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# Efficacy of LASER Photobiomodulation in the Management of Cancer Treatment Induced Oral Mucositis: A Systematic Review

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**ABSTRACT**

Oral mucositis is one of the most severe side effects of cancer treatment. Photobiomodulation therapy is a novel supportive therapy to prevent and manage cancer treatment induced oral mucositis. This review aimed at the assessment of efficacy of Laser photobiomodulation therapy in preventing and managing cancer treatment induced oral mucositis. Methods: An extensive electronic search for in vivo randomized controlled trials via Medline (via PubMed) and The Cochrane Controlled Clinical Trials Register databases from 2007 -2019 was done using MESH terms "stomatitis", "oral mucositis", "low-level light therapy", "light therapy" and "clinical trial". Articles were retrieved and exported to Mendeley Desktop 1.13.3 software. Results: In total, 9 articles were selected for review out of 164 articles retrieved from the search and remaining were

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excluded based on the eligibility criteria. All studies except one demonstrated better pain relief and healing with laser photobiomodulation therapy compared to control group (sham therapy) Conclusion: Photobiomodulation therapy can serve as an effective preventive and therapeutic modality to manage cancer treatment induced oral mucositis.

**Keywords:** Stomatitis; Oral mucositis; Low-level laser therapy; Radiotherapy; Chemotherapy

## Introduction

Oral mucositis is the most common, painful debilitating side effect of non-surgical oncotherapy. Around 30–40% of cancer patients treated with chemotherapy develop mucositis and this rises to almost 90% for head and neck cancer (HNC) patients treated with radio and chemotherapy (Villa & Sonis, 2016). The development and severity of mucositis depends on oncotherapy regimen, doses, number of cycles and patients' characteristics. Some of the known risk factors for mucositis are old age, female gender, high bodyweight, compromised drug clearance conditions and genetic susceptibility (Jones et al.,2006) (Sonis et al.,1978) (Pratesi et al.,2011). Oral mucositis starts within 7 days of onset of radiotherapy and after chemotherapy it starts within a day. The difficulty level of performing the daily chores is very high in people suffering from oral mucositis since it is associated with pain, burning sensation, and bleeding. Oral mucositis causes taste alterations, burning sensation, dysphagia, nutrition deprivation, secondary fungal, bacterial infections and altered speech. The symptoms contribute to compromised treatment leading to discontinuity or delay in taking chemo or radio cycles. Most importantly it causes decreased quality of life of cancer patients. Therefore, good supportive care is necessary to treat oral mucositis (Pratesi et al.,2011) (Hahn et al.,2010).

Management of oral mucositis has been largely palliative although targeted therapeutic interventions have been developed. The Mucositis Study Group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) has developed clinical practice guidelines for the management of mucositis. According to the guidelines, management of oral mucositis comprises of: nutritional support, pain control, oral decontamination, palliation of dry mouth, management of oral bleeding and therapeutic interventions. A range of therapeutic modalities for cancer treatment-induced oral mucositis includes:

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cryotherapy with ice cubes, growth factors like recombinant human keratinocyte growth factor-1,human keratinocyte growth factor-2 and human fibroblast growth factor-2; Antiinflammatory agents like Benzydamine hydrochloride and L-glutamine; Antioxidants like Amifostine and N-acetylcysteine; Immune regulators Dusquetide, SGX942 and natural agents like turmeric (Curcuma longa), essential oils of manuka (Leptospermum scoparium) and kanuka (Kunzeaericoides). However, there are no clear guidelines of managing cancer treatment induced side effects which are usually physically intolerable and mentally unacceptable. Oral care is often ignored over cancer therapy (Verdi,1993) (Rodríguez-Caballero et al.,2011) (Trotti et al.,2003) (Brown & Gupta,2020) (Alvariño-Martín, C., & Sarrión-Pérez, M. G,2014) (Zadik et al.,2019).

Laser photobiomodulation (PBM) is a novel therapy used for treating oncotherapy induced oral mucositis. In 2004, the expert panels of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) considered low level laser therapy, after reviewing literature published from 1966 to May 2002, as a possible option in the management of cancer treatment induced oral mucositis with a level II of evidence and a grade B of recommendation (Zadik et al.,2019). PBM which was previously known as Low Level Laser Therapy (LLLT) is the application of red and near infra-red light(600nm-1000nm) over injuries or lesions to improve wound and soft tissue healing, reduce inflammation and to give relief to both acute and chronic pain. Photobiomodulation devices typically deliver light at 10mW - 500mW power (0.01 -> 0.01 Watts). The power density typically ranges from 0.005W/Cm² -> 5 W/Cm². It is non-invasive, pain free and safe therapy with no associated adverse effects. Many systematic reviews and meta analysis studies which have summarised the efficacy of laser photobiomodulation have included studies done using different types of lasers predominantly focusing on treatment of mucositis rather than prevention of mucositis (Chung et al.,2012) (de Freitas & Hamblin 2016). Thus, this systematic review was planned To systematically evaluate both the prophylactic and therapeutic effects of laser photobiomodulation in patients who might develop or who have developed oral mucositis during chemotherapy or radiotherapy or combined chemo-radiation.

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## Literature Review

### Literature retrieval

An extensive electronic search was made on two data bases namely Medline (via PubMed) and The Cochrane Controlled Clinical Trials Register from 2007 -2019 using MESH terms and Boolean operators as shown in Table 1. Hand searching was performed in the relevant journals. Reference lists of the retrieved were also checked. No restrictions on the language or date of publication were applied during the search.

