UNIVERSIDADE FERNANDO PESSOA

IMPACT OF PHOTODYNAMIC THERAPY IN ORAL MUCOSITIS: SYSTEMATIC REVIEW

Graduation Project

Raman Rasuli

Thesis Advisor:
Professor José Alberto Frias De Vasconcelos Bulhosa

Co-advisor:
Professor Filipa Manuel Moreira Aroso Pinto De Oliveira

07/2025

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" Success is not final, failure is not fatal: it is the courage to continue that counts."

Winston Churchill

Acknowledgments

I would like to express my deepest gratitude to my parents, whose constant support and belief in me allowed me to pursue my dreams even when I doubted myself. My mother's countless sacrifices, immense patience, boundless hope, and strong will taught me how life-changing it is to have someone believe in you. My father's resolute determination and tireless work ethic have always reminded me that perseverance yields results.

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Resumo

A mucosite oral é uma inflamação da mucosa e das membranas mucosas da boca e do trato gastrointestinal. É frequentemente uma consequência de tratamentos como quimioterapia e/ou radioterapia para o câncer de cabeça e pescoço.

Embora temporária, essa condição pode ser dolorosa e trazer riscos médicos, exigindo cuidados pessoais e tratamento professional. Um dos tratamentos propostos para essa condição debilitante é a terapia fotodinâmica; trata-se de uma opção terapêutica que utiliza luz e agentes fotossensibilizantes (como Azul de Metileno, Clorina e6 e hipericina) e que demonstrou ser eficaz na redução da inflamação e alívio da dor, tornando-se uma alternativa terapêutica válida também para outras condições médicas.

Para formular a pergunta de pesquisa, foi utilizado o modelo PICO. O principal objetivo desta revisão sistemática é responder à seguinte pergunta de pesquisa:

"A terapia fotodinâmica é uma opção de tratamento válida para a mucosite oral em pacientes com câncer oral?"

A busca, conduzida segundo as diretrizes PRISMA, abrangeu PubMed, SciELO, B-on e TRIP, utilizando o conector booleano “AND”.

Incluíram-se todos os ensaios clínicos disponíveis sobre o tema; excluíram-se estudos não clínicos ou sem pertinência direta.

Os trabalhos identificados indicam que a PDT, isolada ou associada à fotobiomodulação, diminui a dor, reduz o grau da mucosite e acelera a cicatrização, sem relatar eventos adversos significativos. Contudo, a maioria dos ensaios apresenta amostras pequenas e protocolos heterogéneos, o que faz com que a evidência global seja moderada.

Conclui-se, portanto, que a PDT é segura e potencialmente aplicável na prática clínica diária. Ainda assim, devido ao tamanho reduzido das amostras e à variação dos métodos, são necessários estudos mais amplos, bem planeados e com parâmetros padronizados para confirmar definitivamente a eficácia e definir recomendações clínicas robustas.

Palavras-chave: mucosite oral; terapia fotodinâmica; tratamento; ensaio clínico

Abstract

Oral mucositis is an inflammation of the mucosa and mucous membranes of the mouth and gastrointestinal tract. It is often a consequence of treatments such as chemotherapy and/or radiotherapy for head-and-neck cancer.

Although temporary, this condition can be painful and pose medical risks, requiring self-care and professional treatment. One of the treatments proposed for this debilitating condition is photodynamic therapy; it is a therapeutic option that uses light and photosensitizing agents (such as methylene blue, chlorin e6 and hypericin) and has proved effective in reducing inflammation and relieving pain, thus becoming a valid therapeutic alternative for other medical conditions as well.

To formulate the research question, the PICO model was used. The main objective of this systematic review is to answer the following research question:

"Is photodynamic therapy a valid treatment option for oral mucositis in patients with oral cancer?"

The search, conducted according to PRISMA guidelines, covered PubMed, SciELO, B-on and TRIP, using the Boolean connector "AND".

All available clinical trials on the topic were included; non-clinical studies or those not directly relevant were excluded.

The studies identified indicate that PDT, alone or in combination with photobiomodulation, reduces pain, lowers the grade of mucositis and accelerates healing, without reporting significant adverse events. However, most trials have small sample sizes and heterogeneous protocols, which means the overall evidence is moderate.

It is therefore concluded that PDT is safe and potentially applicable in daily clinical practice. Even so, owing to the small sample sizes and methodological variation, larger, well-designed studies with standardized parameters are required to definitively confirm its efficacy and establish robust clinical recommendations.

