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MARIANA TAKATU MARQUES

Photobiomodulation as a Preventive Strategy for Oral Mucositis in Pediatric Oncology: a systematic review and meta-analysis

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"Conheça todas as teorias, domine todas as técnicas, mas ao tocar uma alma humana, seja apenas outra alma humana."

Carl Gustav Jung

RESUMO

MARQUES, M. T. **Fotobiomodulação como estratégia preventiva para mucosite oral em oncologia pediátrica: uma revisão sistemática e meta-análise.** 2026. Trabalho de Conclusão de Residência (Especialização) - Faculdade de Odontologia, Universidade Estadual Paulista (UNESP), Araçatuba, 2026.

Objetivos: A mucosite oral (MO) é uma das complicações mais frequentes e debilitantes em crianças em tratamento de neoplasias hematológicas. As estratégias atuais de manejo concentram-se em minimizar a gravidade da MO e aliviar os sintomas. Esta revisão sistemática teve como objetivo avaliar a eficácia da fotobiomodulação (FBM) na prevenção da MO em pacientes pediátricos com neoplasias hematológicas submetidos à quimioterapia.

Dados/Fontes: Orientada pelo modelo PICOS, esta revisão abordou a seguinte pergunta de pesquisa: A terapia de FBM é eficaz na redução da incidência e da gravidade da mucosite oral em crianças e adolescentes com neoplasias hematológicas sob tratamento quimioterápico? Foi realizada uma busca abrangente nas bases PubMed, Scopus, Web of Science, Embase e Cochrane até fevereiro de 2025. Foram considerados elegíveis estudos clínicos randomizados envolvendo pacientes de 0 a 22 anos diagnosticados com neoplasias hematológicas, tratados com quimioterapia e submetidos à FBM preventiva para MO.

Seleção dos Estudos: Cinco ensaios clínicos randomizados foram incluídos, englobando pacientes de 4 meses a 22 anos. Destes, 97 receberam terapia com laser de baixa potência (LLLT) e 80 receberam terapia com diodo emissor de luz (LEDT). A FBM foi consistentemente relatada como eficaz na prevenção do surgimento e na redução da gravidade da MO nessa população. Três estudos foram elegíveis para a meta-análise, que demonstrou um benefício estatisticamente significativo da terapia com FBM ($p = 0.04$), com intervalo de confiança de 95% variando de 0.01 a 0.84.

Conclusões: A terapia com FBM mostrou ser uma estratégia preventiva eficaz para mucosite oral em pacientes pediátricos submetidos à quimioterapia para neoplasias hematológicas. Ensaios adicionais, de maior escala, são necessários para estabelecer protocolos padronizados e otimizar os resultados do tratamento.

Relevância Clínica: A terapia com FBM reduz significativamente a incidência e a gravidade da mucosite oral em pacientes pediátricos submetidos à quimioterapia para neoplasias hematológicas. Essa intervenção não invasiva representa uma estratégia preventiva

promissora, melhorando o conforto do paciente e a adesão ao tratamento. Protocolos padronizados de FBM podem aprimorar o cuidado de suporte em cenários de oncologia pediátrica.

Palavras-chave: fotobiomodulação; crianças; laser de baixa potência; mucosite oral; câncer.

ABSTRACT

MARQUES, M. T. **Photobiomodulation as a preventive strategy for oral mucositis in pediatric oncology: a systematic review and meta-analysis.** 2026. Trabalho de Conclusão de Residência (Especialização) - Faculdade de Odontologia, Universidade Estadual Paulista (UNESP), Araçatuba, 2026.

Objectives: Oral mucositis (OM) is one of the most frequent and debilitating complications in children undergoing treatment for hematologic malignancies. Current management strategies focus on minimizing OM severity and alleviating symptoms. This systematic review aimed to evaluate the effectiveness of photobiomodulation (PBM) in preventing OM in pediatric patients with hematologic malignancies receiving chemotherapy.

Data/Sources: Guided by the PICOS framework, this review addressed the following research question: Is PBM therapy effective in reducing the incidence and severity of oral mucositis in children and adolescents with hematologic malignancies undergoing chemotherapy? A comprehensive search was conducted in PubMed, Scopus, Web of Science, Embase and The Cochrane databases through February 2025. Eligible studies were randomized clinical trials involving patients aged 0–22 years diagnosed with hematologic malignancies treated by means of chemotherapy, and undergoing preventive PBM therapy for OM.

Study Selection: Five randomized controlled trials were included, encompassing patients aged 4 months to 22 years. Of these, 97 received low-level laser therapy (LLLT) and 80 received light-emitting diode therapy (LEDT). PBM was consistently reported as effective in preventing the onset and reducing the severity of OM in these populations. Three studies were eligible for meta-analysis, which demonstrated a statistically significant benefit of PBM therapy ($p = 0.04$), with a 95% confidence interval ranging from 0.01 to 0.84**.**

Conclusions: PBM therapy appears to be an effective preventive strategy for oral mucositis in pediatric patients undergoing chemotherapy for hematologic malignancies. Further large-scale trials are warranted to establish standardized protocols and optimize treatment outcomes.

Clinical Significance: PBM therapy significantly reduces the incidence and severity of oral mucositis in pediatric patients undergoing chemotherapy for hematologic malignancies. This non-invasive intervention offers an emerging preventive strategy, improving patient comfort and treatment adherence. Standardized PBM protocols may enhance supportive care in

pediatric oncology settings.

Keywords: photobiomodulation; children; low-level laser therapy; oral mucositis; cancer.

