Emerging Potential of Phototherapy-Induced Antioxidants in Management of Symptomatic Oral Lichen Planus: A Systematic Review of Randomised Controlled Clinical Trials

Abstract: Phototherapy incorporating; photobiomodulation therapy and antimicrobial photodynamic therapy has been utilised in symptomatic OLP management; however, its role of intervention remains controversial. The aim of this systematic review of CRD42021227788 PROSPERO registration reference was to oversee and determine phototherapy efficacy in patients with symptomatic OLP, identifying and bridging the gaps by proposing recommendations for future studies. A search strategy was developed consistent with the PRISMA statement. Various electronic databases were exercised to search for randomised controlled clinical trials (RCTs). PRISMA guidelines and Cochrane Collaboration recommendations followed. Several search engines were employed to analyse a total of 177 studies, of which nine included a wide range of utilised laser and light-emitted diode wavelengths between 630nm-808 nm noted and irradiance ranged between 10-13mW/cm^2. 67% studies reported a high risk of bias and a high heterogeneity obtained from numerical data for quantitative analysis, therefore meta-analysis was impossible to conduct. Despite the inconsistency and diversity in the phototherapy parameters, treatment protocols, photosensitiser (type, concentration and method of application) and outcomes assessment tools, the majority of the included studies showed positive results compared to standard care treatments. Hence, a necessity to perform well-designed RCTs with robust methodology is warranted, after acknowledging the drawbacks and addressing the suggested recommendations highlighted in our review.

1. Introduction

1.1 Oral lichen planus (OLP)

OLP is a chronic inflammatory, autoimmune (T lymphocyte-mediated immunological origin), mucocutaneous condition/disease of the oral mucosa [1-3], associated with a wide range of clinical presentations, including; white reticular patches, erosive/ulcerative and atrophic lesions associated with intense symptoms, which can significantly impair quality of life (QoL) [4-6]. Atrophic form of OLP has a higher potential risk of malignant progression than non-atrophic OLP [7]. The two most important histological features of OLP are as follows: infiltration of the subepithelial band-like inflammatory cell predominated by lymphocytes and destruction of the epithelial basal cell layer [8,9]. It is characterised by abnormalities in the growth and differentiation of the basal keratinocytes whose surface antigens are modified, due to primary autoimmune damage [10], leading to a delay in the mucosal epithelium growth that is responsible for hyperkeratosis and acanthosis [11]. OLP is considered as one of the oral potentially malignant disorders (OPMDs) with transformation into squamous cell carcinoma [12], nevertheless, the rate of malignant transformation is low [13,14]. OLP lesions tend to exhibit relapses and various remissions behaviours [15].

1.2. Pathogenesis of OLP

1.2.1. Role of Oxidative Stress in OLP Pathogenesis

Several studies have shown that oxidative stress (OS) plays an important role in the molecular pathogenesis of OLP [16-20] as it is dependent on T lymphocytes [21]. It has been shown that patients with OLP and OSCC are more susceptible to an imbalance of antioxidant-oxidative stress status [22]. A study by Darczuk et al., 2016 showed lower levels of glutathione and total antioxidants capacity in the saliva of patients with OLP, indicating free radicals and causing oxidative damage, which can ultimately play a vital part in OLP pathogenesis.

An increase in the level of oxidative damage markers such as; thiobarbituric acid reactive substances [23] and matrix metalloproteinase-9 (MMP-9) [24] and activation of oral mucosal keratinocyte heat shock protein (HSP) expression in OLP can contribute in its pathogenesis [25].

Importantly, HSP70 immuno-expression could be an objective marker for the presence of epithelial dysplasia in OLP [26].

1.2.2. Role of reactive oxygen species (ROS) in OLP pathogenesis

It has been proved that reactive oxygen species (ROS) (superoxide, hydroxyl radicals) play an important role in inflammation-mediated carcinogenesis in OLP [27].

A study conducted by Tvarijonaviciute et al., 2017 showed alterations in total antioxidant status and reactive oxygen species (ROS) described in the saliva of patients with OLP [28]. It has been found that ROS produced by keratinocytes, fibroblasts and various inflammatory cells results in an imbalance between the pro-oxidants and antioxidants [36].

Several studies [29,30] showed higher levels of serum malondialdehyde in patients with OLP, indicating an increase in ROS production [29].

1.2.3. Proinflammatory mediators

Histamine, cytokines and bacterial Lipopolysaccharides (LPS) are proinflammatory mediators, which play a role in OLP pathogenesis [31,32].

A study by Salem et al., 2019 [33] showed that the human β-defensin 2 involvement is modulated by the following proteins [27,34]: p53, cycle rBMI, MMPs, transforming necrotic factor-alpha (TNF-α), Interleukin (IL)-6 and cyclooxygenase-2 (COX-2), which ultimately play role in OLP pathogenesis [35].

1.3 Current Pharmacotherapy in OLP Management

Two different approaches can be employed in the management of patients with OLP: a wait and see approach in asymptomatic cases or pharmacotherapy (both topical and systemic delivery routes) in symptomatic cases. [36]. Chamomile has been used to deal with diverse inflammatory disorders, as it has antioxidant, anti-inflammatory, antibacterial and immunoregulatory effects [37]. A RCT study conducted by Lornet et al., 2018 showed that topical chamomile application improved the clinical presentation of OLP [38].

Currently, topical corticosteroids are widely accepted as a standard treatment care [39], but also retinoids, calcineurin inhibitors and other immunosuppressants (azathioprine, cyclosporine) can be administered [40]. Some of these treatment options proved to be ineffective or partially effective and can be associated with side effects [41]. Although strong topical corticosteroid use seems to be therapeutically effective, in the treatment of symptomatic atrophic and erosive OLP [42]long-term usage of corticosteroid therapy can lead to local complications such as; mucosal atrophy, local hyperpigmentation, candidiasis, xerostomia, prolonged healing or mucosal fragility and systemic complications such as; Cushing's syndrome, hyperglycaemia or glycosuria, adrenal insufficiency, gastrointestinal disorders, hypertension and corticosteroids resistance [43-45]. Hence, it is justifiable to seek alternative non-invasive therapies; such as phototherapy.

1.4. Phototherapy in OLP

In view of the above facts, it appears that alternative therapeutic approaches are needed for OLP management. Photonic therapy can be utilised as an alternative non-invasive clinical tool in symptomatic OLP management in form of; photobiomodulation (PBM) therapy and photodynamic therapy (PDT).

1.4.1. Photobiomodulation (PBM) Therapy

PBM is an antioxidant which acts as a free radical scavenger and neutralisess the excess of ROS. Hence, PBM therapy has a potential immunomodulatory, anti-inflammatory and analgesic effect as well as regenerative activities [46-49].

The therapeutic action of PBM is attributed to non-thermal photochemical or photobiological action of light via interaction with a range of endogenous photoreceptors and chromophores of the target tissue [50,51]. Photoreceptors and mediators of the photobiological action of visible and near

infrared (NIR) light include cytochrome c oxidase, nitrosated and flavo-proteins, opsins and ion-gated channels [52-54].

PBM light sources and laser and light emitted diodes (LEDs) are associated with various treatment protocols as well as parameters including: wavelengths, power outputs, fluences and emission modes [55]. LED arrays at optimal wavelengths penetrates tissue at a depth of approximately 23cm. Therefore, LED are an efficient alternative to lasers by being used as a combination of wavelengths with a broader beam width that enables treatments of larger areas with less heat production [55,56].

1.4.2. Photodynamic Therapy (PDT)

PDT is an effective and promising treatment modality in the management of OPMDs [57,58], it PDT is minimally invasive, with high selective tumour destruction preserving the healthy tissue, so is favourable over other conventional methods [57].

PDT is based on activation of a non-toxic, photoactive dye [Photosensitiser (PS)] at a specific wavelength of light from a laser or LED in the presence of oxygen. This results in the formation of toxic reactive oxygen species, such as singlet oxygen and free radicals, causing cellular damage, membrane lysis, and protein inactivation [59]. The illuminated area is attributed to the areas of marked mitotic cell activities of dysplastic or OPM lesions as a result of binding the PS to the nucleic markers [60]. On this note due to the immunomodulatory mechanism of PDT, the immuno-inflammatory pathogenesis of OLP responds effectively leading to photochemical and photobiological effects in OLP management [61].

The wavelength or wavelength bands and their associated photosensitisers (PS) are listed below [62]:

- UVA (400-450nm): Fullerenes (400nm), Titanium dioxide (400-450nm);
- Blue (375-475nm);
- Green wavelengths: Erythrosine (400-550nm), Rhodamine (450-590nm), Rose Bengal (480-600nm)
- Red wavelengths: Porphyrins and derivatives: Aminolaevulinic acid (ALA) (630nm), Methylene blue (MB) and Tolonium chloride or Toluidine blue, (TB) (630-660nm), Chlorins (650-670nm), Phthalocyanines (670-780nm);
- NIR: Bacteriochlorins (730-800nm), Cyanines: Indocyanine green (ICG) (810nm).

1.5 Rationale of conducting the present systematic review and meta-analysis

Utilisation of phototherapy expressed in PBM therapy and aPDT in management of symptomatic OLP can be an effective treatment in modulating pain intensity, reducing inflammation and promoting wound healing [63,64]. Nevertheless, its efficacy remains controversial due to a discrepancy in the reported results. After a comprehensive examination of the literature, the results of the recent six published systematic reviews and meta-analyses of RCTs of which five focused only onaPDT and one concentrated on both PBM therapy and aPDT between 2018-2021, showing a contradiction and a lack of consistency in the reported data. The drawbacks of these reviews are explained below:

A very recent systematic review and meta-analysis conducted by Wang et al., 2021 evaluated aPDT compared to topical steroids [65]. Only nine studies were included in this review and concluded that PBM therapy and aPDT could be effective and reliable alternative treatments to topical steroids in OLP management with no or less severe complications in the short-term. The authors suggested well-designed RCTs with long follow-up periods. However there was no indication of the drawbacks in the design of the included studies. This was supported by a systematic review conducted by Al-Maweri et al., 2018 reporting PDT is effective inthe management of symptomatic OLP [66], but due to the small number of included studies and heterogeneity among them, well-designed RCTs with large data arewarranted .