Keywords: oral mucositis; photodynamic therapy; treatment; clinical trial

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List of Abbreviations, Acronyms, Symbols, or Initialisms

ALL : Acute Lymphoblastic Leukemia

aPDT : antimicrobial Photodynamic Therapy

ChIMES: Children's International Mucositis Evaluation Scale

CT: Chemotherapy

CTCAE: Common Terminology Criteria for Adverse Events

F : Feminine

GI: Gastrointestinal

HSCT: Hematopoietic Stem Cell Transplantation

ICU: Intensive care unit

ISOO: International Society of Oral Oncology

LLLT : Low-Level Laser Therapy

M : Masculine

MASCC: Multinational Association of Supportive Care in Cancer

MT : Meta-analysis

NA : Not available

NCI: National Cancer Institute

OM: Oral Mucositis

PBM: Photobiomodulation**.**

PDT: Photodynamic Therapy

PS: Photosensitizer

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT: Randomized Clinical Trial

ROS: Reactive Oxygen Species

RT: Radiotherapy

SR : Systematic review

WHO: World Health Organization

WCCNR: Western Canadian Cancer Nurses Research

1. INTRODUCTION

According to MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy, Lalla et al. (2014) define mucositis as:

> mucosal damage secondary to cancer therapy occurring in the oral cavity; pharyngeal, laryngeal, and esophageal regions; and other areas of the gastrointestinal tract. Oral mucositis presents as erythema and/or ulceration of the oral mucosa. It is typically very painful, requiring opioid analgesics, and impairs nutritional intake and quality of life. (Lalla et al., 2014, p. 1453)

In this context, it is crucial to explore effective and safe therapeutic alternatives that can help relieve symptoms and speed up the healing of the affected mucosa.

Joseph et al. (2024) emphasize that photodynamic therapy is considered a helpful treatment option for managing oral mucositis, due to its potential to reduce inflammation and control infection in the mouth, improving the healing in oral mucositis by reducing discomfort, while supporting the natural recovery of the affected tissues

Although many studies have looked into this topic, such as Lessa et al. (2023) and Andrade et al. (2022), there's still no clear agreement on how effective photodynamic therapy really is for treating oral mucositis

For this reason, conducting a systematic review of the literature is crucial to better understand the available evidence and determine whether photodynamic therapy could be a valid option for managing mucositis caused by cancer treatment or not. Considering these factors, it is particularly important to address the research question: "Is photodynamic therapy a valid therapeutic option for the treatment of oral mucositis in patients with oral cancer?"

This review aims to contribute to the advancement of scientific knowledge on the topic by providing useful and current data that can support more informed decisions in clinical practice**.**

2. DEVELOPMENT

2.1. Materials and Methods

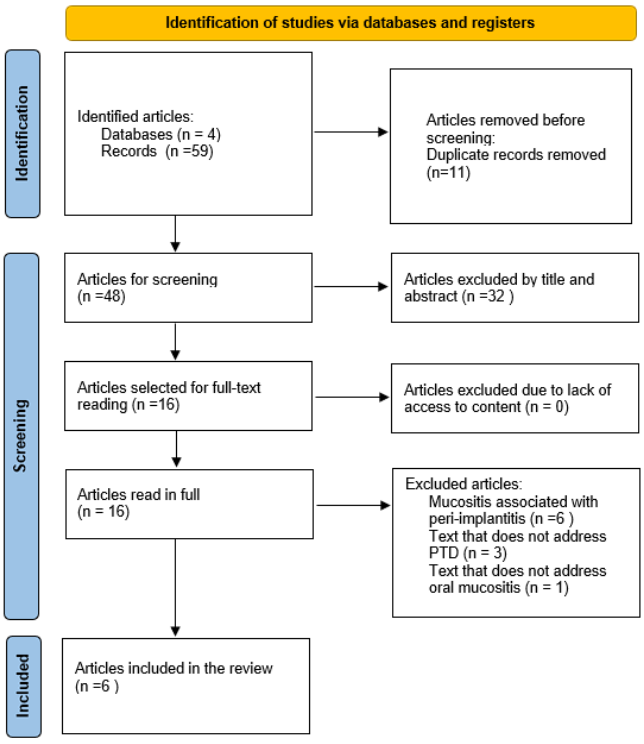
This research is a systematic review, which main objective is to collect, carefully review, and bring together the available information on a specific topic in an organized and clear way.

In this dissertation, the systematic review was used to explore how effective PDT is in treating oral mucositis caused by cancer treatments like chemotherapy and radiotherapy. Mucositis is an important issue because it can seriously affect a patient's quality of life and even lead to delays or interruptions in their cancer treatment due to pain and mouth sores.

2.1.1. Type of study

The methodology adopted was guided by the PRISMA guidelines, which help organize the construction of systematic reviews from the formulation of the research question to the presentation of results.