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SUMÁRIO

1 INTRODUCTION*

Hematologic malignancies, primarily comprising leukemias and lymphomas, represent a significant proportion of childhood cancers, accounting for approximately one-third of all cases diagnosed in the pediatric population. Among these, acute lymphoblastic leukemia (ALL), non- Hodgkin lymphoma (NHL) and acute myeloid leukemia (AML) are the most prevalent, with ALL being the leading subtype [1]. The treatment of hematologic malignancies typically involves chemotherapy, radiotherapy, or a combination of both. Depending on the disease subtype, stage, and patient-specific factors, additional modalities such as surgery, immunotherapy, or hematopoietic stem cell transplantation (HSCT) may also be incorporated into the therapeutic regimen [2]. Although these treatment protocols have significantly improved survival rates, they are frequently associated with a range of adverse effects, including oral mucositis (OM), which can compromise both the efficacy and continuity of cancer care.

OM is one of the most common and distressing complications of antineoplastic therapy in pediatric oncology. It affects approximately 52% to 80% of children receiving chemotherapy and occurs in over 90% of pediatric patients undergoing HSCT [3]. This high incidence in children and adolescents is largely attributed to their higher baseline cellular mitotic rates, which render the rapidly dividing mucosal epithelium more vulnerable to cytotoxic damage. Moreover, the intensity and specificity of pediatric chemotherapy regimens further exacerbate this risk [4]. Among the various chemotherapeutic agents, high-dose methotrexate (MTX), particularly at doses ≥1 g/m², is strongly associated with OM development and is a cornerstone in the treatment of ALL [5, 6].

Clinically, OM is characterized by inflammation, erythema, and ulceration of the oral mucosa. The condition often leads to severe oral pain, making it difficult for patients to eat, drink, or speak, which in turn results in reduced oral intake, weight loss, and a notable decline in quality of life [5-7]. In more severe cases, nutritional support via parenteral feeding may become necessary. Furthermore, the ulcerative lesions associated with OM can serve as portals of entry for pathogens, particularly in immunocompromised patients, increasing the risk of systemic infections that may require hospitalization or interrupt cancer treatment [5,8]. The World Health Organization (WHO) provides a widely adopted grading system for OM, which categorizes its severity from grade 0 (no observable changes) to grade 4 (severe

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ulceration with an inability to feed orally), based on clinical presentation and the impact on oral function [9].

Currently, the management of OM remains largely supportive and focuses on symptom relief and the prevention of secondary infections. Interventions typically include analgesics, topical agents, and antiseptics, which provide limited efficacy and do not directly address the underlying tissue damage [5]. In this context, photobiomodulation (PBM) therapy has emerged as a promising alternative. PBM involves the application of non-ionizing light, typically from low-level lasers or light-emitting diodes (LEDs), at specific wavelengths to modulate biological processes. Several clinical studies have demonstrated that PBM can reduce the severity and duration of OM, as well as alleviate associated symptoms such as pain and discomfort [5-7,10,11].

The therapeutic potential of PBM has been acknowledged in international guidelines. Current guidelines support the use of PBM for the prevention and/or treatment of OM, with scope and strength varying by population and modality. The Children's Oncology Group (COG) Supportive Care Endorsed Guidelines [12] incorporate the pediatric clinical practice guideline by Patel et al. [7], which issues a conditional recommendation (moderate-quality evidence) to consider intraoral PBM in the red spectrum (620–750 nm) for children receiving radiotherapy to the head and neck for non-carcinomatous tumors. In adults, the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) guidelines strongly recommend intraoral PBM to prevent OM in patients receiving head-and-neck radiotherapy and in those undergoing HSCT [12]. Consistent with these positions, the Oncology Nursing Society classifies PBM therapy as 'Recommended for Practice' for mucositis prevention/treatment in head-and-neck cancer and HSCT settings. Recently, prophylactic PBM, particularly using wavelengths in the red to near-infrared spectrum (620–750 nm), has also been incorporated into clinical practice guidelines for the prevention of OM and oropharyngeal mucositis in pediatric patients undergoing HSCT [7]. Collectively, these guidelines highlight the growing role of PBM as a supportive care strategy across both adult and pediatric oncology, while also underscoring that recommendations in children remain most firmly established in the context of head-and-neck radiotherapy. In this context, our synthesis centers on pediatric patients with hematologic malignancies treated with chemotherapy ± HSCT; consequently, while the pediatric radiotherapy-specific COG recommendation does not directly mirror our study cohort, the overall direction and safety profile of PBM across guidelines support the clinical relevance of our study findings

[7,12,13].

PBM is believed to exert its effects through several biological mechanisms, including the modulation of inflammatory pathways, stimulation of cellular proliferation, acceleration of tissue repair, and enhancement of local microcirculation. Its analgesic and regenerative properties make it especially attractive for use in children, as the procedure is minimally invasive, painless, and associated with minimal to no adverse effects [2]. Despite these advantages, standardized and robust clinical protocols for PBM in pediatric patients undergoing chemotherapy remain lacking. Although well-established guidelines are available for children receiving radiotherapy, the absence of chemotherapy-specific recommendations in pediatrics hinders broader implementation and limits comparability across studies.

Given the potential benefits of PBM and the high burden of OM in pediatric oncology, there is a clear need to consolidate current evidence and assess the effectiveness of this intervention more systematically. Therefore, the objective of the present study is to conduct a comprehensive systematic review to evaluate the effectiveness of PBM therapy in preventing OM in pediatric patients diagnosed with hematologic malignancies and undergoing chemotherapy and/or HSCT. By synthesizing the available data, this review aims to provide evidence-based insights that may inform clinical decision-making and contribute to the development of standardized treatment protocols for this vulnerable population.

2 MATERIALS AND METHODS

2.1 Protocol Registration and PICO Strategy

This systematic review followed the guidelines of the Cochrane Collaboration [14,15] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) for its design and planning [16]. The review was prospectively registered in the PROSPERO database under protocol number CRD42024610954.