Another systematic review conducted by Akram et al., 2018 [67], favouring the effects of aPDT in symptomatic OLP management, but the review included a small number of studies according to their eligibility criteria and subsequently no subgroup analyses. Controversially, He et al., 2020 [68] conducted a recent systematic review and meta-analysis of the nine included RCTs comparing aPDT to topical steroids in the management of OPL. The authors concluded that aPDT has the same curative effect as the topical corticosteroids in treating symptomatic OLP. The drawbacks of this review were

that there are an insufficient number of trials that met its inclusion criteria, which ultimately undermined the significance of the results, especially in the subgroup analysis. Additionally, the placebo effect as well as other standard care treatments havenot been explored. Hence, no recommendations were extrapolated. Whereas, a systematic review by Jajarm et al., 2018 showed that aPDT failed to exert any significant effects on the symptoms of OLP [69].

A meta-analysis conducted by Jin et al., 2019 [57] reviewed 22 articles and analysed the effect of PDT on OPMDs, however, only six papers focused on OLP and the authors did not investigate the effect of different factors on PDT efficacy in OLP versus that in all OPMDs in the subgroup analysis. In terms of PBM therapy in OLP management, a systematic review conducted by Akram et al., 2018 [70] concluded that the effectiveness of PBM therapy remains debatable compared to the corticosteroids.

In the line with the above-mentioned notes, it prevails debatable scientific evidence, whether aPDT or PBM therapy is an effective treatment modality in symptomatic OLP management. Hence, it was a rational approach to carry out the present systematic review.

1.6 Aim and Objectives of the Present Review

The present systematic review is aimed to evaluate the existing contextual scientific evidence, rationalising the gaps in the literature and developing a conceptual framework to govern the efficacy of PBM therapy and aPDT in symptomatic OLP management. Whereas, the objectives of this research review were outlined below:

1. To explore the basis and extrapolate the reasons of the inconsistencies among the data.
2. To evaluate the sensitivity of results' methods of assessment and obtain vigorous standardised methodology.
3. To attempt to propose a preliminary empirical consensus of PBM-laser and LEDs dosimetry, and methodology for future randomised clinical trial (RCT) studies
4. To identify the most effective PS and matching wavelengths, taking into consideration the type, dose, route of delivery, incubation period and toxicity.

2. Materials and Methods

2.1. Protocol and PROSPERO Registration

The present systematic review was reported based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement and the Cochrane Collaboration recommendations (Supplementary File S1) [71,72]. A document affirming the protocol followed in this systematic review is published in the Prospective Register Of Systematic Reviews (PROSPERO) (CRD42021227788).

2.2. Population (P), Intervention (I), Comparison (C) and Outcomes (O)-PICO

P: Patients diagnosed with all forms of symptomatic OLP, according to World Health Organisation (WHO) and American Academy of Oral and Maxillofacial Pathology [73,74].
I: Patients were treated with either; PBM therapy or aPDT (LEDs or laser) or combined therapies; aPDT and PBM therapy.
C: Placebo (laser sham) group or any conventional standard care treatments.
O: Clinical parameters including; pain intensity, lesion response and remission or histological or immunological or psychological profile or salivary serum profile.

2.3. Focused Research Questions

1. Does a combined therapy of aPDT and PBM therapy have a synergetic effect compared to monotherapy of PBM therapy or aPDT in terms of clinical, histological or immunological profiles in patients with symptomatic OLP?

2. Does PBM therapy or aPDT have superior effects to pharmacotherapy in terms of; clinical, histological or immunological profiles in patients with symptomatic OLP?

2.4. Search Strategy

The search strategy included only terms related to, or describing, the study domain and intervention, which were conducted by three review authors (R.H., S.D., G.T.) independently. In order to assess inter-reviewer reliability analysis, Kappa (κ) statistics performed with a minimum value of 0.8 was deemed acceptable [75]. In case of any inconsistencies, a third review author (G.T.) was consulted to resolve the matter. The following search engines, using the relevant keywords and Medical Subjective Headings (MeSH) terms were systematically searched: MEDLINE (NCBI PubMed and PMC), EMBASE, CINAHL, Cochrane Library database, ProQuest, Scopus, ClinicalTrials.gov, Trial Registry for RCTs, comparing PMB therapy or aPDT or combinations of the two to placebo (sham) or standard care intervention, Cochrane Central Register of Controlled Trials (CCRCT), ScienceDirect, Google Scholar. Additionally, the following journals were hand searched: Photomedicine and Laser Surgery, Clinical Oral Investigation, Journal of Dental Research, Lasers in Medical Science, Journal of Photochemistry and Photobiology, Photodiagnosis and Photodynamic Therapy, Scientific Report (nature research), Photodermatology Photoimmunology & Photomedicine, Lasers in Medical Sciences. Grey literature sources were also screened. The electronic search thoroughly explored all the available literature data up to January 2022.

2.4.1 Relevant free keywords and MeSH Terms

The objective of the search was to identify all the relevant clinical randomised controlled trials (RCTs). In order to obtain a thorough, sensitive and specific approach for the electronic search, the search strategy included only terms relating to, or describing, the study domain and intervention. The use of relevant free text keywords, as well Medical Subject Heading (Mesh) terms that were logically connected with the help of appropriate Boolean operators, was performed.
"Oral lichen planus" **OR** "Symptomatic oral lichen planus" **OR** "Erosive lichen planus" **OR** "OLP" **OR** "Erosive atrophic oral lichen planus" **OR** "Potentially oral malignant lesion" **OR** "Reticular oral lichen planus"
AND
"Phototherapy" **OR** "Photodynamic therapy" **OR** "Photochemotherapy" **OR** "Photobiomodulation" **OR** "LLLT" **OR** "Photoimmunity" **OR** "low level laser therapy" **OR** "LLLT" **OR** "PDT" **OR** "Antimicrobial photodynamic therapy" **OR** "aPDT" **OR** "Photochemistry" **OR** "Photobiology" **OR "** Photosensitisers"
AND
"Corticosteroids" OR "Oral corticosteroids" OR "Dexamethasone"
AND
"Randomised controlled trials **OR** "RCT"

Each of the below MeSH terms was used to find the relevant literature from the search engines in section 4.2:
Photochemotherapy; photosensitising agents / therapeutic use; antimicrobial photodynamic therapy; photobiomodulation therapy; oral lichen planus; oxidative stress; reactive oxygen species; salivary biomarkers; topical corticosteroids; photosensitising agents; phototherapy; LLLT; PBM.

2. 5. Eligibility criteria

2.5.1. Inclusion criteria

1. *Study in vivo* human RCTs [split-mouth (SM) & parallel (P)] of ≥ 20 recruited subjects.
2. Subjects aged ≥ 18-years-old who where clinically and/or histologically diagnosed with unilateral or bilateral symptomatic OLP lesions based on the criteria proposed by the WHO [Modified World Health Organization (WHO) criteria] and American Academy of Oral and Maxillofacial Pathology (AAOMP) [72,73].
3. Studies recruited patients of ≥ four weeks symptoms of onset.

4. Studies recruited subjects with any form of symptomatic OLP with no. size restrictions.
5. Studies compared the efficacy of aPDT or PBM therapy alone or combined therapy (aPDT + PBM therapy) versus any conventional methods or shame control group.
6. Studies utilised any wavelength of laser or LED light source.
7. Studies with follow-up of at least four weeks.
8. Subjects associated with systematic diseases (ASA I & II) or not, smokers/non-smokers.
9. All forms of symptomatic oral lichen planus lesions with no lesion size restrictions (same as item 4?).
10. Studies utilised any type of PS dye (any dose, incubation period and method of application)
11. Studies utilising any wavelength of any light source (Laser and LEDs) for PBM or aPDT.(same as 6?)
12. Studies reporting at least one of the following parameters, as an outcome variable; clinical (pain intensity, lesion size, recurrence), or microbiological or immunological profile or psychological status
13. Articles published only in English language.
14. All the available published articles up to 31st January 2022.
15. No restriction on recorded or un-reported data or laser parameters of the selected studies.

2.5.2. Exclusion criteria

1. Any of the following types of studies: *In vitro, in vivo* and RCT of < 20 recruited subjects, protocol RCTs, case reports, non-RCT comparative, pilot, case series, abstracts, letters to the editor, opinion articles; abstract; review (narrative and systematic), unpublished articles, conference presentations, protocol, pilot, prospective and retrospective.
2. Studies with follow-up < four weeks
3. Studies compared efficacy of only PS to conventional therapy or to placebo.
4. Studies utilised surgical laser therapy or plants in combination with PBM or aPDT or as a comparative arm.
5. Subjects with lesions treated previously with phototherapy < three months prior to study enrolment.
6. No outcome variable of interest.
7. Subjects with lesions with mild dysplasia, moderate dysplasia, severe dysplasia or carcinoma in situ confirmed histologically.
8. Subjects with OLP lesion associated with other oral mucosal lesions.
9. Subjects with idiopathic plaque-like lichen planus (non-erosive), lichenoid drug eruptions
10. Subjects with asymptomatic oral lichen planus.
11. Immunocompromised patients or patients with systemic diseases of high complexity.
12. Subjects who used probiotic bacteria four weeks prior enrolling in the study.
13. Pregnant and lactating women.
14. Subjects with evidence of oral lichenoid lesions associated with graft-versus-host disease and systemic lupus erythematosus.
15. Subjects with co-existing chronic neuropathic orofacial pain
16. Severe systemic disease (ASA III or ASA IV) and/or some psychiatric conditions which might affect the participation of the study such as; schizophrenia.

2.6. Types of Outcomes Measures

2.6.1. Primary Outcomes

1. Pain intensity (PI) measured on VAS.
2. Clinical Improvement:
   a. Treatment efficacy
   b. Lesion response and improvement
   c. Lesion size or change of area.

