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Review Article

USE OF EXTRAORAL PHOTOBIOMODULATION IN THE MANAGEMENT OF ORAL MUCOSITIS: SYSTEMATIC LITERATURE REVIEW

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Abstract

Oral mucositis (OM) is an adverse effect in oncology patients and photobiomodulation (PBM) improve the quality of life of these patients through OM management. The objective of this study was to evaluate the effects of extraoral PBM on the prevention and/or treatment of OM in oncology patients. This systematic review was registered in PROSPERO, following the PRISMA guidelines. PubMed, Scopus, Science Direct, *LILACS, CAPES*, *BVS* and Google Scholar were consulted, and keywords from DeCS/MeSH were used. The risk of bias was analyzed using RoB2. A total of 1246 studies were identified and two articles were selected. A total of 115 patients were included, and the extraoral PBM promotes preventive and therapeutic action in OM, reduces pain, and is well-tolerated. When comparing intraoral and extraoral PBM, both achieved similar results; moreover, extraoral PBM required a shorter application time. Extraoral PBM prevented/treated OM, and optimized the application time in oncology patients.

Keywords: Mucositis, Laser Therapy, Low-Level Light Therapy, Lasers, Semiconductor.

Statement of Clinical Significance

A extraoral photobiomodulation is an effective in the management of oral mucositis, especially in the post-pandemic context, with the potential to reduce pain and accelerate healing, while also being associated with shorter application time and reduced contact with salivary contaminants.

1. INTRODUCTION

Oral mucositis (OM) is one of the most commonly observed adverse effects in patients undergoing oncological treatment, particularly in individuals with neoplasms in the head and neck region, due to the intensive therapeutic regimen involving radiotherapy with or without cytotoxic chemotherapy.[1] In general,

mucositis is an inflammatory condition where the mucous membranes in the gastrointestinal tract can be damaged and the mitotic cells are more susceptible to the damage. OM involves the appearance of erythematous and/or ulcerated lesions in the oral cavity.[2] Local pain is one of the most recurrent and limiting symptoms of this condition; it hampers chewing, swallowing, and proper oral hygiene, potentially leading to the need for parenteral nutrition and opioid analgesics.[3] Among the various therapeutic resources available for OM management, highlights include the use of anti-inflammatories, analgesics, cryotherapy, growth factors, and photobiomodulation (PBM).[4]

PBM is a preventive and therapeutic method for various medical and dental conditions based on the use of lasers or LED lights. It is a safe and non-pharmacological treatment that has shown beneficial results in OM management by providing comfort and improving the quality of life of oncological patients through the modulation of growth factors, inhibition of pain mediators with the promotion of analgesia, modulation of the inflammatory process, increased angiogenesis, and stimulation of tissue healing.[5-9] These biological effects are mainly attributed to the absorption of light by intracellular photoacceptors, particularly cytochrome c oxidase, resulting in increased adenosine triphosphate (ATP) production, modulation of reactive oxygen species, and activation of signaling pathways involved in tissue repair. The therapeutic response to PBM is influenced by parameters such as wavelength, power output, energy density, irradiation time, and treatment frequency. Both laser and LED devices can be used for PBM, although they differ in coherence and beam collimation characteristics. PBM involves the direct application of laser light to OM lesions using a low-power device, and its preventive and therapeutic potential is well-established in the current literature. [3-4]

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has altered the landscape of both public and private healthcare systems, particularly in oncological care units. The pandemic has generated uncertainties and difficulties in providing care for these patients. In this scenario, a new approach using extraoral PBM has emerged as an alternative resource, because its principle is based on reducing the spread of SARS-CoV-2. Extraoral PBM involves the external application

of a laser or light-emitting diode (LED) light in areas adjacent to the oral cavity, reducing direct contact with oral mucosal tissues and thereby decreasing the risk of viral transmission. This adaptation has enabled the continued assistance to patients with OM in a safe and effective manner during the pandemic.[5]

At the beginning of therapeutic light-based treatments, several acronyms and terms emerged, and then FBM began to be used globally among clinicians and researchers to facilitate communication. The number of studies in this area has increased, however, in the literature, some limitations are still observed, such as the diversity of protocols, few clinical trials that address the topic, mainly the use of extraoral FBM, and because this is a relatively new practice.[10] Even so, extraoral PBM has proven to be a safe, practical, quick, and effective alternative for the prevention and/or treatment of OM in oncological patients, as it minimizes the application time and avoids manipulation of oral tissues.[3] However, as this device has only recently been employed in mucositis, it is still unknown whether this technique has a similar or superior effect on intraoral PBM and what dosimetries can be used to manage this condition. Therefore, the present study aims, through a systematic literature review, to evaluate the effect of extraoral PBM in the prevention and/or treatment of OM in oncological patients.

