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Review article

The potential effect of photobiomodulation on oral mucositis induced by head and neck radio-chemotherapy: A literature review

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Abstract Oral mucositis (OM) is a common side effect of head and neck radio-chemotherapy. It manifests as painful, ulcerative lesions in the oral mucosa, significantly impairing essential functions such as eating, speaking, and maintaining oral hygiene. It finally has adverse effects on the patient's quality of life. Photobiomodulation therapy (PBMT) has emerged as a promising non-invasive modality for preventing and treating OM. Due to controversy among the results of studies, this literature review synthesizes findings from recent randomized controlled trials that evaluated the use of PBMT in adult and pediatric cancer patients. This review also highlights the mechanisms, clinical efficacy, and future challenges of integrating PBMT into routine supportive cancer care. The evidence shows that PBMT significantly reduces the severity and duration of OM, improved patient-reported outcomes, and minimized treatment-related morbidity. By utilizing low-intensity light sources—typically lasers or LEDs—PBMT enhances cellular metabolism, reduces inflammation, alleviates pain, and promotes mucosal healing. Despite its clinical potential, widespread implementation of PBMT is hindered by variability in treatment protocols and limited standardization; in brief, laser protocols — wavelengths (630–980 nm), energy densities (2–6 J/cm^2), and application durations (10–125 s/point) are commonly used for preventing and treating OM induced by head and neck radio-chemotherapy.

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However, future studies with long-term follow-ups will be necessary to standardize PBMT protocols, as standardization is essential to integrate PBMT into routine cancer care.

Introduction

Cancer continues to be a major health problem worldwide, with millions of new cases and deaths reported each year.[1] Among these, head and neck cancer (HNC) is a serious type that affects areas like the mouth, throat, and voice box. Many patients with HNC are treated with radiotherapy, often combined with chemotherapy, a method known as radio-chemotherapy.[2,3] This multimodal strategy has enhanced local tumor control and improved survival rates. However, despite its clinical effectiveness, radio-chemotherapy has various adverse effects that can severely affect patients' quality of life (QoL). Notably, oral mucositis (OM) emerges as one of the most distressing and challenging complications to manage.[4]

OM is characterized by inflammation, erythema, and ulceration of the mucosal lining within the oral cavity. It is primarily triggered by the cytotoxic effects of chemotherapy and ionizing radiation on rapidly dividing epithelial cells.[5,6] The progression of OM typically follows a pathobiological cascade that involves initiating tissue injury, signaling and amplifying pro-inflammatory cytokines, ulceration, and, ultimately, healing.[5] Patients with OM often experience severe oral pain, difficulties in swallowing and speaking, reduced nutritional intake, and an increased risk of infection. These symptoms frequently necessitate the use of potent analgesics, including opioids. They may lead to interruptions or reductions in cancer treatment—highly undesirable outcomes that could compromise therapeutic efficacy.[7,8] There is an urgent need for effective strategies to prevent and manage this complication. Various pharmacologic and non-pharmacologic approaches have been proposed, ranging from anti-inflammatory mouthwashes and cryotherapy to growth factors and coating agents. However, many of these options offer limited benefits or are associated with adverse effects.[9] In recent years, photobiomodulation therapy (PBMT)—formerly referred to as low-level laser therapy—has emerged as a promising modality in supportive cancer care, particularly in the prevention and treatment of OM.[10]

PBMT is a non-invasive and safe technique that involves the application of low-intensity, non-ionizing light sources such as lasers or light-emitting diodes (LEDs). These light waves penetrate tissue without increasing tissue temperature or causing any tissue damage. They are absorbed by intracellular chromophores, particularly within the mitochondria, leading to increased production of adenosine triphosphate (ATP), modulation of reactive oxygen species (ROS), and activation of transcription factors that promote cell proliferation and migration.[11] As a result, PBMT facilitates tissue repair, reduces inflammation, and provides an analgesic effect.[12]

Different studies have explored the clinical applications of PBMT in treating or preventing OM. However, there is controversy regarding the integration of PBMT into routine clinical practice, which faces several challenges, especially due to various PBMT protocols (including variations in light source, wavelength, energy output, and treatment frequency).[13] Therefore, the present study was designed to evaluate the effect of PBMT on OM induced by head and neck radio-chemotherapy.