2.6.2. Secondary Outcome Measures

1. Oral health-related QoL (OHR-QOL).
2. Anxiety and psychological profile.
3. Type of PS and number of aPDT sessions are required to obtain optimal results in post-operative healing of symptomatic OLP.
4. Salivary biomarkers (Histobiochemistry, immunofluorescence)
5. Histopathologic evaluation
6. Long-term stability of the therapy's outcomes
7. Proposing suggested recommendations of PBM therapy and aPDT protocols for future extensive research
8. Offering suggested recommendations for consensus in standardised methodology in studies investigating OLP management.

2.7 Methods of Assessment of Outcomes Measures

2.7.1. Clinical Efficacy Evaluation

The following four outcome measures collected to evaluate the clinical efficacy outcomes are listed below with their associated scoring indices:

2.7.1.1 Clinical Severity Index (SI)

Visual Analogue Scale (VAS) is a self-rated the pain intensity (PI) recorded by the subjects on scale of 0-10, when 0 means no symptoms and 10 severe with a Numeric Rating Scale (NRS) pain score, ranging from 0 -10: "0" for no pain at all, and "10" for the worst imaginable pain. Scores were grouped into three levels of "mild pain" (0–3), "moderate pain" (4–7) and "severe pain" (8-10) [76].

The amount of improvement in experienced pain was calculated by the following formula: N = 100% × (pre-treatment VAS score − post treatment VAS score)/ pre-treatment VAS score by which the results are classified as follows: score 5: a lack of pain or discomfort N = 100%; score 4: marked an improvement of 75% ≤ N < 100%; scores 3 and 2: moderate improvement 25% ≤ N < 75%; score 1: mild improvement 0% < N < 25%; score 0: no improvement N = 0).

2.7.1.2. Treatment Efficacy Indices

For determining the efficacy indices (EI) of the treatment (improvement of lesions), the following formula was used: [100% × (total score of lesions before treatment-total score of lesions after treatment)]/ total score of lesions before the start of treatment. Cut-off levels of 0.85 for the Safety index and 0.80 for the Efficacy index were set to determine successful results at last follow-up for these two indices, respectively.

The EI was rated by patient's self-reported score from 0–10, where 0 score means no symptoms and 10 means severe symptoms perceived by the subject. The, EI was evaluated on a five-rank scale listed below [77]:

E1: 75% substantial improvement.
E2: 75%-50% moderate improvement.
E3: < 50% mild improvement.
E4: 0%, no improvement.

2.7.1.3. Lesion Response Indices

The lesion response indicates the healing and improvement outcome which is as follows: complete response (CR): lack of visible lesion confirmed by clinical evaluation\ and no symptoms by patient-self reported and the remission of all atrophic/erosive lesions regardless of any persisting hyperkeratotic lesions; partial response (PR): at least 20% reduction in size of the lesion but no complete remission of atrophic/erosive areas and symptoms; no response (NR): < 20% reduction in size of the lesion or no changes from the baseline condition [78].

2.7.1.4. Changes in Size and or Area of Lesion and its Clinical Severity

The Digital Caliper Sign Score is utilised to evaluate lesions' size by using a digital caliper (accuracy 0.01 mm).

The severity of the lesion can be recorded based on the presence of reticular/hyperkeratotic, atrophic, or erosive/ulcerative lesion(s), using the reticular-atrophic-erosive (RAE) sores record the clinical signs and symptoms as follows: reticular score: R; atrophic score: A; erosive ulcerative score: E [79].

Thongprasom sign scoring (TSS) [80] is another tool to assess the OLP lesion based on the following scoring signs: score 5: white striae with an erosive/ulcerative area > 1cm^2; score 4: white striae with an erosive/ulcerative area < 1 cm^2; score 3: white striae with keratotic or atrophic or erythematous area > 1 cm^2; score 2: white striae with mixed keratotic and atrophic or erythromatous area < 1 cm^2; score 1: only mild white striae; score 0: no lesions, normal healthy mucosa.

2.7.2. Autoimmune Bullous Skin Disorder Intensity Score

Autoimmune bullous skin disorder intensity score (ABSIS) scoring system is a tool used to classify patients into different severity grades for better management and prognosis. ABSIS 2 scoring system is used to assess the extent of oral lesions on a scale from 0-11, whereas ABSIS3 is utilised to assess discomfort, while eating or drinking on a scale from 0-45. [81].

2.7.3. Functional Scores

Functional scores analysed the chewing function; swallowing, fluid intake and altered sense of taste as described by Lilleby et al. 2014 [82], which are based on the following scale of scoring: no difficulty: 0 points; mild difficulty: 1 point; moderate difficulty: 2 points; severe difficulty: 3 points; impossible: 4 points.

2.7.4. Histopathological Changes

The histological evaluation cannot confirm the diagnosis satisfactorily, the use of immunofluorescent examination is of great importance. Early diagnoses of these conditions are more likely with adjunctive use of immunofluorescent examination [83]. An evaluation of the histological changes [84] by analysing the plasma IL6 and IL8 levels [85].

2.7.5. Salivary Biomarkers

The histobiochemistry and immunofluorescence analyses are useful tools to evaluate the cytokines, OS and cortisol level in the unstimulated saliva samples obtained from patients with symptomatic OLP [86-88].

2.7.6. Anxiety and Psychological Profile

Beck Anxiety Inventory (BAI) [89] is a questionnaire with 21 multiple-choice items, addressing the common symptoms of anxiety. The score ranges from 0 -63 and is classified as follows: minimal anxiety: 0-10; mild anxiety: 11-20; moderate anxiety: 21-30; severe anxiety:31-63

2.7.7. Oral Health-Related Quality of Life

The following measurement tools can be utilised to evaluate the impact of OLP on patients' and Oral Health-Related Quality of Life (OHRQoL) in terms of physical, psychological and social dimensions [90]: Oral health Impact Profile-14 (OHIP-14) (short form) or 49 items (OHIP-49), consisting of only 8 items related to physical, psychological and social performance [91,92]; Chronic Oral Mucosal Disease Quality of Life Index (COMDQ) [94,95]; Oral Impacts of Daily Performance (OIDP) [93].

2.8. Data Extraction

Three reviewers independently [R.H., G.T., S.D.] selected the eligible studies from the search. They performed the review, assessment and data extraction for each eligible study. All eligible studies were given their unique identification with first author's name, publication year and origin. Also, the following additional relevant information was tabulated from each eligible study: journal's impact factor, study design; sample size; demographics of the participants; baseline characteristics; intervention and comparator groups; disease types and location; number of lesions.

Additionally, the other parameters utilised for qualitative synthesis were as follows: wavelength; light source (laser or LEDs); power meter use, power output; exposure time; light-tip diameter; energy density (fluence/dose); treatment interval; number of applications (frequency); treatment duration; PS type used, including the dosage and incubation time; relapse during follow-up; any adverse reactions during the course of treatment; statistical test performed; results; conclusions.

2.9. Qualitative Analysis

The Revised Cochrane Risk-of-Bias (RoB) tool for Randomised trials, Version 2.0 (RoB 2) was utilised to perform a qualitative assessment for each included study. This assessment was conducted independently by two reviewers (R.H. and S.D.) [94-96]. The criteria for assessment were divided under the following five domains:

1. Bias arising from the randomisation process.
2. Bias due to deviations from intended interventions.
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

Based on the fulfilment of questions pertaining to each domain, the studies received an overall score of low, moderate or high RoB. Discussions with a third author (G.T.) helped to mitigate any inter-reviewer disagreements in between the two primary reviewers (R.H. and S.D.). The 'discrepancy check' feature of the RoB 2 software was utilised sequentially in order to obtain a final judgement.

2.10. Statistical Analysis of Data

A statistical analysis of data was planned at the time of project inception. The aim was to assess the improvement in pain reduction (VAS) and clinical severity if any, from baseline visit to final follow-up visit independently for studies utilising aPDT or PBM therapy in comparison to topical corticosteroid (conventional treatment) in the management of OLP. Accordingly, we intended to extract all the available and relevant quantifiable data of interest from the included studies and combine the same for a possible for meta-analysis using RevMan (Version 5.4.1) [97]. A random effects meta-analysis for continuous outcome measures was planned to assess any expected heterogeneity. Since we have grouped studies utilising the two laser therapies namely; aPDT and PBM therapy separately in our project we aimed to conduct a distinctive MA on each. Calculation of the treatment effects would be done through pooled standardised mean differences (SMDs) with 95% confidence intervals (CIs). The statistical analysis for pooled overall effect was considered significant when $p < 0.05$ [5]. Additionally, forest and funnel plot analysis were planned to assess heterogeneity [I^2 statistics for homogeneity that ranged from 0–100% with the following interpretation: 0% = no evidence of heterogeneity; 30–60% = moderate heterogeneity; and 75–100% = high heterogeneity] [98-101].

Here, we would like to emphasise that in spite of all the efforts made to conduct a meaningful MA with significant findings, the authors were unable to collate the results owing to several notable discrepancies amongst the eligible studies. We have highlighted the various shortcomings in a tabular representation in our results.

3. Results

3.1. Study Selection

The search strategy utilised in the present systematic review has been illustrated in the PRISMA flow diagram (**Figure 1**). A total of 177 studies were identified through a combination of electronic database and manual hand searches which included 94 aPDT studies and 83 PBM therapy studies. Furthermore, five studies were additionally obtained through other sources of which two studies were based on aPDT and three studies were based on PBM therapy. Hence, the initial preliminary search included a totally of 182 study titles (inter-reviewer agreement, $\kappa = 0.94$). After scanning all the study titles obtained in the preliminary searches, 100 duplicate studies were excluded which resulted in a sample size of 82 studies (inter-reviewer agreement, $\kappa = 0.92$). A further 31 studies were excluded as these were studies related to asymptomatic OLP and irrelevant to PBM (inter-reviewer agreement, $\kappa = 0.96$). Consequently, 51 studies were included for a further evaluation (inter-reviewer agreement, $\kappa = 0.96$). These included 25 aPDT studies, 15 PBM therapy studies and one study which had combined

aPDT and PBM therapy study protocol. Twenty-five studies were excluded based on their title and abstracts (systematic reviews (n=5) [68,69,102-104], literature reviews (n=3) [66,105,106], aPDT case series/reports (n=8) [60,61,107-112], PBM therapy case series/reports (n=7) [113-119], conference abstract (n=1) [120], letter to editor (n=1) [121]. Therefore, 26 studies qualified for full text reading (aPDT studies: n=17, PBM therapy studies: n=8, aPDT +PBM therapy study: n=1) (inter-reviewer agreement, $\kappa = 0.96$). Eventually, a further exclusion of 17 full text papers (aPDT studies: n=13 and PBM therapy studies: n=4). Exclusion of 13 aPDT studies was performed based on the following reasons; pilot and prospective studies (n= 7) [122-128], no Laser/LED light source (n= 2) [129,130], RCT sample size ≤8 (n= 1) [131], photosensitiser compared to conventional therapy (n= 3) [132-134]. The reason for exclusion of the four PBM therapy studies were; non-RCTs (n= 3) [135-137] and RCT protocol only (n= 1) [138]. A list of all excluded studies has been provided in Supplementary File S3.