2. MATERIAL AND METHODS

2.1 Eligibility criteria

This systematic literature review was conducted from August 2023 to April 2024, seeking randomized clinical trials. The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] Electronic databases such as PubMed, Scopus, ScienceDirect, LILACS, and BVS were searched for this review, all well the Google Scholar gray literature. In addition to the aforementioned platforms, searches were conducted on two clinical trial registration sites: clinicaltrials.gov and The Brazilian Registry of Clinical Trials (ReBEC). The selected strategies included the use of keywords from

the Health Sciences Descriptors (DeCS/MeSH) and terms related to extraoral PBM and OM. These terms were combined using the Boolean operators AND and OR (Table 1). This review was registered on the PROSPERO platform under registration number CRD42023482308.

The study question was, "Does extraoral photobiomodulation prevent and/or treat OM in oncology patients?" The PICOS strategy was used, with P, population: patients with cancer; I, intervention: extraoral PBM for the prevention and/or treatment of OM signs and symptoms; C, comparison: placebo group and/or group receiving intraoral PBM; O, outcome: whether extraoral PBM is capable of promoting the prevention and/or treatment of OM signs and symptoms; and S, study design: randomized clinical trials.

Table 1

Table 1. Search Strategy with Selected Descriptors.

Mucositis	("Mucositis" OR "Stomatitis" OR "Mucositides, Oral" OR "Mucositis, Oral" OR "Oral Mucositides" OR "Oral Mucositis" OR "Oromucositides" OR "Oromucositis" OR "Stomatitides"). "Oromucosite" OU "Oromucosites" OU "inflamação da mucosa" OU "irritação da mucosa" OU "mucosite" OU "mucositides" OU "Oromucosite" OU "Oromucositis".
Lasertherapy	("Low-Level Light Therapy" OR "Laser Therapy" OR "LED Dental Curing Lights"). "Photomobiomodulation extra oral" OR "Led"). "Extra oral laser" OU "Extra oral".

Source: Own authorship, 2023.

2.2 Inclusion criteria

The inclusion process involved randomized clinical trials in which OM was induced by high doses of chemotherapy with or without radiotherapy as a treatment for patients undergoing hematopoietic stem cell transplantation (HSCT), as well as radiation-induced mucositis in the head and neck for the treatment of solid tumors in this region or even the use of cytotoxic chemotherapy for the treatment of solid tumors in other locations. The therapy applied to reduce the symptoms of this condition was extraoral PBM, whether through a laser or LED, compared with placebo and/or intraoral PBM. Studies published in all languages were included. There were no restrictions regarding sex, age, OM or cancer stage, or publication period.

The scales adopted for OM assessment were the World Health Organization (WHO) scale[12] and the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).[13] The WHO scale classifies OM as Grade 0 (absence of mucositis), Grade I (oral soreness and/or erythema), Grade II (oral erythema and ulcers, with the ability to swallow solid food), Grade III (oral ulcers requiring a liquid diet only), and Grade IV (oral alimentation impossible).[12] The NCI-CTCAE scale evaluates OM according to both clinical findings and functional impairment. Grade 1 corresponds to asymptomatic or mild symptoms; Grade 2 indicates moderate pain or ulcers not interfering significantly with oral intake; Grade 3 is characterized by severe pain, extensive ulceration, and significant limitations in oral intake, often requiring nutritional support; Grade 4 represents life-threatening consequences requiring urgent intervention; and Grade 5 corresponds to death related to the adverse event.[13]

2.3 Exclusion criteria

Articles in which the therapeutic approach included other agents, regardless of their association with extraoral PBM or conditions other than OM, were excluded. Studies in which the intervention could not be clearly identified from the abstract were also excluded. Experimental studies on animal models, pilot studies, theses, dissertations, studies without abstracts in databases, editorials, and letters to the editor were excluded because of their low level of scientific evidence.[14]