The objective of this review was to address the following clinical question: Is PBM therapy effective in reducing OM in children and adolescents with hematologic malignancies undergoing chemotherapy? Following the PICO framework, the components were defined as follows:

Population: Children or younger adults (≤22 years old) diagnosed with hematologic malignancies undergoing chemotherapy; *Intervention*: PBM therapy; *Comparison*: Any other preventive strategies for OM; *Outcomes*: Severity of OM, timing and intensity of pain, treatment acceptability, efficacy and adherence to PBM therapy, and other relevant symptoms, such as need for nutritional support and swallowing ability. The duration of PBM's therapeutic effects was also considered relevant for the pediatric population.

2.2 Eligibility Criteria

Inclusion criteria were as follows: randomized controlled trials (RCTs) involving children/young adolescent aged 0 to 22 years diagnosed with hematologic malignancies and receiving oncologic treatment, in which PBM therapy was used as a preventive intervention for OM. Exclusion criteria included literature reviews, clinical case reports or case series, letters to the editor, conference abstracts, and opinion articles.

2.3 Search Strategy

Two independent researchers (M.T.M. and L.T.A.) searched PubMed/MEDLINE, Scopus, Web of Science, Embase and The Cochrane for studies published over the entire period available in each database up to February 2025, applying the eligibility criteria. Boolean operators (AND, OR) were used to combine keywords, refining the search strategy.

All references were exported to the software (Endnote), where duplicates were removed automatically by the software and manually. The search strategy incorporated a range of terns, such as: Child OR Children AND Hematologic Neoplasms OR Hematologic Neoplasm OR Neoplasm, Hematologic OR Hematologic Malignancies OR Hematologic Malignancy OR Hematological Malignancies OR Hematological Malignancy OR Malignancy, Hematological OR Hematological Neoplasms OR Hematological Neoplasm OR Neoplasm, Hematological OR Malignancies, Hematologic OR Malignancy, Hematologic OR Blood Cancer OR Blood Cancers OR Cancer, Blood OR Neoplasms, Hematologic OR Hematopoietic Neoplasms OR Hematopoietic Neoplasm OR Neoplasm, Hematopoietic OR Neoplasms, Hematopoietic OR Hematopoietic Malignancies OR Hematopoietic Malignancy OR Malignancy, Hematopoietic AND Low-Level Light Therapy OR Light Therapies, Low-Level OR Light Therapy, Low-Level OR Low-Level Light Therapies OR Low Level Light Therapy OR Therapies, Low-Level Light OR Therapy, Low-Level Light OR LLLT OR Photobiomodulation Therapy OR Photobiomodulation Therapies OR Therapies, Photobiomodulation OR Therapy, Photobiomodulation OR Photobiomodulation OR Photobiomodulations OR Laser Therapy, Low-Level OR Laser Therapies, Low-Level OR Laser Therapy, Low Level OR Low-Level Laser Therapies OR Laser Biostimulation OR Biostimulation, Laser OR Laser Irradiation, Low-Power OR Irradiation, Low-Power Laser OR Laser Irradiation, Low Power OR Laser Phototherapy OR Phototherapy, Laser OR Laser Therapy, Low-Power OR Laser Therapies, Low-Power OR Laser Therapy, Low power OR Low-Power Laser Therapies OR Low-Level Laser Therapy OR Low Level Laser Therapy OR Low-Power Laser Irradiation OR Low Power Laser Irradiation OR Low-Power Laser Therapy OR Low Power Laser Therapy AND Stomatitis OR Stomatitides OR Oral Mucositis OR Mucositides, Oral OR Oral Mucositides OR Mucositis, Oral OR Oromucositis OR Oromucositides.

2.4 Study Selection

Two independent reviewers (M.T.M. and L.T.A.) independently screened titles and abstracts for eligibility. Full-text articles were retrieved for references with insufficient titles or abstracts to determine inclusion or exclusion. Cohen's Kappa coefficient was used to assess inter-reviewer agreement, with an acceptable threshold value of 0.86. Any disagreements at any stage of the selection process were resolved through discussion and consensus with a

third reviewer (L.H.T.). No discrepancies were observed between the two primary reviewers during study selection.

2.5 Risk of Bias Assesment

Risk of bias was assessed using the Cochrane Collaboration tool [14,15]. For each domain, the risk of bias was classified as follows: (1) low risk of bias (when all criteria were adequately met); (2) unclear risk (when insufficient information was provided to make a judgment); and (3) high risk of bias (when two or more criteria were not met). These domains were applied to each included study. Two reviewers (M.T.M. and L.T.A.) independently conducted the quality assessment, and any disagreements were resolved through consultation with a third investigator (L.H.T.). The following domains were evaluated and rated as adequate (+), inadequate (−), or unclear (?):

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcome assessment (patient-reported outcomes);
5. Blinding of outcome assessment (all-cause mortality);
6. Incomplete outcomes (short-term [2–6 weeks]);
7. Incomplete outcomes (long-term [>6 weeks]);
8. Selective outcome reporting.

2.6 Data Synthesis and Meta - Analysis

A meta-analysis using a random-effects model was conducted to compare the effectiveness of PBM therapy. The DerSimonian-Laird method was applied to minimize the impact of heterogeneity among the included studies. Odds ratios were used to assess the likelihood of developing OM with or without PBM therapy.

Heterogeneity was assessed using Cochran's Q test and quantified using the I^2 statistic. An I^2 value below 25% indicates low heterogeneity, between 25% and 75% indicates

moderate heterogeneity, and above 75% indicates high heterogeneity. All analyses were performed using RevMan 5.4 software (Cochrane IMS, Copenhagen, Denmark).

Two studies included in the systematic review did not provide sufficient data for inclusion in the quantitative synthesis [6,17]. Additionally, the study by Guimarães et al. [6] lacked a control group and included two intervention groups low-level laser therapy (LLLT) and light-emitting diode therapy (LEDT), which may introduce potential bias in the results.