Thus, after conducting a meticulous search strategy based on a robust selection criterion, nine studies [139-147] qualified for a qualitative analysis in our systematic review (inter-reviewer agreement, $\kappa = 1$). These nine studies included four aPDT studies [139-141,143], four PBM therapy studies [144-147] and one study [142] had combined aPDT and PBM therapy study protocol. The PRISMA flowchart illustrates the above analysis (**Figure 1**).

3.2. Demographical Characteristics of the Data

3.2.1 Characteristics of Study Population:

3.2.1.1 Sample size

The sample of the included studies was classified as follows; n= 20 [140], n=25 [139], n= 30 [141,143,144], n=34 [147], n=42 [145], n=45 [142], n= 120 [146] (**Table 1**).

3.2.1.2 Gender distribution

In terms of gender distribution, seven studies included more than 50 femalesin their respective studies [139,141-143,145-147], whereas two studies [140,144] failed to provide any information on the gender distribution (**Table 1**).

3.2.1.3 Age Distribution

Two studies [144,147] mentioned the age of their study population to be under 20 years of age. The mean age range was 40-50 years in four studies [139,141,142,146] whereas the mean age range was 50-60 in one study [145]. while two study failed to provide any information on the age distribution of their study population [140], one study mentioned the age range of their study population as 33-76 years [143] (**Table 1**).

3.2.1.4 Characteristics of the Lesion: Type of Lesion/ Mean Lesion Size (cm^2)/ Site/ No. of Lesion(s)

The type of lesion was classified as; erosive [140], erosive atrophic [139,142,144], erosive reticular [141], erosive atrophic reticular [145-147], erosive erythematous [143]. Whereas the mean lesion size was mentioned in 4 studies [140,142,143,146] and it was ≤ 3 cm^2 in three studies [140,142,146] and 17.8 cm^2 in one study [143]. Five studies [139,141,144,145,147] failed to provide any information on the mean lesion size. Five studies stated in their respective studies that the site of lesion was the tongue and buccal mucosa [139,140,142,144,146].

One study stated that the lesions were found on the tongue, gingivae and buccal mucosa [143], one study mentioned the lesion sites as; tongue, labial mucosa, gingivae, palatal, alveolar ridge, floor mouth [145] and one study mentioned the lesion sites as; buccal mucosa, gingivae, tongue, palate, lips, alveolar ridge, floor mouth [147]. Only one study [141] failed to provide any information about the lesion site. While the number of lesions were mentioned as 51 in one study [143] and 224 in another study [145], whereas the remaining seven studies failed to provide this information [139-142,144,146,147] (**Table 1**).

3.2.2. Study Characteristics:

3.2.2.1 Country of Origin

Three studies were conducted in Iran [139,141,144], two studies each in Saudi Arabia [140,142] and Brazil [145,147] and one study each in Poland [143] and Turkey [146] (**Table 1**).

3.2.2.2 Study Design

Seven of the included studies have conducted a parallel-controlled RCT [139-142,144-146], whereas the remaining two studies have conducted a split-mouth RCT [143,147] (**Table 1**).

3.2.2.3 Intervention groups

Seven studies had two intervention groups [139-141,143-145,147] in which four of them were aPDT and control group [139-141,143], whereas in the remaining three studies, the intervention groups were LLLT and control group [144,145,147]. One study had three intervention groups namely; aPDT, LLLT and control group [142] whereas, one study had four intervention groups namely; LLLT, two positive control groups and one negative control group [146]. The various positive control groups were steroid which was utilised in all nine included studies [139-147], but one study also used ozone [146] (**Table 1**).

3.3. Documentation of aPDT Parameters vs Conventional Therapy

This section focuses on four out of the nine included studies [139-141,143] which utilised aPDT compared to conventional therapy in symptomatic OLP management (**Table 2**).

3.3.1. Utilised Wavelength [Wavelength (nm)/ laser or LED/ C or NC/ Laser-tissue distance]

Two [139,141] out of four studies [139-141,143] have utilised 630 nm wavelength whereas one study each has utilised 660 nm [140] and 650 nm [143] wavelength. Three out of these four studies [139,140,143] have utilised a diode laser, whereas one study has utilised LED as the light source [141]. Furthermore, three studies have mentioned the use of 'non-contact' mode for aPDT treatment [139-141], whereas one study has failed to provide this information. All four studies have failed to mention the laser tip-tissue distance [139-141,143].

3.3.2. Photosensitiser (PS) Characteristics [Type of PS/ concentration/incubation time (min) /applied method]

In terms of the type of PS and its concentration, three out of four studies have utilised 5% MB photosensitiser dye [140,141,143] whereas 1 study has utilised 1 mg toluidine blue dye [139]. The PS incubation time was ten minutes in three studies [139,141,143] and five minutes in one study [140]. Three out of four studies utilised a PS in mouthwash formulation; TB mouthwash [139], MB mouthwash [140,141], whereas one study utilised MB topical application of the PS [143].

3.3.3 Reported Energy (J)

All the four studies failed to provide this information [139,141,143,144].

3.3.4 Reported Power Output (W)

All the four studies failed to mention this information [139,140,141,143], but based on the reported parameters, we managed to calculate the power out in only two studies [139,142], which was 10mW for both of them.

3.3.5 Emission Mode

Three out of four PBM studies have utilised the continuous wave emission mode (CW) [139-141], whereas one study has failed to mention this specific information [143].

3.3.6 Use of Power Meter

All the four studies have failed to mention any information regarding the utilisation of a power meter [139-141,143].

3.3.7 Spot Size/ Fibre Tip Diameter

The spot size/fibre tip diameter information in the four studies was categorised as follows; 1 cm^2 [139], 0.8 cm^2 [143] and 8000 μm [141], whereas, one study failed to provide any relevant information [140].

3.3.8 Energy density [Fluence (J/cm^2)]

The reported energy density [Fluence] in three studies was; 1.5 J/cm² [139], 7.2-14.4 J/cm² [141] and 120 J/cm² [143]. One study failed to provide any relevant information [140].

3.3.9 Power Density [Irradiance (mW/cm²)]

The reported power density [Irradiance] in three studies was; 10 mW/cm² [139], 100–130 mW/cm² [140] and 1034 mW/cm² [143]. One study failed to provide any relevant information [141].

3.3.10 Irradiation Exposure Time (min/s)

All four studies have reported the irradiation exposure time as follows; 70 s [140], 120 s [141], 150 s [139] and 277 s [143].

3.3.11 Number of Sessions/ Duration (Week)

With regards to the number of sessions/ duration (week), the following information could be summarised from the four studies; eight sessions (twice a week/ four weeks) [139], eight sessions (once a week/ eight weeks) [140], four sessions (on days; 1, 4, 7, 14) [141], four sessions (on days; 1, 3 ,6 ,9 with every two-three days interval) [143].

3.4 Documentation of PBM Therapy Parameters vs Conventional Therapy

This section focuses on four out of the nine included studies [144-147] which have utilised PBM therapy in comparison to conventional therapy in the management of symptomatic OLP.

3.4.1. Utilised Wavelength [Wavelength (nm)/ laser or LED/ C or NC/ Laser-Tissue Distance

All four studies have utilised diode laser for PBM therapy [144-147]. With regards to the wavelength, two studies utilised 660 nm [145,147], whereas one study each utilised 630 nm [144] and 808 nm [146]. Furthermore, one study utilised the 'non- contact' mode with a laser -tissue distance as 0.5-1 cm [146], whereas, two studies utilised contact mode of application [145,147], where laser-tissue distance is not applicable. Only one study [144] failed to provide neither the method of application nor the laser-tissue distance [144].

3.4.2. Reported Energy (J)

Two studies have reported the energy as follows; total 0.24 J [145] and 0.5 J [147], whereas two studies failed to mention the energy parameter utilised in their respective study protocol [144,146].

3.4.3. Reported Power Output (W)

Three studies have reported the power output as follows; 40 W [145] 100 mW [146,147], whereas one study failed to provide this information [144].

3.4.4. Emission Mode

Three out of four studies have utilised the continuous wave emission mode [144,146,147], whereas only study failed to provide this information [145].

3.4.5. Use of Power Meter

All four studies have failed to mention any information regarding the utilisation of a power meter [144-147].

3.4.6. Spot Size/ Fibre tip diameter

The spot size/fibre tip diameter information in the four studies was categorised as follows; 1 cm² [144,146], 0.4 cm² [145] and 0.00283 cm² [147].

3.4.7. Energy Density [Fluence (J/cm²)]

The reported energy density [Fluence] in the four studies was; 1.5 J/cm² [144], 6 J/cm² /point [145] and 1.5 J/cm² /point and total 120 J/cm² [146], 176.671 J/cm² [147].

3.4.8. Power Density [Irradiance (mW/cm²)]

The power density [Irradiance] was reported in all four studies and was categorised as follows; 10 mW/cm^2 [144,146], 35.335 mW/cm^2 [147] and 1000 mW/cm^2 [145].

3.4.9. Irradiation Exposure Time (min/s)

All fourstudies have reported the irradiation exposure time as follows; 2.5 mins [144,146], 6 s [145] and 5s [147].