2.4 Study selection

The study selection procedure was divided into three stages. In phase 1, the reference management's list of potential studies were organized using Microsoft Word (version 2018). Two blinded authors (ESB and TLDJ) reviewed titles and abstracts independently. Based on them, these authors chose articles that met the inclusion criteria. The same authors assessed the full text of all selected articles in Phase 2 and excluded studies that did not meet the inclusion criteria. The exclusion of articles followed ethical criteria and a transparent methodology as per the predefined design. A third search was conducted to identify specific articles

and enrich the theoretical foundation. Studies meeting these criteria have focused on clinical trials investigating the use of PBM in managing OM in patients with cancer. The disagreements between these authors were initially settled through consensus. When they couldn't agree, a third author (JBLD) was brought in to make the final decision.

2.5 Methodological quality and risk of bias

The risk of bias (RoB) was assessed based on the methodological design of the included studies. The CONSORT guidelines were used to validate the necessary information in randomized clinical trials and develop an organized, accurate, reproducible, and transparent study[15]. The Cochrane Collaboration's RoB 2 tool was used to assess potential bias risks in randomized clinical trials.[16]

2.6 Data extraction

Data extraction was performed by two examiners (ESB and TLDJ) individually. They searched for variables such as the year and country of publication, article authors, research objectives, sample description and total quantity, methodology employed, PBM characteristics (dosage, frequency, and administration time), characteristics of the comparative group(s) (dosage/dosimetry, frequency, and administration time), assessment of OM, results, and outcome measurement. We conducted a descriptive analysis of the studies.

3. RESULTS

After searching the databases, 305 articles were found on the PubMed platform, including 124 on Scopus and ScienceDirect, 215 on BVS, 34 on LILACS, and 568 on Google Scholar, totaling 1.246 studies. After the initial screening based on exclusion criteria, the number of studies was reduced to three, which were read in full. Of these, only two studies met the inclusion criteria as outlined in the flowchart based on the PRISMA model (Figure 1).[11] One study was excluded because did not specify the therapy used in the abstract.

