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Informative title: **Topical photodynamic therapy in the treatment of benign oral mucosal lesions: a systematic review**

Running title: Topical PDT for benign oral mucosa lesions

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ABSTRACT

Background: The introduction of Photodynamic therapy (PDT) in various branches of the dental field such as endodontics, implantology, periodontology, and restorative dentistry and oral medicine has become useful in recent decades. This systematic review presents an overview of the literature to evaluate the usefulness of topical PDT for the treatment of benign oral soft tissue lesions and to identify limitations in prior studies to improve PDT applications. **Methods**: We performed a review of the literature using different search engines (PubMed, ISI Web of Science, and the Cochrane Library) employing MeSH terms such as "Photodynamic therapy" and "PDT" in conjunction with other terms. We utilized the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) method to define our study eligibility criteria. **Results**: Initial results were 1513. Finally, there were only 21 studies that met our selection criteria. We divided the 21 selected items into two groups: inflammatory diseases and infective diseases. **Conclusions**: Although topical PDT is an easy to perform and well-tolerated treatment and appears to be a

valid method with promising results in the treatment of benign lesions of the oral cavity's soft tissues, further studies are needed to complete the current knowledge of this technique.

***Key Words*:** Photodynamic therapy, PDT, Oral, benign lesions.

1. INTRODUCTION

Photodynamic therapy (PDT) relies on the interaction between a photosensitizer, the appropriate activating wavelength of light, and oxygen. The reaction generates reactive oxygen species (ROS), causing cell death by necrosis or apoptosis, but minimally affects the surrounding tissue[1]. Furthermore, PDT can directly alter immune cells' function (cytokine production, cell signaling events, and surface receptor expression) and, therefore, relieve immune-mediated disease[2].

Also, photodynamic therapy effectively treats infectious diseases of viral, fungal, and bacterial origin because it indirectly impacts the DNA and RNA synthesis, stages of the mitosis cycle, and protein excretion[3–5]. The wavelength range that can be exploited in the PDT is between 600 and 900 nm[6]. Photosensitizers can be administered systemically or topically[7]. Systemic photosensitizers currently in use are characterized by very low systemic toxicity in the absence of light; however, the administration of these drugs determines a period of undesirable residual photosensitization, which must be managed as long as the drug is not deleted[8]. On the other hand, the absorption of drugs for topical PDT is reduced; they cause more limited adverse effects, such as pain and swelling. Furthermore, the total absence of residual systemic photosensitivity means that patients are not forced to avoid exposure to sunlight. The limit of topical therapy is linked to the transcutaneous absorption of drugs, limiting the possibility of application to more superficial lesions[9, 10].

PDT is a tool that allows a minimally invasive approach with satisfactory results both in the medical and dental fields[11, 12]. It is mainly used in various branches such as endodontics, implantology, periodontology, restorative dentistry, and oral medicine[13–19]. The use of PDT in the treatment of oral mucosal lesions has focused mainly on treating premalignant lesions[20]. More recently, the research has focused on inflammatory and infective diseases[19, 21, 22]. The purpose of this review is to evaluate topical photodynamic therapy's efficacy in the treatment of benign oral soft tissue lesions.

2. MATERIALS AND METHODS

A systematic review of the literature was carried out by inserting the MeSHs listed in Table 1 in different databases (ISI Web of Science, PubMed, and the Cochrane Library) following the PRISMA checklist. The research was completed in September 2020. The articles were acquired by three reviewers (AR, FF, and DDS), the duplicates were eliminated, and subsequently, following the reading of the abstracts, the articles that did not meet the inclusion criteria were eliminated. The selection criteria used to include the studies

were: studies on patients with benign oral soft tissue lesions treated topically with photodynamic therapy, in vivo, available full text and published in English. Reviews were excluded. The remaining articles were evaluated by two other reviewers (AL and EG) to insert only relevant articles into this review. This systematic review has been conducted using the "PICOS" approach[23]: population (P) was men and women with benign oral soft tissue lesions; intervention (I) was topical photodynamic therapy; comparison (C) was other conventional therapies; the outcome (O) was to evaluate the efficacy of topical photodynamic therapy in the treatment of inflammatory and infective diseases, and the study designs (S) included randomized control trials (RCTs), prospective comparison studies, retrospective cohort studies, case-control studies, and case series.