3.4.10. Number of Sessions/ Duration (week)

With regards to the number of sessions/duration (week), the following information could be summarised from the four studies as follows; eight sessions (twice a week/ four weeks) [147], 10 sessions (twice a week/ five weeks) [144,146], 12 sessions (three times a week/ four weeks) [145].

3.4. Documentation of PBM and aPDT Utilised Parameters vs Conventional Therapy

Only one study out of the nine included studies has utilised PBM therapy and aPDT in comparison to conventional therapy in the management of symptomatic OLP [142]. All the laser parameters utilised in this study have been summarised as follows; a 630 nm diode laser was utilised for both aPDT and PBM therapy and there was no information regarding the method of application, as well as the laser-tissue distance for both therapies. The aPDT utilised in this study had the following PS characteristics; 1 mg/ml toluidine blue PS dye utilised as a mouthwash. There was no information regarding the PS incubation time [142]. The energy was not reported for both PBM therapy and aPDT [142]. The utilised power output was 10 mW in both PBM therapy and aPDT.

A continuous wave emission mode was utilised in both aPDT and PBM therapy [142]. There was no information regarding the use of a power meter in the study protocol. The spot size/ fibre diameter was 1 cm^2 for both aPDT and PBM therapy. The energy density (fluence), power density (irradiance) and irradiation exposure time for both therapies were 1.5 J/cm^2, 10 mW/cm^2 and 150 s each, respectively. The number of sessions/duration (week) for aPDT was eight sessions (twice a week/ four weeks) and for PBM therapy was 10 sessions (twice a week/ five weeks) (**Table 2**).

3.6. Main Outcomes of Included Studies

3.6.1 Key Characteristics of the Outcomes Assessment tools

Based on the available data, a graphical representation of the assessment tools has been depicted in **Figure 2**. All assessment tools were broadly classified under three categories namely; pain assessment tools, functional improvement tools and anxiety/depression and QoL assessment tools. Furthermore, each tool was sub-categorised as; qualitative and quantitative tools based on the data obtained from **Table 3**, which is the proposed suggested recommendations by the authors of the present systematic review obtained from the included studies (**Table 1**) and the available literature data.

Depending on the tool utilisation in the total number of studies an overall graphical representation and percentage tool utilisation score based on the qualitative and quantitative outcome measures was derived. It was observed that the various pain and functional improvement assessment tools were the most commonly assessed methods amongst the three categories. Both these tools were assessed in all nine included studies [139-147]. Furthermore, it was noted that all the included studies have utilised only VAS as a qualitative outcome measure and received a 100% tool utilisation score. With regards to the functional improvement tools, one out of the nine studies [143] has utilised ABSIS 3, as a qualitative outcome measure (11%), whereas all nine studies have utilised the following quantitative outcome measures: RAE, TSS and lesion size (100%). The anxiety/depression and QoL tools were utilised in two out of the nine studies [143,145] and these were the following qualitative outcome measures: OHIP-14, OHRQoL and BAI (22%).

3.6.2. Antimicrobial Photodynamic Therapy Versus Conventional Therapy

The following are the various outcome measures in the studies which have compared aPDT to conventional therapy in the management of OLP; Jajarm et al., 2015 [139] [VAS, RAE, TSS, EI/pain

intensity, lesion size, RR], Mostafa et al.,2017 [140] (VAS, DD, PI, lesion size), Bakhtiari et al.,2017 [141] (VAS, EI, RAE, SI, TSS, PI, treatment efficacy, lesion size), Zborowski et al., 2021 [143] (TSS, ABSIS, VAS, OHIP-14, OHRQoL/ PI, FS, lesion size).

Table 4 illustrates the relationship in between the aPDT protocol followed in the four included studies in comparison to the results obtained by the authors. The results in the above table have been described in terms of level of significance (significant/ not significant) for clinical outcomes of various methods of assessment for aPDT group which have been elaborated in **Tables 1 and 3**.

It can be appreciated that two out of four studies utilised 650-660 nm diode laser wavelengths, along with 5% MB for aPDT [140,143]. One study utilised 630nm diode laser and 1 mg/ml TB, whereas the other study utilised 630nm-LED and 5% MB. In terms of the level of significance for clinical outcomes, the three studies which have utilised MB as PS irrespective showed statistically significant results irrespective of the light source [140,141,143], whereas the authors of the study that utilised TB, as PS along with 630 nm diode laser have reported insignificant results for aPDT [139].

3.6.3. PBM Therapy Versus Conventional Therapy

The following are the various outcome measures that were utilised in the included studies, comparing PBM therapy to conventional therapy in the management of OLP; Jajarm et al., 2015 [144] [VAS, TSS, RAE, EI, PI, lesion size, RR], Dillenburg et al.,2014 [145] [BAI, VAS, FS, TSS, PI, clinical score, lesion size, lesion response], Kazancioglu & Erisen 2015 [146] [VAS, RAE, TSS, EI, PI], Ferri et al., 2020 [147] [VAS, TSS, photographs/ PI, clinical score, clinical resolution, RR].

3.6.4. PBM therapy and aPDT Versus Conventional Therapy

Only one study has compared PBM therapy and aPDT to the conventional therapy in OLP management [142] and the following tools of assessment were assessed: VAS, EI, RAE, TSS/PI, RR.

3.7. Quality Assessment of the Included Studies.

An assessment of the study's quality was conducted using the RoB 2 tool, which is specially designed for *in vivo* PG and SM human RCTs [94-96]. **Figure 3** outlines the risk of bias results of the individual studies based on the five domains as mentioned in the methodology section. **Figure 4** is a graph which depicts the RoB score for each risk domain based on cumulative percentage data obtained from the nine included studies using the abovementioned tools. The information provided in these figures is based on the consensual answers of two independent reviewers (R.H. and S.D.). The results were verified using the 'Discrepancy check' feature of RoB 2 tool, across (inter-reviewer agreement, $\kappa = 0.92$) any discrepancy was resolved by a discussion with a third author (G.T.).

In terms of the randomisation process, 44% of included trials were at a high and low risk of inadequate randomisation each, whereas 12% had some concerns, respectively. 56% of the included studies were at a high risk of deviations from intended interventions, whereas 44% of them were at a low risk of bias. There was substantial evidence (100%) for reporting missing outcome data along with a low risk in all the included studies. 44% of the studies report high RoB arising from reporting outcome measurement and 56% reported a low RoB. In terms of selective reporting of the results, all included studies showed a low risk (100%). Overall, 67% studies reported a high risk of bias and 33% low risk of bias.

3.8. Follow-up evaluation

All studies performed an initial baseline evaluation in their respective studies. With regards to the follow-up evaluation in the included studies of this systematic review, a diverse report was collated from the available information which has been presented in **Table 1**. In the studies which utilised the aPDT protocol, the follow-up duration after treatment completion was classified as four weeks [139], two-months) [140], Days 15, 30, 60 & 90 [141] and three-months [143]. In the studies which utilised the PBM therapy protocol the follow-up duration after treatment completion was classified as; one study has utilised the following protocol; PBM therapy group- during treatment: weekly and after treatment:

three-months, six-months and 12-months, whereas the control group: weekly during the treatment (one-month) [144] whereas one study utilised the following protocol; during treatment: once a week, (days seven, 14, 21 & 30) and after treatment: four weeks (day 30), eight weeks (day 60) [145]. Furthermore, one study has utilised the following follow-up protocol after treatment completion; one-month, three-months and six-months [146], whereas one study has utilised the following protocol; once a week during treatment, 30, 60 and 90 days [147]. In the study which utilised aPDT and PBM therapy protocols compared to the conventional treatment, the following follow-up protocol after treatment completion was utilised; one-month and 12-months) [142].

3.9 Quantitative assessment

As stated in our study methodology section, the authors of this systematic review had planned to perform a meta-analysis of the reported outcomes in order to assess the improvement in pain reduction (VAS) and clinical severity if any, from baseline visit to final follow-up visit independently for studies utilising aPDT or PBM therapy in comparison to topical corticosteroid (conventional treatment) in the management of OLP, after thorough scrutinisation of the available data in the included studies.

Table 5 is an overview of the limitations which we noted during meta-analytical numerical data extraction and after performing qualitative analysis of the eligible studies. During our assessment, the following confounding factors were detected with a dissimilar representation amongst the eligible studies; study design, high risk of bias based on qualitative analysis of each study, diversity in the assessed outcome measures and variations in presentation/absence of quantifiable data in the individual study results. Since the numerical data was not uniformly documented in the aPDT studies, a statistical analysis of numerical data could not be performed. Furthermore, for the PBM therapy cohort, relevant numerical data for analysis on pain assessment (VAS) was extracted from three studies, which have utilised the PBM therapy protocol in comparison to the conventional topical steroid therapy for the management OLP namely; Jajarm et al., 2011 [144], Dillenburg et al., 2014 [145] and Kazancioglu & Erisen 2015 [146] and on clinical severity from two studies namely, Jajarm et al., 2011 [144] and Kazancioglu & Erisen 2015 [146].

A highly heterogenous set of results was obtained after the numerical data was analysed in the MA software. Owing to the high risk of bias in two out of three abovementioned studies [144,145], the high heterogeneity obtained from MA results could not be mitigated using a subgroup or sensitivity analysis. The presence of all the above-mentioned confounding features amongst the eligible studies made it difficult for us to collate the numerical data for quantitative analysis. Hence, a decision to negate the entire MA was decided upon after a discussion with all the authors of this project.

Discussion

The therapeutic management of symptomatic atrophic/erosive OLP lesions, which are potentially malignant oral lesions, is of great challenge despite the presence of various pharmacotherapy which ultimately are not all successful in alleviating OLP symptoms [148,149] and are associated with adverse effects on long-term use such as; secondary candidiasis, mucosal atrophy and dryness, bad taste and delayed healing [41]. Hence, phototherapy has been examined to be a possible non-invasive alternative treatment modality to pharmacotherapy. In the present systematic review, we have scrutinised the available data to evaluate the effectiveness of PBM therapy and aPDT as a monotherapy or combined, compared to the conventional standard care treatment, with the possible reproducibility of the following parameters: treatment protocols, light dosimetry, methodology, outcomes measures and assessment tools and ultimately proposed suggested recommendations for future studies. Within this standpoint, our rigor and comprehensive review has unwrapped the fundamental RCTs' shortfalls and drawbacks, which are detailed below and we have provided proposed recommendations based on evidence-approach in science and practice to prevail over them.

