients' quality of life. **Objective:** To determine the efficacy of probiotics in preventing and treating oral mucositis in cancer patients undergoing chemotherapy or radiotherapy. **Method:** A meta-review was conducted following PRISMA guidelines. Articles published between 2019 and 2024 were searched in four databases. **Results:** Probiotics significantly reduced the incidence of oral mucositis (RR = 0.84) and severe oral mucositis (RR = 0.65). Multi-strain probiotics were more effective than single-strain ones, with greater efficacy observed in Asian populations. **Conclusions:** Probiotics are a promising strategy for preventing and treating oral mucositis in cancer patients, significantly reducing its incidence and severity. Further studies are needed to optimize strain selection, establish optimal doses and durations, and understand mechanisms of action across diverse populations and cancer types.

**Keywords:** Mucositis; Mouth neoplasms; Probiotics; Radiotherapy; Drug therapy; Meta-Analysis.

### RESUMEN

**Introducción:** la mucositis oral es una complicación frecuente y dolorosa del tratamiento oncológico que afecta significativamente la calidad de vida de los pacientes. **Objetivo:** determinar la eficacia de los probióticos en la prevención y tratamiento de la mucositis oral en pacientes con cáncer sometidos a quimioterapia y/o radioterapia. **Método:** se realizó una meta-revisión siguiendo las directrices PRISMA. Se buscaron artículos publicados entre 2019 y 2024 en cuatro bases de datos. **Resultados:** los probióticos redujeron significativamente la incidencia de mucositis oral (RR = 0,84) y mucositis oral severa (RR = 0,65). Los probióticos multi-cepa fueron más efectivos que los de cepa única, con mayor eficacia observada en poblaciones asiáticas. **Conclusiones:** los probióticos son una estrategia prometedora para prevenir y tratar la mucositis oral en pacientes con cáncer, mostrando una reducción significativa en su incidencia y gravedad. Se necesitan más estudios para optimizar la selección de cepas, establecer dosis y duraciones óptimas, y entender los mecanismos de acción en diversas poblaciones y tipos de cáncer.

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## INTRODUCTION

Oral mucositis (OM) is a frequent and painful complication of cancer treatment, characterized by inflammation and ulceration of the oral mucosa.<sup>1,2</sup> It occurs due to oxidative stress, DNA damage, and dysregulated immune responses, causing significant pain and difficulties in eating and swallowing.<sup>3,4</sup> This condition affects patients' quality of life and can interrupt or modify oncological treatment, potentially compromising its efficacy.<sup>5-7</sup>

The incidence of OM varies according to the type of cancer treatment:

- 20-40% of patients receiving conventional chemotherapy
- 60-85% of patients undergoing hematopoietic stem cell transplantation
- Up to 90% of head and neck cancer patients receive combined chemo- and radiotherapy.<sup>6,8-11</sup>

These high percentages underscore the urgent need for effective strategies to prevent and treat OM.<sup>12-14</sup>

Probiotics are live microorganisms that confer health benefits to the host when administered adequately.<sup>15-19</sup> In recent years, there has been growing interest in their use as a potential strategy to prevent and mitigate the side effects of cancer therapy, including OM.<sup>20-24</sup>

Several studies have shown promising results, including a significant reduction in the incidence and severity of diarrhea in cancer patients undergoing radiotherapy, especially with the use of *Lactobacillus* spp.<sup>25</sup> Protection against oral mucositis has also been observed in patients receiving chemoradiotherapy for nasopharyngeal carcinoma.<sup>26-29</sup>

However, significant knowledge gaps still exist. Most studies have yet to provide detailed information on the specific strains used or response times, limiting the direct applicability of these findings in clinical practice. Furthermore, the diversity in probiotics and treatment regimens complicates direct comparisons between studies. These knowledge gaps hinder the identification of the most effective strategies for the prevention and management of chemotherapy and radiotherapy-induced OM.<sup>27,28,30,31</sup>

This study's primary aim was to conduct a comprehensive meta-review, synthesizing recent scientific literature to unveil the most effective probiotic strategies for preventing and managing oral mucositis in cancer patients undergoing chemotherapy and radiotherapy. By systematically analyzing and integrating evidence from multiple systematic reviews, we sought to paint a more holistic and current picture of the field. This innovative approach allowed us to distill complex findings into actionable insights, potentially bridging the gap between laboratory discoveries and clinical practice. Our goal was not just to summarize existing knowledge, but to provide a springboard for future research and to equip healthcare providers with the most up-to-date evidence for improving patient care in oncology.

The findings of this study could have significant implications for improving the management of this frequent complication of cancer treatment, potentially enhancing patients' quality of life and the efficacy of oncological treatment.