Quality assessment of Non-randomized Studies will be based on Bias's Risk in Non-randomized Studies of Intervention (ROBINS-I) assessment tool[24].

This review was submitted and registered on PROSPERO (registration number: CRD42020166928).

3. RESULTS

The initial search yielded 1513 results; 936 articles were excluded as they were duplicates. Another 519 articles were excluded following the reading of titles and abstracts. Of the 58 remaining articles, two were excluded (they were not available in full text), and 35 because they did not meet our inclusion criteria. At the end of the selection, 21articles were included in this systematic review (Figure 1). We decided to allocate the 21 selected items into two groups: inflammatory diseases and infective diseases. Information about the 21 selected articles and their main contents is summarized in Table 2.

3.1 Risk of bias in individual studies

When assessed with ROBINS-I (Table 3), two studies were graded as serious-risk RoB and 14 as moderate RoB. Mainly, concerning selection bias, five studies recruited only volunteers; for bias due to deviations from intended interventions and bias in the measurement of outcomes, in all the studies, there was no blinding both of participants and healthcare providers and of outcome assessors. In conclusion, all the studies provided sound evidence, and none presented a critical RoB in any domain.

3.2 Inflammatory Diseases

Oral lichen planus (OLP)

Aghahosseini et al.[25] in 2006 published a case report concerning two patients who underwent a single session of PDT, performed with methylene blue (MB) activated by a diode laser. After only seven days, the

Authors obtained complete healing of the lesion, an atrophic area with white striae of the gingiva vestibule present in one of the two patients; the other patient instead presented three keratotic lesions in buccal mucosa and tongue. In this case, after one week, there was a reduction in the size of the buccal mucosa lesions; however, the tongue's lesion did not respond to the therapy. Results obtained were stable at two months.

Kvaal et al.[26] treated 17 OLP patients by performing PDT only in one region of the oral cavity, while they used the remaining parts as control. PDT involved the use of methyl 5-aminolevulinate (MAL) cream and a light-emitting diode (LED) light source. The treatment comprised one session of PDT. One month after the treatment, no clinical differences could be detectable between the two regions, but statistically significant improvement on the PDT treated side manifested itself both on the third and the sixth month after the start of the therapy. This improvement trend has persisted in the next 4-year follow-up period.

In a comparative study produced by Jajaram et al.[27], a group of 11 OLP patients underwent two sessions of PDT with toluidine blue (TB) and a Gallium-Aluminum-Arsenide (GaAlAs laser). According to this protocol, another group of patients (14 controls) received conventional drug therapy: dexamethasone and nystatin. The authors did not find statistically significant differences between the two groups of patients.

Malothet al.[28] aimed to compare traditional drug therapy for OLP with PDT. To this end, 8 cases with 20 OLP lesions were subdivided into two groups (each including four patients): a traditional drug therapy(kenacort 0.05%) control group and a PDT study group. At the end of the therapy, both in the case of PDT and conventional drug therapy, 80% of the lesions showed partial response (PR), while 20% of the lesions showed no response (NR) at all. Nevertheless, the mean reduction in size score differences was significantly better in the PDT group ($P < 0.001$).

To carry out their case-control study about OLP therapy, Bakhtiari et al.[29] used PDT with 5% MB combined with a LED light to treat 15 patients, while the second group of 15 patients underwent traditional therapy with corticosteroids. Authors developed the treatment and assessment plans basing on the timing proposed by Sadaksharam[30]. As a result, the Authors found that PDT effectiveness was comparable to traditional corticosteroid treatment, but PDT was more beneficial as it requires fewer applications than the drug and causes fewer complications. The use of PDT is also suggested as an auxiliary to corticosteroids therapy.