4.1. Methodology Quality

4.1.1. Recruited Populations: Demographic and Characteristics and Sample Size.

All nine included studies have utilised an equal number of recruited subjects in each interventional and conventional/sham/control groups except in one study [139] where 11 recruited in aPDT and 14 in the conventional group. In terms of the sample size and gender distribution, one study [140] had the lowest recruited subjects of 10 in each group and all the nine studies exhibited unequal distribution of gender across the groups, where more? females were recruited than males. This is concise with the literature which shows that age and gender distribution leaned towards middle-aged females (who are particularly affected by OLP) [42,150]. However, it has not been yet conclusively clarified what the cause is of the higher OLP prevalence in female patients. The most prevalent location of OLP in the present systematic review was the buccal mucosa, in agreement with the available published literature [151,152].

4.1.2. Assessment of the Diagnostic Criteria

There has been a debate on the best diagnostic criteria of symptomatic OLP. Some authors have reported that the clinical and the histological criteria are sufficient for an accurate diagnosis including the cases associated with erosive OLP [153,154]. Whereas others have recommended immunofluorescence assessment when the histopathological evaluation is insufficient, as well when there is a need to rule out particular autoimmune diseases such as; pemphigus vulgaris and mucous membrane pemphigoid (MMP) [155].

Based on the abovementioned notes and the evidence-based science and practice that we have gathered from our systematic review, we have proposed a suggested recommendation for OLP diagnostic criteria, which illustrated in **Table 6**. We have emphasised on the main compulsory and supplementary diagnostic criteria. The main compulsory diagnostic criteria are focused on the clinical presentation [156] and histopathological analysis [155], whereas the following supplementary diagnostic tools are focused on: Immunofluorescence (IF) assessment (Direct IF (DIF)/Indirect IF (IIF)] [155,157] and salivary profile [158,159] and biomarkers [160], reflectance confocal microscopy [161] and time-resolved fluorescence spectroscopy [162].

A work by Aziz et al., 2012 has demonstrated evidence of lower salivary and plasma levels of total antioxidant status in patients with erosive OLP compared with healthy controls, as well-infiltration of inflammatory cells, mainly of $CD4^+$ lymphocytes, which is a well-known source of ROS [163]. Combinations of several salivary proteins such as; C3c, fibrinogen fragment D and cystatin SA can be useful to diagnose OLP [164,165]. These diagnostic tools are considered as supplementary criteria to the main one (**Table 6**).

In summary, histopathologic diagnosis confirms the clinical diagnosis of OLP. The correlation between clinical presentation and histopathologic diagnosis is crucial for the definitive diagnosis of OLP. OLP necessitates an additional biopsy for DIF assessment and/or histopathologic evaluation, so continued clinical follow-up after the initial biopsy is essential. For a clear and precise definitive diagnosis, a thorough history and clinical presentation of lesions and histological assessment should be correlated with one or more of the complex assessment methods when it is required: histopathological, DIF, IIF, salivary biomarkers, reflectance confocal microscopy and fluorescence spectroscopy (**Table 6).** Extensive research work is needed to validate further the diagnostic criteria, perhaps by designing a homogeneous group of patients with OLP, which could lead to more accurate diagnosis strategies being unanimously accepted and applied. Moreover, it is important to highlight that WHO through the Global Oral Health Program (GOHP) had classified OLP as a premalignant condition back in 2005 [155]. Nevertheless, the malignant potential of OLP is still debated, due to a lack of consensus on accurate diagnostic criteria, thus the diagnosis being based only on clinical presentation in some cases [149,166]. Further work needs to address this to reach to diagnostic consensus.

4.2 Evaluation of the interventional treatment vs Conventional Treatment/Control/sham

4.2.1. PBM Therapy Effectiveness Versus Conventional Treatment

All four studies compared PBM therapy to corticosteroid as a control arm [144-147], exceptt two studies [144,146], which compared PBM to corticosteroid and nystatin (Antifungal) mouthwash as

a control [144] and PBM to ozone and corticosteroid as control groups and to placebo as a negative group [146]. It is noteworthy that all of the four studies have utilised different laser-PBM parameters with wavelengths ranging between 630nm-808 nm, irradiance (power density) between 10 mW/cm^2 - 1000 mW/cm^2 and dose (energy density) between 1.5 J/cm^2-120 J/cm^2. The results of these studies were controversial. There were a wide range of diversity in the outcomes among these four studies (**Table 1**).

An RCT conducted by Dillenburg et al., 2014 [145] showed a significant improvement in signs, symptoms and reduced recurrence rates of erosive OLP in patients treated with 660nm-laser PBM compared those treated with clobetasol propionate based on 30-and 60-days follow-up timepoints. This was supported by a case series study conducted by Cafaro et al., 2010 [119], demonstrating the effectiveness of PBM in the management of unresponsive OLP compared to standard care treatment. They reported a significant reduction in lesion size and in reported pain with LLLT when the following laser treatment protocol utilised: 904nm pulsed diode laser; dose: 4 J/cm^2, exposure time: 60s; spot size: 0.8 cm. They concluded that LLLT could be a possible treatment option for patients with unresponsive OLP.

Interestingly, an RCT study by Jajarm et al., 2011 [144], on the other hand, demonstrated that PBM was as effective as a topical corticosteroid therapy without any adverse effects, and could be considered as an alternative treatment for erosive-atrophic OLP in the future, and this was supported by an RCT conducted by Ferri et al. 2020 [147] where both corticosteroid (control) and PBM groups presented with similar clinical resolution & RR. This coincided with a study conducted by Akbulut et al., 2013 [167], comparing topical steroid effectiveness versus PBM therapy, where 63% of patients who were treated with PBM therapy had more than 50% lesion improvement; nevertheless, they concluded that PBM therapy was as effective as the topical corticosteroid therapy in reducing pain intensity and severity scores with no significant differences found between the two therapies. Controversially, Kazancioglu & Erisen 2015 [146] showed that corticosteroid therapy was associated with significant improvement of OLP compared to PBM and this was supported by studies conducted by El-Shenawy *et al.*, 2015 [135] and Othaman *et al., 2016 [137].*

Interestingly, a study by Mutafchieva et al., 2018 reported a greater reduction in pain and burning sensation in 12 patients with erosive-atrophic OLP compared to the lesion size when they were treated with 810nm-laser PBM at a power output of 0.5W, three times a week for a month [118]. Whereas, Mahdavi et al., 2013 [168] reported two cases of erosive OLP treated with 630nm laser-PBM and there was a significant reduction in pain and lesion size. They suggested that PBM therapy can be considered as a long-term maintenance therapy for symptomatic OLP. In this context, the authors of the present review are in agreement with the above authors, as PBM therapy is a non-invasive and non-accumulative dose therapy with significant value in reducing the clinical signs in patients with symptomatic OLP, including the erosive-atrophic form. This is due to the biological activities in enhancing proliferation, differentiation and migration of fibroblasts ultimately leading to stimulation of epithelial cells, which are considered the key influencers in the healing process of oral mucosa tissues [169].

Dose and irradiance of PBM application appear to play a fundamental role in therapeutic clinical outcomes, nevertheless, taking into consideration the diversity in laser parameters effective fluence and irradiance with precise values have not yet been established. Determining the number of irradiated points depends on the size of the lesion, therefore, a robust methodology in achieving a standardised protocol needs to be taken into consideration, as none of the included studies in this review reported the number of the irradiated points.

The treatment protocols of the included studies in this review were varied, and were associated with a high risk of bias, due to the lack of sample size calculation, methods of randomisation and treatment masking.

Taking all the above-mentioned notes and due to the lack of a well-designed RCT, evaluating the efficacy of PBM in symptomatic OLP compared to the standard care treatments remains unclear and debatable as to whether PBM therapy is a viable alternative option in treating symptomatic OLP, as the scientific evidence is weak. Hence, there is an urgent need for rigorous clinical RCTs studies to validate the efficacy of PBM in OLP.

4.2.2. Evaluation of aPDT Effectiveness Versus Conventional Therapy

All four included studies have shown to be controversial in aPDT effectiveness compared to the conventional therapy, which was corticosteroid [140,141,143] /corticosteroid and nystatin [139].

The wavelengths ranged between diodes laser 630-660 [139,140,143], whereas only one study by Bakhtiari at al., 2017 utilised LED 630nm [141]. Types of utilised PS, their concentrations, methods of administration and incubation period were as follows respectively: TB, 1mg/ml, mouthwash, 10 mins [139], MB, 5%, mouthwash, five mins [140], MB, 5%, mouthwash, 10 mins [141] and MB, 5%, topical application, 10 mins [143].

It is noticeable that the RCT of 30 subjects (15 in each group) by Zborowski et al., 2021 [143] that utilised 5% MB in a topical form at an incubation period of 10 mins has shown aPDT is more effective than topical steroid in reducing pain and lesion size with no side effects, compared to the steroid group which exhibited the following adverse effects: 14.3% of transient local burning sensation at the first two days and 9.5% of GIT. However, in this study, most of the essential laser parameters were unreported, therefore, it would be a great challenge to be reproducible. The other two studies that utilised 5% MB, as a mouthwash, but with incubation period of fivemins [140] (20 subjects) and 10mins [141] showed controversial results. An RCT study by Mostafa et al., 2017 (20 subjects) [140] showed that aPDT is more effective than corticosteroid group, whereas Bakhtiari et al., 2017 [141] (30 subjects) showed no significant differences between the two groups in relation to all the symptoms' improvement. The 4th study by Jajarm et al., 2015 [139] utilised TB (1mg/ml) as a mouthwash for 10mins showed that corticosteroid was more effective than aPDT in reducing pain and the RAE score was significantly lower in corticosteroid group compared to aPDT group.