Figure 1
PRISMA Flow Diagram



A total of 59 articles were initially identified through searches in four databases (PubMed, Scielo, B-on, and Trip Database). After removing 11 duplicates, 48 articles remained for screening. Of these, 32 were excluded based on the analysis of titles and abstracts. 16 articles were selected for full-text reading. After reviewing the full texts, 10 articles were excluded: six focused on mucositis associated with peri-implantitis, three did not consider photodynamic therapy as the primary intervention, and one did not refer to oral mucositis. In total, six studies met the inclusion criteria and were included in the final review.

2.1.2. Research Question and PICO Strategy

The PICO model helps to define a clear structure for organizing the components of a research question. In this case, the population (P) refers to patients with oral mucositis, the intervention (I) is photodynamic therapy, the comparison (C) was not defined, as the review did not aim to compare different interventions, and the outcome (O) selected was the healing of oral lesions, considered the main clinical parameter for evaluating the effectiveness of the therapy.

Table 1
PICO model

Population	oral mucositis
Intervention	photodynamic therapy
Comparison	undefined
Outcome	healing

2.2. Oral Mucositis in Oncology Patients

According to Pulito et al. (2020):

> inflammation response of epithelial mucosa to chemo- radiotherapy cytotoxic effects leads to mucositis, a painful side effect of antineoplastic treatments. About 40% of the patients treated with chemotherapy develop mucositis; this percentage rises to about 90% for head and neck cancer patients (HNC) treated with both chemo- and radiotherapy. 19% of the latter will be hospitalized and will experience a delay in antineoplastic treatment for high-grade mucositis management, resulting in a reduction of the quality of life, a worse prognosis and an increase in patient management costs. (Pulito et al., 2020, p. 1)

According to Sonis (2007) this process unfolds in five distinct stages:
1. Initiation: The first damage happens when cancer therapy directly injures the DNA of epithelial cells in the oral mucosa.

2. Primary signaling: These initial injuries activate inflammatory pathways, especially the NF-κB pathway, which stimulates the release of inflammatory molecules such as TNF-α, IL-1β, and IL-6.

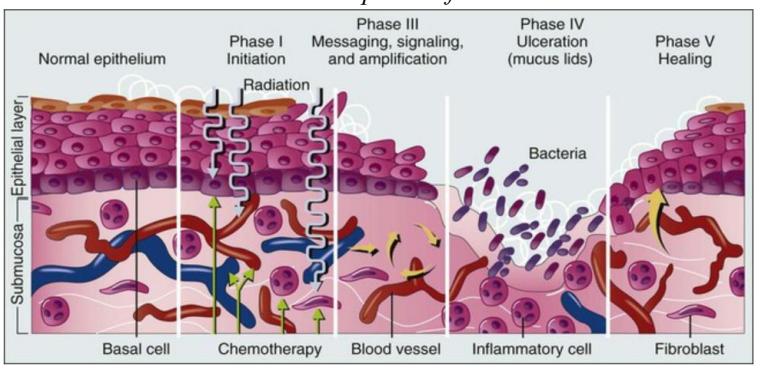
3. Amplification: These inflammatory signals intensify the response, worsening cellular damage and expanding the area of affected tissue.

4. Ulceration: At this stage, the mucosal surface breaks down, forming painful ulcers and leaving the tissue vulnerable to infections.

5. Healing: Once treatment ends or becomes less aggressive, the body begins to repair the damaged tissue. The mucosa gradually regenerates, restoring its protective function.

Figure 2

Phases in the development of oral mucositis



Note. Adapted from Peterson DE, "New strategies for management of oral mucositis in cancer patients", *J Support Oncol,* 2006.

2.2.1. Risk Factors Related to Oncologic Therapy

The risk and severity of mucositis associated with CT and RT depend on several factors, as discussed by Wang et al. (2024) and Wardill et al. (2020), including:

1) Radiation Dose and Field: Radiotherapy involving the head and neck region, presents a high risk due to direct damage to oral mucosal cells.

2) Combined Modality Therapy: When chemotherapy and radiotherapy are used together, the risk increases significantly, often resulting in earlier development, more severe symptoms, and a longer recovery period.

3) Metabolic and Systemic Conditions: Systemic factors such as diabetes mellitus and significant weight loss during treatment ($\geq 5\%$) are associated with impaired tissue repair and higher mucositis susceptibility.

4) Patient Demographic and Behavioral Factors: Individual characteristics, including female sex and smoking history, have been linked to increased mucositis risk, possibly due to biological and inflammatory response.