Erosive-atrophic OLP was the subject of the study by Mostafa et al.[31]. Two groups of 10 patients underwent drug therapy with cortisone kenakort A-orabase and PDT with 5 %MB and diode laser once a week for two months, respectively. According to results, MB-PDT has shown a greater efficacy both in pain reduction and lesion regression.

Mizra et al.[32] also dealt with 45 erosive-atrophic OLP patients, comparing three types of approaches: PDT, low-level laser therapy (LLLT), and topical corticosteroid application. Although all three groups showed improvements after the respective treatments' initiation, there was a statistically significant difference in terms of the score changes between the PDT group and the LLLT group against the corticosteroids group. Furthermore, the efficacy index of the PDT group was significantly better than the other two groups. Instead, conventional therapy produced a significant improvement in pain.

Jurczyszyn et al.[33] enrolled 35 patients; among them, 9 had OLP for a total of 14 lesions. LP achieved complete remission (CR) in 7 of all lesions (50%), a partial response was observed in 5 lesions (35.7%), and two lesions (14.3%) had no response to PDT. Symptoms of OLP, such as burning pain, sensitivity to spicy foods, and discomfort during speaking, disappeared in all of the patients. Sulewska et al.[34] treated 50 patients with 124 OLP lesions. Upon completing the study, 109 out of 124 lesions (87,9%) showed a clinical improvement; 46 of them (37,1%)achieved a complete remission. Statistical analysis of the lesion size revealed a significant difference with the mean size reduction that ranged from 62,9% at the end of the therapy to 78,7% one year after the therapy.

Lavaee et al.[35] compared PDT to triamcinolone acetonide 0.1% using toluidine blue as PS. Clinical outcomes were evaluated using the Thongprasom score, Efficacy Index, Clinical Severity Index, and VAS score. The data analysis highlighted that TH, SI, and EI difference between the intervention and the control sides were significantly different. VAS reduction was statistically significant in both intervention and control samples. Romano et al.[36] evaluated the efficacy of toluidine blue mediated PDT using RECIST criteria, achieving 4 complete remissions (CR = 80%) and a decrease in lesion size of 54% (PR = 20%). Cosgarea et al.[37] evaluated 20 OLP patients' clinical features underlining the significant improvement between day one and day 28 (14 days after the last session of PDT), which correlated with the significant improvement of ABSIS I score assessed during day 42 and day 56. The authors also used Thongprasom and Carrozzo-Gandolfo scores to estimate lesion severity; the study's main findings seem to suggest a shift from severe lesions to softer ones, using Thongprasom score, and a size reduction that can be considered as complete or partial remission according to Carrozzo-Gandolfo score. Statistical analysis also revealed a significant reduction in burning sensation and improvement in self-performed oral hygiene in concordance with the decrease of the ABSIS II score from the baseline to day 56. Saleh et al.[38] performed a case-control study comparing MB-PDT with topically applied corticosteroids using the subjective score (VAS) and objective score (Thongprasom score). In both groups, the authors found a statistically significant difference in symptom reduction after two weeks and four weeks from the baseline. Objective measurement also detected a significant decrease of the Thongprasom score after four sessions of PDT, further decreased after eight sessions (4 weeks).

Recurrent aphthous stomatitis (RAS)

In 2017, Casu et al.[39] applied PDT for the treatment of recurrent aphthous stomatitis (RAS). Since standard RAS therapy may include analgesics, antibiotics, corticosteroids, and immunosuppressive drugs, the Authors researched an alternative to alleviate symptoms, reduce ulcer number and size, and prolong the periods of absence of lesions, avoiding the appearance of drug-related side effects. The authors treated a female patient who presented an aphthous lesion on the buccal mucosa, refractory to topical therapy with cortisone. The lesion was treated with TB and a diode LED 10 consecutive times with 30 seconds cycles. The first effects were found already a few hours after the session, with a reduction in symptoms. Clinical healing had a centrifugal pattern, originating from the ulcer's center towards the lesion margins and was observable already after a few days. The mucosa was free of injury after a week.