In light of the above notes and the extrapolated data that is documented in the present review it is very challenging to justify whether aPDT or pharmacotherapy is more effective in symptomatic OLP. However, a systematic review conducted by Jaram et al., 2018 has shown that the method of PS administration and its incubation time play a crucial role in optimising the clinical outcomes [69].

4.2.3. Effectiveness of Combined aPDT and PBM Therapy Versus Conventional Treatment

An RCT study by Mirza et al., 2018 [142] tried to assess the efficiency of PBM therapy and aPDT compared to corticosteroid and nystatin mouth wash as a control group in the management of erosive OLP. Although the efficiency index was highest for PDT the maximum reduction in pain and burning sensation was obtained with topical dexamethasone.

It is reported that treating symptomatic OLP with aPDT has been shown to have better results in shorter-lived lesions versus more persistent lesions [170]. Therefore, we strongly believe that the effectiveness of combined therapies; aPDT and PBM therapy is more significant than monotherapy in improving the clinical signs and symptoms in patients with more persistent erosive/atrophic OLP compared to steroid therapy with no adverse-effects. Hence, further RCT are warranted to validate our hypothesis.

4.3. Suggested Recommendations Based on Science and Authors' experiences

4.3.1 Recommendations for PBM Reporting Parameters and PS choice for aPDT

A discrepancy between the interventional and control groups in terms of the follow-up timepoints was observed in all the included studies [139-147], which is shown in **Table 1** and documented in section 3.8. Therefore, a standarisation follow-up protocol should be implemented for both the interventional and control/sham groups in future clinical RCT studies in order to have valid, reliable and reproducible outcomes.

In the present systematic review, none of the nine included articles used a power meter (**Table 2**). It is important to emphasise the crucial role of using a power meter prior to the illumination process in order to establish the therapeutic power output reaching the target tissue and taking into consideration the optical properties of the lesion. Thereby, the investigator would obtain precise parameters to record, so that a standardised protocol can be provided [171-174].

In the light of above-mentioned notes, we could not produce a suggested recommendation for phototherapy protocols due to the following reasons: small sample size across the board, inadequate methods of randomisation and absence of treatment masking. Additionally, there is no consensus in

terms of; the optimal parametric dosimetry, power meter usage to measure the therapeutic power output reaching the target tissue, characteristic of PS and its method of administration and treatment protocol (number of sessions, time intervals between sessions, duration of treatment, length of follow-up period) for OLP patients treated with PBM therapy and aPDT. Nevertheless, we have suggested a recommendation on how to report the essential and desirable PBM treatment parameters, which is illustrated in **Table 7** [175]. This ultimately would assist in reproducibility of the future studies. Additionally, we have produced a suggested recommendation on reporting the essential aPDT treatment parameters regimen for future scholars and investigators to follow, which is illustrated in **Table 8.**

4.3.2 Proposed Suggestions of Outcome Measures and Assessment Tools

In order to obtain significant results the outcomes assessment tools need to be robust and reproducible, thereby, we have proposed suggested recommendations of outcomes measures and tools of assessment to be employed in extensive future studies based on various qualitative and quantitative measurements for primary and secondary outcomes utilised in the selected studies of this review and literature data, with consideration for salivary analysis to evaluate the levels of OS, NO, cytokines have been described below.

Table 3 illustrates the summary of the outcome measures assessment, which was categorised under six domains namely; qualitative [patient reported outcomes (subjective), quantitative (objective), salivary profile, immune-histology, histological analysis, direct immunofluorescence.

The qualitative outcome measures were classed under primary and secondary outcomes. Pain intensity reduction was the qualitative primary outcome measure, which was assessed by the following methods in the included studies; VAS, numerical scale of pain, OHIP questionnaire, McGill pain questionnaire and SSI. The qualitative secondary outcome measures were subdivided into two categories namely; functional improvement (assessment methods- atient-specific Functional scale, ABSIS 3) and Anxiety/depression & QoL [assessment methods- Beck anxiety inventory (BAI), Beck Depression Inventory (BDI), LISS, STAI, HADS, HAM-A, MACL, DASS, SCL-90, Pain distress scale/Euro Qol-5D-5L, OHRQoL, OHIP-14] and patient-reported outcomes measures (PROMs) [176].

The quantitative outcome measures, on the other hand, are classified as; primary and secondary outcomes measures. Pain intensity reduction is the primary outcome where the following assessment methods can be utilised: Kaplan-Meier method, pressure pain threshold *(PPT),* dial algometer [142], power algometer. Whereas, the secondary outcome measures are related to functional improvement, which can be evaluated by using the following assessment tools: digital caliper (lesion size), clinical severity index (SI), RAE score (lesion severity), ABSIS 2 (lesion severity), TSS (lesion ulceration status), lesion response indices and functional score scale (0-4 scoring).

The salivary profile was assessed under the following quantitative outcomes- enzyme-linked immunosorbent assay (ELISA) to assess oxidative stress, IL-1, 2, 4, 6, 8, 10, 17 and 18), TNF-α & β, MM-1,2 and 9, vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1), Insulin-like growth factor-I (IGF-I), IFN-γ, CXCL8, NO, sTNGR-2, Th17, Th1 to evaluate the level of cortisol, ELISA, CLIA and RIA. Whereas Serum levels of IL-1β, IL-6, IL-8, IL-10 and TNF-α can be analysed from blood sample and evaluated via ELISA.

The immunohistological assessment can be carried out for the following quantitative outcomes; high levels of CD207 and increase number of Langerhans cells. Additionally, histological assessment can be conducted in order to evaluate the lesion improvement and any dysplastic transformation [177].

The direct immunofluorescence was assessed quantitatively using the following methods; shaggy fibrinogen at the basement membrane zone (BMZ) with IgM deposition on the colloid bodies followed by shaggy fibrinogen along BMZ [178].

The serum and salivary levels of IL-6, IL-10, IL-1β, INF-γ and tumour necrosis factor-α can be evaluated by ELISA. Studies have shown that salivary analysis of NF-kappa B-dependent cytokines may be applied to monitoring the therapeutic response of OLP [179,180]. A work conducted by Rhodus et al., 2005 [181] proposed the determination of salivary cytokines, as a method of monitoring the evolution of OLP lesions. Further examination of these cytokines would expand our knowledge in understanding the molecular signalings and the biological mechanisms triggered by PBM.

It is noteworthy that the role of OS in OLP has been investigated [182] and the pathogenesis of this disease has been related to NO and ROS [183]. Numerous studies have described higher salivary

NO levels in patients with OLP than in healthy individuals [184] and elevated levels have been associated with a more severe disease progression through the production of mucosal lesions [183,185]. Hence, it would be crucial to measure the NO and OS to evaluate the effectiveness of PBM therapy in patients with symptomatic OLP and monitor the progression of OLP.

It is significant to mention that transient receptor potential ankyrin 1 (TRPA1) is activated by noxious stimuli such as; OS products, inducing pain and a release of proinflammatory mediators. This was shown in a study by Kun et al., 2017 [186] where the extra-neuronal presence and upregulation of the proinflammatory TRPA1 receptor in buccal samples of patients with OLP. This may be linked to the ion channel in OLP pathomechanism.

4.3.3. The Relationship Between OLP Phenotype and Wavelength's Choice

The authors of the included studies in the present review have employed a wide range of laser and LED wavelengths for PBM therapy and aPDT between 630-808nm wavelength, where reduction of pain intensity and lesion size were observed in almost all the wavelengths except at 660 nm where reduction in the OLP lesions frequency was reported in the study conducted by Dillenberg et al., 2014 [145]. It is noteworthy to highlight the relationship between the penetration depth of the wavelength photonic energy and the optical properties of the OLP phenotype.

OLP is characterised by sub-epithelial inflammation mediated by auto-immunity. Reticular OLP is characterised by Wickham striae, which is formed by an increase in the granular cell layer in the epithelium, hence, PBM wavelength of deeper penetration depth in tissue should be considered, as more structures have to be penetrated in reticular OLP. Whereas, erosive/ulcerative OLP is characterised by a defect in the epithelium that makes the penetration possible with a wavelength of a shallow penetration depth. In this context, red wavelengths are more easily absorbed by tissue surface components than infrared wavelengths. The absorbed energy can be dissipated in the form of heat around the skin surface. Conversely, the infrared wavelengths can penetrate deeply into the body tissues, which have lower scattering and absorption properties [187]. Another key contributor to the light penetration depth is the treatment area or spot size employed by the device. Spot size has important clinical implications due to its effect on light penetration and dispersion in the tissue [188].

In summary some of the key factors determining the light depth of penetration are as follows: target optical properties consistency, structure, thickness, skin colour, absorption/scatter coefficient) [189]/ type of the pathological lesion [190] (light source, wavelength, shape of laser beam, spot size, duration of irradiation exposure and applied tissue pressure. This can be considered as a guidance in choosing PBM parameters, according to OLP phenotype.

4.4. Phototherapy Safety and Patient Compliance Versus Corticosteroids Therapy

One of the advantages of PBM therapy in the management of OLP is patients' good compliance [16], as PBM is a non-invasive treatment modality that accelerates oral mucosal healing, reduces pain intensity and upregulates immunological cytokines [171,172,191].

Also, it is well-tolerated among paediatric patients. A case report by Pedro et al., 2018 demonstrated that PBM therapy was well-tolerated by an eight-year-old female patient with OLP with no evidence of lesion recurrence after a two-year follow-up period [192].

Interestingly, all the included studies have not reported any adverse effects with phototherapy groups, whereas, an RCT study by Zborowski et al., 2021 [143] reported 14.3% of transient local burning sensation at the first two days of treatment and 9.5% was related to GIT disturbances. This coincided with few reported documentations in literature [193,194].

Carcinogenesis in OLP may be regulated by the integrated signal from various tumour inhibitors (TGF-β1, TNF-α, IFN-γ, IL-12) and promoters macrophage migration inhibitory factor (MIF), and MMP-9 [51]. On this note, blocking these signals or up-regulating TGF-β1 activity in OLP may be a path for therapeutic strategies, in which PBM therapy can be one of them. On this note, extensive research works have shown the crucial role of PBM in activation of the endogenous latent TGF-β1 for accelerating wound healing [195,196] and the safety use of PBM in management of side-effects induced by oncology therapies in head and neck cancers [197].