### Criteria for article selection:

Research question framed was ″What is the efficacy of laser photobiomodulation in the management of cancer therapy induced oral mucositis?”. Articles were retrieved based on PICOS criteria: (Table 2)

### Criteria for inclusion of studies

1. Low-level laser of red and infrared wavelength diode lasers used for the treatment of cancer therapy induced oral mucositis.
2. In -vivo randomised controlled trials
3. Outcome measures were pain relief, reduced inflammation and wound healing assessed through visual analogue scale and histological examination of oral mucositis lesions.

### Criteria for exclusion of studies

1. Review articles, letters to editor, editorials, observational studies, commentaries, in-vitro and animal studies.
2. Studies which used other than diodes lasers for photobiomodulation such as Light emitting diodes,$CO_2$ lasers, Nd: YAG lasers, etc. for treatment of oral mucositis

Each study was reviewed by four authors independently and any difference of opinion was resolved by reaching a consensus and if necessary, resolved by a fifth reviewer. The reviewing authors were not blinded to authors, institution or journals. All full-text papers that were retrieved were similarly screened. All the studies which were excluded were recorded with reasons for exclusion.

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**Data extraction and management**

Data and quality information was extracted and fed into Revmann 5.3 software (Lorenzetti & Ghali, 2013). The year of publication and country of origin were recorded. Inclusion/exclusion criteria were specified and a detailed description of interventions was given. All outcomes were reported in trials at different intervals.

**Assessment of risk of bias in included studies**

The studies were assessed for risk of bias by using the Cochrane risk of the bias assessment tool (Higgins et al.,2011). The domains assessed for each included study were: sequence generation, allocation concealment, blinding of outcome assessment, completeness of outcome data, risk of selective outcome reporting, risk of other potential sources of bias. A description of the risk of bias domains was tabulated for each included trial, along with a judgment of no risk (procedure followed) and unclear (not mentioned) risk of bias, using the Revman 5.3 review manager software.

**Results**

The search strategy yielded a total of 164 articles. (Figure 1) Post removal of duplicates, articles were retrieved, and their materials and methods were scanned and reviewed for PICOS criteria and eligibility criteria. This yielded a total of 9 articles which were systematically reviewed.

**Characteristics of the studies:** Studies included in systematic review were reported in India, Italy, France, Spain, Iran and Brazil. All the studies followed an in-vivo, randomized controlled design. All studies compared photobiomodulation with sham treatment except the study by Carvalho et al where the control group was also given PBM therapy with different dosage compared to the test group (Carvalho et al., 2011). The Laser parameters, mode of application, and duration of therapy used in the studies varied and are listed in Table 3. Majority of the studies identified and included in this review used visible red wavelengths within the 632.5–660 nmrange (Carvalho et al., 2011) (Gautam et al., 2012) (Gautam et al., 2015) (Kalati et al., 2015) (Legoute et al., 2019). In addition, other studies used wavelengths within the range of 780–970nm (Cruz et al.,

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2007) (Kuhn et al.,2009) (Amadori et al.,2016) (Conde et al.,2018). Majority of the studies used a small optical spot size of only 0.04 $cm^2$ with a probe in contact with or near-contact to the target tissues. The number of points of application for these studies varied from 15 to 80, with a declared fluence at each point of 1 to 83 $J/cm^2$, and an irradiance of 0.024 to 13.8 $W/cm^2$. Few studies were done among paediatric patients (Cruz et al., 2007) (Kuhn et al.,2009) (Amadori et al.,2016) and the rest were among adults. Outcome measures assessed across different studies were grading of oral mucositis, pain, use of analgesics, dysphagia, xerostomia, quality of life, breaks in radiotherapy and chemotherapy cycles and recurrence of mucositis. Majority of studies used WHO - NCI-CTC ( National Cancer Institute -common toxicity criteria) scale followed by Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) scale for grading of mucositis (Sroussiet al.,2017) (Soni S,2012) (Gussgaurd et al.,2014).

**Outcome of studies**: All studies except study by Cruz et al,2007 demonstrated beneficial effect of Laser photobiomodulation in decreasing the severity of oral mucositis (Kuhn et al., 2009) (Amadori et al.,2016) (Conde et al.,2018) (Carvalho et al., 2011) (Gautam et al.,2012) (Gautam et al., 2015) (Kalati et al.,2015) (Legoute et al.,2019). In few studies there was decrease in the intensity of pain associated with mucositis with photobiomodulation therapy (Kuhn et al.,2009) (Amadori et al.,2016) (Conde et al.,2018)(Carvalho et al.,2011) (Gautam et al.,2012) (Gautam et al., 2015) (Kalati et al.,2015) (Legoute et al.,2019). Few studies demonstrated decreased xerostomia, improved quality of life, decreased dysphagia, less use of morphine analgesic, lesser breaks in radio-chemo cycles and decreased recurrence of oral mucositis associated with photobiomodulation therapy (Gautam et al.,2012) (Gautam et al., 2015) (Amadori et al.,2016). Risk of bias was unclear in majority of the studies. (Figure 2)

**Table 1 -Search strategy of studies**

| **Database** | **Search strategy** | **Articles retrieved** |
|---|---|---|

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| | | |
|---|---|---|
| PubMed | "Stomatitis"[MeSH Terms] OR "stomatitis"[All Fields] OR ("oral"[All Fields] AND "mucositis"[All Fields]) OR "oral mucositis"[All Fields]) AND ("low-level light therapy"[MeSH Terms] OR ("low-level"[All Fields] AND "light"[All Fields] AND "therapy"[All Fields]) OR "low-level light therapy"[All Fields] OR ("low"[All Fields] AND "level"[All Fields] AND "laser"[All Fields] AND "therapy"[All Fields]) OR "low level laser therapy"[All Fields]) AND Clinical Trial[ptyp] | 53 |
| Cochrane | Oral mucositis and laser therapy, light therapy | 111 |