3.3 Infective Diseases

Oral Candidiasis

In their study, de Oliveira Mima et al.[40] compared the use of PDT with topical antifungal therapy for the treatment of denture stomatitis (DS). Two groups of 20 patients were treated respectively with nystatin and with PDT, spraying the denture with 500 mg / L of Photogem, before of irradiation with a LED light. The comparison of mycological cultures taken from dentures and palates and of the photographs of the palates taken at baseline (day 0), after treatment (day 15), and during the follow-up period (days 30, 60, and 90) revealed the presence of Candida species and showed a reduction of the mycological CFU / mL at the end of the treatments and on day 30 ($p < 0.05$). The mycological efficacy in the first and the second group was attested by a success rate of 53% and 45%, respectively, revealing that both therapies were also effective for DS treatment.

Scwingelet al.[41] enrolled twenty-one HIV-positive patients suffering from oral candidiasis, splitting them into three groups (seven patients for each group). The first group was treated with conventional oral antifungal fluconazole therapy; the second group was subjected to only low-level laser therapy in single irradiation. The study group underwent a PDT protocol. After thirty days, the low-level laser therapy group did not significantly improve the clinical appearance of oral candidiasis; recurrence of signs and symptoms was observed in 72% of patients treated with oral fluconazole. Instead, the PDT group achieved remarkable results both for the improvement of clinical conditions and for yeast cell eradication.

Potential PDT inactivation of oral fungal colonization was investigated by Abduljabbar et al.[4], who examined 22 subjects affected by palatal denture stomatitis; exfoliative cytology was performed, and

samples confirmed the presence of fungal hyphae. 500 mg / L haematoporphyrin derivative of Photogem was delivered directly upon the dentures through a sterile spray bottle; then irradiation was performed by two light-emitting diode sources (122 J/cm2) for 20 minutes. Differences between Colony forming units per milliliter (CFU/ml) before and after the treatment were evaluated: at 3-months follow-up, there was a significant decrease in mean CFU/ml values, and palatal mucosae showed no clinical signs of candidiasis superinfection. De Senna et al.[42] also explored PDT efficacy in inactivating candida's superinfection, through comparing it with conventional antifungal pharmacological therapy. According to their protocol, for the study group, methylene blue solution was applied both upon prosthesis and palatal mucosae for ten minutes; then, irradiation was performed by using GaAlAs diode laser. The control group's patients were treated with miconazole oral gel, 2%. Both groups achieved significant clinical improvement and decreased CFU/ml; therefore, no statistically significant differences were observed between PDT protocol and conventional miconazole therapy.

Nystatin therapy, instead, was compared to PDT inactivation by Alrabiah et al.[43]. In their study, 36 patients suffering from denture stomatitis were randomly allocated into two groups: the control group was subjected to 100.000 IU oral nystatin four times daily for two weeks; the PDT group underwent methylene blue application and GaAlAs diode laser, twice a week for four weeks. Unlike the previous study by De Senna et al. [42], 30 and 60 days after treatments, a significant reduction in Candida spp was observed on both palates and dentures in the nystatin group only.

Afroozi et al.[44] also aimed to compare conventional nystatin therapy with PDT, enrolling 66 patients. The control group was treated with oral nystatin drop. PDT group was treated in combination with nystatin mouthwash; PDT protocol used foresaw 1mg/mL Indocyanine green application for ten minutes, and then irradiation by 810 nm diode laser (56 J/cm2). At the end of the follow-up period, the mean reduction achieved by the PDT + nystatin group was significantly higher than the nystatin alone.

Paracoccidioidomycosis

Ribeiro et al.[45] reported a single case of PDT treatment for an oral lesion caused by Paracoccidioides brasiliensis. Histological and serologic confirmation of Paracoccidioidomycosis (PCM) was previously obtained. The palatal ulcerated lesion underwent PDT protocol, consisting of topical Toluidine Blue dye application on the affected site for 5 minutes; then, a continuous 660 nm InGaAlP irradiation was performed in contact mode, with an energy density of 100 J/cm2 and 40 mW of power. Forty days after the treatment, the affected area showed a total regression of the lesion, and the patient reported a total absence of symptoms. Six months after the therapy, the serologic test was performed again, achieving a negative result.