Pathophysiology of oral mucositis

OM follows a dynamic and multifactorial biological sequence that can be conceptualized in five interrelated stages: initiation, upregulation and message generation, signal amplification, ulceration, and healing.[14] The initiation phase begins immediately after exposure to chemoradiation, with DNA damage and generation of ROS. These molecules activate transcription factors such as nuclear factor kappa B (NF-κB) and p53, leading to the release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL (interleukin)-1β, and IL-6. The signal amplification phase enhances this inflammatory cascade, recruiting immune cells and amplifying tissue injury. As epithelial integrity breaks down, ulceration occurs, often with bacterial colonization that further intensifies inflammation. Healing, the final phase, requires the resolution of inflammation, angiogenesis, fibroblast proliferation, and epithelial regeneration.[14,15] This multiphase complexity makes OM a challenging condition to manage and presents a rational target for PBMT. Unlike surface-based symptomatic agents, PBMT can interact with mitochondrial chromophores such as cytochrome *c* oxidase, modulating ROS, ATP production, and inflammatory signaling at a cellular level.[16] Therefore, PBMT is suited to interfere with multiple stages of OM progression.

Clinical evidence on photobiomodulation therapy for oral mucositis

Over the past two decades, numerous randomized clinical trials have assessed the effectiveness of PBMT in preventing and treating OM in cancer patients (see Table 1). In the

Table 1 Description of the reviewed studies.