**Table 2-PICOS format (Population, Intervention, Control, Study design) to identify studies pertaining to research question search strategy of studies**

| | |
|---|---|
| Population | Patients suffering from cancer therapy induced oral mucositis |
| Intervention | Laser photobiomodulation for Cancer therapy induced oral mucositis |
| Control | Patients receiving placebo, local or systemic analgesics |
| Outcome | Analgesia, wound healing, decreased inflammation |
| Study design | Randomized controlled trials |

**Table 3-Characteristics of studies selected for review**

| **Author /Year/ Country** | Type of malignancy and treatment | Sample size (n) | Mean age of participants (years) | Control group | Test Group | Therapy Duration | Laser Diode parameters | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Wavelength | Energy Density | Power | Time |
| Cruz et al 2007 Brazil | Leukemia,lymphoma,solid tumors HSCT | Test (n) = 29 Control(n)= 31 | 8.7 ±4.3 | No therapy | Laser PBM | 5 consecutive days from initiation of chemotherapy | 780nm | 4 J/cm2 | 60mW | 66sec |

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|---|---|---|---|---|---|---|---|---|---|---|
| Kuhn et al 2009 Brazil | Leukemia,lymphoma,solid tumors CT or HSCT | Test (n) = 9 Control(n)= 12 | 8.1±3.1 | Sham therapy | Laser PBM | 5 consecutive days after development of chemotherapy induced oral mucositis. | 830nm | 4 J/cm2 | 100mW | 40sec |
| Carvalho et al 2011 Brazil | Oral /Oropharyngeal neoplasm RT+CT | Test (n) = 35 Control(n)= 35 | G1:56.2± 14.5 G2:58.1± 10.1 | Group 2: PBM with 660 nm/ /1.3 J/c/cm2/ | Group 1:Laser PBM with (660 nm/3.8 J/cm2 | Daily, five consecutive days per week, starting on the first day of radiotherapy (before the radiation sessions) | 660nm | 3.8J/cm2 (Group1) 1.3J/cm2 (Group 2) | 15mW 5mW | 252sec 260sec |
| Gautam et al 2012 India | HNC with oral or oropharyngeal involvement CRT | Test (n) = 115 Control(n)= 124 | 55.18 ± 11.70 | Sham Therapy | Laser PBM | 5 sessions/week for 45 days prior to radiotherapy at six anatomical sites in the oral cavity (buccal mucosa, lateral and ventral tongue, labial mucosa, floor of the mouth, and palate excluding cancer site) | 632.8nm | 3J/cm2 | 24mW | 125sec |
| Kalati et al 2015 Iran | HNC CT | Test (n) = 24 Control(n)= 24 | 44.5 ± 4.04 | Sham therapy | Laser PBM | One session prior to every chemotherapy session. Each session 10 spots in oral cavity were irradiated: two spots on the cheeks, two on the tongue, two on the floor of the mouth, one on the soft palate and one on the hard palate | 630nm | 5 J/cm2 | 30mW | 166 sec |
| Gautam et al 2015 India | Primary HNC RT | Test (n) = 22 Control(n)= 24 | 55.18 ± 11.70 | Sham therapy | Laser PBM | 5 fractions/week, total 33 fractions for 6.5 weeks prior to radiotherapy at six anatomical sites bilaterally i.e. 12 locations, total dose/session=36 J, | 632.8nm | 3 J/cm2 | 24mW | 125 sec |
| Amadori et al 2016 Italy | Hematologic malignancies,Solid tumors CT | Test (n) = 62 Control(n)= 61 | 9.8 ± 3.25 | Sham therapy | Laser PBM | Laser therapy started on day 1 of the diagnosis of OM and continued for another 3 consecutive days (4 days in total). Laser irradiated at the sites of OM (buccal mucosa, lip mucosa, tongue, floor of mouth and soft palate) | 830nm | 4.5 J/cm2 | 150mW | 30 sec |

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| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Conde et al 2018 Spain | Squamous cell carcinoma oral/oropharyngeal<br><br>CRT | Test (n) = 18 Control(n)=18 | 60.89±9.9 | Sham therapy | Laser PBM | Total 12 sessions of Laser therapy were carried out. At each session,post radiation therapy,laser beam was directed on the mucosa, perpendicular to the irradiated surface. The irradiations were performed intraorally, avoiding the area of the tumour. The laser was applied at a total of 72 identified points :12 points were on the buccal mucosa (right and left), eight on the mucosa of the upper and lower lip, 12 on the hard palate, four on the soft palate, 12 on the lingual surface of the tongue, 10 on the left and right lateral edges of the tongue, eight on the ventral surface of the tongue, four on the floor of the mouth, and one on each labial commissures. | 940nm | 4.5J/cm2 | 500mW | 9sec |
| Legoute et al 2019 France | Advanced HNC<br><br>CRT | Test (n) = 41 Control(n)= 41 | 58 (53-65) | Sham therapy | Laser PBM | All anatomic sites with moderate or severe OM (OMS scale grade ≥ 2) were treated daily after radiotherapy session,<br>1 session / day, 5 times / week from day of grade II OM occurrence to day of grade II OM resolution. Interval between treatments 1 or 2 days | 658nm | 4 J/cm2 | 100mW | 40sec |

## Table 4: Results of studies selected for review

| Author | Outcome assessed | Method of assessment | Results | Summary |
|---|---|---|---|---|
| **Cruz et al** | 1.Grade of oral mucositis | WHO - NCI-CTC ( National Cancer Institute - common toxicity criteria) | No significant difference was observed between groups concerning the grades of mucositis on day 8 (P = 0.234) or on day 15 (P = 0.208). | No evidence of benefit of Laser PBM |