4. DISCUSSION

The articles in the literature concerning benign lesions of the oral mucosa treated with PDT have shown promising results obtained with this method. Most of the studies focused on the use of PDT in the treatment of OLP and comparing this alternative therapy with traditional therapy. Corticosteroid therapy is the one most commonly used for the treatment of OLP lesions. Although this therapy works in most patients, it is not free from adverse reactions and cannot be given to all patients due to comorbidities. From the results of this study, it appears that PDT may be effective in treating the signs and symptoms of OLP without the adverse effects associated with corticosteroids[46].

In some cases, such as the one treated by *Casu et al.*[39] on RAS, patients are not responsive to traditional therapy and, in particular, to corticosteroids; in these cases, PDT is a valid alternative method. Furthermore, PDT has also effectively treated infectious diseases in other medicine branches, with only a few studies dealing with this tool applied to the oral mucosa[47-49]. Although the results look promising, further studies are needed on this topic. The literature analysis has highlighted a heterogeneity of the protocols; in fact, the authors use different types of photosensitizers, light sources, and different protocols regarding the time of irradiation of the lesion and the duration of the latter. Given the lack of articles on this topic, it is not yet possible to establish which of these is the most appropriate. Besides, since the studies are relatively recent and the follow-ups are not long enough, it is not yet possible to say that the results are stable and there are no recurrences at a distance of a long time.

In conclusion, topical PDT is minimally invasive, economical, easy to perform, and well tolerated by patients, and at present, no severe adverse reactions are reported in the literature. Although further studies are needed, PDT fits perfectly into the panorama of alternative methods to traditional therapies in treating benign lesions of the soft tissues of the oral cavity.

Conflict of interest

Authors declare no conflict of interest.

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Table **1** The entire list used in the search and the combinations used in the research phase

Searchtopic	**Searchterms (September 2020)**		
PotodynamicTherapy or PDT	and #2	and #3	and #4
			and #5
			and #6
#1	and #2	and #7	and #4
		and #8	and #4
		and #9	

		and #10	
		and #11	
		and #12	
		and #13	
		and #14	
		and #15	
		and #16	
		and #17	
		and #18	
		and #19	
		and #20	
		and #21	

1. Photodynamic therapy or PDT; 2. Topical; 3. Oral; 4. Mucosa; 5. Lesion; 6. Lesions; 7. Mouth; 8. Buccal; 9. Lip; 10. Lips; 11. Tongue; 12. Lingual; 13. Palate; 14. Palatal; 15. Cheek; 16. Cheeks; 17. oral floor; 18. Gum; 19. Gums; 20. Gingiva; 21. Gingival.

Table **2** Study characteristics of the 21 included studies.

