



# Effectiveness of methylene blue photosensitizers compared to that of corticosteroids in the management of oral lichen planus: a systematic review and meta-analysis

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This study aimed to systematically review the effectiveness of methylene blue (MB) photosensitizers in the management of symptomatic oral lichen planus (OLP). Electronic online databases and manual searches were performed for randomized controlled trials (RCTs) published in English between January 2010 and February 2022. RCTs comparing photodynamic therapy (PDT) and corticosteroid therapy at baseline and follow-up period were identified. The Cochrane risk of bias tool was used to assess the quality of the included studies. A meta-analysis was performed regarding visual analog scale (VAS) scores, Thongprasom sign scores, lesion size, response to treatment, and exacerbation of lesions after therapy. The clinical severity was analyzed qualitatively. Five RCTs consisting of 180 samples fulfilled the inclusion and exclusion criteria. All parameters of VAS score, Thongprasom sign score, lesion size, and response to treatment were statistically non-significant. Our results indicate that both MB-PDT and corticosteroid therapy are effective for the management of OLP. Moreover, MB-PDT is an effective alternative treatment option for OLP when corticosteroids are contraindicated. However, conclusive evidence cannot be ascertained owing to the heterogeneity among the studies.

**Keywords:** Corticosteroid; Oral Lichen Planus; Photodynamic Therapy.

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## INTRODUCTION

Oral lichen planus (OLP) is a chronic immune-mediated, inflammatory, and psychosomatic disease involving the oral mucosa in a standard bilateral pattern that is characterized by discomfort and burning sensation. OLP is a relatively common disease affecting 0.5%–2.2% of the general population [1-8]. Although the precise etiopathogenesis of OLP is unclear, current research indicates that an inflammatory cell-mediated immune

response to an unknown stimulus can be the probable cause [4,7,9].

OLP can be categorized into three clinical forms—reticular, erosive, and atrophic. Reticular lesions are the most common, are usually asymptomatic, and do not require surgery. However, patients with erosive–atrophic OLP often seek treatment due to pain and irritation. Erosive–atrophic patterns appear as diffuse, erythematous spots surrounded by fine white lines (Wickham striae), with certain lesions progressing to malignancy [2,9-11], although the possibility of malignant transformation is

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low, at only 1.4% [2,4,8].

OLP can be treated with various treatments including local and systemic corticosteroids, laser therapy, and surgery [12]. However, long-term application of corticosteroids has been linked to candidiasis, mucosal atrophy, adrenal insufficiency, stomach problems, hypertension, and diabetes [13]. Photodynamic therapy (PDT) has the potential to overcome many of the currently unmet clinical effects. Although still emerging, PDT is a clinically successful therapeutic modality used as an alternative treatment strategy for OLP [14].

PDT causes cytotoxic effects by forming biochemical interactions and producing singlet oxygen and free radicals, which trigger cellular, vascular, and immunological responses. The fundamental effects of PDT include cellular degradation, membrane lysis, and protein inactivation [15]. The application of PDT in the treatment of different forms of oral diseases such as tumors, leukoplakia, erythroplakia, and mucosal hypertrophy has been steadily increasing due to its numerous advantages, such as selective toxicity against inflamed or cancerous tissues, low risk of complications, low invasiveness, and unusual side effects. Its efficacy can range from total regression to no response [6,7,13,14,16].

Currently, there is no consensus on the efficacy of PDT for the treatment of OLP [1,5,7,8,10-12,13-15,17]. PDT has been shown to play role in the symptomatic treatment of OLP [9]; however, a systematic review found no conclusive evidence to support the use of PDT for the treatment of OLP [18]. The type of photosensitizer (PS) used is a factor that can affect the effectiveness of PDT. Most previous reviews have only evaluated the efficacy of PDT in the treatment of OLP; however, none have clarified the type of PS used or the impact of confounding factors, such as the location of the lesion, type of PS used, wavelength used, or duration of irradiation, on therapeutic responses. Additionally, the efficacy of methylene blue (MB) for the treatment of OLP is unclear. Therefore, this systematic review aimed to determine the efficacy of MB-PSs in the treatment of OLP to develop a deeper understanding of treatment protocols for future

trials.

## METHODS

**Protocol development:** This systematic review was written and completed according to the PROSPERO Declaration on Preferred Reporting Products for Systematic Reviews and Meta-Analyses (PRISMA; registration number: CRD42021231518) 2020 guidelines. The focus of this study was to evaluate the effectiveness of MB-PSs compared to that of local or topical corticosteroid/placebo therapy in the management of OLP.

**Eligibility criteria:** Randomized controlled trials (RCTs) published in English between January 1, 2010 to February 17, 2022 were included in the study. Case reviews, case series, animal experiments, research articles, letters to the editor, abstracts, studies reporting unpublished data, non-RCTs, and controlled or comparative clinical trials were excluded.

**Participants/population:** Adult patients ( $\geq 18$  years) clinically and/or histologically diagnosed with symptomatic OLP according to the World Health Organization criteria.

**Intervention(s)/exposure(s):** Hospital inpatients and outpatients diagnosed with OLP lesions treated with MB-PS and irradiated with lasers, LED, or light.

**Comparator(s)/control:** Hospital inpatients and outpatients diagnosed with OLP lesions treated with topical ointments, intralesional injections/mouth washes, or rinsing corticosteroids.

**Main outcome(s):** Changes in visual analog scale (VAS) score for pain, Thongprasom sign scores, clinical severity, lesion size, response/efficacy to treatment from baseline to last available follow-up, and exacerbation of lesions after therapy.

**Search strategy:** From January 1, 2010 to February 17, 2022, researchers (MW and PR) searched the PubMed/MEDLINE, PMC, Cochrane, clinical trial registry, Google Scholar, Science Direct, and Directory

of Open Access Journals (DOAJ) databases for relevant RCTs and manually searched the references of included studies.