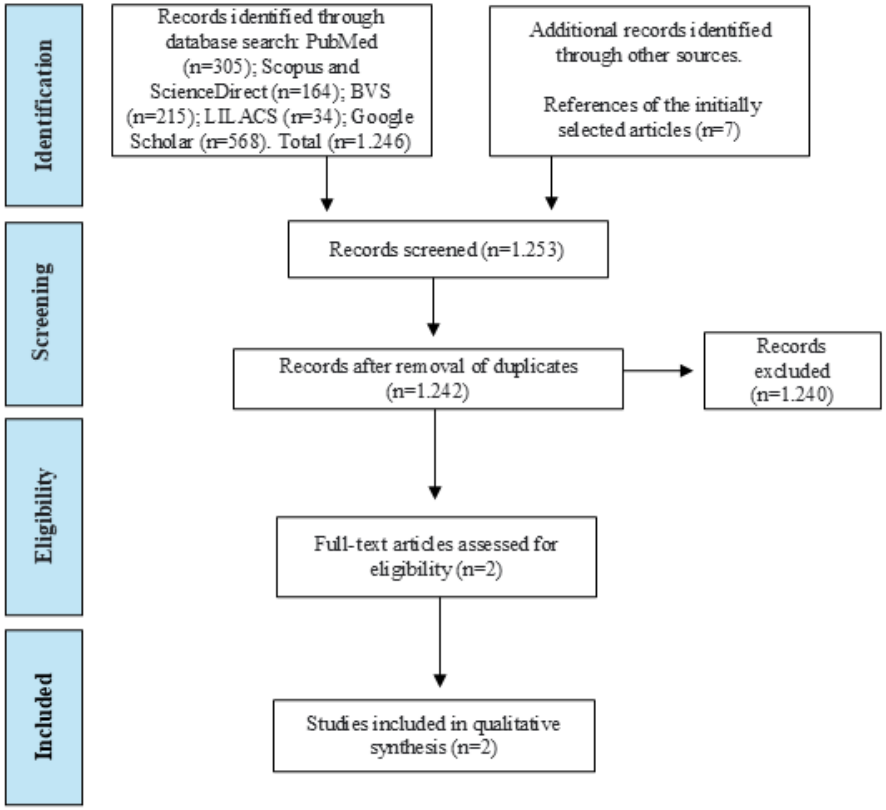

Figure 1

The clinical trials included in this systematic review were published in 2021. One study compared the effect of extraoral PBM with placebo in patients with OM and oropharyngeal mucositis induced by curative radiotherapy (60–70 Gy total, with a dose of 2.0–2.12 Gy/day, in five sessions per week) as a single modality or in combination with chemotherapy, in patients with advanced-stage squamous cell carcinoma (SCC) of the mouth and oropharynx (stages III or IV).[17] The other study comparatively evaluated extraoral and intraoral PBM in patients undergoing HSCT.[3] The included studies totaled 115 patients and these trials were conducted in patients aged > 18 years, with a male predominance, representing 71.3% of the total sample (n = 82).

In the study by Fontes *et al*. (2021),[17] the OM affected 19 individuals. In contrast, in the study by Ramos-Pinto *et al*. (2021),[3] 13 individuals in the extraoral PBM group and 12 individuals (n = 25) in the intraoral PBM group were affected by this condition. According to the World Health Organization (WHO) scale, only one patient experienced dysphagia due to grade IV OM. This patient belonged to the extraoral PBM group and declined one scheduled PBM session.[3] Pain in the oral cavity was assessed using a visual analog scale (VAS) ranging from zero to 10. In Fontes *et al*.'s study (2021),[17] the highest average pain score was 2.8 during the fifth week of radiotherapy. In a trial by Ramos-Pinto et al. (2021),[3] the highest pain scores occurred on the eighth day after TCTH administration in the intraoral PBM group and seventh day in the extraoral PBM group.

Regarding the methodology adopted, Fontes *et al*. (2021)[17] applied prophylactic extraoral PBM daily for five consecutive days (Monday to Friday) throughout radiotherapy treatment. Extraoral PBM was administered using a THOR LX2 device equipped with a red and near-infrared LED probe. The probe contained 69 LEDs, consisting of 35 × 850 nm (near-infrared, 30 mW) and 34 × 660 nm (red, 10 mW), with a total output power of 1390 mW, an outer diameter of 70 mm, an output area of 63 mm, and an average power density of 50 mW/cm^2. This therapy was administered directly to the patient's face and neck for 60 seconds per point at five different locations. The placebo group received LED applications with an inactivated probe but followed the same standard application model to ensure blinding. The protocol employed by Ramos-Pinto *et al*. (2021)[3] was initiated on the first day of the conditioning regimen and ended on the fifth day after

transplantation. Extraoral PBM involved the use of a pulsed diode laser (Gemini®, Azena Medical, LLC, distributed by Ultra Dent Products, Inc.) at wavelengths of 810 and 980 nm. Extraoral PBM was performed at six sites, whereas intraoral PBM utilized continuous application of the InGaAlP diode laser at 3300 mW/cm^2 at 34 points.

Fontes *et al*. (2021)[17] evaluated the patients' mucositis weekly according to the National Cancer Institute (NCI) scale. All included individuals manifested some degree of OM; however, in the placebo group, the lesions developed during the first week of oncological treatment in 19% of patients, whereas in the extraoral PBM group, the lesions appeared only in the second week. By the third week, all patients in the placebo group exhibited some degree of OM, whereas in the extraoral PBM group, the same result was observed only in the sixth week. Except for the last week of radiotherapy, where both groups showed the same degree of OM, in all other weeks, the incidence of severe mucositis (grade ≥ 3) was higher in the group that did not receive PBM. Thus, extraoral PBM delayed the onset of OM lesions, reduced pain levels, and was well tolerated by oncology patients.[17]

Ramos-Pinto *et al*. (2021)[3] assessed OM daily from the first day of conditioning until marrow engraftment. Mucositis was assessed using the WHO and NCI scales. According to the WHO scale, patients subjected to intraoral PBM exhibited grade I OM between days four and 12, whereas the extraoral PBM group demonstrated the same grade between days two and 10. Grade II was observed in the intraoral PBM group between days five and 10, and the same grade was observed in the extraoral PBM group between days three and 11. Severe grade (III) developed between days six and 11 and between days four and 12 in the intraoral and extraoral PBM groups, respectively. The recovery process of patients with ulcerated OM (grades II-IV) after transplantation, according to the NCI scale, averaged 9.35 days in the intraoral PBM group and 8.44 days in the extraoral PBM group. According to these findings, both therapeutic modalities yielded similar results for the prevention and treatment of OM. Table 2 summarizes the results of the studies included in this systematic review.