2.2.2. Classifications of Mucositis

WHO – World Health Organization Criteria

The WHO criteria for oral mucositis are widely used to determine severity and to guide clinical management in cancer patients. According to the World Health Organization (1979), oral mucositis is classified as follows:

1. Grade 0 (None): This indicates that the patient has no signs or symptoms of oral mucositis despite receiving cancer treatment.
2. Grade 1 (Mild): The patient has soreness or erythema (redness) in the oral mucosa, but there is no ulceration or significant tissue loss and usually does not require significant intervention.
3. Grade 2 (Moderate): Erythema and ulcers are present in the oral cavity, leading to some pain and difficulty with eating. This stage often necessitates more intensive management, such as the use of local treatments or pain control.
4. Grade 3 (Severe): Extensive ulceration and bleeding may occur, significantly affecting the patient's ability to eat or speak. Patients may require hospitalization due to the severe symptoms.
5. Grade 4 (Very Severe): Represents life-threatening mucositis with extensive ulceration and potentially the involvement of other tissues in the oral cavity and gastrointestinal tract; this stage requires urgent medical intervention, possibly including supportive care in an ICU.

Table 2
World Health Organization Oral Mucositis Classification

Mucositis - Oral Toxicity Scale (WHO)	
Grade 0	No alterations
Grade I	Pain and erythema
Grade II	Erythema and ulcers
Grade III	Ulcers (liquid diet only)
Grade IV	Unable to feed

Note. Adapted from Cleverson et al.," Clinical assessment of oral mucositis and candidiasis compare to chemotherapic nadir in transplanted patients", *Brazilian Oral Research,* 2014.

NCI – National Cancer Institute Scale

Compared to the WHO scale, the NCI criteria focus slightly more on functional impact and need for medical support, focusing on the presence of symptoms and their impact on a patient's ability to eat, speak, or perform daily activities. As reported by National Cancer Institute (2009), oral mucositis is categorized in:

1. Grade 0: No symptoms of mucositis.
2. Grade 1: Asymptomatic or mild symptoms; slight soreness or redness in the mouth without any ulcers; does not require intervention.
3. Grade 2: Moderate pain or ulceration, but the patient can still eat and swallow solid foods. Some modifications to the diet may be needed.
4. Grade 3: Severe pain; ulcerations that make eating solid food difficult or impossible, requiring a liquid or soft diet. Medical intervention is typically needed
5. Grade 4: Extreme pain and ulceration, such that the patient cannot eat or drink at all by mouth. Feeding must be done via tube (enteral) or intravenously (parenteral).
6. In the CTCAE classification system, Grade 5 refers exclusively to death directly caused by an adverse event. However, this grade is not applicable to oral mucositis, as mucositis alone is not considered a direct cause of mortality.

Table 3
NCI/CTCAE Scale

0	None
1	Asymptomatic or mild symptoms; intervention not indicated
2	Moderate pain; not interfering with oral intake; modified diet indicated
3	Severe pain; interfering with oral intake
4	Life-threatening consequences; urgent intervention indicated
5	Death

Note. Adapted from NIH CTCAE v4.03, 2010, p. 45.

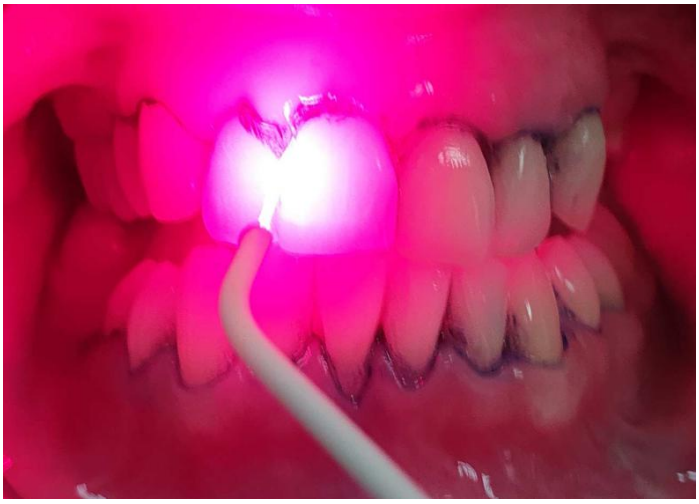
2.3. Photodynamic Therapy (PDT)

Suresh et al. (2024) refer to photodynamic therapy as "a rapidly evolving, non-invasive treatment modality with considerable promise in dental pharmacotherapeutics"

According to Correia et al. (2021), PDT consists of administering a photosensitizer (PS)—topically or intravenously—that selectively accumulates in tumor tissue during the drug–light interval, followed by exposure to light of an appropriate wavelength. The PS itself does not react with biomolecules; upon illumination, energy is transferred to molecular oxygen to generate reactive oxygen species (ROS). These cytotoxic photoproducts trigger a cascade of biochemical events that can damage and ultimately kill the target tissue. What makes PDT especially appealing, compared with chemotherapy or radiation, is its highly targeted action, focusing only on the area that needs treatment.

