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LUIZA DEITOS MENTI

# LÍQUEN PLANO ORAL: UMA OVERVIEW DE REVISÕES SISTEMÁTICAS

Porto Alegre
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Trabalho de Conclusão de Residência apresentado ao Programa de Residência Integrada em Saúde Bucal, da Faculdade de Odontologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para obtenção do título de Especialista em Estomatologia.

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CD Esp. em Estomatologia Mariana Klein
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“Faltar na própria vida é uma dessas ausências impossíveis de explicar. A conexão consigo mesmo, com o outro, com a natureza, com o mundo à sua volta e com o que cada um de nós considera sagrado exige, antes de tudo, um estado de presença.”

Ana Cláudia Quintana Arantes

## RESUMO

O líquen plano oral (LPO) é uma doença inflamatória imunologicamente mediada que acomete cerca de 0,89% da população mundial e sua apresentação clínica clássica é representada por estriações brancas localizadas principalmente em mucosa jugal bilateral, geralmente assintomáticas. Porém, dois terços dos pacientes que apresentam essa doença desenvolvem sintomatologia, podendo interferir significativamente na qualidade de vida destes indivíduos. Atualmente o tratamento de primeira escolha para o LPO sintomático é o uso de corticoides tópicos. Porém, diversas outras modalidades de tratamento estão descritas na literatura, especialmente opções que representem menos efeitos adversos e que tragam benefícios para casos refratários. Diante disso, o objetivo deste trabalho foi realizar uma overview de revisões sistemáticas acerca das modalidades terapêuticas para o LPO e propor um protocolo de tratamento com vistas a auxiliar na conduta do cirurgião-dentista. A busca nas bases de dados Scopus, Embase, Web of Science e Pubmed resultou em 428 estudos que, após remoção dos duplicados e triagem, foram incluídas 74 revisões sistemáticas para análise qualitativa final. Destes artigos, 35 estudos englobaram o uso de agentes naturais, 26 inibidores de calcineurina, 21 corticoides, 15 terapia fotodinâmica, 12 retinoides, 10 outras drogas imunossupressoras, 9 fotobiomodulação, 8 fototerapia com luz ultravioleta e 13 outras modalidades terapêuticas. Baseado nos resultados dos estudos incluídos na presente overview, o uso de corticoides tópicos é considerado como primeira linha de tratamento para as lesões de LPO, sendo que não há evidências de superioridade entre medicamentos desta mesma classe terapêutica. Em lesões refratárias, é recomendado o uso de inibidores de calcineurina, como tacrolimo e pimecrolimo. Em lesões múltiplas mucocutâneas, os corticoides sistêmicos são recomendados, pelo menor tempo que seja necessário para reduzir os potenciais efeitos adversos. Agentes naturais, retinóides tópicos e laserterapia podem ser empregados como adjuvantes em lesões refratárias à corticoterapia. O manejo com irradiação UV não é recomendado devido ao seu potencial oncogênico. A remoção cirúrgica ou com laser de dióxido de carbono para manejo do LPO somente é recomendada em lesões persistentes, pequenas e localizadas, não sendo recomendadas como possibilidade terapêutica de rotina. Os retinóides sistêmicos, outras drogas imunossupressoras e as demais modalidades terapêuticas citadas neste trabalho devem ser avaliadas com cautela devido aos efeitos adversos importantes. Além disso, carecem de evidência científica robusta que suportem a sua indicação no manejo das lesões de LPO. O risco de viés foi considerado baixo em 58,1% das revisões sistemáticas, moderado em 20,27% e alto em 21,62%. Apesar da heterogeneidade

encontrada na literatura em relação às diferentes modalidades e doses terapêuticas para o manejo do LPO, neste trabalho foi proposto um protocolo para auxiliar o cirurgião-dentista frente a casos de pacientes com LPO. Este protocolo foi concebido para fornecer uma abordagem estruturada e baseada em evidências para o manejo eficaz de casos de LPO, com ênfase particular naqueles que se mostram refratários aos tratamentos convencionais.

Palavras-chave: líquen plano bucal; terapêutica; revisão sistemática.