Ramos-Pinto *et al*. (2021)[3] found that the application of extraoral FBM had a daily average of 1.67 minutes, while intraoral FBM was approximately 5.97 minutes.

Fontes *et al.* (2021),[17] obtained a total daily duration of 2 minutes of extraoral FBM application, as well as the placebo group.

Table 2

Table 2 - General characteristics of included studies.

Author/Year /Country	Objective	Sample (n) Description of Sample	Oncologic therapy	Intervention group (Extraoral PBM) and therapeutic protocol	Control or comparison group	Assessment of OM	Results	Outcome	The CONSORT score
Pinto *et al.* (2021)[3] **Blinded Controlled Clinical Trial** **Brazil.**	To determine the most effective and least uncomfortable PBM protocol for patients in managing OM.	Total of 60 adults (18 to 40 years). Groups: Intraoral PBM (n=30) Extraoral PBM (n=30).	ASCT (autologous or allogeneic) with myeloablative conditioning regimen, non-myeloablative conditioning, or reduced-intensity conditioning.	Extraoral PBM with LBP (407 mW/cm2 x 10s=4.07 J/cm2); Intraoral PBM with LBP (3300 mW/cm2 x 10s=33.3 J/cm2). Daily application from the first day of the conditioning regimen until the fifth day after transplantation.	Intraoral PBM was applied following the same parameters as the extraoral PBM.	WHO and NCI (daily).	No significant differences were observed between the groups regarding the recovery of patients with OM grade II to IV (NCI) after transplantation (p = 0.424). According to the NCI scale, the incidence of OM was lower in the extraoral PBM group (p = 0.021),.	The extraoral PBM and intraoral PBM exhibited similar results in the prevention and treatment of OM, with a slight superiority of the extraoral PBM.	22/25 items 88%.
Fontes *et al.* (2021)[17] **Double-blind Randomized Controlled Trial** **Brazil.**	To evaluate the safety and efficacy of prophylactic extraoral PBM in preventing OM and oropharyngeal mucositis.	A total of 55 patients with SCC of the oral cavity and oropharynx were allocated into two groups. Groups: Extraoral PBM (n=29); Placebo (n=26).	Curative RT (60–70 Gy/ 2.0–2.12 Gy/day, five sessions/week) as a single dose daily or in combination with CT.	Prophylactic extraoral PBM with LED (50 mW/cm2 × 60 s=3.0 J/cm2 per site). Daily application five days per week, from the first to the last day of RT.	The placebo group received daily applications with deactivated LED and probe, following the same application model as the extraoral PBM.	NCI 4.0 version (days 5, 20, 25, 30, 30, 35, 45).	The incidence of severe OM was higher in the Placebo group in all the weeks, except for the last week of RT, where both groups presented the same grade of OM.	The extraoral PBM was well tolerated and did not cause any adverse effects. It demonstrated preventive action on OM, and reduced pain levels.	23/25 items 92%.

Legends: ASCT (Autologous Stem Cell Transplantation); cm2 (Square centimeter); CT (Chemotherapy); Gy (Gray); J/cm2 (Joule per square centimeter); LBP (Low-Level Laser Therapy); LED (Light-Emitting Diode); mW (Milliwatts); OM (Oral Mucositis); NCI (National Cancer Institute); PBM (Photobiomodulation); RT (Radiotherapy); s (seconds); SCC (Squamous Cell Carcinoma); WHO (World Health Organization).

The risk of bias assessed using the RoB2 tool was considered low in both of the included studies. There was also a slight decrease in methodological quality due to the lack of information in the analyzed articles, such as the randomization process, intervention deviations, and outcome measurements. However, these biases did not hinder the reproducibility of the methodologies employed in the studies. Figure 2 displays the assessment of bias risk according to the five established criteria for RoB2.