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| | | | | |
|---|---|---|---|---|
| **Kuhn et al** | 1.Grade of oral mucositis | WHO – NCI-CTC Scale | Mean duration of oral mucositis post therapy was<br>5.8±2 days in laser group and 8.9±2.4 days in control group (p=0.004). | Photobiomodulation with LLLT reduced the severity of mucositis in patients treated with chemotherapy |
| **Carvalho et al** | 1.Grade of oral mucositis<br>2.Pain | 1.WHO- NCI-CTC Scale<br>2.visual analog scale (VAS) | Post therapy, patients in Group 1 presented mucositis(grade 2) at mean time of 13.5 days (range 6–26 days) while in Group 2 at mean time of 9.8 days (range 4–14 days)( $p = 0.005$). Group 2 patients presented a higher mucositis grade than Group 1 at weeks 2 ($p = 0.019$), 3 ($p = 0.005$) and 4 ($p = 0.003$) for WHO scale and weeks 2 ($p = 0.009$) and 4 ($p = 0.013$) for NCI scale. The patients in Group 1 reported lower pain levels ($p = 0.004$) | Photobiomodulation with LLLT was effective in control of the intensity of mucositis and in the pain related to the mucositis in patients treated with radio- chemotherapy. |
| **Gautam et al** | 1.Grade of oral mucositis<br>2.Pain<br>3.Dysphagia | 1.Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) scale<br>2.Visual analogue scale<br>3.Functional Impairment Scale | There was significant reduction in incidence of severe oral mucositis (F=16.64, df=8876, p<0.0001) and its associated pain (F=25.06, df=8876, p<0.0001), dysphagia (F=20.17, df=8876, p<0.0001) and opioid analgesics use (p<0.0001) in laser than placebo group patients. | Photobiomodulationdecreased the incidence of chemoradiotherapy induced severe oral mucositis and its associated pain, dysphagia and opioid analgesics use |
| **Kalati et al** | 1.Grade of oral mucositis<br>2.Pain<br>3.Xerostomia | 1.WHO- NCI-CTC Scale<br>2.visual analog scale (VAS)<br>3.LENT SOMA scale | Photobiomodulation significantly reduced, mucositis intensity (p<0.001), Xerostomia(p<0.001) and pain (p<0.001) at 2 weeks post chemotherapy till 14 weeks compared to control group. | Photobiomodulation was able to decrease the effect of chemotherapy on oral mucositis, xerostomia and pain. |
| **Gautam et al** | 1.Grade of oral mucositis<br>2.Pain | 1.EORTC Scale<br>2.VAS scale | Significant reduction in the incidence and duration of severe OM (p=0.016) and severe pain (p=0.023) and weight loss (p=0.004) was observed in laser than placebo group. No difference was found for enteral feeding use (p=0.667) between two groups. | Photobiomodulationdecreased the severity of oral mucositis and oral pain in elderly Head and neck cancer patients receiving radiotherapy. Lesser weight loss, morphine analgesic use and radiation break was observed in laser group. |

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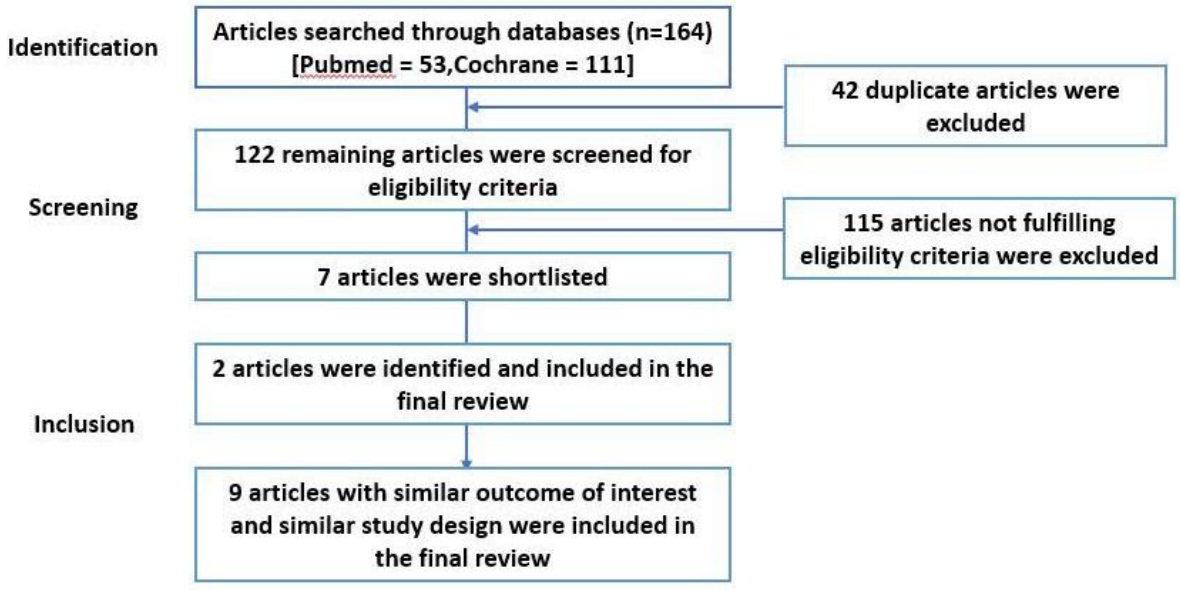
| **Amadori et al** | Grade of oral mucositis | 1.WHO- NCI-CTC Scale | The difference in the decline of OM grading between the two groups was not statistically significant ($p = 0.07$). A statistically significant difference in pain reduction between two groups both at T1 and at T2 ($p < 0.005$) was observed. | Photobiomodulation demonstrated efficacy in reducing pain due to chemotherapy-induced oral mucositis in children, while no significant benefit was noted in reducing OM grade. |
| **Conde et al** | Grade of oral mucositis | RTOG/EORTC Scale | There was significant($p<0.05$) increase in prevalence of normal mucosa (grade 0 mucositis) in laser group (72.7%) compared to control group (20%) | Photobiomodulation reduces the incidence and severity of mucositis in patients treated with radio- chemotherapy. |
| **Legoute et al** | 1.Grade of oral mucositis<br>2.Pain<br>3.Quality of life<br>4.Recurrence of mucositis | 1.WHO- NCI-CTC Scale<br>2.visual analog scale (VAS)<br>3."EORTC QLQ-H&N35 questionnaire<br>4. Recurrence-Free Survival (RFS), and Overall survival (OS) | Acute oral mucositis (grade ≥ 3) was observed in 54.8 % of the active laser group versus 43.9% in the control group (modified intend to treat, $p =0.32$). Median time before occurrence of OM ≥ grade 3 in half of the patients was 8 weeks in active laser group vs. 9 weeks in control group. .95% of patients exhibited a very good tolerance of laser photobiomodulation | photobiomodulation reduced the incidence and severity of mucositis in patients treated with radiochemotherapy. It was well tolerated with a good safety profile. |