Figure 3

Safe and effective photodynamic therapy



Note. Adapted from Dentistry, "Safe and effective photodynamic therapy", 2023.

2.3.1. Key Components

As outlined by Cai et al. (2025), the general mechanism of PDT involves three primary elements: light with a specific wavelength, a photosensitizer, and molecular oxygen.

1. Photosensitizer: A photosensitizing agent selectively accumulates in the target tissue. Common examples include methylene blue and porphyrins.
2. Light: For PDT to be effective, the photosensitizer must be exposed to light of a specific wavelength, usually from a laser or LED. The light energy excites the photosensitizer, triggering the production of ROS.
3. Oxygen: Oxygen concentration in the tissue affects the effectiveness of PDT, as lower oxygen levels can reduce ROS production and therapeutic efficacy.

2.3.2. Mechanisms of Action of PDT

Robertson et al. (2009) point out that the two most important aspects of PDT are the processes of light absorption and energy transfer. A ground-state photosensitizer (PS) has two electrons with opposite spins in a low-energy molecular orbital; this is known as the singlet state. Following the absorption of light (photons), one of these electrons is promoted to a higher-energy orbital, while retaining its spin, forming the first excited singlet state. This state is transient and dissipates its energy either by emitting fluorescence or by internal conversion to heat.

As described by Rodrigues and Correia (2023), two types of photodynamic reactions can occur in PDT:

1. Type I reactions- the activated photosensitizer transfers energy to nearby molecules, generating free radicals that react with oxygen to produce ROS, which help destroy harmful cells.

2. Type II reactions- which happen more often in PDT, involve the photosensitizer passing energy directly to oxygen. This creates a special kind of reactive oxygen called singlet oxygen, which can damage important parts of the cell like fats, proteins, and DNA.

3. RESULTS

Regarding the type of study, among the six articles reviewed, four are randomized clinical trial (including two pilot studies) one is a triple-blind trial, and one is a systematic review with meta-analysis.

The selected studies involved oncology patients with therapy-induced oral mucositis across all age groups, with three studies conducted exclusively in pediatric populations (10 months to 18 years) and the remaining three focused on adults, whose mean ages, ranged from 18 to 65 years and in one case extending up to 81 years.

Based on the collected studies, sex distribution was reported in three cases: two adult trials showed a predominance of male participants (one clearly marked and the other moderate) while one pediatric study showed a balanced distribution; the remaining studies did not report sex data.

Table 4
Simplified overview table of the included studies

Author/year	Country	Type of article	Measurement bias	N° of participant Sex (M/F)	Age	Type of cancer and location	Onco treatments
Andrade, R.C.D.V. *et al* (2022).	Brasil	RCT	The study was registered in the Brazilian Clinical Trials Registry under number RBR 2bhf37x..	Total: 30 .Control group: 10/0 .PBM group: 8/2 .aPDT group: 8/2	.Control group: 60,1 ± 10,6 years .PBM group : 57,3 ± 7,2 years .aPDT group: 60,5 ± 6,8 years	Oral cancer : .Tongue (40%,ventral-lateral) . Floor of the mouth (30%) .Lower lip (30%)	. Radiotherapy and chemotherapy
Oliveria, A.B. *et al.* (2021)	Brasil	SR with MT	Data were extracted by two independent reviewers who were blinded to the identity of the studies; disagreements were resolved by a third reviewer (κ = 0.92).	Total: 85 .Gender no disclosed	.Pediatric (≤18 years old) to adults (26–81 years old)	.Lymphatic system cancer (60%) .Breast cancer (40%)	.Radiotherapy and/or chemotherapy
Lavaee, F. *et al* (2020).	Iran	RCT single-blind pilot	Split-mouth design: one side was treated while the other received a sham treatment, ensuring that effects were compared within the same patient.	Total: 15 .9/6	.Mean :34 years old (age > 4 years)	NA	Chemotherapy