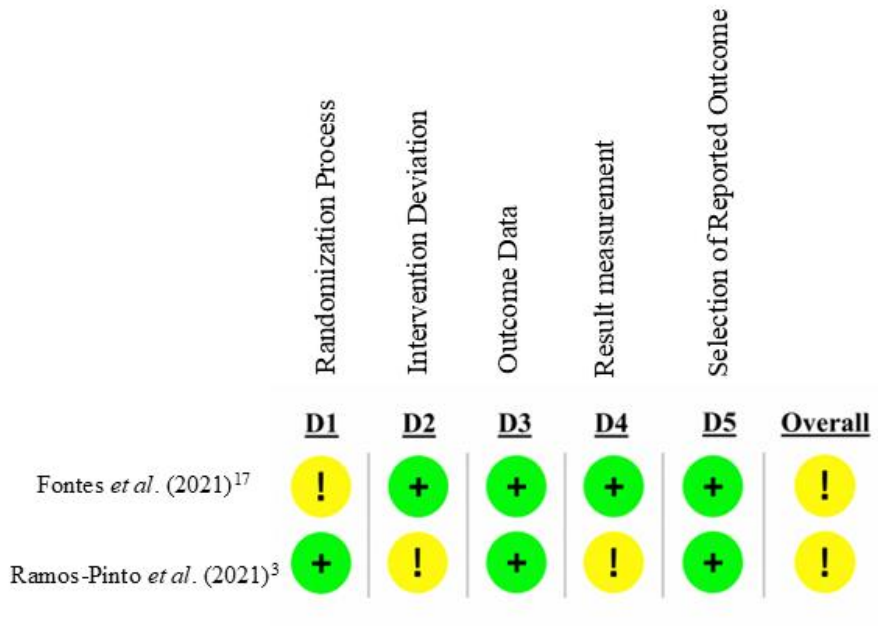

Figure 2

According to the 25 items of the CONSORT strategy (Table 2), the scores obtained were 88% in the study by Ramos-Pinto *et al*. (2021),[3] where 22 criteria were met, with limitations in the following criteria: test design, recruitment, results, and estimation, and 92% in the study by Fontes *et al*. (2021),[17] with limitations

restricted to statistical methods, results, estimation, and generalization (Supplementary Material), demonstrating the quality and transparency of the included clinical trials.

4. DISCUSSION

The present study aimed to conduct a systematic literature review on the efficacy of extraoral PBM in managing OM through an analysis of clinical trials. The PICOS strategy (Patient, Intervention, Comparison, and Outcomes) was used to evaluate the information provided by the studies.[18] The included trials suggest that extraoral PBM delays the onset of OM, reduces discomfort associated with mucositis, such as pain, in both patients undergoing radiotherapy[17] and those undergoing conditioning regimens for HSCT,[3] and allows for shorter session times than intraoral applications.

The participants in the clinical trial by Ramos-Pinto *et al*. (2021)[3] underwent HSCT (autologous or allogeneic) under different conditioning regimens, while the other study included patients diagnosed with advanced stage (III or IV) SCC of the oral cavity and oropharynx who were treated with curative radiotherapy.[17] It is important to acknowledge that the two included studies evaluated distinct clinical scenarios. Ramos-Pinto *et al*. (2021)[3] investigated patients undergoing HSCT, in whom OM is primarily associated with high-dose conditioning regimens and profound immunosuppression, whereas Fontes *et al.* (2021)[17] evaluated patients with head and neck cancer receiving radiotherapy, in whom OM results from gradual cumulative radiation-induced tissue damage. Differences in the pathophysiology, severity, clinical course of OM may influence treatment response and limit direct comparisons between the findings of the studies.