The search terms were adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials, where available. The following mesh terms and keywords were used for the electronic database search:

- PubMed/Medline: ((“photochemotherapy” [MeSH Terms] OR “photochemotherapy” [All Fields] OR (“photodynamic” [All Fields] AND “therapy” [All Fields]) OR “photodynamic therapy” [All Fields] OR (“photochemotherapy” [MeSH Terms] OR “photochemotherapy” [All Fields] OR “photochemotherapies” [All Fields])) AND (“lichen planus, oral” [MeSH Terms] OR (“lichen” [All Fields] AND “planus” [All Fields] AND “oral” [All Fields]) OR “oral lichen planus” [All Fields] OR (“oral” [All Fields] AND “lichen” [All Fields] AND “planus” [All Fields]))) AND (2010/1/1:2022/2/17[pdat]).
- PMC: (((photodynamic therapy) OR photochemotherapy)) AND oral lichen planus filters: Publication date from 01/01/2010 to 02/17/2022.
- Cochrane Library: ((Photodynamic therapy OR photochemotherapy (AND oral lichen planus)).
- ClinicalTrials.gov: Oral lichen Planus AND Photodynamic therapy
- Science Direct: Oral lichen Planus, Photodynamic therapy
- Google Scholar Advanced Search: all in title: “photodynamic therapy,” “Oral lichen planus” Filter uses 2010 to 2021 [with all of the words: “photodynamic therapy” with the exact phrase: “Oral lichen planus”]: Return articles dated between 2010 and 2021.
- DOAJ (all fields): photodynamic therapy and oral lichen planus  
[https://doaj.org/search/articles?ref=homepage-box&source=%7B%22query%22%3A%7B%22query\\_string%22%3A%7B%22query%22%3A%22photodynamic%20therapy%20and%20oral%20lichen%20planus](https://doaj.org/search/articles?ref=homepage-box&source=%7B%22query%22%3A%7B%22query_string%22%3A%7B%22query%22%3A%22photodynamic%20therapy%20and%20oral%20lichen%20planus)

%22%2C%22default\_operator%22%3A%22AND%22%7D%7D%2C%22track\_total\_hits%22%3Atrue%7D

**Screening process:** Two independent reviewers (MW and PR) conducted the search and screening processes. After the removal of duplicates, the titles and abstracts and of all extracted papers were initially screened, and unrelated studies were excluded. For possible data retrieval, the full text of the qualifying studies was collected and carefully reviewed according to the eligibility criteria (inclusion/exclusion). The authors of the included studies were contacted by email to confirm any concerns or missing details.

**Data extraction and synthesis:** Relevant data from the included publications were collected from the data extraction files. Prior to scoring, all reviewers tested the rating forms. The reviewers first determined the eligibility of each study for inclusion in the systematic review based on the reported parameters. The following information was collected: author details, year of publication, study population, type of OLP, description of therapy, outcome measurements, results, adverse effects, and study conclusions. Data from the included studies were summarized during the follow-up period.

Both qualitative and quantitative syntheses were considered when the data were combined. Meta-analysis was performed to evaluate the significant differences in the outcomes of PDT and corticosteroid therapy. The mean differences in (MDs) VAS scores, Thongprasom sign scores, lesion size, risk ratio of response to treatment, and any exacerbation of lesions after both therapies were calculated. A fixed effects model, in which the heterogeneity was low ( $I^2 \leq 50\%$ ), and a random-effects model, in which the heterogeneity was high ( $I^2 > 50\%$ ), were used. All analyses were performed using RevMan Manager software (version 5.3; Cochrane, London, UK).

**Quality assessment:** The overall quality of each included study was evaluated using the Cochrane Risk of Bias tool (ROB-2 tool) (<http://ohg.cochrane.org>) for RCTs [19]. The overall risk of bias was determined as low, some concerns, or high risk. Disagreements between