**Figure 1:Flow chart of study design**



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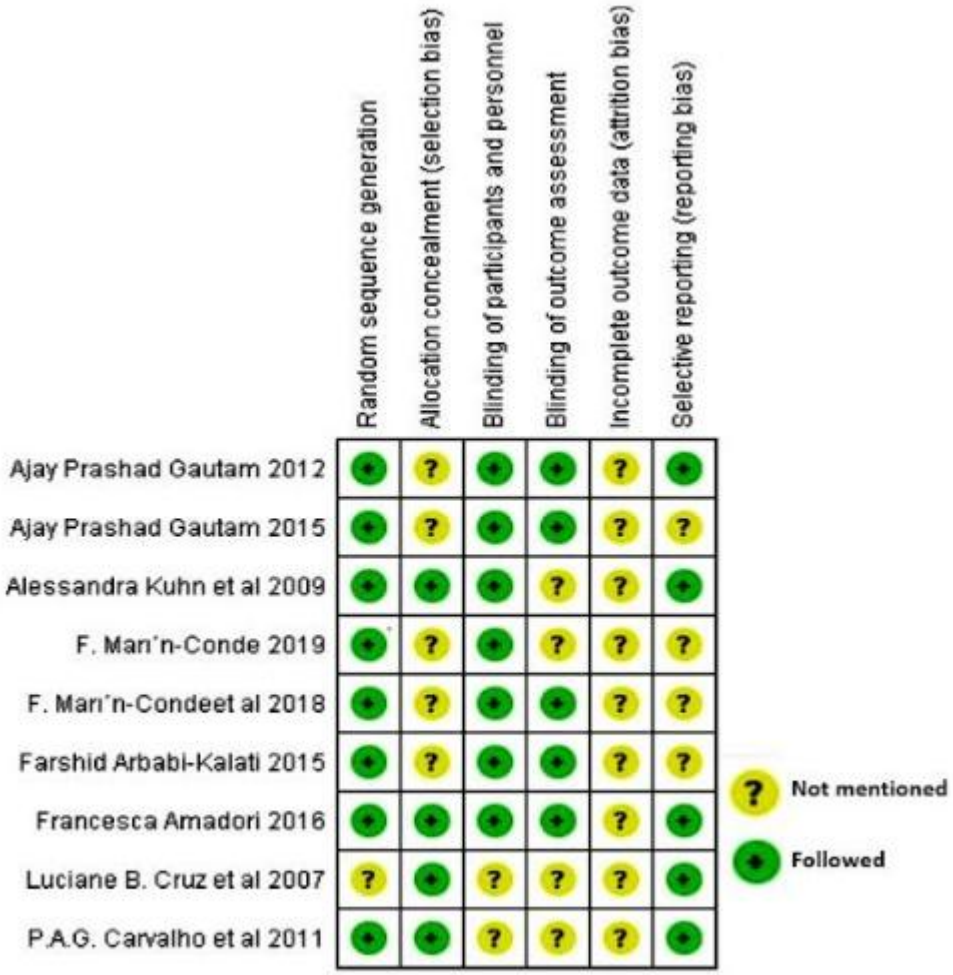


**Figure 2.Risk of Bias assessment**

## Discussions

Oncologic therapy has major side effects which include oral mucositis. Literature suggests there are many treatment modalities to control oral mucositis but so far no effective therapy has been found. Standard guidelines are needed to manage oral mucositis. This systematic review analysed the efficacy of laser photobiomodulation as a possible supportive therapy to prevent and treat oral mucositis. Majority of the studies in this systematic review demonstrated decrease in the severity of oral mucositis and pain associated with head and neck cancer treated with chemotherapy, radiotherapy, and patients undergoing hematopoietic stem-cell transplantation using photobiomodulation therapy (Kuhn et al.,2009) (Amadori et al.,2016) (Conde et al.,2018) (Carvalho

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et al.,2011) (Gautam et al.,2012) (Gautam et al., 2015) (Kalati et al.,2015) (Legoute et al.,2019). The mechanism of photobiomodulation starts with the transfer of photonic energy to a cellular target, which subsequently affects intra-cellular organelle metabolism. This takes place in the mitochondria, which respond to the absorption of red to near-infra-red (IR) wavelengths of light by an increase in activity of the electron transport respiratory chain thereby resulting in an increase in the production of ATP and nitric oxide along with some changes beneficial to cellular metabolism like selective uptake of pro-inflammatory cytokines and an inhibition of COX-2 activity, perfusion of tissues with oxygenated blood, increased production of pro-collagen and growth factors, increase in cellular motility and rate of division, reduction in nociception and selective inhibitory effects on axonal transmission. Photobiomodulation can influence cytoplasmic reactive oxygen species (ROS) levels and enhance immune response at the target site. In this process, endorphins and enkephalins are released which block membrane depolarization that prevents nerve impulse transmission. (Heiskanen & Hamblin, 2018).