Silva, V.C.R. *et al* (2020)	Brasil	RCT blind pilot	The Chi-square, Fisher exact, Student *t*, and Mann-Whitney tests and the mixed linear regression model were used for comparison between the groups, with the maximum error admitted of 5%.	Total: 29 .Gender no disclosed	.10 months to 18 years.	NA	Chemotherapy
Silva, V.C.R. *et al* (2020)	Brasil	RCT triple-blind	The Chi-square test, Fisher exact test, Student *t* test and Mann-Whitney *U* test, in addition to the mixed linear regression and Poisson models, were used for comparison, with the maximum error admitted of 5%	Total: 54 .Gender no disclosed	.10 months to 18 years.	NA	Chemotherapy
Silva, V.C.R. *et al* (2018)	Brasil	RCT single-blind pilot	The Chi-square, Exact Fisher, Student's-t and Mann-Whitney tests, and the mixed linear regression model were used for comparison between the groups, with the maximum error admitted of 5%.	Total: 29 .Grupo A: 7/7 .Grupo B: 8/7	.10 months and 18 years	.Acute Lymphoid Leukemia (69%) .Non-Hodgkin Lymphoma (13.8%) .Osteosarcoma (17.2%)	Chemotherapy

In terms of the severity of oral mucositis, two clinical trials reported initial levels explicitly: one pediatric study identified grade II and III mucositis in all participants, while one adult study showed most patients began treatment at grade II. Additionally, the systematic review included five studies describing severity levels ranging from I to IV, with a predominance of grades II and III. The remaining articles did not provide specific grades on mucositis; however, all studies used recognized clinical grading scales such as the WHO or the NCI-CTCAE scale.

Regarding the treatment protocols, photodynamic therapy administrated was typically in combination with low-level laser therapy, with variations in photosensitizers, irradiation parameters, and session frequency.

The photosensitizing agents most commonly used were methylene blue and curcumin, with incubation times ranging from 3 to 10 minutes before irradiation.

Light sources operated primarily at wavelengths of 450 nm and 660 nm, with power outputs varying between 25 and 100 mW, and delivered doses between approximately 19 and 142 J/cm². The number of treatment sessions varied considerably, ranging from 3 to 12, with some protocols applying therapy daily until clinical resolution and others spacing sessions weekly. Control groups generally received photobiomodulation alone, often following the same treatment schedule as the experimental group to ensure comparability.

The clinical outcomes evaluated primarily included pain reduction, healing time, regression of mucositis grade, and need for nutritional support, all of which were positively influenced by PDT in all studies, with pediatric populations additionally showing better treatment tolerance, reduced reliance on systemic analgesics, and shorter recovery periods.

Table 5
Table of detailed overview of the included studies

Author /year	Mucositis grade	Complementary treatments	Type of device	Protocol	Results	Adverse effects	Follow-up
Andrade, R.C.D. V. *et al* (2022).	**7 days:** .Control group:1,90 ± 0,88 .PBM group:1,50 ± 0,53 .aPDT group:2,30 ± 1,16 **14 days:** .Control group: 2,70 ± 0,95 .PBM group:1,70 ± 1,06 .aPDT group:2,30 ± 1,06 **21 days:** .Control group: 2,90 ± 0,74 .PBM group:1,90 ± 1,10 .aPDT group:1,70 ± 0,68 **30 days:** .Control group: 2,90 ± 0,88 .PBM group:1,50 ± 0,85 .aPDT group:1,20 ± 0,42	PBM and aPDT	**PBM group:** Low-level laser device (red light) **aPDT group:** LED light device (blue light)	**PBM group :** Total sessions :12 3 times per week for 30 days Irradiation time of 03 s per point, over the entire length of the lesion with an equidistance of 1 cm between the points. **aPDT group:** Total sessions : 4 1 time per week for 30 days Application of the curcumin solution, 10-minute waiting, blue LED for 10 minutes.	**PBM (red laser) :** beneficial but slower in effect compared to aPDT, while the control group showed no significant improvement **aPDT** (curcumin + blue LED) most effective, providing faster improvement and greater pain relief by day 30	None	NA

Oliveria, A.B. *et al.* (2021)	.Grade III and IV: n15 .Grade II and III: n28 .Grade I and III: n15 .Grade I,II,III and IV: n28	.LLLT .PDT .LLLT+PDT	**PDT :** .Red light-emitting diode LED (660-810 nm) .Blue light-emitting diode LED (400-470 nm) **LLLT :** .Low-level laser (660-810 nm)	**PTD group :** Total Total session : 3 to complete remission of lesion Application of Methylene Blue, 3 to 10 minutes waiting, laser irradiation for 30 seconds to 10 minutes **LLLT+PTD group:** Total session : 4 to 8 Application of curcumin (mouthwash) or Methylene Blue, 10 minutes waiting, laser irradiation 90 s to 5 minutes	**PDT + LLLT** healed 4.84 days faster than those receiving LLLT alone. **PDT** also reduced microbial load, contributing to improved tissue healing.	None	NA