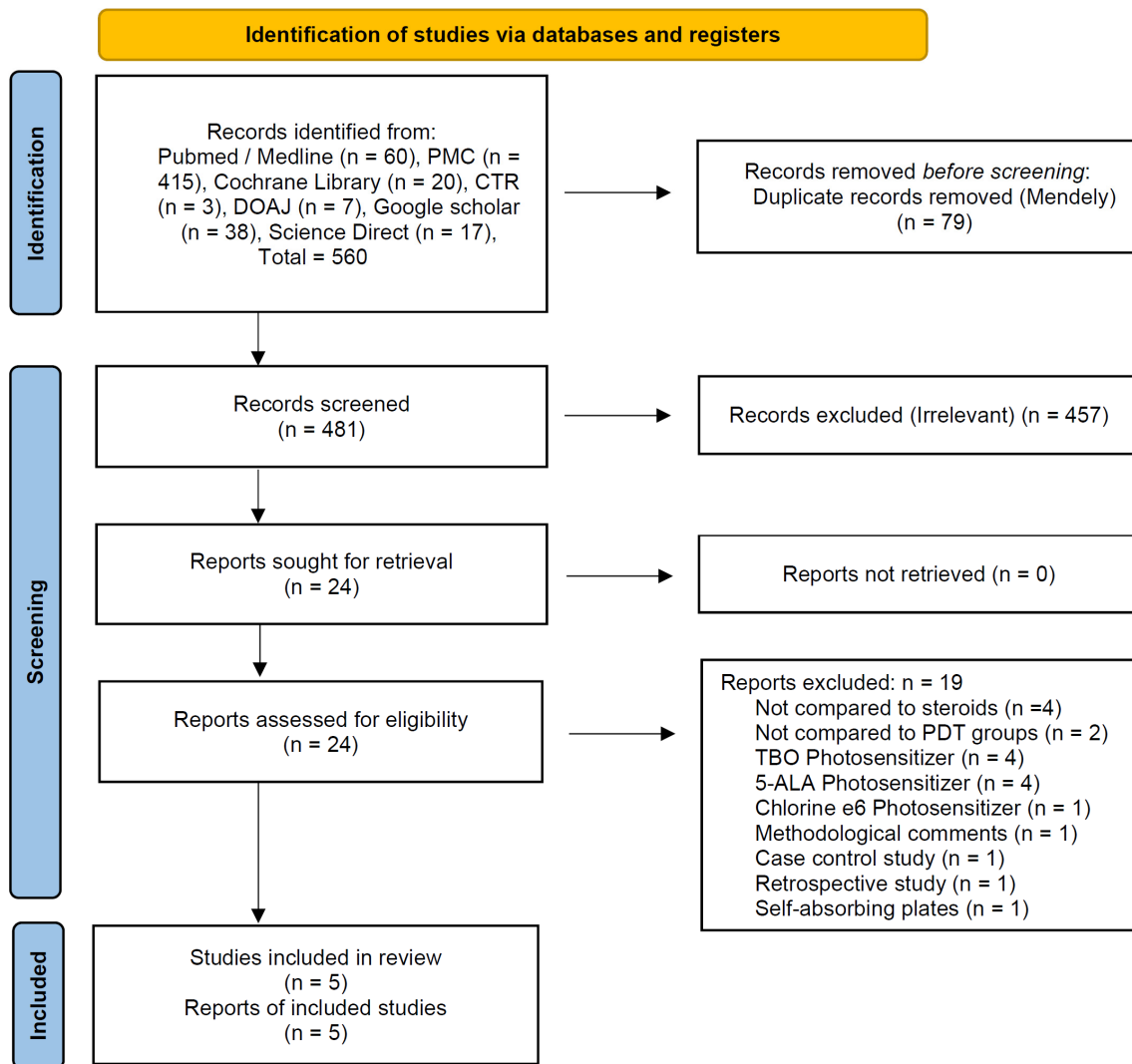


Fig. 1. Flow diagram of the search according to the PRISMA 2020 guidelines. ALA, aminolevulinic acid; CTR, clinical trial registry; DOAJ, Directory of Open Access Journals; n, number; PDT, photodynamic therapy; PMC, PubMed Central; TBO, toluidine blue ortho.

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Zborowski et al. 2021	+	+	+	+	+	+
	Jurczyszyn et al. 2021	+	+	+	+	+	+
	Saleh et al. 2020	-	+	+	+	+	-
	Mostafa et al. 2017	-	+	+	+	+	-
	Bakhtiari et al. 2017	-	+	+	+	+	-

Domains:  
 D1: Bias arising from the randomization process.  
 D2: Bias due to deviations from intended intervention.  
 D3: Bias due to missing outcome data.  
 D4: Bias in measurement of the outcome.  
 D5: Bias in selection of the reported result.

Judgement  
 - Some concerns  
 + Low

Fig. 2. Risk of bias in the included studies

Table 1. Description of included studies

Study	OLP type	Patients	Case description	Outcome measurements	Outcomes	Adverse effects	Conclusion
Bakhtiari S, et al., 2017 [13]	Erosive and ulcerative	30 (17 f/ 13 m) (mean age: 47.2 yrs and dexamethasone- 53.4)	Case (15) : 5% methylene blue using Fotosan device for 30 seconds (630 nm wavelength and 7.2-14.4 J/cm <sup>2</sup> dose) for 4 sessions in the days 1,4,7,14. <b>Control (15):</b> 0.5mg tab dexamethasone solution in 5cc water, rinsed 4 times in a day within two weeks	Thongprasom sign score VAS - symptoms scores (pain), clinical severity and treatment efficacy were measured at the days 15, 30, 60, 90 after beginning of the treatment	Thongprasom sign score In PDT gp Baseline: S1-0, S2-3(20%), S3-4(26%), S4-5(33%), S5-3(20%) At 90 days: S1- 0(0%), S2-4(26.7%), S3-5(33.3%), S4-4(26.6%), S5-2(13.3%) In Dexa gp: Baseline: S1-1(6.7%), S2-2(13.3%), S3-4(26.7%), S4-7(46.7%), S5-1(6.7%) At 90 days: S1-0(0%), S2-3(20%), S3-4(26.7%), S4-7(46.7%), S5-1(6.7%) <b>VAS symptoms scores (pain):</b> NS at 90 days <b>Clinical severity:</b> PDT gp - Baseline: 21.76 ± 19.61 at 90 days: 20.06 ± 18.11 Dexa gp - Baseline: 17.76± 17.93at 90 days: 17.33 ± 17.93 <b>Treatment efficacy</b> PDT gp: 15 days : No improvement : 9 (60%), Mild improvement - 4 (26.7%), Moderate improvement - 2 (13.3%) At 90 days : No improvement - 9 (60%), Mild improvement - 4 (26.7%), Moderate improvement - 2 (13.3%) Dexa gp: 15 days : No improvement : 12 (80%), Mild improvement - 2 (13.3%), Moderate improvement - 1 (6.7%) At 90 days : No improvement - 6 (40%), Mild improvement - 5 (33.3%), Moderate improvement - 4 (26.7%)	Nil	Both treatment options are effective in the treatment of oral lichen planus. PDT could be used as a safe modality in the treatment of oral lichen planus lesions.
Mostafa D, et al., 2017 [15]	Erosive	20 (17 females and 3 males) Case: 39-60 years with a mean of 48.6 ± 5.25 Control: 36-56 years with a mean of 47.0±6.94	<b>Case (10):</b> PDT mediated by MB once a week for 2. Patients were instructed to gargle 5% MB solution in water for 5 minutes Then, diode laser (660 nm, 100-130 mW/cm <sup>2</sup> ) was performed. The lesion and 0.5 cm of its surrounding marginal zone was illuminated with multiple spots (70 sec for each spot). <b>Control (10):</b> Conventional TC in Orabase (Kenakort A-Orabase). They were educated to put a very thin layer of TC three times a day without eating or washing for 30 mins after application (after meals and before bed time).	sign scores (lesion size) and symptoms (pain) scores	symptoms (pain) scores assessed by VAS: PDT - Baseline v/s 2 months: 8.8 ± 1.55 v/s 1.5 ± 3.17 (P = 0.436) Steroid - Baseline v/s 2 months: 8.7 ± 1.16 v/s 5.8 ± 3.43 (P = 0.004)  Thongprasom sign scores: PDT - Baseline v/s 2 months: 5.00 ± 0.00 v/s 1.84 ± 1.80 (P = 0.0001) Steroid - Baseline v/s 2 months: 4.79 ± 0.42 v/s 3.79 ± 2.04 (P = 0.022)	PDT: three lesions (16%) showed exacerbation. Control: five lesions (26%) had exacerbated.	In PDT group eight patients (80%) showed excellent pain improvement, one patient (10%) showed fair improvement and one patient (10%) showed poor improvement. While in control group three patients (30%) showed poor improvement of pain, five patients (50%) showed fair improvement and only two patients (20%) showed excellent improvement. The mean lesion size scores after 2 months of treatment with baseline, a highly notable reduction was observed (P = 0.0001) in PDT. In PDT group: seven lesions (37%) healed completely, eight lesions (42%) showed reduction in size score, one lesion (5%) had no response and <b>Control group:</b> four lesions (21%) healed completely, three lesions (16%) revealed reduction in lesion size score, seven lesions (37%) had no change in size score