## METHOD

The meta-review was based on PRISMA recommendations [Preferred Reporting Items for Systematic Reviews and Meta-Analyses].<sup>32</sup> The review question was: In cancer patients treated with chemotherapy or radiotherapy, what is the effectiveness of probiotics compared to placebo or absence of probiotics in preventing and treating oral mucositis and reducing the severity of its symptoms? The protocol, developed according to PRISMA-P

guidelines,<sup>32</sup> was registered with PROSPERO (CRD42024581119).

**Eligibility:** The PICO strategy was employed.<sup>33</sup> P: Cancer patients treated with chemotherapy or radiotherapy. Use of probiotics as an intervention to prevent and treat oral mucositis. C: Comparison with placebo or absence of probiotics in treatment. O: Evaluation of the effectiveness of probiotics in reducing the severity of oral mucositis symptoms.

This meta-review applies the PRISMA Statement guidelines for systematic reviews and meta-analyses. Full texts published in four databases were used in this study, including Pubmed, ScienceDirect, EBSCOhost, and Clinicalkey, from 2019 to 2024. The literature search was conducted using relevant keywords and Boolean operators. The following Boolean search terms were used: (probiotics OR probiotic OR Lactobacillus OR Bifidobacterium) AND (Treatment OR Prevention OR Management) AND ("oral mucositis" OR stomatitis). Boolean operators such as AND, NOT, and OR were employed in various combinations to refine and optimize the search results. This comprehensive search strategy was designed to capture a wide range of relevant studies addressing the use of probiotics in treating, preventing, or managing oral mucositis or stomatitis.

**Inclusion criteria:** Complete articles published in any language, including systematic reviews and meta-analyses on probiotic treatment in patients with oral mucositis during cancer treatment.

**Exclusion criteria:** Single-arm experimental studies, commentaries, case series, letters to the editor, in vitro or animal research, in vivo studies, randomized and non-randomized clinical trials, comparative studies, and longitudinal clinical studies were excluded.

**Data collection process:** Two observers conducted the research, with a third observer acting as an independent mediator in case of differences of opinion. Initially, titles and abstracts of retrieved articles were reviewed for selection. Then, all eligible studies were thoroughly examined, and a final decision was made on whether to include each study in the analysis.

Data were obtained using a standardized form previously tested in a pilot test. This form included the following elements: authors' names, year of publication, country of origin of the study, research objective, materials and methods, results, and conclusions drawn from the results.

**Quality assessment of studies and risk of bias:** Two researchers independently evaluated the literature and reviewed the original texts thoroughly. In case of evaluation discrepancies, a third researcher acted as a mediator. Differences in evaluation scores were discussed until a final consensus score was agreed upon, using the Joanna Briggs Institute (JBI) checklist.<sup>34</sup>

**Ethical considerations:** Considering that this study employs retrospective documentary research techniques and methods and does not perform any intervention or modification in biological, physiological, psychological, or social variables to study participants - including review of medical records, interviews, questionnaires, and others that do not identify or deal with sensitive aspects of their behavior - it is considered a risk-free study, according to resolution 008430 of 1993 of the Ministry of Health of Colombia.<sup>35</sup>

## RESULTS

A comprehensive database search was conducted on April 20, 2024, utilizing Clinicalkey, Ebsco host/dentistry, Pubmed, and ScienceDirect. The combination of keywords yielded nine results in Pubmed, 202 in ScienceDirect, 74 in ClinicalKey, and 16 in Ebscohost. After removing duplicates, a total of 264 unique results were obtained. After applying specific exclusion criteria, 259 articles were eliminated from consideration. This rigorous selection process resulted in 5 articles being included in the final systematic review. This methodical approach ensures that the review focuses on the most relevant and high-quality studies, providing a solid foundation for analysis and conclusions regarding the use of probiotics in preventing and treating oral mucositis in cancer patients undergoing chemotherapy or radiotherapy.

### Characteristics of included studies

The following table summarizes the key characteristics of the five studies included in this systematic review (Table 1).