**ABSTRACT**

Oral lichen planus (OLP) is an immunologically mediated inflammatory disease that affects approximately 0.89% of the world's population. Its classical clinical presentation is characterized by white striae mainly located on the bilateral buccal mucosa, called ‘Wickham striae’, usually asymptomatic. Nevertheless, two-thirds of patients with this disease experience symptoms that can significantly interfere with their quality of life. Currently, the first-line treatment for symptomatic oral lichen planus is the use of topical corticosteroids. Diverse other treatment modalities are described in the literature, particularly options that have fewer adverse effects and that provide benefits for refractory cases. The objective of this study was to conduct an overview of systematic reviews on therapeutic modalities for oral lichen planus and propose a treatment protocol to assist dental practitioners in its management. The search in the Scopus, Embase, Web of Science, and PubMed databases resulted in 428 systematic reviews, of which 74 articles were included for final qualitative analysis. Of these articles, 35 covered the use of natural agents, 26 calcineurin inhibitors, 21 corticosteroids, 15 photodynamic therapy, 12 retinoids, 10 other immunosuppressants, 9 photobiomodulation, 8 phototherapy with ultraviolet light and 13 other therapeutic modalities. Based on the results of these systematic reviews, the use of topical corticosteroids is considered the first-line treatment for OLP lesions, and there is no evidence of superiority between this therapeutic class. In refractory lesions, the use of calcineurin inhibitors, such as tacrolimus and pimecrolimus, is recommended. In multiple mucocutaneous lesions, systemic corticosteroids are recommended, for as short a time as necessary to reduce potential adverse effects. Natural agents, topical retinoids and laser therapy can be used as adjuvants in lesions refractory to corticosteroid therapy. Management with UV irradiation is not recommended due to its oncogenic potential. Surgical removal or with carbon dioxide laser to manage OLP is only recommended in persistent, small and localized lesions and is not recommended as a routine therapeutic possibility. Systemic retinoids, other immunosuppressive drugs and other therapeutic modalities mentioned in this work must be evaluated with caution due to important adverse effects. Furthermore, they lack robust scientific evidence to support their indication in the management of OLP lesions. The risk of bias was considered low in 58.1% of systematic reviews, moderate in 20.27% and high in 21.62%. Despite the heterogeneity found in the literature in relation to different modalities and therapeutic doses for the management of OLP, in this work a protocol was proposed to assist the dentist when dealing with cases of patients with OLP. This protocol was designed to provide a structured,

evidence-based approach to the effective management of OLP cases, with particular emphasis on those that prove refractory to conventional treatments.
Keywords: oral lichen planus; therapeutics; systematic review.

## LISTA DE ILUSTRAÇÕES

**SUMÁRIO**

# 1 INTRODUÇÃO

O líquen plano (LP) é uma doença mucocutânea inflamatória imunologicamente mediada que afeta o epitélio estratificado escamoso principalmente da pele, mucosa oral e mucosa genital (SCULLY, 2009). Estima-se que essa condição acometa 0,89% da população mundial, sendo frequente na prática clínica do cirurgião-dentista (LI et al., 2020). A apresentação clínica típica do líquen plano oral (LPO) manifesta-se como estrias brancas reticulares bilaterais, denominadas de 'Estrias de Wickham', mas a doença pode apresentar-se também na forma erosiva com eritema e ulcerações que causam sintomatologia dolorosa ao paciente. Após a confirmação do diagnóstico através do exame clínico juntamente com realização de biópsia e análise histopatológica, o manejo é realizado pelo acompanhamento clínico de lesões assintomáticas e, nos casos sintomáticos, pela terapia tópica ou sistêmica (RAJ; RAJ, 2021).

As evidências sobre formas de manejo da sintomatologia de lesões orais de LPO são diversas na literatura e incluem uso de corticoides tópicos e sistêmicos, imunossupressores, fitoterápicos, bem como fotobiomodulação com laser de baixa potência (NOSRATZEHI, 2018). Porém, com essa ampla gama de recursos terapêuticos e constante surgimento de novas evidências na literatura, há uma dificuldade para padronização e estabelecimento de protocolos mais eficazes para o tratamento.

As revisões sistemáticas sobre esse tema representam um alto nível de evidência científica pois englobam todos estudos clínicos primários a fim de responder de forma robusta questões acerca do LPO e modalidades de tratamento. No entanto, há uma heterogeneidade da evidência disponível até o momento. Nesse sentido, uma overview desempenha um papel importante ao reunir análises utilizando um método transparente e sistemático com objetivo de agrupar as evidências sobre determinado tema. Com isso, o objetivo deste trabalho foi realizar uma overview de revisões sistemáticas sobre LPO e suas modalidades terapêuticas, agrupando as evidências cientificas acerca do tema e propor um protocolo clínico para facilitar a conduta do cirurgião-dentista frente a casos de LPO.