(continued)

Study	OLP type	Patients	Case description	Outcome measurements	Outcomes	Adverse effects	Conclusion
Saleh W, et al., 2020 [5]	Erosive	Total 20 patients PDT (10) v/s Topical betamethasone (10) Age: 34-58 yrs (mean 52.4 in PDT & 48.6 yrs in controls). Total: 16 females & 4 males	PDT: 5% MB in H <sub>2</sub> O mouth path for 5 mins. After 10 mins irradiated with LASERs (660 nm, 100-130 mW/cm <sup>2</sup> , 2 mins- twice/week for 4 weeks. Control: topical betamethasone valerate ointment 100 mg - 3 times/day for 4 weeks, refrain from eating or drinking for 30 mins thereafter	Follow-up - 4 weeks. VAS scale for subjective pain assessment. Objectively, Thongprasom sign score to assess in reduction of size. Ulceration, erythema, Reticulation areas & total area	VAS: PDT - 3(2-2) v/s 1 (2-0), P = 0.01 Control - 3 (3-2) v/s 1 (3-0), P = 0.01 Sign score: PDT - 5 (5-4) v/s 3 (5-0), P = 0.01 Control - 5 (5-4) v/s 3 (5-1), P = 0.01 AU: PDT - 38 (12-68) v/s 0 (0-20), P = 0.01 Control - 24 (8-70) v/s 0 (0-60), P = 0.01 AE: PDT - 52 (0-100) v/s 13 (0-54), P = 0.09 Control - 76 (0-100) v/s 32 (0-64), P = 0.04 AR: PDT - 98 (0-225) v/s 48 (0-220), P = 0.01 Control - 139 (0-300) v/s 111 (0-304), P = 0.01 Total area of lesion: PDT - 226 (52-306) v/s 97 (8-226), P = 0.01 Control - 222 (16-450) v/s 137 (0-328), P = 0.01	Not available	Statistically significant difference in both groups from pre-operative to 4 weeks post-operative follow-up. MB-PDT showed a higher degree of improvement than topical corticosteroids between time zero and the 4th week of treatment. PDT is safe and effective treatment modality
Zborowski, et al., 2021 [20]	Bilateral erythematous / erosive	Total 28 samples Age: 33-76 yrs with Mean age 61.9 ± 10.9 yrs	PDT: 5% MB for 10 mins followed by diode laser (spot size 0.8 cm <sup>2</sup> at 650 nm, 120 J/cm <sup>2</sup> and power density 1034 mW/cm <sup>2</sup> for 227s. (four session severy 2-3 days on days 1, 3, 6, 9 days) Control: Daily application 0.05% triamcinolone acetonide over a period of 9 days.	Follow-up: 12-weeks. The size of lesions, Thongprasom, ABSIS, and VAS scale	Relatively high rates of complete remission of lichen were demonstrated: immediately after treatment, 33.3% with PDT and 22.2% with TA, and after 3 months, 54.2% with PDT and 62.9% with TA. After 3 months of treatment, a reduction in the area of evaluated lesions of 52.7% for PDT and 41.7% for TA was achieved. After 3 months of treatment, a reduction in the area of evaluated lesions of 52.7% for PDT and 41.7% for TA was achieved. No significant covariations between pre- and post-treatment clinical relations were found between VAS and OHIP-14 before treatment (R = 0.56, P = 0.001).	An exacerbation of OLP inflammatory lesions, slight swelling, and increased pain after the first or second PDT session, resulting in disagreement with continuing therapy on this side of the mouth - 4 patients. Abandoned self-administration of the polymer carrier with TA as a result of technical problems with drug insertion - 1 patient. One patient reported exacerbation of halitosis in relation to treatment - 1 patient.	In situations of topical or general contraindications to oral corticosteroids, resistance to them, or the need for repeated treatment in a short period of time, PDT appears to be a very promising treatment option.
Jurczyszyn, et al., 2021 [21]	Bilateral erythematous / erosive	Total 28 samples Age: 33-76 yrs with Mean age 61.9 ± 10.9 yrs	PDT: 5% MB carrier for 10 mins followed by diode laser (spot size 0.8 cm <sup>2</sup> at 650 nm, 120 J/cm <sup>2</sup> and power density 1034 mW/cm <sup>2</sup> for 227s. (3 session severy 3 days) Control: Daily application 0.05% triamcinolone acetonide over a period of 8 days.	Follow-up: 12-weeks. The size of lesions, fractal dimensional & texture analysis	<b>Size of lesion &amp; Texture analysis:</b> Statistically non-significant differences were found before and after treatment (P = 0.1469) <b>Fractal Dimensions:</b> Statistically significant differences were found before and after treatment in the photographs taken in 405 + 450 nm wavelength.	2 lesions enlarged after PDT therapy and 5 after using steroid therapy	PDT and topical steroid therapy are effective methods for treating OLP. Use of carrier offers more predictable and effective method of drug delivery into the mucous membrane.

ABSIS, autoimmune bullous skin disorder intensity score; AE, area of erythema; AR, area of reticulations; AU, area of ulceration; Dexa, dexamethasone; LASER, light amplification by the stimulated emission of radiation; MB, methylene blue; OHIP, oral health impact profile; OLP, oral lichen planus; PDT, photodynamic therapy; TA, triamcinolone; TC, topical corticosteroids; VAS, visual analogue scale; v/s, versus; yrs, years.