3 RESULTS

3.1 Study Selection

A total of 299 articles were initially identified. After removing duplicates, 113 unique studies remained. Title screening led to the exclusion of 83 articles that did not meet the eligibility criteria. The abstracts of the remaining studies were reviewed, resulting in 30 articles selected for full-text evaluation. After detailed analysis, 25 studies were excluded. Ultimately, five studies met inclusion criteria. Three provided sufficient, compatible data for quantitative synthesis (meta-analysis); the remaining two studies were synthesized narratively (Figure 1).

This review incorporated five prospective randomized trials: two conducted in Brazil [6, 18], one in the Republic of Belarus [17], one in the United States [11], and one in Egypt [19]. Sample sizes ranged from 33 to 80 participants, undergoing various chemotherapy cycles. Participant ages ranged from 4 months to 22 years. Three studies compared PBM therapy to a control group without treatment [11,17,18]. One study compared the preventive efficacy of LEDT with LLLT [6], and another compared PBM with a placebo (simulated irradiation) [19].

The initiation of PBM therapy varied across studies. Elkady et al. [19] began PBM one day before chemotherapy infusion, whereas de Castro, Boris, and Guimarães started on the day of chemotherapy [6,17,18]. In the study by Pritchard et al., PBM was initiated on the first day of conditioning and continued daily until Day +20 or until engraftment [11].

3.2 Clinical Treatment Characteristics

Five prospective randomized clinical trials were included and are summarized in Table 1. When laser/LED parameters or results were not reported in the publication, the authors were contacted for clarification [11]. Table 2 summarize all the laser/LED parameters and outcomes of the included studies.

Boris et al. [17] compared a prophylactic PBM intervention group with a no-treatment control group in children diagnosed with ALL or lymphoma receiving high-dose MTX. They reported that PBM significantly reduced the frequency of OM during chemotherapy cycles, 30% in the intervention group versus 67.4% in the control group. The authors noted an 88%

reduction in the risk of developing OM with PBM therapy during MTX treatment. Additionally, the intervention group had fewer severe cases (8% vs. 17%), lower pain intensity on a visual analog scale, and shorter OM duration (5 days vs. 8 days).

Castro et al. [18] evaluated patients with ALL receiving high-dose MTX, comparing a prophylactic PBM group (divided into red and infrared light) with a therapeutic PBM group (also subdivided into red and infrared light, applied after lesion onset). A statistically significant difference was found: 40% of patients in the prophylactic group developed OM compared to 75% in the therapeutic group, indicating that prophylactic treatment was more effective than treatment after lesion onset.

Guimarães et al. [6] compared the preventive effects of LED therapy (LEDT) and LLLT in children with ALL treated with high-dose MTX (5 g/m²). Both groups showed favorable and similar outcomes. Only 12.5% in the LEDT group (one patient grade 3, three grade 2, one grade 1) and 10% in the LLLT group (one patient grade 3, two grade 2, one grade 1) developed OM. Both therapies reduced episode duration and pain levels.

Pritchard et al. [11] assessed PBM using LEDT devices in children with ALL and AML admitted for HSCT. This study employed a distinct OM assessment scale. Significant differences were observed between groups in the duration of grade 1 and 2 OM, total hospitalization days, and mucositis severity, with the PBM group exhibiting milder mucositis than the control group.

Elkady et al. [19] examined the effects of PBM therapy in preventing chemotherapy-induced OM in children with AML. The study compared PBM therapy and placebo groups and showed that PBM therapy reduced OM prevalence on all days assessed. Only one case of grade 3 OM was observed in the placebo group, with no severe lesions reported in the PBM group, demonstrating its efficacy in reducing lesion severity.

3.3 Risk of Bias Assessment

All discrepancies regarding study quality were reviewed before finalizing the risk of bias summary (Figure 2). Using the Cochrane risk-of-bias tool, two studies [6,19] were classified as having a low risk of bias, as they provided sufficient methodological detail across all domains. One study [18] was rated as having an unclear risk of bias. Two studies [11,17] were classified as having a high risk of bias. Common concerns included incomplete reporting

of allocation concealment and blinding, and missing outcomes (short-term).

3.4 Main Results of the Meta-Analysis

Of the 30 studies reviewed in full, three were eligible for inclusion in the meta-analysis. Forest plots were used to illustrate effect sizes and 95% confidence intervals (CIs). Statistical significance was set at two-tailed $p < 0.05$. Heterogeneity was assessed using Cochran's Q test and quantified with the I^2 index.

Analyses were performed for patients with grade 1–2 OM (Figure 3), grade 3–4 OM (Figure 4), and any grade of OM (Figure 5). Studies evaluating patients with any OM and those with grade 1–2 OM showed heterogeneity levels of 85% ($p = 0.01$) and 70% ($p = 0.07$), respectively. However, studies of patients with grade 3–4 OM showed no heterogeneity ($I^2 = 0\%$, $p = 0.46$). In the forest plot analysis, results favored PBM therapy ($p = 0.04$) in all grades of OM.

4 DISCUSSION

OM is one of the most prevalent and distressing complications encountered during the treatment of hematologic malignancies in pediatric patients, affecting both the clinical course and the overall well-being of affected individuals [7]. The painful ulcerations, nutritional limitations, and increased risk of systemic infection associated with OM often lead to treatment interruptions, prolonged hospital stays, and increased healthcare costs. In this context, the implementation of effective preventive strategies is essential. Reducing the incidence and severity of OM not only preserves treatment continuity but also contributes to better therapeutic outcomes and improved quality of life for children undergoing cancer therapy, including radiotherapy of head and neck and chemotherapy [20].

The primary aim of this systematic review was to investigate whether PBM therapy, when applied prophylactically, offers superior clinical benefits over conventional management alone in children and adolescents receiving chemotherapy or HSCT for hematologic malignancies (focusing in patients receiving chemotherapy not radiotherapy). The findings of the included studies support this hypothesis, advocating that PBM therapy may serve as a valuable adjunct in mitigating the adverse effects of cytotoxic treatments. Specifically, the results of the meta-analysis revealed a statistically significant benefit in favor of PBM therapy over conventional care in reducing OM prevalence. However, when OM severity was stratified by grade, the difference between treatment and control groups did not reach statistical significance, highlighting the need for more data in future investigations.