Condition		Sample size	Age (mean ± SD)	Gender (male/female)	Comparison Group	Photobiomodulation parameters							Aim of using laser	Outcome	Refs
Type of cancer	Type of treatment					Light source	Wavelength	Power	Energy density	Wave mode	Time	Session			
Digestive tract cancer	Chemotherapy (FOLFOX, XELOX)	45	N/A	27\18	Placebo laser (OFF) + Basic oral care only	Diode	635 (intraoral) 980 (extraoral)	200 mW	4 J/cm^2	Continuous	20 s/spot	One session (before chemotherapy)	Preventive	↓ OM severity ↑ QoL	17
Squamous cell carcinoma	Radio-chemotherapy (cisplatin + radiotherapy)	36	60.83 years	63.9 % male	Placebo laser (OFF) + Diphenhydramine + Almgs mouthwash	Diode	810 nm	200 mW	6 J/cm^2	N/A	30 s/spot	4 consecutive days (After OM onset)	Treatment	↓ Pain ↓ OM grade	18
Head and neck cancer	Radiotherapy ± Chemotherapy	80	68 years	67/13	Placebo laser (OFF)	N/A	660 nm 810 nm Both	100 mW	6 J/cm^2	N/A	N/A	Daily (42 days)	Preventive and treatment	660 + 810 nm showed best OM reduction.	19
Solid tumors (mainly breast and GI)	Chemotherapy	287	56 years	58/229	Placebo laser (OFF)	Diode	630 nm	30 mW	2 J/cm^2	Continuous	N/A	Once per cycle (Before each chemo cycle)	Preventive	↓ OM incidence and severity	20
Pediatric leukemia (Acute lymphoblastic leukemia)	Chemotherapy (High-dose methotrexate)	80	9.4 years	51/29	Laser/LED	InGaAlP LED	660 nm	100 mW 5 mW	2 J/cm^2	Continuous	36 s 120 s	Daily during hospital stay until discharge	Preventive and treatment	Similar efficacy between LED and laser.	21
Oral cavity and oro/ hypopharyngeal cancers (stage III or IV)	Radio-chemotherapy	83	N/A	N/A	Placebo laser (OFF)	He–Ne laser	658 nm	100 mW	4 J/cm^2	Pulsed <50 Hz	40 s/spot	5x/week during radio-chemotherapy	Treatment	No significant difference from placebo	22
Squamous cell carcinoma	Radio-chemotherapy (cisplatin + radiotherapy)	26	60.89 ± 9.99	20/6	Placebo laser (OFF)	Diode	940 nm	0.5 W	0.5 J/s	N/A	360 s (5 s/point)	12 sessions	Preventive and treatment	↓ OM incidence and severity	3
Head and neck cancer	Radio-chemotherapy	94	53.5 ± 6.9 (PBMT) 55.7 ± 8,6 (Control)	82/12	Placebo laser (OFF)	InGaAlP	660 nm	100 mW	4 J/cm^2	Continuous	40 s/point	Before each radiotherapy session	Preventive	Improved clinical outcomes	23
Patients undergoing hematopoietic stem cell transplantation	Chemotherapy	51	42 years (PBMT) 41 years (Control)	26/25	Placebo laser (OFF) + Basic oral care only	InGaAlP	660 nm	40 mW	4 J/cm^2	Continuous	4 s/point	Daily from first day until the seventh post-transplant day	Preventive and treatment	↓ OM severity ↓ CXCL8	24
Head and neck cancer (elderly)	Radiotherapy	46	71.57 ± 7.27 (PBMT) 69.67 ± 8.68 (Control)	39/7	Placebo laser (OFF)	He–Ne	632.8 nm	24 mW/cm^2	3 J/point	Continuous	125 s/point	5x/week during RT (6.5 weeks)	Preventive	↓ OM, ↑ Swallowing and oral intake	25
Pediatric and young cancer patient (Hematological tumor Solid tumor)	Chemotherapy	67	15.6 ± 12.0 (PBMT) 14.8 ± 7.8 (Control)	41/26	Placebo laser (OFF)	AlGaIAs	940 ± 15 nm	0.3 mW	4.2 J/cm^2	Pulse	30 s/point	Daily from first chemotherapy day	Preventive	↓ Pain ↓ OM severity	26
Head and neck cancer	Radiotherapy	25	N/A	21/4	Placebo laser (OFF)	InGaAlP	660 nm	25 mW	6.2 J/cm^2	Continuous	10 s/point	35 sessions (3 times a week)	Treatment	↓ OM severity ↓ Inflammatory cytokines	27
Head and neck cancer	Radio-chemotherapy (cisplatin + radiotherapy)	220	55 ± 11.52 (PBMT) 56 ± 11.80 (Control)	189/31	Placebo laser (OFF)	He–Ne	632.8 nm	24 mW/cm^2	3 J/point	Continuous	125 s/point	Daily before each RT session	Preventive	↓ OM severity Improved QoL	28

Abbreviation: GaAlAs, Gallium-aluminum-arsenide; He–Ne, Helium-neon; InGaAlP, Indium-gallium-aluminum phosphide; J, Joule; J/cm^2, Joules per square centimeter; J/s, Joule per second; LED, Light-emitting diode; mW, Milliwatt; mW/cm^2, Milliwatt per square centimeter; N/A, Not applicable; Nd:YAG, Neodymium-doped yttrium aluminum garnet; Nm, Nanometer; OM, Oral mucositis; QoL, Quality of life; Refs, References; S, Seconds.

following, we reviewed the studies based on several key factors: the aim of using laser (preventive vs. therapeutic), laser parameters, timing of the application, and clinical outcomes.