Lavaee, F. *et al* (2020).	NA	PDT	**PTD group** :diode laser (660nm) **Control group :** sham laser (placebo)	Total session : 3 (Day 1, Day 3 and Day 5) Application of Methylene Blue on both lesion sides, waiting time 10 minutes, 1) Intervention Side: Irradiation with diode laser,10 minutes per session 2) Control Side: sham laser ,10 minutes per session	Both groups showed improvement in oral mucositis over time, with the PDT group demonstrating significantly faster and greater healing.	None	Day 12 (a week after last session of PDT)

Silva, V.C.R. *et al* (2020)	NA	PBM and PDT	**aPDT group:** red laser of 660 nm in combination with 0.01% methylene blue as a photosensitizer **PBM group :** red laser of 660 nm	**aPDT group:** 0.01% Methylene Blue solution, and application of Laser **PBM group :** Direct application of red Laser	aPDT and PBM showed no significant difference in healing time or pain reduction, but both treatments significantly reduced pain within their respective groups.	None	NA
Silva, V.C.R. *et al* (2020)	NA	PBM and PDT	**PTD group :** red laser of 660 nm in combination with 0.01% methylene blue as a photosensitizer Control group : red laser of 660 nm	**PTD group :** Methylene Blue solution,applicati on of Laser **Control group :** Direct application of red Laser	Both groups experienced a significant reduction in pain and difficulty with swallowing or chewing	None	Daily, until clinical cure of the lesions

Silva, V.C.R. *et al* (2018)	.Grade II (23 patients) .Grade III (6 patients)	LLLT and PDT	**Group A:** Red Laser (660 nm) + Methylene Blue (0.01%) as a photosensitizer **Grupo B :** Red Laser (660 nm)	**Group A :** Methylene Blue solution, 3-minute waiting period, Laser Irradiation 30 seconds per point,daily application until clinical healing. **Group B :** Direct application of red laser 10 seconds per point, daily application until clinical healing	Resolution of mucositis .Group A: 11/14 .Group B: 14/15	.One patient stopped PDT due to discomfort from the photosensitiz er (Methylene Blue), not the laser	NA

4. DISCUSSION

A total of six articles were analyzed, including 243 patients (50 male, 24 female, and 169 not reported) with mucositis. Four studies—Silva et al. (2018), Lavaee et al. (2020), and both clinical trials by Silva et al. (2020)—involved patients treated exclusively with chemotherapy. One study, Andrade et al. (2022), included patients who underwent both chemotherapy and radiotherapy, whereas Oliveira et al. (2021) involved patients treated with chemotherapy and/or radiotherapy.

The mucositis reported in these articles was caused by the treatment of a wide range of cancers, including hematologic malignancies (such as acute lymphoblastic leukemia and lymphomas), osteosarcoma, and various solid tumors including head and neck, breast, and gastrointestinal cancers.

The photodynamic therapy protocols employed, used methylene blue or curcumin as photosensitizers, either alone or in combination with photobiomodulation. The devices used included red diode lasers and blue LED systems, depending on the study design and photosensitizer selected.

The impact of these therapeutic approaches becomes more evident when looking at the clinical outcomes:

Lavaee et al. (2020) reported significant improvement in mucositis severity scores (WCCNR and NCI) after just one session of PDT ($p = 0.049$), with continued healing observed throughout the follow-up period. Similarly, Andrade et al. (2022) observed a significant decrease in mucositis severity and pain, particularly from the 21st day onward. In this study, the PDT group outperformed both the control and PBM groups in terms of early pain relief and lesion resolution.

The combination of PDT with PBM/LLLT appears to improve these benefits. The systematic review and meta-analysis highlighted that this combined therapy reduced healing time by approximately 4.8 days compared to PBM alone, suggesting a synergistic effect on tissue regeneration and lesion duration.

The pediatric studies by Silva et al. (2018, 2020) showed that both PDT and PBM were effective in reducing pain and mucositis severity, with no significant differences in the number of sessions needed for lesion resolution. These trials also highlighted good tolerability among children, with no reported adverse effects, making PDT a safe and viable approach in younger populations.

The analyzed data confirm that PDT combines antimicrobial action with photobiological stimulation, which together contribute to the modulation of inflammation and promotion of tissue regeneration. These effects help reduce the clinical severity of oral mucositis, promoting earlier pain relief, and preserving essential functions such as eating and speaking, facilitating the continuation of oncologic treatment without interruption.