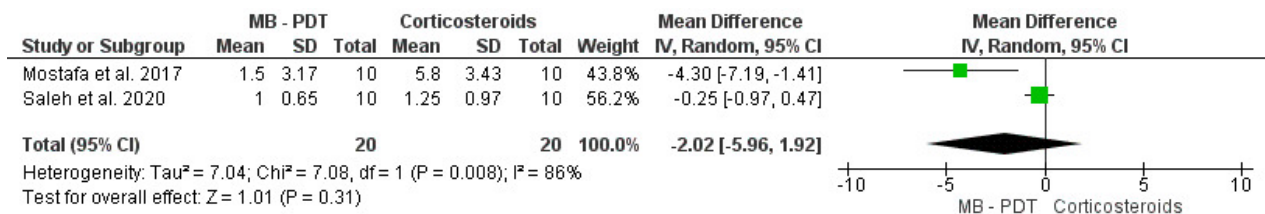


Fig. 3. Forest plot of overall VAS score in patients with OLP. CI, confidence interval; MB, methylene blue; OLP, oral lichen planus; PDT, photodynamic therapy; SD, standard deviation; VAS, visual analogue scale.

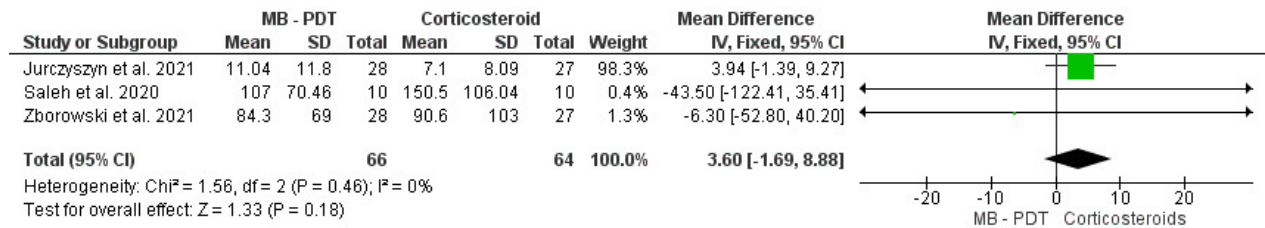


Fig. 4. Forest plot of size of lesion in patients with OLP. CI, confidence interval; MB, methylene blue; OLP, oral lichen planus; PDT, photodynamic therapy; SD, standard deviation.

the reviewers regarding the risk of bias in particular studies were resolved by discussion with a third reviewer whenever necessary.

## RESULTS

The systematic search of the electronic databases yielded 560 studies. After removal of duplicate records (n = 79) using Mendeley software and screening of titles and abstracts, 24 full-text studies were evaluated. Five studies were included in the final review for qualitative and quantitative assessment. The PRISMA flowchart for the inclusion of studies is shown in Figure 1. The findings of this meta-analysis were based on five RCTs comprising 180 patients (MB-PDT group = 91 and corticosteroid group = 89) [5,13,15,20,21].

Two studies had a low risk of bias [20,21], while the other three showed some concerns due to the unclear randomization of the samples [5,13,15] (Fig. 2).

Table 1 provides comprehensive information about the included studies. Two studies assessed erosive OLP [5,15], two studies evaluated bilateral erythematous or erosive OLP [20,21], and one study evaluated erosive and ulcerative OLP [13]. Corticosteroid prescriptions included

0.5 mg in 5 ml dexamethasone solution (5 cc rinsing qid/2 weeks) [13], topical application of 0.05% triamcinolone acetonide [15,20,21], or topical betamethasone ointment (100 mg, qid/4 weeks) [5] for a period of 8 or 9 days to 2–3 months. Five percent MB application for 5–10 mins was used in all five studies [5,13,15,20,21]. Diode lasers using wavelengths of 630–660 nm with a power density of 1.034 or 100–130 mW/cm<sup>2</sup> at dose of 7.2–14.4 J/cm<sup>2</sup> up to 120 J/cm<sup>2</sup> for a minimum of 30 s to a maximum of 227 s per session were used. Laser irradiation was performed every 2–3 days for 8–9 days [20,21] or once weekly for 1 month [5,13] to 2 months [15].

Only two studies evaluated the VAS score [5,13]. The other studies either did not evaluate pain (VAS scale) before and after a specific treatment modality [20] or did not report the data [13]. Therefore, these data were not included in the quantitative assessment. The MD in VAS scores was statistically non-significant based on the random model effect with high heterogeneity (-2.02, P = 0.31, 95% confidence interval [CI] = -5.96–1.92, Fig. 3).

Three studies evaluated the lesion size [5,20,21]. The MD in the size of the lesion before and after treatment was statistically non-significant based on the random effects model (3.60, P = 0.18, 95 % CI = -1.69–8.88).

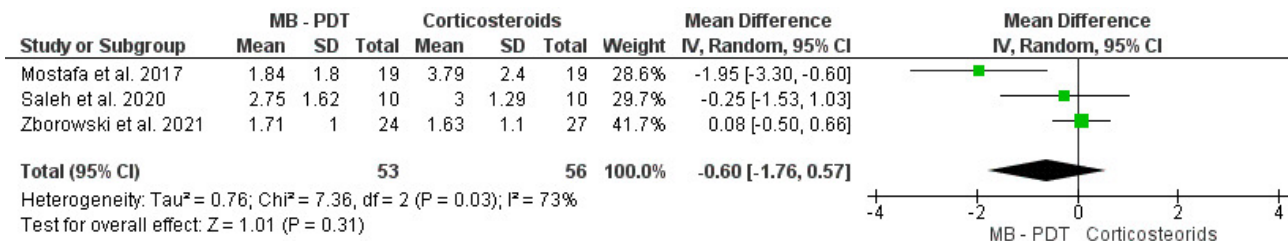


Fig. 5. Forest plot of Thongprasom sign score in patients with OLP. CI, confidence interval; MB, methylene blue; OLP, oral lichen planus; PDT, photodynamic therapy; SD, standard deviation.