The study population consisted of a wide age range of adults over 18 years, and the scales used to assess OM were from the WHO[17] and NCI.[3,17] Both grading systems are among the most commonly used,[19,20] as shown in the study by Dantas *et al*. (2020),[19] which used the WHO scale, and the experiment by Martins *et*

al. (2021),[20] which adopted both scales. According to a scoping review of the last 20 years,[10] the NCI and WHO have been the predominant scales in recent years. This is because these grading systems are easy to reproduce, quick to administer, and address the signs and symptoms associated with OM.[19]

The clinical trials included in this study adopted the use of extraoral PBM in managing OM according to the established inclusion criteria. However, both studies employed different PBM protocols, which was anticipated because of the use of different devices: one study used extraoral and intraoral laser devices,[3] while the other used LED devices.[17] The average duration of PBM sessions was 5.97 minutes in the intraoral PBM group and 1.67 minutes in the extraoral PBM group, representing a reduction of approximately four minutes in application time with the extraoral protocol, thus demonstrating improved treatment efficiency.[3] Adnan *et al*. (2021)[21] asserted that extraoral PBM offers the benefit of simple handling and the ease of light delivery at multiple points simultaneously. Kunh *et al*. (2009)[22] highlighted that an advantage of extraoral PBM is its ability to access the oropharyngeal region. The effectiveness of extraoral PBM depends on the ability of light to penetrate biological tissues and reach deeper target structures. Although part of the incident energy is inevitably absorbed, reflected, or scattered by the skin, subcutaneous tissue, and facial musculature, near-infrared wavelengths have demonstrated greater tissue penetration than shorter wavelengths. Therefore, adjustments in irradiation parameters, including wavelength, power output, energy density, and application time, may be necessary to compensate for energy losses and ensure adequate light delivery to deeper tissues. The biological effects induced by the fraction of light reaching the target tissues include mitochondrial stimulation, increased ATP production, modulation of inflammatory mediators, improved microcirculation, and enhanced tissue repair. Therefore, the clinical benefits of extraoral PBM are not solely dependent on direct irradiation of mucosal lesions but may also result from the modulation of biological processes within adjacent tissues[21,22].

Kunh *et al*. (2009)[22] aimed to evaluate the use of intraoral PBM in 21 children and adolescents with cancer undergoing chemotherapy for HSCT. This therapy was well tolerated, and no adverse side effects attributable to its use have been reported. To corroborate this finding, Ramos-Pinto *et al*. (2021)[3] demonstrated

that diode lasers were well accepted, and no toxicity was reported. The intraoral and extraoral PBM protocols have been shown to be efficient in preventing OM. In addition, Fontes *et al*. (2021)[17] reported that extraoral PBM was also considered a well-tolerated, simple, and easily applicable intervention. More recently, Ferrari et al. (2025)[23] reported favorable outcomes with prophylactic PBM in 118 patients with head and neck cancer undergoing radiotherapy or chemoradiotherapy. The authors observed a cumulative incidence of severe OM (grade 3/4) of only 28.0%, supporting the role of PBM as an effective preventive strategy in routine oncological care. In addition, the intervention was implemented across multiple cancer centers, reinforcing the feasibility and clinical applicability of PBM in real-world settings. These findings are consistent with the recommendations of the World Association for Photobiomodulation Therapy (WALT)[24], which recognizes a robust body of evidence supporting PBM for the prevention and management of OM in patients undergoing cancer therapy. Furthermore, WALT emphasizes that PBM is a safe, well-tolerated, and clinically effective supportive care intervention when evidence-based protocols are followed.

Soto *et al*. (2015)[25] conducted a pilot study with 24 children undergoing HSCT, in which a protocol of intraoral PBM combined with extraoral PBM was used. The total sample was divided into two experimental groups: the first group comprised 12 children who received combined PBM (intra- and extraoral) four times a week, with an average duration of 22 days; the second group was the placebo group, which did not receive any photobiomodulatory therapies. The intraoral PBM device used was the InGaAIP Diode Laser (Therapy XT, DMC® Equipment Ltd., São Carlos, Brazil), 35 mW/cm^2 × 10 s = 6.65 J/cm^2, applied at 19 points. The extraoral PBM was administered with a GaAIAs laser (Therapy XT, DMC® Equipment Ltd., São Carlos, Brazil), 80 mW/cm^2 × 30 s = 14.4 J/cm^2, applied at six points. The combination therapy group showed significantly lower OM scores than the placebo group (p=0.004). The authors suggested that a combined PBM protocol may reduce the severity of OM in pediatric patients undergoing HSCT. The simultaneous evaluation of both forms of PBM was not the focus of this systematic review; however, the studies included here exhibited the positive effects of both extraoral[3,17] and intraoral[3] laser when used individually.