Preventive and therapeutic use

An important distinction among the studies is whether PBMT was used to prevent mucositis before it occurred or to treat established lesions. Out of the thirteen trials analyzed, 10 employed PBMT as a preventive measure.[3,17,19–21,23–26,28] They consistently reported benefits such as delayed onset of OM, reduced severity scores, and improved patient-reported outcomes, which included better pain control and QoL. Among these studies, Kuhn-Dall'Magro et al., Guimaraes et al., Marín-Conde et al., and Salvador et al. included preventive and therapeutic goals in their study protocols.[3,19,21,24] Notably, Kuhn-Dall'Magro's study demonstrated superior outcomes for patients who received treatment from the onset of radiotherapy, especially when using a dual-wavelength protocol, suggesting a synergistic effect when PBMT is applied proactively.[19] On the other hand, Barati et al., Legouté et al., and Oton-Leite et al. applied PBMT therapeutically after OM had developed.[18,22,27] Barati et al. noted a significant reduction in pain and severity within days of starting therapy, while Legouté et al. found no statistically significant improvement.[18,22] This divergence underscores the greater consistency and reliability of PBMT when used for prevention, although its therapeutic benefits may still be context-dependent.

Laser parameters

Laser specifications —particularly the wavelength, energy density, and frequency of application— varied significantly among trials and impacted outcomes. Most studies employed red or near-infrared wavelengths ranging from 630 to 980 nm, often using diode, aluminium gallium indium phosphide and helium-neon (He–Ne) sources. Preventive protocols, like those in Gautam et al. and Ahmed et al., used lower energy densities (2–4 J/cm^2) delivered daily during radiation or chemotherapy cycles.[25,26,28] Conversely, therapeutic studies such as Barati et al. applied higher doses (6 J/cm^2) in fewer sessions after OM manifestation.[18] Notably, Legouté et al. also used a 658 nm laser at 4 J/cm^2 but did not observe clinical benefit, likely due to variability in timing and perhaps suboptimal energy delivery.[22] The combination of 660 and 810 nm wavelengths evaluated by Kuhn-Dall'Magro et al. showed enhanced efficacy compared to either wavelength alone, suggesting that wavelength synergy may optimize tissue penetration and biological response.[19]

Timing and frequency of application

Effective PBMT protocols generally started at or before the initiation of chemoradiation and continued at least three to five times per week. For example, Khalil et al. applied a single preconditioning session with 635/980 nm light before chemotherapy and reported a statistically significant delay in OM onset.[17] In contrast, Legouté et al., who started PBMT only after OM was clinically evident, achieved no clear benefit.[22] Moreover, studies incorporating daily treatment, such as those by Gautam et al. and Ahmed et al., reported greater mucosal protection and more consistent symptom reduction consistency.[25,26,28] These findings support the concept that timing and regularity are critical determinants of PBMT success and that inconsistency in protocol adherence may explain negative findings in otherwise well-designed trials.

Target population

PBMT has shown utility across age groups. Ahmed et al. and Guimaraes et al. specifically studied pediatric populations receiving high-dose chemotherapy.[21,26] Both found that PBMT significantly reduced OM severity and improved functional outcomes (e.g., oral intake and reduced analgesic need). Guimaraes et al. also evaluated LED therapy alongside laser therapy and found comparable efficacy, suggesting that cost-effective light sources may offer similar clinical benefits in pediatric patients.[21] In older adults, Gautam et al. demonstrated that PBMT significantly reduced mucositis incidence and pain, enabling patients to maintain oral feeding during radiotherapy.[25] These findings affirm the broad applicability of PBMT across the age spectrum, though tailored parameters may be necessary.

Patient-reported outcomes and quality of life

Patient-reported outcomes are critical in evaluating supportive cancer care interventions. Several randomized trials have demonstrated that PBMT significantly improves patient-reported outcomes by reducing pain, improving oral intake, and limiting the need for analgesics. In the study by Khalil et al., patients who received a single preventive PBMT session before chemotherapy reported lower pain levels, reduced mucositis scores, and improved functional parameters like eating and speaking.[17] Similarly, Gautam et al. observed that patients undergoing daily PBMT sessions during radiotherapy experienced fewer treatment interruptions and improved overall QoL compared to control groups.[28] Barati et al. further confirmed that PBMT significantly reduced the need for narcotics and enhanced patient comfort.[18] In pediatric populations, studies such as those by Ahmed et al. and Guimaraes et al. showed decreased anxiety, better compliance, and improved daily functioning with PBMT, making it particularly suitable.[21,26] Overall, these findings emphasize that PBMT targets the biological mechanisms of OM and positively influences patients' daily experiences, reinforcing its value in comprehensive oncology care.