Multiple therapeutic modalities have been proposed for the prevention and management of OM, including mucosal protectants, anti-inflammatory agents, and topical or systemic antimicrobials [5,6,20]. Despite their frequent use, most of these strategies lack robust clinical evidence to support routine implementation in pediatric oncology protocols. In contrast, PBM therapy, particularly using LLLT or LEDT, has demonstrated promising anti-inflammatory, regenerative, and analgesic effects. PBM acts by modulating the inflammatory response, accelerating tissue repair, and reducing pain, making it especially suitable for pediatric use due to its non-invasive nature and low risk of adverse effects [7]. Additionally, the use of longer wavelengths, such as the 830 nm infrared laser, enables deeper tissue penetration, facilitating extraoral application and enhancing acceptability, particularly in younger or non-cooperative children [10].

Despite the growing interest in PBM, relatively few clinical trials have specifically

evaluated its use as a preventive measure in pediatric oncology patients with hematologic malignancies [6,11,17-19] under chemotherapy treatment. Importantly, none of these studies reported intolerance or adverse effects related to PBM therapy, reinforcing its safety profile. In support of these findings, Abramoff et al. [21] reported that even children with severe OM lesions tolerated PBM therapy well, and no participants discontinued treatment due to discomfort or lack of adherence.

The clinical efficacy of PBM is influenced by several technical parameters, including energy dosage, wavelength, power output, exposure time, and frequency of application. Notably, low- energy doses have been shown to be effective in preventing mucosal injury, consistent with recommendations by the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) [12]. For example, Castro et al. [18] used 1 joule of energy with a power output of 100 mW; Guimarães et al. [6] applied 0.6 joules at 100 mW; Boris et al. [17] employed 0.36 joules at 30 mW; and Elkady et al. [19] used 0.25 joules at 25 mW in their LLLT protocols. These findings underscore the importance of standardizing treatment parameters to improve reproducibility and maximize therapeutic benefit.

The frequency and timing of PBM applications also varied across studies. While Elkady et al. [19] initiated PBM therapy one day prior to chemotherapy infusion, other studies, such as those by Castro et al. [18], Boris et al. [17], and Guimarães et al. [6], began PBM therapy on the same day as chemotherapy. Pritchard et al. [11] began PBM application on the first day of conditioning and continued daily until Day +20 or engraftment. Treatment sessions were conducted either daily or on alternate days. Despite these differences in protocol design, all included studies reported favorable clinical outcomes, suggesting that both prophylactic and therapeutic PBM can effectively reduce OM incidence and severity in pediatric patients. However, these variations also highlight the urgent need for standardized clinical guidelines to ensure consistency across treatment settings.

The biological rationale for PBM therapy is supported by its ability to convert photonic energy into metabolic energy, leading to enhanced mitochondrial activity, increased synthesis of adenosine triphosphate (ATP), and elevated nitric oxide (NO) production. NO functions as a vasodilator, improving local microcirculation and facilitating the delivery of oxygen and nutrients essential for tissue repair [10]. These cellular and molecular effects provide a plausible mechanistic explanation for the observed clinical improvements. Similar wound healing responses have been reported in pediatric oncology patients treated with PBM

during chemotherapy, as demonstrated by Cruz et al. [5].

In addition to PBM, meticulous oral hygiene and mucosal hydration play pivotal roles in the prevention of OM [22]. The American Academy of Pediatric Dentistry [23] recommends maintaining oral hygiene two to three times daily using a soft-bristled toothbrush and fluoridated toothpaste. Regular use of lanolin-based lip balms and thorough evaluation of oral conditions before and during cancer treatment are also advocated [24]. Although OM is a non-infectious inflammatory condition, poor oral hygiene and local infections can exacerbate mucosal injury and increase susceptibility to ulceration [7]. This reinforces the importance of including oral care protocols as integral components of OM prevention strategies. Consistent with this, studies by Castro et al. [18] and Boris et al. [17] emphasized oral hygiene practices, while Pritchard et al. [11] and Elkady et al. [19] also highlighted the value of mucosal hydration to prevent dryness and mucosal fissures. Only Guimarães et al. [6] did not explicitly mention hygiene-related measures, representing a potential gap in care.

Because conditioning regimens for HSCT are associated with a substantially higher baseline risk of OM compared with high-dose MTX–based chemotherapy protocols, direct comparisons across these regimens should be interpreted with caution. In this review, findings from the HSCT cohort [11] were synthesized narratively to reflect this elevated risk and the unique clinical context, whereas quantitative analyses focused on chemotherapy-only studies to minimize clinical heterogeneity and ensure more reliable comparisons. This approach allows for a clearer assessment of PBM efficacy while accounting for regimen-specific differences in OM susceptibility.

The present results align with contemporary guidance and implementation reports indicating that PBM is feasible and safe in pediatric programs, particularly around HSCT, and may reduce OM burden [7,13]. In addition, major U.S. supportive-care organizations, including the Oncology Nursing Society, recognize PBM as a recommended intervention for mitigating OM in pediatric head-and-neck radiotherapy [12]. Reports indicate that PBM implementation has led to reductions in the severity and duration of mucositis, decreased reliance on opioid analgesics, and shorter hospital stays, reflecting both improved patient comfort and potential health system benefits [25]. These findings underscore the growing evidence base and clinical confidence supporting PBM therapy as a safe and effective component of pediatric HSCT supportive care especially for children under radiotherapy treatment [25].