Studies by Ramos-Pinto *et al*. (2021)[3] and Fontes *et al*. (2021)[17] were conducted in 2021, a period when the world was experiencing a pandemic, and extraoral PBM became a potentially effective alternative because it reduced the application time and manipulation of potentially contaminating oral tissues.[5] In a pilot study conducted by Costa *et al*. (2021)[26] with 30 patients with head and neck cancer aged > 18 years from a high-complexity oncology unit in the public health network, adherence to the preventive PBM protocol was evaluated. Therapy began at the first session of radiotherapy using a semiconductor diode laser device (AsGaAl, Twin Flex®, MM Optics, São Carlos, Brazil) three times a week, with parameters: 86.7 mW/cm^2 × 10s = 1 J, wavelength 660 nm continuously, at 28 points. Patient adherence to PBM was moderate, with 50% of patients missing sessions. However, even with moderate adherence, the implementation of PBM in public health services helps minimize the signs and symptoms associated with OM, improves the quality of life of oncology patients, and reduces costs by reducing morbidity and mortality rates. Moreover, there is a high unmet demand within the Brazilian Unified Health System (SUS). Extraoral PBM, once implemented owing to its faster application time compared to intraoral PBM protocols, will allow greater access to low-income populations.

Despite the scarcity of studies in the literature, the clinical trials included here were pioneers in addressing mucositis using extraoral PBM, as it is a relatively innovative technique. The CONSORT and RoB2 tools revealed similar results between studies. Regarding the CONSORT guidelines, 92% of the recommendations were implemented in the study by Fontes *et al*. (2021)[17] and 88% in the study by Ramos-Pinto *et al*. (2021).[3] Similar data were found after the RoB2 analysis, with a slight decrease in the methodological quality of both studies due to a lack of information in the articles, such as intervention deviations, randomization process, and outcome measurement. Despite the slight limitations, they were not sufficient to interfere with the orderly and transparent reproduction of the clinical trials; therefore, the risk of bias was considered low, and the methodological quality was satisfactory.

The results of this review suggest that extraoral PBM may be an effective approach for preventing OM in patients undergoing different antineoplastic therapies. The available evidence indicates potential benefits, including reduced application time compared with intraoral PBM, delayed onset of pain, good tolerability,

and absence of reported adverse effects. In addition, the ability of extraoral PBM to reach anatomical regions that are difficult to access intraorally, may represent an important clinical advantage. This aspect is particularly relevant because oropharyngeal mucositis is frequently associated with dysphagia, nutritional impairment, reduced quality of life, and, in severe cases, interruption or modification of cancer treatment.

Although a broad initial search identified many studies, only two randomized clinical trials met the eligibility criteria for inclusion. This reflects the emerging nature of extraoral PBM as a therapeutic approach for OM and highlights the current scarcity of high-quality evidence in this field. Furthermore, differences in patient populations, oncological treatments, PBM devices, and irradiation protocols limited direct comparisons between studies and precluded quantitative synthesis of the findings. Therefore, the results should be interpreted with caution. Nevertheless, the included studies were methodologically sound and provided valuable insights into the clinical applicability of extraoral PBM. This review contributes to the current body of knowledge by summarizing the available evidence and emphasizing the need for further well-designed randomized clinical trials.

5. CONCLUSION

This systematic review suggests that extraoral PBM may be an effective approach for the prevention and management of OM in oncology patients with hematological malignancies and solid tumors of the oral cavity and oropharynx. The available evidence indicates that this therapy may reduce application time compared with intraoral PBM, delay the onset of pain, and be well tolerated without reported adverse effects. However, given the limited number of randomized clinical trials available, these findings should be interpreted with caution. Further well-designed clinical studies are needed to confirm the effectiveness and optimize the clinical protocols of extraoral PBM for OM management.

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AUTHORS' CONTRIBUTIONS

TLDJ and ESB had the idea for the article, performed the literature search, data collection and participated the text writing. JFF, LALA, JSVN and DASS colaborated in the data analysis, article review assay, english proofreading and critical review. JBLD guided all stages of the work, had the idea for the article, performed the literature search, data collection, participated in the text writing and critically revised the work.

CONFLICT OF INTEREST STATEMENT

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Ethics approval:

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