**Table 1.** Characteristics of Included Studies

Authors	Method	Results	Conclusions	Study Quality
Liu <i>et al.</i> <sup>31</sup>	Eight RCTs reviewed involving 708 patients	Probiotics significantly reduced oral mucositis, severe mucositis, and the need for enteral nutrition in cancer patients.	Probiotics prevent/treat oral mucositis in cancer therapy. They improve quality of life and reduce adverse effects. Probiotics are recommended in the comprehensive management of oncological patients.	11/11
Minervini <i>et al.</i> <sup>36</sup>	Three RCTs reviewed 213 patients involved.	Probiotics significantly reduce mucositis and adverse effects in cancer. Optimizing quality of life and results is recommended.	Probiotics are a practical option for treating oral mucositis caused by chemotherapy in head/neck cancer—more studies are needed to confirm mechanisms.	10/11
Feng <i>et al.</i> <sup>26</sup>	12 RCTs reviewed patients not specified.	Probiotics significantly reduced diarrhea, oral mucositis, and severe forms during cancer chemotherapy.	Oral probiotics significantly reduced diarrhea and oral mucositis in cancer chemotherapy versus control. No serious adverse effects or related deaths.	11/11
Shu <i>et al.</i> <sup>37</sup>	5 RCTs reviewed 435 patients involved.	Probiotics reduce oral and severe mucositis and do not affect treatment completion. Slightly reduce severe mucositis in chemoradiotherapy.	Probiotics reduce the incidence and severity of oral mucositis in cancer patients, especially those with head and neck cancer. However, more trials are needed to optimize their use.	
Allenby <i>et al.</i> <sup>38</sup>	16 RCT articles included 2027 patients involved.	A high-fiber diet improves diarrhea in pelvic cancer. Enteral nutrition prevents malnutrition in the head/neck. Vitamins C/ $\beta$ -carotene reduce xerostomia, but vitamin E	More research is needed for evidence-based nutritional guidelines that limit radiotherapy toxicities in cancer.	9/11

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increases mortality.

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This table provides a concise overview of the methodologies, key findings, conclusions, and quality assessments of the included studies, facilitating comparison and synthesis of the evidence.

### **General efficacy of probiotics**

Liu YC *et al.*<sup>31</sup> conducted a meta-analysis demonstrating the efficacy of probiotics in preventing and treating oral mucositis in cancer patients. Key findings included a significant reduction in the incidence of oral mucositis (RR=0.84, 95%CI 0.77-0.93) and severe oral mucositis (RR=0.65, 95%CI 0.53-0.81).

### **Probiotic strains and treatment duration**

The probiotics used varied between studies, including *Lactobacillus brevis* CD2, combinations of *Bifidobacterium*, *Lactobacillus* and *Enterococcus*, *Bacillus clausii*, *Lactobacillus lactis* and *Lactobacillus rhamnosus* GG. Treatment durations varied, in some cases lasting up to a week after completing cancer treatment.

### **Single-strain vs. multi-strain probiotics**

Feng *et al.*<sup>26</sup> compared single-strain versus multi-strain probiotics in chemotherapy cancer patients. The study included 12 articles evenly divided between those using a single bacterial species and those using multiple strains.

Results showed that multi-strain use was generally more effective in reducing side effects. Multiple strains showed an RR of 0.76 for all-grade diarrhea, while single strains did not reach statistical significance. Multiple strains were more effective in severe diarrhea, with an RR of 0.49.

Both approaches showed efficacy for all grades of oral mucositis, with a slight advantage for single strains (RR: 0.78 vs RR: 0.90 for multiple strains). However, for severe oral mucositis, multiple strains were significantly more effective (RR: 0.41).

### **Response time**

Most studies did not provide detailed information on the exact response time. However, Lipták *et al.*<sup>39</sup>, although not included in these meta-analyses, observed positive effects from the first month of treatment with Cervitec Plus®.

### **Effects on enteral nutrition**

Liu *et al.*<sup>31</sup> reported that only Sanctis *et al.*<sup>40</sup> evaluated the need for enteral nutrition, showing a significant reduction with probiotics (OR=0.34, 95%CI 0.13-0.92).

### **Regional differences in probiotic efficacy**

Feng J *et al.*<sup>26</sup> analyzed probiotic efficacy by region, finding significant differences. In Asian populations, probiotics significantly reduced the incidence of diarrhea and severe oral mucositis. No significant effects were observed in European and American populations.

### **Effects on different types of cancer treatment**

Shu Set *al.*<sup>37</sup> and Allenby *et al.*<sup>38</sup> performed subgroup analyses for chemoradiotherapy patients. Although a trend towards reduced risk of severe oral mucositis was observed, it did not reach statistical significance.

### **Efficacy of probiotics vs. placebo**

Meta-analyses by Shu *et al.*,<sup>37</sup> Liu *et al.*,<sup>31</sup> and Allenby *et al.*<sup>38</sup> show notable concordance in the efficacy of probiotics in reducing the incidence of oral mucositis in cancer patients.

### **Limitations and Future Considerations**

Most studies should have provided information on specific strains, limiting direct applicability in clinical practice. The lack of data on response time suggests this aspect was not a primary focus of the meta-analyses or that individual studies needed to provide consistent information on this aspect.

Although results are promising, more research is needed to determine the most effective probiotic strains, optimal treatment duration, and exact mechanisms of action. Efficacy may vary depending on the type of cancer treatment and the population studied.