Despite these positive outcomes, a number of factors may help explain the variation in results across studies:

1. Photosensitizer differences

   In the reviewed studies, methylene blue was the most frequently used photosensitizer (Lavaee et al., 2020; da Silva et al., 2018, 2020), showing consistent results in reducing inflammation and lesion severity. In contrast, Andrade et al. (2022) used curcumin in mouthwash form. Although curcumin has known photodynamic properties, it has different absorption peaks (≈ 450 nm) and reduced tissue penetration compared with methylene blue (≈ 664 nm). These pharmacological and photophysical differences may influence antimicrobial efficacy and healing potential, which can partly explain why studies using methylene blue showed faster improvement in deeper lesions.

2. Irradiation protocols

   The studies varied in laser wavelength (450 nm for curcumin vs. 660 nm for methylene blue), light dose (≈19–142 J/cm²), and power (25–100 mW). Longer wavelengths, such as 660 nm, penetrate tissues more deeply, which may be more effective in treating lesions in thicker mucosa. For example, Lavaee et al. (2020), using red light and methylene blue, achieved rapid clinical improvement after a single session. In contrast, Andrade et al. (2022), using blue light and curcumin, observed improvements only after multiple sessions. This supports the hypothesis that deeper penetration improves PDT efficacy in more severe cases.

3. Application schedule and number of sessions

   The number and frequency of PDT sessions varied considerably across the studies. Lavaee et al. (2020) conducted three sessions over a short period, da Silva et al. (2018, 2020) implemented daily applications until complete lesion remission, whereas the Andrade et al. (2022) protocol extended to 21 days.

   This variation in session timing and treatment continuity may affect the cumulative therapeutic impact, making outcomes difficult to compare directly—particularly in cases of grade III–IV mucositis, where more frequent interventions may be required.

4. Clinical scales and mucositis classification

   Not all studies reported the mucositis grade at baseline, and evaluation methods varied across studies: da Silva et al. (2018, 2020) used the WHO and ChIMES scales, while Lavaee et al. (2020) used the NCI and WCCNR scales, which provide more detailed evaluation, including lesion size, inflammation, and bleeding.

   Andrade et al. (2022) did not specify the initial severity level for each patient but indicated overall improvement based on the WHO scale. In contrast, studies that used WHO grading alone might have captured fewer subtle changes, affecting the interpretation of short-term results. The inconsistent use of grading systems across studies may reduce the sensitivity of clinical comparisons, especially in early-stage improvements.

5. Population differences

   The studies on pediatric populations (da Silva et al., 2018, 2020) consistently reported good treatment tolerance, faster healing, and fewer adverse effects. Children and adolescents generally present fewer pre-existing conditions and a higher capacity for tissue regeneration compared with adults. In contrast, adult-focused studies—such as Andrade et al. (2022) and Lavaee et al. (2020)—involved participants with diverse oncologic profiles, including chemotherapy/radiotherapy combinations and more severe baseline conditions, which could have influenced treatment response.

Although the results look promising, the overall strength of the evidence is still moderate. Five of the six papers was labelled as randomized, yet only one clearly explains how treatment randomization process was kept hidden, so some selection bias remains possible. Measurement bias were better controlled: two small pediatric pilots used a triple-blind set-up, another study blinded the outcome examiner, and one trial ran a split-mouth design, so each patient served as his or her own control. Only two trials were registered in public clinical trial databases, which makes it harder to detect selective reporting and limits transparency.

Three of the trials are pilots with very small samples, which limits statistical power, and the treatment protocols differ widely in doses, wavelengths, number of sessions making the studies hard to compare.

This heterogeneity in treatment protocols reinforces the urgent need for standardized guidelines to ensure reproducibility and optimize clinical outcomes.

Such efforts are essential to validate photodynamic therapy as a reliable and standardized approach for managing oral mucositis in oncology settings and to support its broader clinical implementation.

5. CONCLUSION

Photodynamic therapy is not just a promising supportive therapy for oral mucositis ,but it reveals to be a practical tool that can be incorporated into the everyday care of people undergoing cancer treatment.

This study shows that when photodynamic therapy's practical requirements (appropriate equipment, treatment settings, and simple disinfection steps) are integrated into a dental clinic's everyday workflow, it can be used safely without buying new devices or making major changes to infection-control protocols.

Taken together, the six studies reviewed form a moderately reliable foundation: all report favorable clinical outcomes and no meaningful adverse events, but they vary in methodological rigor and treatment parameters.

The existing studies collectively suggest benefit but still leave some uncertainty due to modest sample sizes and varied protocols. Future large, well-standardized trials will therefore be essential to move PDT from a promising option to a firmly established component of supportive cancer care.

Getting these practical details right is essential since dentists typically serve as the initial clinicians to identify oral mucosal pathology and, after systemic therapy ends, remain the primary providers of ongoing support for these patients.

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