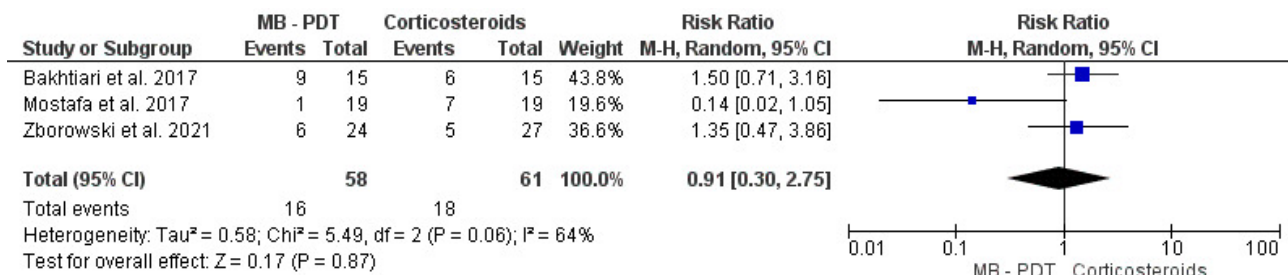
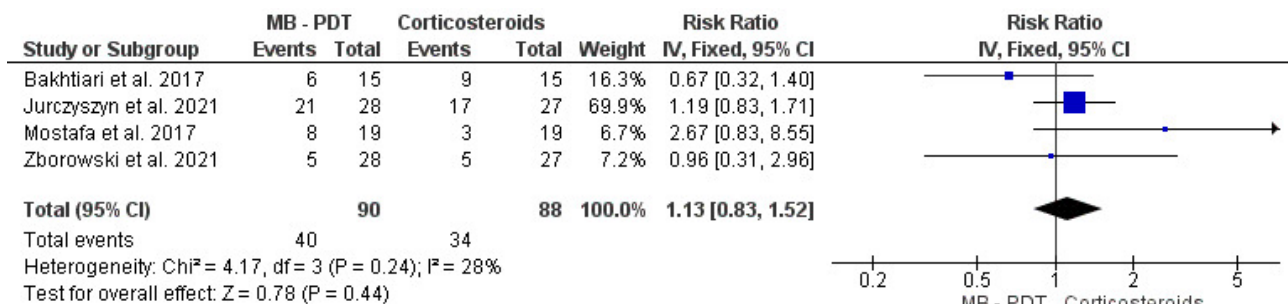
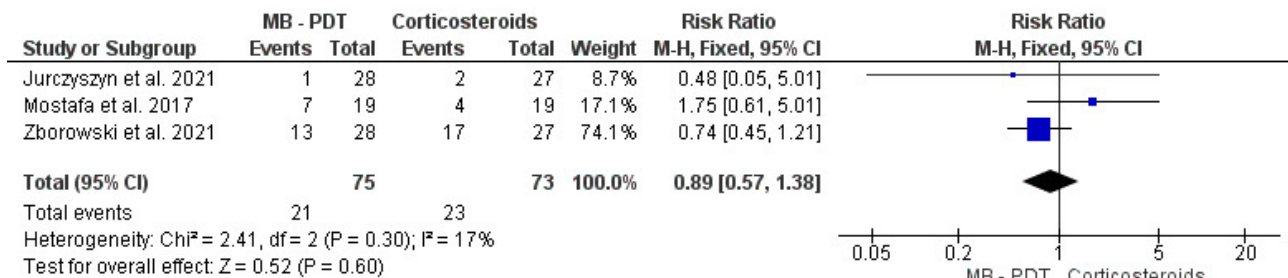


Fig. 6. Forest plot of summary of treatment response to OLP therapy. CI, confidence interval; MB, methylene blue; OLP, oral lichen planus; PDT, photodynamic therapy.

There was no heterogeneity; however, a high CI was reported (Fig. 4). Similarly, the MD in the Thongprasom sign scores between the intervention and control groups was statistically non-significant, with high heterogeneity (-0.60, P = 0.31, 95% CI = -1.76-0.57, Fig. 5).

Responses to interventional and conventional treatments were analyzed as complete, partial, or no response. Four studies evaluated the response to treatment

[13,15,20,21]. The risk ratios (RRs) showed no statistically significant differences (complete response: 0.89, P = 0.60, 95% CI = 0.537-1.38; partial response: 1.13, P = 0.44, 95% CI = 0.83-1.52; and no response: 0.91, P = 0.87, 95% CI = 0.3-2.75). The fixed effects model was used to analyze complete and partial responses to treatment as the heterogeneity was ≤ 50%, and the random effects model was used to assess no response to



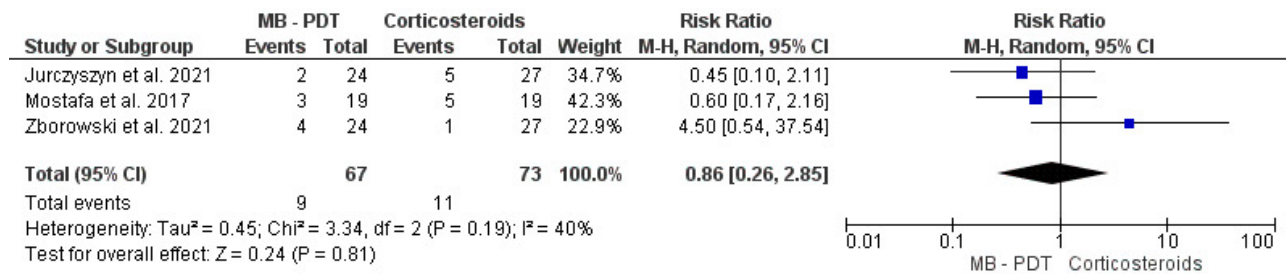


Fig. 7. Forest plot of exacerbated response to OLP treatment. CI, confidence interval; MB, methylene blue; OLP, oral lichen planus; PDT, photodynamic therapy.

treatment due to high heterogeneity ( $\geq 64\%$ , Fig. 6). Only three studies reported exacerbation of lesions after MB-PDT and corticosteroid administration [15,20,21]. Both treatment modalities resulted in similar exacerbation of lesions, which was statistically significant based on the random effect model (RR = 0.86, P = 0.81, 95% CI = 0.26–2.85, Fig. 7).

One study assessed the clinical severity index (CSI) at baseline and at 15, 30, 60, and 90 days after treatment and found no major intergroup differences [13]. There was a significant reduction in the CSI from day 1 to days 15 and 30 after treatment, although there was no substantial improvement in the clinical severity in the PDT group [13].

Three patients complained of discomfort with PDT during the treatment, according to Bakhtiari et al. [13]. Two patients with erosive OLP complained of pain during the first and second PDT sessions due to probe tip movement in the affected region, and one patient complained of pain during the second and third sessions [13].