Few studies in the review demonstrated improved analgesia with PBM (Kuhn et al., 2009) (Amadori et al., 2016) (Conde et al.,2018) (Carvalho et al.,2011) (Gautam et al.,2012) (Gautam et al., 2015) (Kalati et al.,2015) (Legoute et al.,2019). The light energy of wavelength range 600-1000nm gets absorbed by the tissues which modulates the descending pain pathway with the help of natural endogenous analgesics which causes partial or selective pain inhibition at the synaptic pathway between neurons of the descending pathway and neurons of the ascending pathway. The mechanism also leads to blocking of the ascending pain pathway and stimulation of the descending pain pathway which increases the release of natural endogenous analgesics like serotonin, beta-endorphin which reduces pain or even block nociception. Many studies suggested that the light which is having deeper tissue penetration provides a better analgesic effect. (Sousa et al.,2018) (de Freitas & Hamblin,2016).Majority of studies showed improved and faster healing of mucositis lesions. The cellular mechanism of action for wound healing occurs in the second phase where the light gets absorbed by the tissues, and activates the coagulation pathway and stimulates platelet aggregation which leads to proliferation and degranulation of mast cells. This causes stimulation of cytokine and growth factors which initiates proliferation of keratinocytes and fibroblast leading to neovascularization and angiogenesis leading to reepithelization, repair, and regeneration. (Moscaet al.,2019) (Sousa et al.,2018). The beneficial effect of photobiomodu-

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lation was more pronounced among adult population compared to pediatric population. In comparison to adults, the development of mucositis is quite severe in young patients. The incidence and severity of mucositis are higher in pediatric patients as there is rapid cell division and proliferation rates compared to adults. 80% of the pediatric patients undergoing chemotherapy experience oral mucositis although the incidence differs depending upon the type of malignancy and treatment regimen. (Miller et al.,2012) (Naidu et al.,2004) Vokurka et al suggested that, gender could be an independent risk factor and predictor for oral mucositis in high-dose chemotherapy settings. Females appear to be more susceptible to mucositis post-chemotherapy compared to males (Vokurka et al.,2006).

Recent MASCC (Multinational Association of Supportive Care in Cancer) protocol suggested that prophylaxis can help in preventing the severity and occurrence of oral mucositis in patients undergoing cancer therapy. The treatment of cells and tissues before chemo or radiotherapy is helpful as it increases the cell's capacity to withstand the damage or stress caused by external chemo agents or radiation (Chemo protective - Radio Protective). The suggested prophylaxis dosage of PBM ranges from 2-8J/cm2, as it is the dose-related response which is biphasic where lower energy is associated with stimulation and higher energy is related to pain inhibition. The cells become more resilient to the chemotherapeutic drugs or the radiation used. At the cellular level when cells are pretreated with the light there is an optimal enhancement of the electron transport chain which accelerates the aerobic metabolism. The aerobic metabolism enhances the optimal production of ATP and Nitric oxide which makes the cells more resilient to stress caused by external chemotherapeutic drugs or radiation. Also, the survival of the cell is enhanced by activation of the cellular protective mechanisms induced by light. However, some downstream effects can also be seen if there is increased production of reactive oxygen species which can reduce the production of ATP by causing decoupling of the electron transport chain (Cronshaw et al.,2020) (Zadik et al.,2019).

According to the NICE guidelines, intraoral photobiomodulation before radiation or chemotherapy is suggested as Standard of care in HSCT (hematopoietic stem cell transplantation) patients who need high dose chemotherapy with or without full body irradiation. As per the supportive evidence, the beneficial wavelength ranges between 630 to 660 nm (red part of the electromagnetic spectrum). Two protocols are suggested - one using 632.8nm wavelength of light on

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18 sites at a distance less than a centimetre, daily from the start day of HSCT till its' cessation. The second protocol suggests the use of 650nm wavelength of light on 54-70 sites in contact mode, daily from the start day of HSCT till 7-13days post-HSCT. Extra-oral PBM for the management of oral mucositis is also reported to have a beneficial effect (Zadik et al.,2019)

Studies by Zecha JA et al (2016), Bensadoun RJ et al (2018) and Zadik Y et al (2019) have suggested dosimetric clinical practice and safety considerations for photobiomodulation therapy in preventing and managing cancer treatment induced oral mucositis.

## Conclusion

Photobiomodulation seems to be a novel, safe, well tolerated therapy for management of cancer treatment induced oral mucositis. There was heterogeneity in the parameters presented by various studies included in this review. More systematic reviews involving trials based on standard protocols of photobiomodulation may clarify its promising potential in the management of cancer treatment induced oral mucositis.

## Limitations and Recommendations

Although majority of studies in the review showed beneficial effects of PBM for management of oral mucositis, the evidence should be considered with the heterogeneity of the studies. As oral mucositis development and severity depends upon various factors like the type of malignancy, chemo drug used, dose, type of radiation, chemo –radio cycles, frequency, duration, age, sex, etc. evidence related to studies standardised for confounding factors and effect modifiers need to be considered. Multi centric trials, with longer follow-up period should be designed. This may enable in formulating a standard dosimetry protocol and clinical practice guidelines for photobiomodulation therapy.