The diversity in probiotics used and treatment regimens makes direct comparisons between studies difficult. This underscores the need for more research to determine the most effective strains or combinations for oral mucositis in cancer patients.

## **DISCUSSION**

This systematic review has unveiled compelling evidence supporting the use of probiotics as a promising strategy for both preventing and treating oral mucositis in cancer patients undergoing chemotherapy or radiotherapy. The results demonstrate a significant reduction in the incidence and severity of oral mucositis, alongside a decreased need for enteral nutrition in patients treated with probiotics.<sup>25–27</sup> These findings underscore the potential of probiotics to substantially improve the quality of life for cancer patients during treatment.

Notably, the review highlighted that multi-strain probiotics appear to be more effective than single-strain formulations. This observation suggests a synergistic effect between different probiotic strains, potentially modulating multiple biological pathways simultaneously to enhance their protective capabilities.<sup>26</sup> Interestingly, greater efficacy was observed in Asian populations, pointing to possible influences of genetic, dietary, or environmental factors on the intestinal microbiota composition and, consequently, on the effectiveness of probiotic interventions.<sup>38–40</sup>

The protective effects of probiotics can be attributed to several mechanisms. Their anti-inflammatory and

immunomodulatory properties play a crucial role in mitigating the adverse effects of cancer therapies. Moreover, probiotics have demonstrated an ability to restore the balance of intestinal microbiota, which is often disrupted during cancer treatment.<sup>25,26,31</sup> This restoration of microbial equilibrium may contribute to overall gut health and systemic well-being, potentially explaining the observed reduction in treatment-related side effects.

These findings corroborate and expand upon previously reported benefits of probiotics in alleviating other side effects of cancer therapy, such as diarrhea.<sup>41–44</sup> The consistent positive outcomes across various studies strengthen the case for incorporating probiotics into standard cancer care protocols. By potentially reducing treatment interruptions and improving patients' ability to tolerate full doses of chemotherapy or radiotherapy, probiotics could indirectly contribute to better oncological outcomes.<sup>6–8</sup>

From a clinical perspective, the implications of these results are significant. Probiotics represent a relatively safe and low-cost intervention that could be readily integrated into existing treatment regimens.<sup>15–17</sup> This accessibility makes them an attractive option for many health systems, potentially democratizing access to supportive care in oncology across different resource settings.

A key strength of this review lies in its focus on recent literature, providing an up-to-date perspective on this rapidly evolving field. The inclusion of recent meta-analyses allowed for a robust assessment of probiotic efficacy, lending weight to the conclusions drawn.<sup>29,45</sup> However, it's important to acknowledge certain limitations. The heterogeneity among studies in terms of design, cancer types, treatment regimens, and probiotic compositions may hinder the generalization of results.<sup>46</sup> Additionally, the predominant focus on head and neck or gastrointestinal cancers limits the direct applicability of findings to other cancer types.<sup>47</sup>

Looking ahead, several avenues for future research emerge. Long-term studies are needed to evaluate the potential effects of prolonged probiotic use, addressing any concerns about safety or efficacy over extended periods.<sup>48</sup> Identifying the most effective probiotic strains and determining optimal treatment doses and durations for different populations and cancer types should be a priority.<sup>49</sup> Furthermore, investigating the specific mechanisms of action and efficacy in various clinical contexts is crucial, recognizing that not all probiotics are equally potent or suitable for all situations.<sup>50</sup>

## CONCLUSIONS

Probiotics emerged as a promising strategy for preventing and treating oral mucositis in cancer patients undergoing chemotherapy or radiotherapy. This meta-review demonstrates significant reductions in the incidence and severity of oral mucositis, with multi-strain probiotics showing greater efficacy, particularly in Asian populations.

These findings align to identify optimal probiotic strategies for managing oral mucositis. Incorporating probiotics into cancer treatment protocols could improve patients' quality of life and enhance oncological outcomes.

However, further research is needed to address limitations. Future studies should expand to cover a broader range of cancer types and treatment regimens, conduct long-term evaluations, identify the most effective probiotic strains, and determine optimal dosages for different populations. Investigating specific mechanisms

of action and exploring regional differences in efficacy are also crucial.

Addressing these limitations will provide more comprehensive guidelines for using probiotics in cancer care, potentially improving treatment outcomes and patient quality of life.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

## AUTHOR CONTRIBUTIONS

**JPR** participated in study conceptualization and design, data collection, statistical analysis, literature review, manuscript drafting, and final approval.

**MGR** participated in study conceptualization and design, data collection, statistical analysis, literature review, manuscript drafting, and final approval.

**GGR** conducted data collection, statistical analysis, manuscript drafting, and final approval.

**LTO** conducted data collection, statistical analysis, manuscript drafting, and final approval.

**ADC** participated in study design, instrument validation, manuscript drafting, and final approval.

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