The COG Supportive Care Guidelines [13] incorporate the pediatric clinical practice guideline by Patel et al. [7], which issues a conditional recommendation (moderate-quality evidence) for intraoral PBM in the red spectrum (620–750 nm) for children receiving radiotherapy to the head and neck for non-carcinomatous tumors. Similarly, the MASCC/ISOO guidelines strongly recommend intraoral PBM for adults undergoing head-and-neck radiotherapy or HSCT [4]. The Oncology Nursing Society also classifies PBM as "Recommended for Practice" for the prevention and treatment of mucositis in both head-and-neck cancer and HSCT for pediatric patients, in line with MASCC/ISOO guidance [7,13]. Our study focused on pediatric patients with hematologic malignancies receiving chemotherapy, with or without HSCT, rather than radiotherapy. While the COG pediatric recommendation is specific to radiotherapy and conditional in strength, it aligns with the broader guideline framework and real-world pediatric HSCT data supporting PBM therapy as feasible, safe, and increasingly adopted. Nonetheless, caution is warranted when generalizing radiotherapy-specific guidance to chemotherapy or HSCT contexts [26]. Therefore, larger, rigorously conducted pediatric randomized controlled trials are needed to optimize PBM parameters, including dose, wavelength, and treatment schedule, and to strengthen the certainty of its therapeutic effect across different treatment regimens.

Several limitations of the present review should be acknowledged. First, the number of high- quality studies evaluating PBM specifically in pediatric populations remains limited. Second, the small sample sizes in most studies constrain the generalizability of the findings and reduce statistical power. Although the majority of the included trials demonstrated low risk of bias and enrolled similar patient populations, three studies did not fully describe their study design, particularly in terms of randomization and blinding. This lack of methodological transparency may impact the external validity of their findings. Moreover, the heterogeneity in PBM protocols, including differences in wavelength, power, treatment duration, and frequency, complicates direct comparisons and limits the ability to define optimal parameters for clinical use and further constrains generalizability and precluded broader pooling. Therefore, the certainty of evidence is limited by all these limitations. Finally, with fewer than 10 studies, we did not perform formal assessments of small-study effects or funnel-plot analyses. Consequently, our effect estimates should be interpreted with appropriate caution and viewed as supportive rather than definitive.

Despite these limitations, the available evidence consistently supports the use of PBM as an effective adjunctive therapy for the prevention of OM in children undergoing

chemotherapy or HSCT for hematologic malignancies. From a clinical standpoint, successful prevention can be defined as the complete absence of OM or the restriction of mucositis severity to grade II or lower, where oral intake remains possible and hospitalization is unnecessary. In addition to PBM, addressing potential infectious foci in the oral cavity and maintaining stringent hygiene practices are critical to achieving optimal preventive outcomes.

As research on PBM advances, its integration into pediatric oncology care protocols is expected to increase. The low-risk, noninvasive nature of PBM, combined with demonstrated clinical benefits of both LLLT and LEDT, makes it a highly emerging therapeutic tool. PBM has the potential to improve treatment adherence, reduce complications, and enhance overall quality of life in pediatric patients. Specifically, PBM has been shown to reduce the incidence and severity of OM in children undergoing therapy for hematologic malignancies.

5 CONCLUSION

In conclusion, this systematic review supports the clinical utility of PBM therapy, whether using LLLT or LEDT, in reducing the incidence and severity of OM in pediatric patients with hematologic malignancies treated with high-dose methotrexate. Furthermore, integrating oral hygiene and mucosal hydration protocols alongside PBM therapy is strongly recommended to optimize therapeutic outcomes. Together, these strategies offer a comprehensive, evidence-based approach to minimizing the burden of OM and improving the quality of life of vulnerable pediatric oncology patients.

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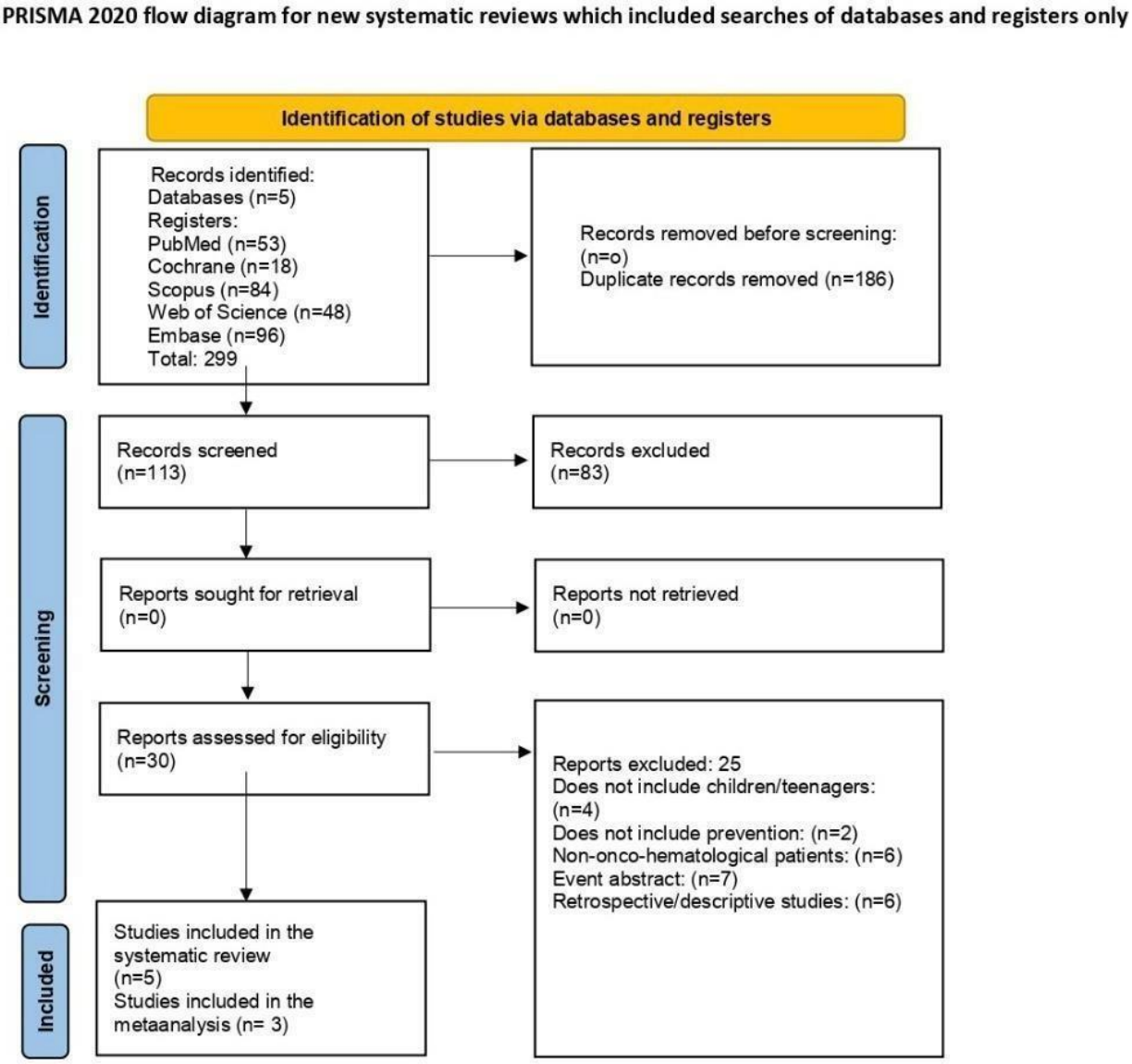