Authors	Year of publication	Lesions	Cases and controls	Photosensitizer drug	Photoactivator light tool	Protocol timing	Comparison
Abduljabbar[4]	2017	Denturestomatitis	22 cases	Haematoporphyrin derivative (Photogem, Photogem LLC Co, Moscow, Russia) 500 mg/L	LED (LXHL-PR09; Luxeon III Emitter, Lumileds Lighting, San Jose, CA, USA); wavelength: 440 nm - 460 nm and 102 mW/cm2 power (122 J/cm^2 fluence)	Number of session: NS. Exposure time: 20 minutes.	___
Afroozi[44]	2019	Denturestomatitis	28 cases and 28 controls	Indocyanine green (ICG) (Diagnostic Green GmbH, Germany)1 mg/ mL	810 nm diode laser (Polaris2, Poland) 56 J/cm^{2}fluence	Number of sessions: one a week for two weeks. Exposure time: NS.	Nystatin 100,000 IU, 20 drops 3 times a day for 15 days
Aghahosseini[25]	2006	OLP	2 cases	MB solution (0.05 gr per 100 cc)	Diode laser (Lumina®, Russia; light exposure dose: 100 J/cm^2; wavelength: 632 nm)	Number of sessions: 1 session. Exposure time: NS.	___
Alrabiah[43]	2019	Denturestomatitis	18 cases and 18 controls	450 µg/mL MB solution	GaAlAs diode laser emitting at λ= 660 nm, 100 mW power; energy density at 28 J/cm^2	Number of sessions: 2 a week for 4 weeks. Exposure time: 280 seconds.	Nystatin 100,000 IU, 4 times a day for two weeks (for 60 s and expectorate).
Bakhtiari[29]	2017	OLP	15 cases and 15 controls	5% MB solution	LED (Fotosan, Denmark; light exposure dose: 7.2–14.4 J/cm^2; wavelength: 630 nm)	Number of sessions: 4 sessions (in the days of 1, 4, 7, 14). Exposure time: irradiating lesions for 30 s	Dexamethasone (0.5 mg in 5 ml) of aqueous mouthwash for 2 min, 4 times a day for two weeks. (Nystatin

						up to 2 min (spot technique).	100.000 unit for 5 min prevented oral candidiasis).
Casu[39]	2017	RAS	1 case	TB solution (0.1 mg/ml)	LED (FotoSan 630, CMS dental, Denmark, Dentalica; fluence rate: 2000 to 4000 MW mW/cm^2; wavelength: 630 nm)	Number of sessions: 1. Exposure time: 30 seconds cycles in 10 consecutive times.	___
Cosgarea[37]	2020	OLP	20 cases	HELBO® Blue photosensitizer	HELBO® eraLite Laser (Bredent® Medical GmbH&Co.KG, Senden, Germany): 200 mW/cm^2 output power; 660 nm emission	Number of sessions: 4 sessions at days 1, 3, 7, and 14. Exposure time: 30 seconds/spot.	___
de Oliveira Mima[40]	2012	Candida species	20 cases treated with PDT; 20 cases treated with topical antifungal therapy	Photogem 500 mg/L	LED (light exposure dose: 37.5 and 122 J/cm^2; wavelength: 455 nm)	Number of sessions: three times a week for 15 days. Exposure time: NS.	Nystatin oral suspension 100,000 IU, 1 min gargle and expectorate, 4 times a day for 15 days.
de Senna[42]	2019	Denturestomatitis	18 cases and 18 controls	450 µg/mL MB solution	GaAlAs diode laser emitting at λ= 660 nm, 100 mW power; energy density at 28 J/cm^2	Number of sessions: 2 a week for 4 weeks. Exposure time: 280 seconds.	miconazole oral gel 2%, 3 times a day during a month
Jajarm[27]	2015	OLP	11 cases and 14 controls	TB solution (1 mg/ml)	GaAlAs laser (Mustang 2000, Russia; KLO3 probe; fluence rate: 10 mW/cm^2; wavelength: 630 nm)	Number of sessions: 2 sessions, two times a week for 1 month. Exposure time: 2.5 min in continuous wave.	Dexamethasone (0.5 mg in 5 ml water) mouthwash for 5 min, 4 times a day for a month (Nystatin 100.000 unit -30 drops - for 5 min prevented oral