## References

1. Alvariño-Martín, C., &Sarrión-Pérez, M. G. (2014). Prevention and treatment of oral mucositis in patients receiving chemotherapy. Journal of clinical and experimental dentistry, 6(1), e74–e80.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 5259 - 5278
Received 25 April 2021; Accepted 08 May 2021.

2. Amadori, F., Bardellini, E., Conti, G., Pedrini, N., Schumacher, R. F., & Majorana, A. (2016). Low-level laser therapy for treatment of chemotherapy-induced oral mucositis in childhood: a randomized double-blind controlled study. Lasers in medical science, 31(6), 1231–1236.
3. Arbabi-Kalati, F., Arbabi-Kalati, F., &Moridi, T. (2013). Evaluation of the effect of low level laser on prevention of chemotherapy-induced mucositis. Acta medica Iranica, 51(3), 157–162
4. Bensadoun R. J. (2018). Photobiomodulation or low-level laser therapy in the management of cancer therapy-induced mucositis, dermatitis and lymphedema. Current opinion in oncology, 30(4), 226–232.
5. Brown, T. J., & Gupta, A. (2020). Management of Cancer Therapy-Associated Oral Mucositis. JCO oncology practice, 16(3), 103–109.
6. Carvalho, P. A., Jaguar, G. C., Pellizzon, A. C., Prado, J. D., Lopes, R. N., & Alves, F. A. (2011). Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. Oral oncology, 47(12), 1176–1181.
7. Chung, H., Dai, T., Sharma, S. K., Huang, Y. Y., Carroll, J. D., & Hamblin, M. R. (2012). The nuts and bolts of low-level laser (light) therapy. Annals of biomedical engineering, 40(2), 516–533.
8. Cronshaw, M., Parker, S., Anagnostaki, E., Mylona, V., Lynch, E., &Grootveld, M. (2020). Photobiomodulation and Oral Mucositis: A Systematic Review. Dentistry journal, 8(3), 87.
9. Cruz, L. B., Ribeiro, A. S., Rech, A., Rosa, L. G., Castro, C. G., Jr, &Brunetto, A. L. (2007). Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy. Pediatric blood & cancer, 48(4), 435–440.
10. de Freitas, L. F., & Hamblin, M. R. (2016). Proposed Mechanisms of Photobiomodulation orLow-Level Light Therapy. IEEE journal of selected topics in quantum electronics : publication of the IEEE Lasers and Electro-optics Society, 22(3), 7000417.
11. de Sousa, M., Kawakubo, M., Ferraresi, C., Kaippert, B., Yoshimura, E. M., & Hamblin, M. R. (2018). Pain management using photobiomodulation: Mechanisms, location, and repeatability quantified by pain threshold and neural biomarkers in mice. Journal of biophotonics, 11(7), e201700370.
12. Gautam, A. P., Fernandes, D. J., Vidyasagar, M. S., Maiya, A. G., &Vadhiraja, B. M. (2012).

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 5259 - 5278
Received 25 April 2021; Accepted 08 May 2021.

Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients - a triple blinded randomized controlled trial. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology, 104(3), 349–354.

13. Gautam, A. P., Fernandes, D. J., Vidyasagar, M. S., Maiya, A. G., &Guddattu, V. (2015). Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial. Journal of photochemistry and photobiology. B, Biology, 144, 51–56.
14. Gussgard, A. M., Hope, A. J., Jokstad, A., Tenenbaum, H., & Wood, R. (2014). Assessment of cancer therapy-induced oral mucositis using a patient-reported oral mucositis experience questionnaire. PloS one, 9(3), e91733.
15. Hahn, T., Zhelnova, E., Sucheston, L., Demidova, I., Savchenko, V., Battiwalla, M., Smiley, S. L., Ambrosone, C. B., & McCarthy, P. L., Jr (2010). A deletion polymorphism in glutathione-S-transferase mu (GSTM1) and/or theta (GSTT1) is associated with an increased risk of toxicity after autologous blood and marrow transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, 16(6), 801–808.
16. Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., Savovic, J., Schulz, K. F., Weeks, L., Sterne, J. A., Cochrane Bias Methods Group, & Cochrane Statistical Methods Group (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed.), 343, d5928.
17. Heiskanen, V., & Hamblin, M. R. (2018). Photobiomodulation: lasers vs. light emitting diodes?. Photochemical & photobiological sciences : Official journal of the European Photochemistry Association and the European Society for Photobiology, 17(8), 1003–1017.
18. Jones, J. A., Avritscher, E. B., Cooksley, C. D., Michelet, M., Bekele, B. N., &Elting, L. S. (2006). Epidemiology of treatment-associated mucosal injury after treatment with newer regimens for lymphoma, breast, lung, or colorectal cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 14(6), 505–515.
19. Kuhn, A., Porto, F. A., Miraglia, P., &Brunetto, A. L. (2009). Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in child-

ren. Journal of pediatric hematology/oncology, 31(1), 33–37.

20. Legouté, F., Bensadoun, R. J., Seegers, V., Pointreau, Y., Caron, D., Lang, P., Prévost, A., Martin, L., Schick, U., Morvant, B., Capitain, O., Calais, G., &Jadaud, E. (2019). Low-level laser therapy in treatment of chemoradiotherapy-induced mucositis in head and neck cancer: results of a randomised, triple blind, multicentre phase III trial. Radiation oncology (London, England), 14(1), 83.

21. Lorenzetti, D. L., &Ghali, W. A. (2013). Reference management software for systematic reviews and meta-analyses: an exploration of usage and usability. BMC medical research methodology, 13, 141.