Mechanism of photobiomodulation therapy

The mechanism of action of PBMT involves a complex sequence of photophysical and photochemical processes that begin at the cellular level and include its local biological effects.[16] These effects are typically described in three interrelated stages (Fig. 1): primary, secondary, and tertiary responses.[29]

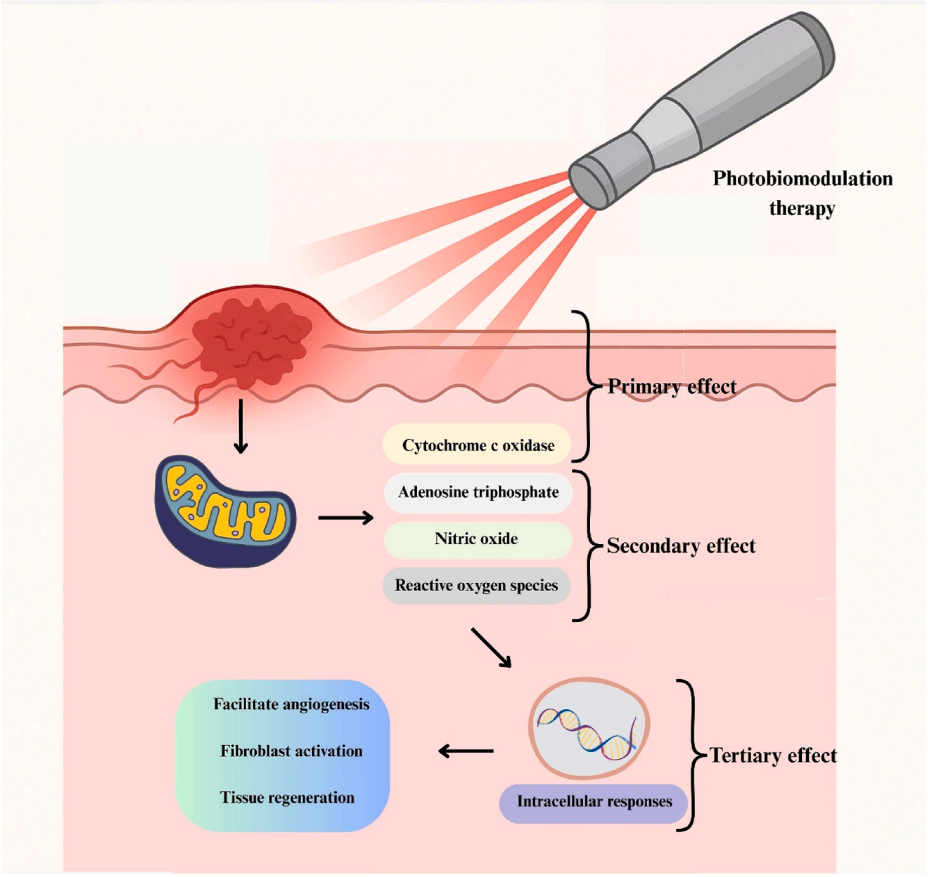

Figure 1 Mechanism of photobiomodulation therapy.