## DISCUSSION

Although there are many treatment options for OLP, none have been shown to be completely successful. Nevertheless, corticosteroids have been recognized as the primary treatment of choice; however, there are several side effects associated with their use, which has led to the emergence of newer treatment modalities.

PDT is a simple and safe treatment involving the use

of PS and light. The light penetration of most PSs ranges from 0.5 cm (for 630 nm) to 1.5 cm (for 700 nm) [19,22]. Based on these properties, the therapeutic effect of various PSs has been described for different pathological conditions and tumors, achieving different total light doses, dose rates, and tissue destruction rates for different tissues and PSs [23]. The effectiveness of PDT in reducing the clinical symptoms of OLP, such as lesion size and symptoms, has been analyzed, with mixed results being reported [1,2,4,8,9,13,15,20,21,24]. Furthermore, there is no evidence that PDT affects the histological or immunological effects associated with OLP [16].

The meta-analysis of this systematic review revealed that both MB-PDT and conventional corticosteroid therapy are effective in treating erythematous or erosive-atrophic OLP lesions without significant adverse effects. Moreover, MB-PDT may be considered a safe and effective alternative therapy for OLP when long-term corticosteroid therapy is not indicated. Currently, there are no clear recommendations on the type of PS or length of PDT exposure to be used for the treatment of OLP. Light sources with different powers, variable wavelengths, energies, densities, and irradiation times cause discrepancies when comparing the actual effects of treatments.

MB-PSs have been analyzed in various studies for the treatment of OLP [13,15,25,26]. MB has immunomodulatory properties and triggers apoptosis in hyperproliferating inflammatory cells through a mitochondrial-dependent pathway in which reactive oxygen species interact with mitochondria, causing an imbalance in their development and antioxidant ability.

Owing to MB-PDT-mediated oxidative stress, mitochondrial integrity and function are compromised, leading to cell death [27,28]. Furthermore, PDT causes upregulation of interleukin (IL)-6 and IL-1 [29]. Damage to nucleic acids, proteins, and lipids has also been identified and rationalized in the literature. Both type I and II processes are thought to cause this damage [28]. Therefore, this systematic review evaluated the efficacy of MB as a PS in PDT.

Al-Maweri studied the effects of PDT, corticosteroids, and placebo and found that PDT with PSs such as MB, toluidine blue, and ALA was successful in treating erosive OLP [30]. However, this study did not provide clear evidence on the type of PS used in the management of OLP. According to Jajarm et al., low-level laser therapy can have a major impact on pain levels and sign scores [18]. However, in the current systematic review, the impact of MB as a PS on pain, lesion size reduction, and Thongprasom sign scores was compared, and the results were not significant from baseline to postoperative follow-up.

In few studies, the gargling or rinsing method was used for the application of PSs [5,13,15], while recent studies have pointed out that mucosa-adhesive porous polymer matrices can be used as desirable solutions to many clinical difficulties [20,21]. A high concentration at the target site was achieved using mucoadhesive patches. Therefore, the effective dose might have a significant impact on the healing of the lesions. Similarly, the mode of steroid administration varied among the included studies. In one study, dexamethasone rinses were used [13], while Mostafa et al. [15] used adherant triamcinolone acetonide, and Saleh et al. [5] used betamethasone ointment; porous adhesive polymer matrices were used in other studies [20,21]. Such varied modes of topical application of steroids could also affect the comparison of the results.

A few methodological differences were noted in published studies. A few studies used a parallel RCT design to compare the efficacy of PDT and topical steroid therapy in OLP [5,13,15], while others used split-mouth

RCT [20,21]. Such differences could also act as a significant factor to compare the impact of study results.

Both MB-PDT and corticosteroid therapy were found to be effective. Complete response to treatment was similar in both groups in all studies. The following parameters should be considered when evaluating the treatment response: older patient age and faster remission. The surface of the lesion also influences the response to treatment; the smaller the surface area, the better the resolution [20].

The findings of this meta-analysis were based on five RCTs. Two studies reported a high quality of evidence owing to the overall low risk of bias [20,21], while the remaining three studies showed problems with randomization, which limited the evidence [5,13,15]. Furthermore, high heterogeneity was observed in a few studies. Nevertheless, the findings of this systematic review should be interpreted with caution because of the possibility of bias in the included studies.

This study has several limitations. First, the number of clinical trials performed was inadequate, which reduced the validity of the findings. The mean VAS score for pain was not reported in a study, although no significant differences were reported [13]. The outcome indicators of the trials differed, making data analysis difficult. Further, the clinical severity score was measured in only one study [13]. The administration of steroids also differed, which may have influenced the findings. Despite these limitations, the findings provide clinicians with a detailed picture of PDT efficacy in OLP. However, high-quality clinical trials are needed to enhance the reliability of the results.

In conclusion, both MB-PDT and corticosteroid therapy are effective in the management of OLP. PDT using MB as a PS was found to have similar efficacy to that of conventional corticosteroid therapy in the management of OLP and may be considered an alternative choice of treatment when steroids are contraindicated. However, conclusive evidence cannot be ascertained owing to the heterogeneity among these studies. Due to the small number of clinical trials, no

definitive evidence exists to determine the possible effects of PDT in the treatment of OLP. The findings of this meta-analysis cannot be generalized, and further research is required to determine the precise effects of PDT with MB.