22. Mosca, Rodrigo Crespo ., Ong, Adrian A.,Albasha, Omar., Bass, Kathryn.,Arany, Praveen (2019).Photobiomodulation Therapy for Wound Care: A Potent, Noninvasive, Photoceutical Approach, Advances in Skin & Wound Care,32(4),157-167.

23. Marín-Conde, F., Castellanos-Cosano, L., Pachón-Ibañez, J., Serrera-Figallo, M. A., Gutiérrez-Pérez, J. L., & Torres-Lagares, D. (2019). Photobiomodulation with low-level laser therapy reduces oral mucositis caused by head and neck radio-chemotherapy: prospective randomized controlled trial. International journal of oral and maxillofacial surgery, 48(7), 917–923.

24. Miller, M. M., Donald, D. V., & Hagemann, T. M. (2012). Prevention and treatment of oral mucositis in children with cancer. The journal of pediatric pharmacology and therapeutics: JPPT : the official journal of PPAG, 17(4), 340–350.

25. Naidu, M. U., Ramana, G. V., Rani, P. U., Mohan, I. K., Suman, A., & Roy, P. (2004). Chemotherapy-induced and/or radiation therapy-induced oral mucositis--complicating the treatment of cancer. Neoplasia (New York, N.Y.), 6(5), 423–431.

26. Pratesi, N., Mangoni, M., Mancini, I., Paiar, F., Simi, L., Livi, L., Cassani, S., Buglione, M., Grisanti, S., Almici, C., Polli, C., Saieva, C., Magrini, S. M., Biti, G., Pazzagli, M., & Orlando, C. (2011). Association between single nucleotide polymorphisms in the XRCC1 and RAD51 genes and clinical radiosensitivity in head and neck cancer. Radiotherapy and oncol-

ogy : journal of the European Society for Therapeutic Radiology and Oncology, 99(3), 356–361.

27. Rodríguez-Caballero, A., Torres-Lagares, D., Robles-García, M., Pachón-Ibáñez, J., González-Padilla, D., & Gutiérrez-Pérez, J. L. (2012). Cancer treatment-induced oral mucositis: a critical review. International journal of oral and maxillofacial surgery, 41(2), 225–238.
28. Sonis S.T. A Comparison and Assessment of Scoring Scales for Mucositis. In: Handbook Oral Mucositis. Chap 6,pp 39-46,2012. Springer Healthcare, Tarporley.
29. Sonis, S. T., Sonis, A. L., & Lieberman, A. (1978). Oral complications in patients receiving treatment for malignancies other than of the head and neck. Journal of the American Dental Association (1939), 97(3), 468–472.
30. Sroussi, H. Y., Epstein, J. B., Bensadoun, R. J., Saunders, D. P., Lalla, R. V., Migliorati, C. A., Heaivilin, N., &Zumsteg, Z. S. (2017). Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer medicine, 6(12), 2918–2931.
31. Trotti, A., Bellm, L. A., Epstein, J. B., Frame, D., Fuchs, H. J., Gwede, C. K., Komaroff, E., Nalysnyk, L., &Zilberberg, M. D. (2003). Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology, 66(3), 253–262.
32. Verdi C. J. (1993). Cancer therapy and oral mucositis. An appraisal of drug prophylaxis. Drug safety, 9(3), 185–195.
33. Villa, A., & Sonis, S. T. (2016). Pharmacotherapy for the management of cancer regimen-related oral mucositis. Expert opinion on pharmacotherapy, 17(13), 1801–1807.
34. Vinesh E., Jeyapriya S M., Kumar M S., Arunachlam M. (2017).Photobiomodulation and oral wound healing.Indian J Multidiscip,7(2),129-34.
35. Vokurka, S., Bystrická, E., Koza, V., Scudlová, J., Pavlicová, V., Valentová, D., Visokaiová,

M., & Misaniová, L. (2006). Higher incidence of chemotherapy induced oral mucositis in females: a supplement of multivariate analysis to a randomized multicentre study. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer, 14(9), 974–976.

36. Zecha, J. A., Raber-Durlacher, J. E., Nair, R. G., Epstein, J. B., Sonis, S. T., Elad, S., Hamblin, M. R., Barasch, A., Migliorati, C. A., Milstein, D. M., Genot, M. T., Lansaat, L., van der Brink, R., Arnabat-Dominguez, J., van der Molen, L., Jacobi, I., van Diessen, J., de Lange, J., Smeele, L. E., Schubert, M. M., … Bensadoun, R. J. (2016). Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 24(6), 2781–2792.

37. Zadik, Y., Arany, P. R., Fregnani, E. R., Bossi, P., Antunes, H. S., Bensadoun, R. J., Gueiros, L. A., Majorana, A., Nair, R. G., Ranna, V., Tissing, W., Vaddi, A., Lubart, R., Migliorati, C. A., Lalla, R. V., Cheng, K., Elad, S., & Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) (2019). Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 27(10), 3969–3983.

**Abbreviations**: PBMT- Photobiomodulation therapy, LLLT – Low-Level Light Therapy, HSCT- Hematopoietic Stem Cell Transplant, HNC- Head & Neck Cancer, RCT- Randomized Controlled Trials, OM- Oral Mucositis, CRT- Chemo Radiotherapy, RT-Radiotherapy, CT-Chemotherapy, RTOG- Radiation Therapy Oncology Group, EORTC -the European Organization for Research and Treatment of Cancer NCI-CTC National Cancer Institute -common toxicity criteria, MASCC -Multinational Association of Supportive Care in Cancer ,ATP Adenosine Tri-Phosphate, ISOO International Society for Oral Oncology, VAS Visual Analog Scale and ROS Reactive Oxygen Species.