It has been documented that symptomatic OLP that is not responding to corticosteroid therapy for a period of three-months or more are considered unresponsive lesions [40,198]. However, it is not yet clear, why OLP lesions can develop a resistance to corticosteroid treatments. Two explanations have been given in literature, suggesting that subpopulation of $CD4^{+}$T lymphocytes can develop resistance to the anti-proliferative effects of corticosteroids with prolonged use [163], where other authors suggested that the *p53* gene mutation may be responsible for certain cases of OLP resistance [199,200].

Most importantly, an OLP lesion that suddenly becomes unresponsive to topical steroids, after an initial responsiveness implies the potential of harbouring dysplastic features and increasing the possibility of malignant transformation [201], hence, the authors of this review strongly believe that PBM can be an alternative safe therapy to steroid in symptomatic OLP management, especially in cases that require long-term management.

In light of the above-mentioned notes, PBM plays a crucial role in reducing the possibility of malignant transformation of an erosive form of OLP by reducing pain or burning sensation and/or the lesion size or both. This ultimately can lead to transforming an erosive OLP lesion to an atrophic or a reticular type, which is a significant improvement, as the risk of malignant transformation is greatly reduced at both cellular and molecular levels along with the burning sensation [40].

One of out of the four studies showed 40% of those treated with 5% MB-aPDT for OLP one day after treatment were described to have a slight oedema [140]. This may be a form of phototoxic inflammation associated with histamine release [202]. This was supported by work conducted by Kvaal et al., 2013 reporting a mild burning sensation on the day of treatment and persistent discomfort for several days [203]. This is due to the formation of ROS and NO immediately after irradiation, as well as the release of pro-inflammatory cytokines and histamine and a neurogenic mechanism related to the activation of TRP receptors [202]. Controversially, other authors have reported that aPDT demonstrates consistent improvement in clinical presentations of symptomatic OLP without any adverse effects, regardless of the type of utilised PS such as; MB [204], photolon [205] or porphyrin [206].

Despite the above unpleasant adverse-effects of aPDT it remains a safe treatment modality in symptomatic OLP management and an alternative to topical corticosteroid therapy which has several serious adverse effects based on long-term use [66-68,207]. Moreover, there is insufficient evidence to consider the LED light profile as safer in this regard compared to the laser beam, whereas modulation of power density during radiation may provide a solution to this clinical problem [202].

4.5. Study Limitations

4.5.1. Quantitative Analysis of Eligible Studies

A systematic review conducted by Jajarm et al., 2018 [69] on 13 clinical trials (RCTs before and after trials) and a further meta-analysis on seven RCT respectively, in order to assess the effects of different phototherapy treatments on OLP. Sign score (Thongprasom) (three studies), pain (VAS) (three studies) and severity (two studies) were the outcomes which were assessed before and after LLLT in their quantitative analysis. Important conclusions made by the authors were; PBM therapy was effective in pain and clinical signs alleviation for OLP patients, whereas lesions treated with aPDT did not show any statistically significant clinical improvement. When compared to corticosteroids PBM therapy showed similar efficacy in pain and sign score improvement although PBM therapy was more effective in decreasing the severity of the lesion than corticosteroids. The authors have also highlighted the subjective nature of the measured outcomes which resulted in highly heterogenous results [69].

In the systematic review and meta-analysis conducted by He et al., 2020 [68], the authors have assessed PDT efficacy in the treatment of OLP and compared the efficacy of aPDT with steroid therapy. The authors have included the original articles, the clinical studies and the case series in their analysis.

Qualitative analysis of 16 studies followed by a quantitative analysis of 13 studies was performed by the authors. Lesion size (Six studies), Sign score (TSS) (Six studies) and pain (VAS) (Five studies) were assessed for outcome before and after aPDT, in their analysis. The authors have highlighted the presence of an insufficient number of trials meeting their inclusion criteria. Also, varying presentations of the outcome measures affected the data combination and this noticeably reduced the significance of the results, especially in the subgroup analysis and comparison with topical corticosteroids [68].

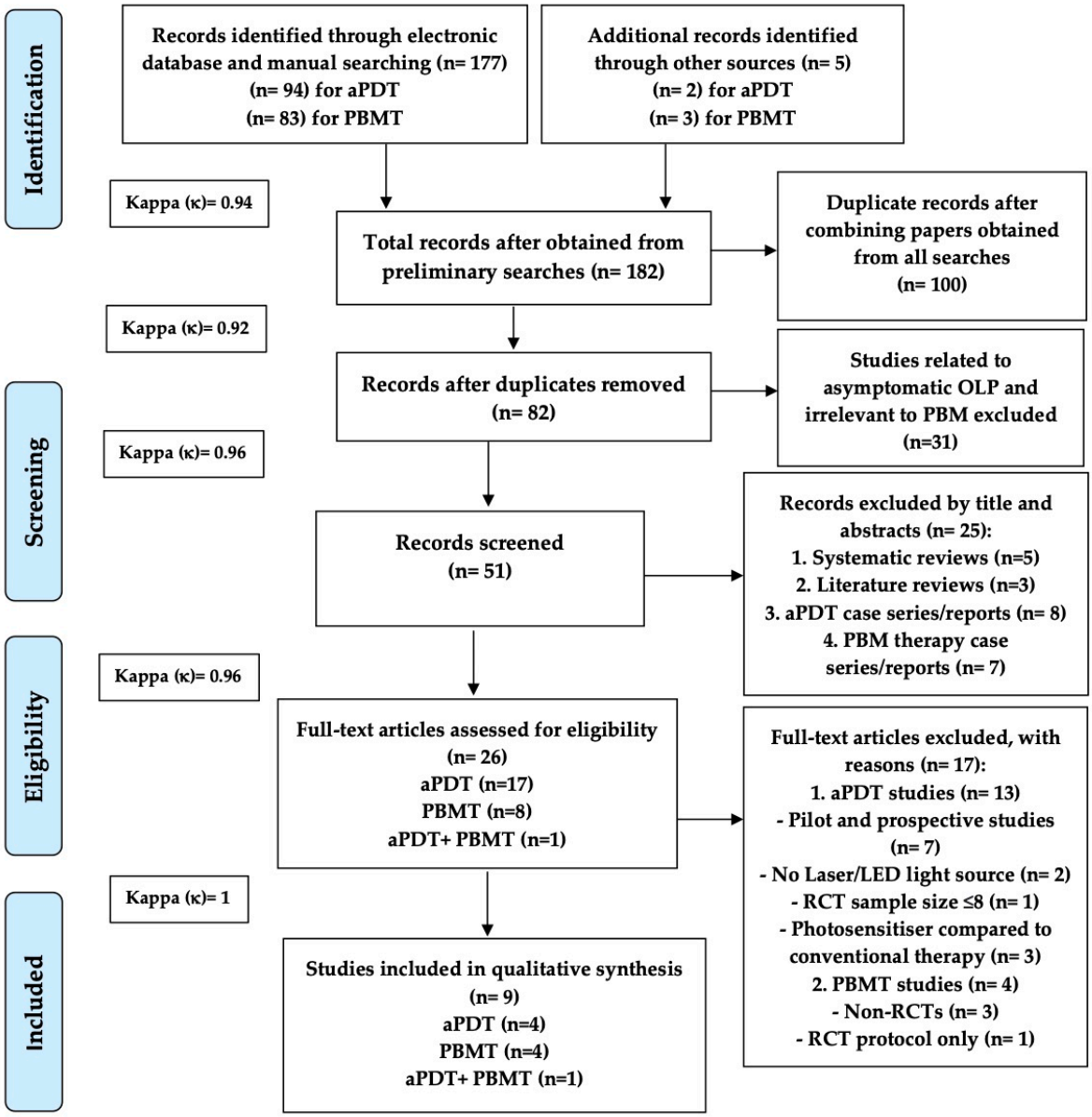
A systematic review on nine RCTs and meta-analysis on seven RCT conducted by Wang et al., 2021 [65], evaluating the efficacy of PBM therapy and PDT in the treatment of OLP. The results of this review reported a high RoB in five out of nine included studies along with no significant differences for sign scores (Thongprasom), pain score (VAS) and severity score for both PBM therapy and aPDT in comparison to the conventional corticosteroid treatment after one-month of follow-up period. The authors have supported the short-term application of PBM therapy and aPDT with no or less severe complications and as reliable alternatives to topical corticosteroids for OLP management and have also emphasised on the need for long-term well-designed RCTs for future research.

Some striking differences between the present systematic review and existing systematic reviews and meta-analyses [65,68,69] were as follows: study selection criteria resulting in variations in sample size and eligibility of included studies, the inclusion of PBM therapy and aPDT as treatment modalities for OLP, variation in protocol designed for quantitative analysis.

As highlighted in our results, we believe that the shortcomings and hindrances we experienced in conducting a potential meta-analysis with meaningful outcomes were also noted by the authors of previous studies [65,68,69] and these points should be addressed in future RCTs.

5. Conclusions and Future Directions

Phototherapy encompassed of aPDT and PBM therapy is considered a safe and effective advanced treatment modality for symptomatic OLP, even the erosive-atrophic forms, giving a remarkable and significant reduction in the symptoms and a fundamental improvement in patients' functionality and QoL without any adverse effects. However, due to the confined number of relevant published RCTs, limited sample size, heterogeneity in the phototherapy protocols, lack of standardised robust methodology and short follow-up periods, we could not formulate proposed treatment protocols. Nevertheless, we have provided recommendations for valid outcome measures with robust tools of assessments and a possible reproducible methodology and OLP diagnostic criteria for future extensive clinical RCTs, evaluating PBM therapy and aPDT effectiveness as a monotherapy or combined therapies, as well as examining the synergistic effects of the latter based on a long-term follow-up to ensure sustainability of phototherapy effects. Moreover, genetic studies to understand further OLP pathogenesis related to genetic polymorphism of some genes are warranted.



PRISMA flow-diagram of the study selective criteria.