Primary effect: The primary effect of PBMT is attributed to the peak absorption of red (600—700 nm) and near-infrared (NIR; 760—900 nm) photonic energy by cytochrome *c* oxidase (CCO), a key mitochondrial photoreceptor. This interaction initiates a cascade of biological responses, beginning with enhanced mitochondrial activity. Consequently, the therapeutic window for PBMT is typically defined within the 600—900 nm range, applied at low power levels (usually 1—500 mW).[29,30]

Secondary effect: Following photon absorption, the secondary effects emerge, involving significant changes in ATP production, nitric oxide (NO) release, and ROS modulation. These biochemical changes are closely linked to the photonic interaction with CCO and are modulated by light dosage and the cell's redox state.[31,32] ATP levels generally increase, supporting enhanced cellular metabolism, while NO dissociation from CCO contributes to improved respiration and vasodilation. Simultaneously, ROS levels are regulated—either attenuated to reduce oxidative stress or maintained to sustain redox signaling.[30]

Tertiary effect: The tertiary effects extend these initial changes to influence various cellular signaling pathways. These downstream responses are cell type-specific and vary according to tissue context. PBMT exerts direct and indirect effects on the cell membrane and nucleus, modulating gene transcription and subsequently impacting cellular behaviors such as proliferation, migration, apoptosis, and the inflammatory response.[30,32] For instance, PBMT is known to downregulate pro-inflammatory mediators like TNF-α and IL-6 while simultaneously upregulating growth factors such as vascular endothelial growth factor. These effects collectively facilitate angiogenesis, fibroblast activation, and tissue regeneration.[33]

Clinical studies have substantiated these mechanistic layers. For example, Salvador et al. reported significant reductions in salivary IL-8 and nitrite levels following PBMT treatment.[24] Another study demonstrated that PBMT application increased antioxidant enzyme activity, notably superoxide dismutase.[20] These changes in biomarkers were associated with clinical improvements, providing robust evidence for the mechanistic plausibility of PBMT's role in modulating OM.

Safety

In this review of 13 randomized clinical trials, PBMT was consistently found to be a safe, painless, and well-tolerated treatment option. No documented adverse events, tissue damage, or complications were associated with laser exposure. Importantly, PBMT did not interfere with the effectiveness of chemotherapy or radiotherapy,

and no studies reported any evidence of tumor stimulation or negative impacts on oncological outcomes. This safety profile was observed across all age groups, including pediatric patients and elderly populations.[21,25,26] The non-invasive nature of PBMT, its localized application, and its lack of systemic pharmacological effects make it especially appealing for immunocompromised patients or those at risk of secondary infections.

Future and challenges

While the evidence supporting the use of PBMT for preventing and treating OM is encouraging, several challenges persist. A significant issue is the absence of standardized protocols for PBMT, including optimal wavelength, dosage, treatment duration, and frequency of application. Different studies have utilized various light sources and treatment regimens, complicating comparisons of results across the literature. Future research should establish the most effective PBMT parameters for preventing and treating OM. Additionally, further studies could investigate the potential synergistic effects of combining PBMT with other interventions, such as topical treatments or pharmacological agents, to enhance its therapeutic benefits.

Conclusion

In conclusion, PBMT is a promising, non-invasive method for preventing and treating OM in patients undergoing chemotherapy and radiotherapy, particularly those with HNC. Evidence from randomized clinical trials encompassing both adult and pediatric populations consistently supports the effectiveness of PBMT in reducing the severity of mucositis, accelerating healing, and improving patients' QoL. PBMT achieves these positive outcomes by modulating inflammatory cytokines, enhancing antioxidant defenses, and stimulating tissue repair. Furthermore, patient-reported outcomes confirm its role in improving daily functioning and reducing the need for pain management and treatment delays. However, a significant barrier to the widespread adoption of PBMT is the lack of standardized protocols, particularly concerning wavelength, energy density, treatment duration, and application frequency. Future studies should focus on establishing evidence-based guidelines and exploring the long-term effects of PBMT on cancer treatment outcomes. Given its safety, ease of use, and proven effectiveness, PBMT should be considered a standard supportive care measure for managing treatment-induced mucositis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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