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#### REFERENCES

- Jajarm HH, Falaki F, Sanatkhani M, Ahmadzadeh M, Ahrari F, Shafae H. A comparative study of toluidine blue-mediated photodynamic therapy versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus: a randomized clinical controlled trial. *Lasers Med Sci* 2015; 30: 1475-80.
- He Y, Deng J, Zhao Y, Tao H, Dan H, Xu H, et al. Efficacy evaluation of photodynamic therapy for oral lichen planus: a systematic review and meta-analysis. *BMC Oral Health* 2020; 20: 302.
- Panta P, Andhavarapu A, Patil S. A holistic intervention for oral lichen planus. *J Contemp Dent Pract* 2019; 20: 765-7.
- Sadaksharam J, Nayaki KP, Selvam NP. Treatment of oral lichen planus with methylene blue mediated photodynamic therapy - a clinical study. *Photodermatol Photoimmunol Photomed* 2012; 28: 97-101.
- Saleh W, Tageldin S, Khashaba E, Darwish M, Elnagdy S, Khashaba O. Could photodynamic therapy be utilized as a treatment modality for oral lichen planus? *Photodiagnosis Photodyn Ther* 2020; 30: 101677.
- Prasanna SW, Ingle E, Aruna PR, Pravada C, Koteeswaran D, Ganesan S. Photodynamic therapy of oral leukoplakia and oral lichen planus using methylene blue: a pilot study. *J Innov Opt Health Sci* 2015; 8: 1540005.
- Lavaee F, Shadmanpour M. Comparison of the effect of photodynamic therapy and topical corticosteroid on oral lichen planus lesions. *Oral Dis* 2019; 25: 1954-63.
- Maloth KN, Velpula N, Kodangal S, Sangmesh M, Vellamchetla K, Ugrappa S, et al. Photodynamic therapy - a non-invasive treatment modality for precancerous lesions. *J Lasers Med Sci* 2016; 7: 30-6.
- Akram Z, Javed FD, Hosen M, Al-Qahtani MA, Alshehri F, Alzahrani AI, et al. Photodynamic therapy in the treatment of symptomatic oral lichen planus: a systematic review. *Photodermatol Photoimmunol Photomed* 2018; 34: 167-74.
- Mirza S, Rehman N, Alrahlah A, Alamri WR, Vohra F. Efficacy of photodynamic therapy or low level laser therapy against steroid therapy in the treatment of erosive-atrophic oral lichen planus. *Photodiagnosis Photodyn Ther* 2018; 21: 404-8.
- Sabry MA, El-Housiny Saafan AM, El-Shenawy HM, Hussine AA, Abd El-Aziz DM, Abdel Fadeel DA. Effect of photodynamic therapy on pain control in patients with erosive / atrophic oral lichen planus. *Eurasian J Biosci* 2020; 14; 7455-60.
- Singh AR, Rai A, Aftab M, Jain S, Singh M. Efficacy of steroidal vs non-steroidal agents in oral lichen planus: a randomised, open-label study. *J Laryngol Otol* 2017; 131: 69-76.
- Bakhtiar S, Azari-Marhabi S, Mojahedi SM, Namdari M, Rankohi ZE, Jafari S. Comparing clinical effects of

- photodynamic therapy as a novel method with topical corticosteroid for treatment of Oral Lichen Planus. *Photodiagnosis Photodyn Ther* 2017; 20: 159-64.
14. Sobaniec S, Bernaczyk P, Pietruski J, Cholewa M, Skurska A, Dolińska E, et al. Clinical assessment of the efficacy of photodynamic therapy in the treatment of oral lichen planus. *Lasers Med Sci* 2013; 28: 311-6.
  15. Mostafa D, Moussa E, Alnouaem M. Evaluation of photodynamic therapy in treatment of oral erosive lichen planus in comparison with topically applied corticosteroids. *Photodiagnosis Photodyn Ther* 2017; 19: 56-66.
  16. Cosgarea R, Pollmann R, Sharif J, Schmidt T, Stein R, Bodea A, et al. Photodynamic therapy in oral lichen planus: A prospective case-controlled pilot study. *Sci Rep* 2020; 10: 1667.
  17. Salva KA. Photodynamic therapy: unapproved uses, dosages, or indications. *Clin Dermatol* 2002; 20: 571-81.
  18. Jajarm HH, Asadi R, Bardideh E, Shafae H, Khazaei Y, Emadzadeh M. The effects of photodynamic and low-level laser therapy for treatment of oral lichen planus-a systematic review and meta-analysis. *Photodiagnosis and photodynamic therapy*. 2018; 23: 254-60.
  19. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.
  20. Zborowski J, Kida D, Szarwaryn A, Nartowski K, Rak P, Jurczyszyn K, et al. A comparison of clinical efficiency of photodynamic therapy and topical corticosteroid in treatment of oral lichen planus: a split-mouth randomised controlled study. *J Clin Med* 2021; 10: 3673.
  21. Jurczyszyn K, Trzeciakowski W, Kozakiewicz M, Kida D, Malec K, Karolewicz B, et al. Fractal dimension and texture analysis of lesion autofluorescence in the evaluation of oral lichen planus treatment effectiveness. *Materials* 2021; 14: 5448.
  22. Kübler AC. Photodynamic therapy. *Med Laser Appl* 2005; 20: 37-45.
  23. Konopka K, Goslinski T. Photodynamic therapy in dentistry. *J Dent Res* 2007; 86: 694-707.
  24. Kvaal SI, Angell-Petersen E, Warloe T. Photodynamic treatment of oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; 115: 62-70.
  25. Sadaksharam J, Nayaki KP, Selvam NP. Treatment of oral lichen planus with methylene blue mediated photodynamic therapy-a clinical study. *Photodermatol Photoimmunol Photomed* 2012; 28: 97-101.
  26. Aghahosseini F, Arbabi-Kalati F, Fashtami LA, Djavid GE, Fateh M, Beitollahi JM. Methylene blue-mediated photodynamic therapy: A possible alternative treatment for oral lichen planus. *Lasers Surg Med* 2006; 38: 33-8.
  27. Chen Y, Zheng W, Li Y, Zhong J, Ji J, Shen P. Apoptosis induced by methylene-blue-mediated photodynamic therapy in melanomas and the involvement of mitochondrial dysfunction revealed by proteomics. *Cancer Sci* 2008; 99: 2019-27.
  28. Tardivo JP, Del Giglio A, de Oliveira CS, Gabrielli DS, Junqueira HC, Tada DB, et al. Methylene blue in photodynamic therapy: From basic mechanisms to clinical applications. *Photodiagnosis Photodynamic Therapy* 2005; 2: 175-91.
  29. Gollnick SO, Owczarczak B, Maier P. Photodynamic therapy and anti-tumor immunity. *Lasers Surg Med* 2006; 38: 509-15.
  30. Al-Maweri SA, Ashraf S, Kalakonda B, Halboub E, Petro W, AlAizari NA. Efficacy of photodynamic therapy in the treatment of symptomatic oral lichen planus: a systematic review. *J Oral Pathol Med* 2018; 47: 326-32.