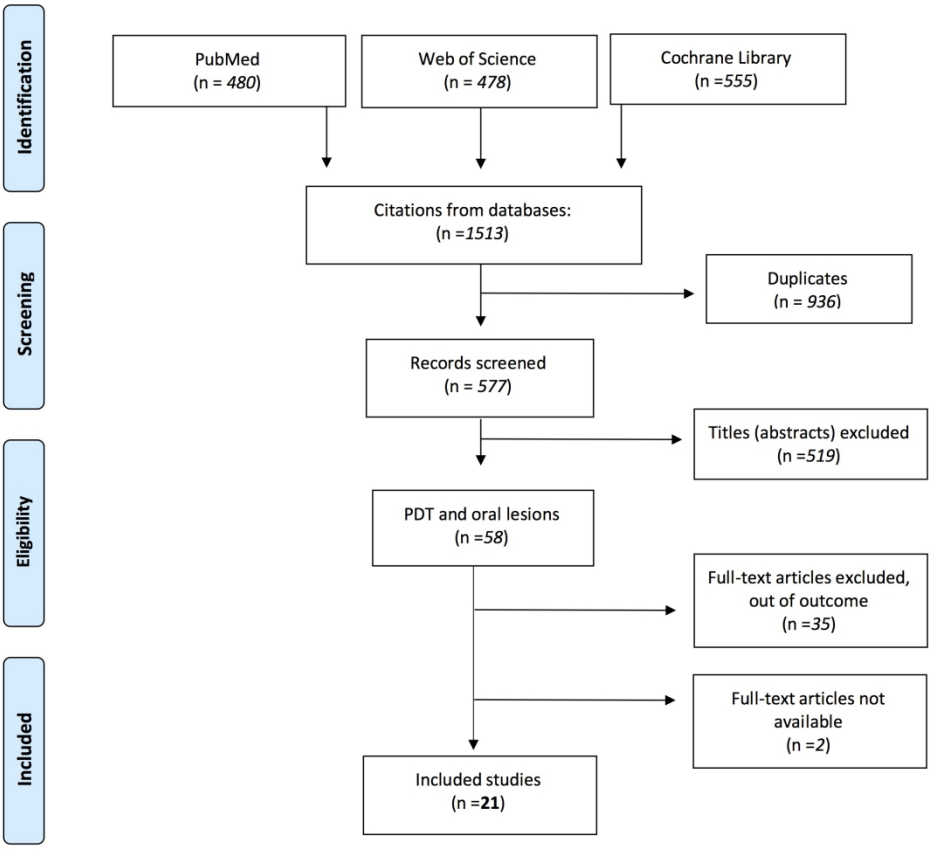
							candidiasis)
Jurczyszyn[33]	2018	OL, OLP	15 M and 20 F; 26 cases of OL and 9 OLP.	20% 5-ALA solution	LED red light (635 nm, Viofor PDT lamp); 120 J per lesion	Number of sessions and exposure time not specified. Each session was repeated every 3 weeks.	___
Kvaal[26]	2013	OLP	17 cases	MAL cream	LED (Luxeon I Emitter, Lumileds, San Jose, CA; fluence rate: 100 to 130 mW/cm2; light exposure dose: 75 J/cm^2; wavelength: 600 to 660 nm)	Number of sessions: 1 session. Exposure time: NS.	Only 1 side of the mouth was treated with MAL-PDT; the other side was left as a control.
Lavaee[35]	2019	OLP	11 cases and 11 controls	TB solution (1 mg/ml)	diode laser InGaAlP 660 nm 25 mW, fluence: 19.23 J/cm^2	Number of sessions: 3 session. Exposure time: 10 minutes.	Topical triamcinolone acetonide 0.1% three times a day (Nystatin 100.000 unit -40 drops - for 4 min prevented oral candidiasis)
Maloth[28]	2016	OLP, OL	OLP = 4 cases and 4 controls; OL = 7 cases and 6 controls	98% ALA solution	LED (QHL 75, Dentsply; fluence rate: 500 mW/ cm^2; wavelength: 420 nm)	Number of sessions not specified. Exposure time: 10 min (fractionated therapeutic time at 3 min).	Conventional therapy (NS)
Mirza[32]	2018	OLP	45 cases: 15 PDT, 15 LLLT, 15 DT	TB solution (1 mg/ml)	GaAlAs laser (fluence rate: 10 mW/cm2; light exposure dose: 1.5 J/cm^2; wavelength: 630 nm)	Number of sessions: Two sessions, two times a week for 1 month. Exposure time: 2.5 min in continuous wave.	Dexamethasone (0.5 mg in 5 ml water) mouthwash 5 min 4 times a day for 1 month (Nystatin 100.000 unit -30 drops - for 4 min