Fig. 1 PRISMA flowchart of the included studies and general characteristics of the included studies.

De Castro et al. 2013 [18]	*Boris et al. 2016 [17]*	*Guimaraes et al. 2021 [6]*	*Pritchard et al. 2024 [11]*	*Elkady et al. 2025 [19]*	
?	-	+	-	+	Random sequence generation
+	-	+	-	+	Allocation concealment
-	-	+	-	+	Blinding of participants and professionals
-	-	+	-	+	Blinding of outcome assessment
?	-	+	-	+	Outcome assessment blinding (all-cause mortality)
+	?	+	+	+	Incomplete outcomes (short term [2-6 weeks])
+	?	+	+	+	Incomplete outcomes (long term [> 6 weeks])
+	-	-	-	?	Selective internship report

Fig. 2 Evaluation of risk of bias of the included randomized clinical trials. Green + color means low risk of bias (when all criteria were properly met); yellow? color means unclear risk (when there was insufficient information to make a judgment); red−color means high risk of bias (when two or more criteria were not met).

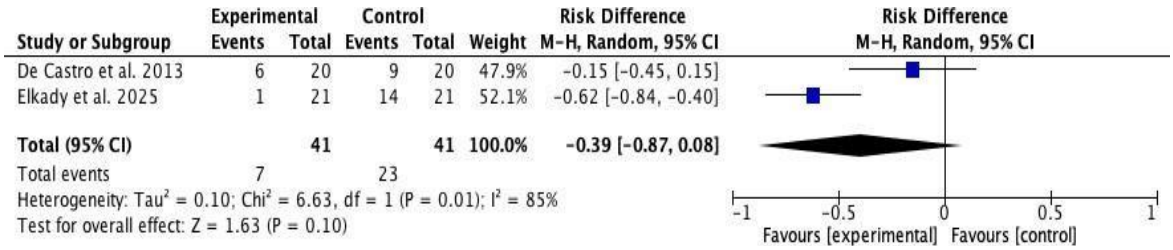

Fig. 3 Forest plot comparing the effect of PBM therapy versus control on the incidence of OM in pediatric patients. The analysis includes two randomized controlled trials [18, 19]. Risk difference (RD) with 95% confidence intervals (CI) was calculated using a random-effects model. Negative values indicate a reduction in events favoring the experimental group (PBM). The pooled estimate suggests a beneficial effect of PBM therapy, although not statistically significant (RD = –0.39; 95% CI: –0.87 to 0.08; $p = 0.10$).

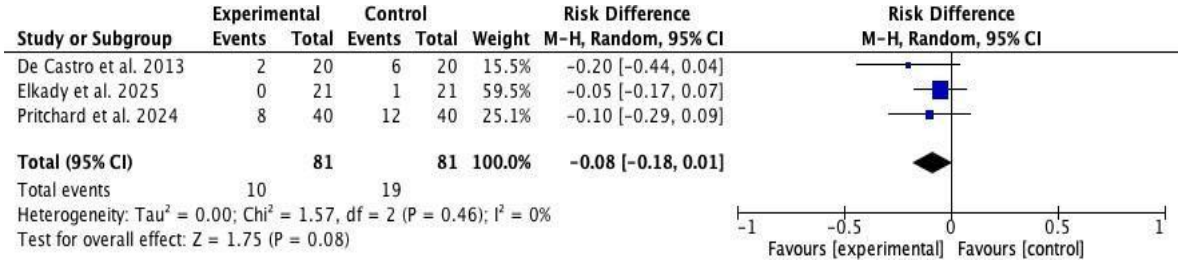

Fig. 4 Forest plot evaluating the effect of PBM therapy compared with control on the incidence of OM in pediatric patients undergoing cancer therapy. Data from three randomized controlled trials [11, 18, 19] were pooled using a random-effects model. Risk difference (RD) with 95% confidence intervals (CI) is presented. Negative values favor PBM therapy, indicating a reduction in OM incidence. The pooled analysis suggested a trend toward benefit with PBM therapy (RD = –0.08; 95% CI: –0.18 to 0.01; $p = 0.08$), with no heterogeneity observed ($I^2 = 0\%$).

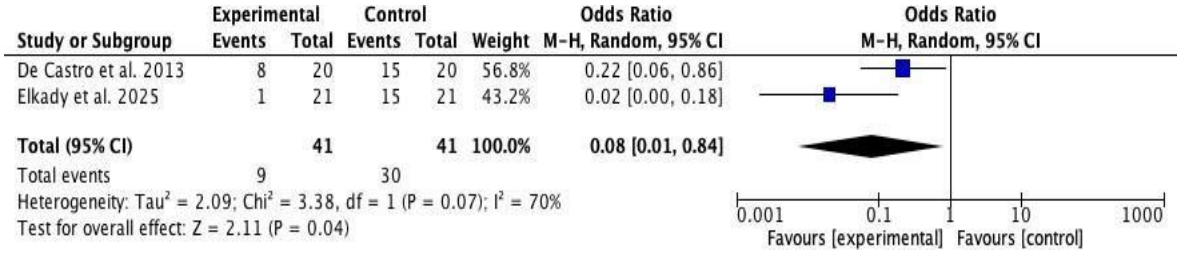

Fig. 5 Forest plot assessing the effect of PBM therapy versus control on the risk of developing OM in pediatric patients undergoing cancer therapy. Data from two randomized controlled trials [18, 19] were pooled using a random-effects model. Odds ratios (OR) with 95% confidence intervals (CI) are shown. Values less than 1.0 favor PBM, indicating a protective effect. The pooled analysis demonstrated a statistically significant reduction in OM incidence with PBM therapy (OR = 0.08; 95% CI: 0.01–0.64; $p = 0.04$), with moderate heterogeneity ($I^2 = 70\%$).

Table 1 General characteristics of the included studies.

First Author & Year	Study Design	Region / Study Period	Sample Size (n)	Age Range	Intervention / Control	Diagnosis	Treatment Regimen	OM Definition	Application Days
Castro et al., 2013 [18]	Prospective clinical trial	Brazil (Jan–Dec 2010)	40	1–18 years	LLLT (preventive) vs. LLLT (therapeutic)	ALL	CT (HD-MTX)	WHO criteria	Day 1–5 of CT
Boris et al., 2016 [17]	Prospective, randomized, controlled, longitudinal study	Belarus (Dec 2013 – Dec 2014)	33	1–17 years	LLLT (preventive) vs. no LLLT	ALL and NHL	CT (HD-MTX)	WHO criteria	Days 1, 3, 5, 7, and 9 of CT
Guimarães et al., 2021 [6]	Prospective, randomized, controlled clinical trial	Brazil (Period not reported)	80	4–12 years	LLLT (preventive) vs. LEDT (preventive)	ALL	HSCT protocol with CT (HD-MTX)	WHO criteria	Daily from Day 1 of CT until hospital discharge
Pritchard et al., 2024 [11]	Prospective clinical trial	USA (Feb 2020 – May 2021)	80	4 months– 22 years	LEDT (preventive) vs. no LEDT	ALL and AML	HSCT protocol	CTCAE v5.0	Daily from first day of conditioning through Day +20 or until engraftment
Elkady et al., 2025 [19]	Prospective, randomized, double- blind, placebo-controlled trial	Egypt (Date not reported)	42	3–18 years	LLLT (preventive) vs. placebo	AML	CT with Cytarabine / Mitoxantrone	WHO and NCI CTCAE v4.0	One day before CT and Days 1–4 of CT

Fonte: Elaborada pela própria autora.

Abbreviations: LLLT: low-level laser therapy; LEDT: light-emitting diode therapy; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin lymphoma; AML: acute myeloid leukemia; CT: chemotherapy; HD-MTX: high-dose methotrexate; HSCT: hematopoietic stem cell transplantation; WHO: world health organization; CTCAE: Common Terminology Criteria for Adverse Events; NCI: National Cancer Institute

Table 2 Summary of laser parameters and outcomes of included studies.

First author & year of publication	Laser type	Wavelength (nm)	Fluency (J/cm²)	Points	Power (mW)	Energy (J)	Spot size (cm²)	Patients Grade 1 and 2 OMS	Patients Grade 3 and 4 OMS	Results
Castro et al., 2013 [18]	LLLT InGaAlP diode	660 or 830	TG: 35 J/cm² CG: 70 J/cm²	GE: 19 intraoral GC: Over the lesions	GE: 100 mW GC: 100 mW	GE: 1 J GC: 2 J	0.028	GE: 6 GC: 9	GE: 2 GC: 6	PBM was effective in preventing OM, and there was no statistical difference between the wavelengths
Boris et al., 2016 [17]	LLLT InGaAlP diode	670	GE: 5.16 J/cm² GC: 21.24 J/cm²	GE: 13 points GC: Over the lesions	30 mW	0.36 J	0.5			PBM proved to be a safe, effective, and accessible method for the prevention of OM
Guimarães et al., 2021 [6]	GE: LLLT InGaAlP diode GC: LEDT (6 LEDs)	GE: 660 GC: 660	GE: 2 J/cm² GC: 2 J/cm²	GE: 42 intraoral GC: 42 intraoral	GE: 100 mW GC: 5 mW	GE: 0.6 J GC: 0.6 J	GE: 0.03 GC: 0.785	GE: 3 GC: 4	GE: 1 GC: 1	LLLT and LEDT showed equivalent positive preventive effects in the prevention of OM
Pritchard et al., 2024 [11]	LEDT Diode	660 and 850	3 J/cm²	6 points (externally) and 1 lollipop	50 mW/cm²	----	-----	Not reported	GE: 8 GC: 12 CTCAE	PBM was effective in the prevention of OM
Elkady et al., 2025 [19]	LLLT Diode laser	660	----	40 points	25 mW	0.25 J	0.08	GE: 1 GC: 14 (Dia 19)	GE: 0 GC: 1 (Dia 19)	PBM reduced the incidence and severity of OM

Abbreviations: LLLT: low-level laser therapy; LEDT: light-emitting diode therapy; InGaAlP = Indium Gallium Aluminum Phosphide; PBM: photobiomodulation; OM: oral mucositis; CTCAE: Common Terminology Criteria for Adverse Events.