							prevented oral candidiasis)
Mostafa[31]	2017	OLP	10 cases and 10 controls	5% MB solution	Diode laser (fluence rate: 100–130 mW/cm^2; wavelength: 660 nm)	Number of sessions: one session a week for 2 months. Exposure time: multiple spots (70 s for each spot).	Topical triamcinolone acetonide 0.1% 3 times a day
Ribeiro[45]	2016	PCM	1 case	37.5mg/L TB	InGaAlP wavelength 660 nm; 40mW power; 100 J/cm^2 fluence.	Number of sessions: NS. Exposure time 100 seconds per point (8 points).	___
Romano[36]	2019	OLP	5 cases	TB	LED FotoSan® 630 device (CMS Dental, Elmevej, Denmark)	Number of session: variable. Exposure time: 150 seconds.	___
Saleh[38]	2020	OLP	10 cases and 10 controls	5% MB mouthpath	Focal red light (wavelength 660 nm, Intensity 100−130 m W/ cm^2)	Number of session: 2 a week for 4 weeks. Exposure time: 120 seconds (spot technique).	Betamethasone valerate ointment 100 mg three times per day for four weeks
Scwingel[41]	2012	Candida species and Denture stomatitis	7 cases and 14 controls	450µg/mL MB	(Twin Laser, MM Optics), wavelength 660 nm, 30 mW power, and 7.5 J/cm^2 fluence	Number of session: NS. Exposure time: 10 seconds per point (spot technique).	Fluconazole, 100 mg/day during 14 days
Sulewska[34]	2018	OLP	50 cases	5% 5- ALA gel solution	LED emitting light diode lamp (Seoul Semiconductor R11292); 630 nm wavelength, 300 mW power and 150 J/cm^2 fluence.	Number of session: 10 weekly sessions. Exposure time: NS.	___

Table **3** Risk of bias assessment for individual studies.

	Bias due to confounding	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall bias**
Abduljabbar (2017)	UR	MR	LR	UR	LR	LR	LR	**MR**
Afroozi (2019)	LR	LR	LR	LR	LR	LR	LR	**LR**
Aghahosseini (2006)	UR	MR	MR	MR	LR	MR	MR	**SR**
Alrabiah (2019)	UR	LR	LR	LR	LR	LR	LR	**LR**
Bakhtiari (2017)	UR	LR	LR	LR	LR	LR	LR	**LR**
Casu (2017)	UR	MR	MR	MR	LR	MR	MR	**SR**
Cosgarea(2020)	UR	LR	MR	MR	LR	LR	LR	**MR**
de Oliveira Mima (2012)	UR	MR	LR	LR	LR	LR	LR	**MR**
de Senna (2019)	UR	LR	LR	LR	LR	LR	LR	**LR**
Jajarm(2015)	UR	LR	LR	LR	LR	LR	LR	**LR**
Jurczyszyn (2018)	UR	MR	LR	MR	LR	LR	LR	**MR**
Kvaal (2013)	UR	LR	LR	LR	LR	MR	LR	**MR**
Lavaee (2019)	UR	LR	LR	UR	LR	MR	LR	**MR**
Maloth (2016)	UR	MR	LR	MR	LR	MR	LR	**MR**
Mirza (2018)	UR	LR	LR	UR	LR	MR	LR	**MR**
Mostafa (2017)	UR	LR	LR	LR	LR	MR	LR	**MR**
Ribeiro (2016)	UR	MR	LR	MR	LR	LR	MR	**MR**
Romano (2019)	UR	LR	LR	LR	LR	MR	MR	**MR**
Saleh (2020)	UR	LR	LR	LR	LR	MR	LR	**MR**
Scwingel (2012)	UR	MR	LR	LR	LR	LR	MR	**MR**
Sulewska (2018)	UR	MR	LR	LR	LR	MR	LR	**MR**

Figure **1** The flowchart summarizes the steps in the selection process.



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