## 1.1 Contexto Histórico

O termo líquen plano foi cunhado através da palavra grega "*leichen*", que remete às características semelhantes ao 'musgo de árvore' e da palavra "planus", que em latim significa plano, também remetendo ao aspecto clínico das lesões (BOCH et al., 2021).

O LP foi descrito pela primeira vez pelo médico inglês Erasmos Wilson em 1869 e, em 1895, o francês Louis-Frédéric Wickham complementou as observações acerca das lesões em pele quando percebeu a presença de estrias brancas reticulares, que ficaram denominadas de 'estrias de Wickham' e que são comumente vistas na prática clínica (GUPTA; JAWANDA, 2015; CHARLES; DUPREE, 2004; MARCUCCI, 2016).

## 1.2 Etiopatologia

O LP é uma doença sistêmica crônica inflamatória e imunologicamente mediada que apresenta períodos de remissão e exacerbação. Essa doença afeta o epitélio escamoso principalmente de pele, unhas, mucosa genital e mucosa oral (PARASHAR, 2011; CASSOL-SPANEMBERG et al., 2018). Mulheres de meia-idade apresentam uma maior predisposição para desenvolver o LPO, quando comparado a homens, em uma proporção de 3:2 (CANTO et al., 2010; FARHI; DUPIN, 2010; NEVILLE, 2016; SCULLY, 2009). Apesar de ser raro o acometimento em crianças, a doença pode manifestar-se também nessa população. A presença de antígenos intrínsecos ou extrínsecos – como por exemplo infecções virais, uso de medicamentos, alteração da microbiota e fatores psicológicos - é capaz de alterar as células da camada basal do epitélio, levando à liberação de citocinas pró-inflamatórias e recrutando linfócitos T (CD4 e CD8), o que desencadeia a apoptose das células da camada basal e as demais alterações teciduais encontradas no LPO (SCULLY, 2009; VIČIĆ et al., 2023).

Sua etiologia não é totalmente elucidada, porém sabe-se que há uma característica multifatorial envolvida e que a imunidade desempenha um papel importante no seu desenvolvimento (CANTO et al., 2010). Foram realizados estudos para avaliação da susceptibilidade genética ao desenvolvimento desta doença. Apesar de terem sido observados alguns casos familiares de LPO e a ocorrência desta doença em gêmeos monozigóticos, não há estudos que elucidem o exato papel do componente genético (BOCH et al., 2021; MUKHOPADHYAY et al., 1996; VALSECCHI et al., 1990). Porém, atualmente é descrito que o papel genético é mais provável em determinar a reatividade dos pacientes do que outros fatores etiológicos (VIČIĆ et al., 2023). Quanto aos fatores ambientais, há uma forte associação com o vírus da hepatite

C (HCV), onde essa infecção seria capaz de modificar antígenos próprios dos queratinócitos da camada basal do epitélio ou alterar o equilíbrio imunológico do local, provendo uma inflamação liquenoide (BOCH et al., 2021). Além disso, há estudos epidemiológicos demonstrando que indivíduos com LPO apresentam maior risco para soropositividade de HCV quando comparado aos controles (LODI et al., 2010). Contudo, a associação ainda é incerta e necessita de maiores estudos para sua elucidação (GUPTA; JAWANDA, 2015). Outros vírus também foram associados ao desencadeamento do LPO, como os vírus da família do herpes vírus (mais especificamente dos tipos 6 e 7), papiloma vírus humano (HPV), vírus da hepatite B (HBV), e Epstein-Barr vírus (EBV) (BOCH et al., 2021; FARHI; DUPIN, 2010; VIČIĆ et al., 2023). Além disso, desequilíbrios da microbiota podem estar relacionados ao desencadeamento de lesões de LPO (VIČIĆ et al., 2023).

O papel de fatores psicológicos na etiologia do LPO é controverso, mas alguns autores afirmam que pacientes com LPO apresentam maiores níveis de ansiedade e depressão quando comparados aos controles saudáveis (KORAY et al., 2003; SOTO et al., 2004). Além disso, estudos apontam que estes distúrbios psiquiátricos podem induzir o aparecimento das formas sintomáticas de OLP, bem como agravar a severidade das lesões em períodos de maior estresse (BLANCO-CARRIÓN et al., 2008; CHAUDHARY, 2004).

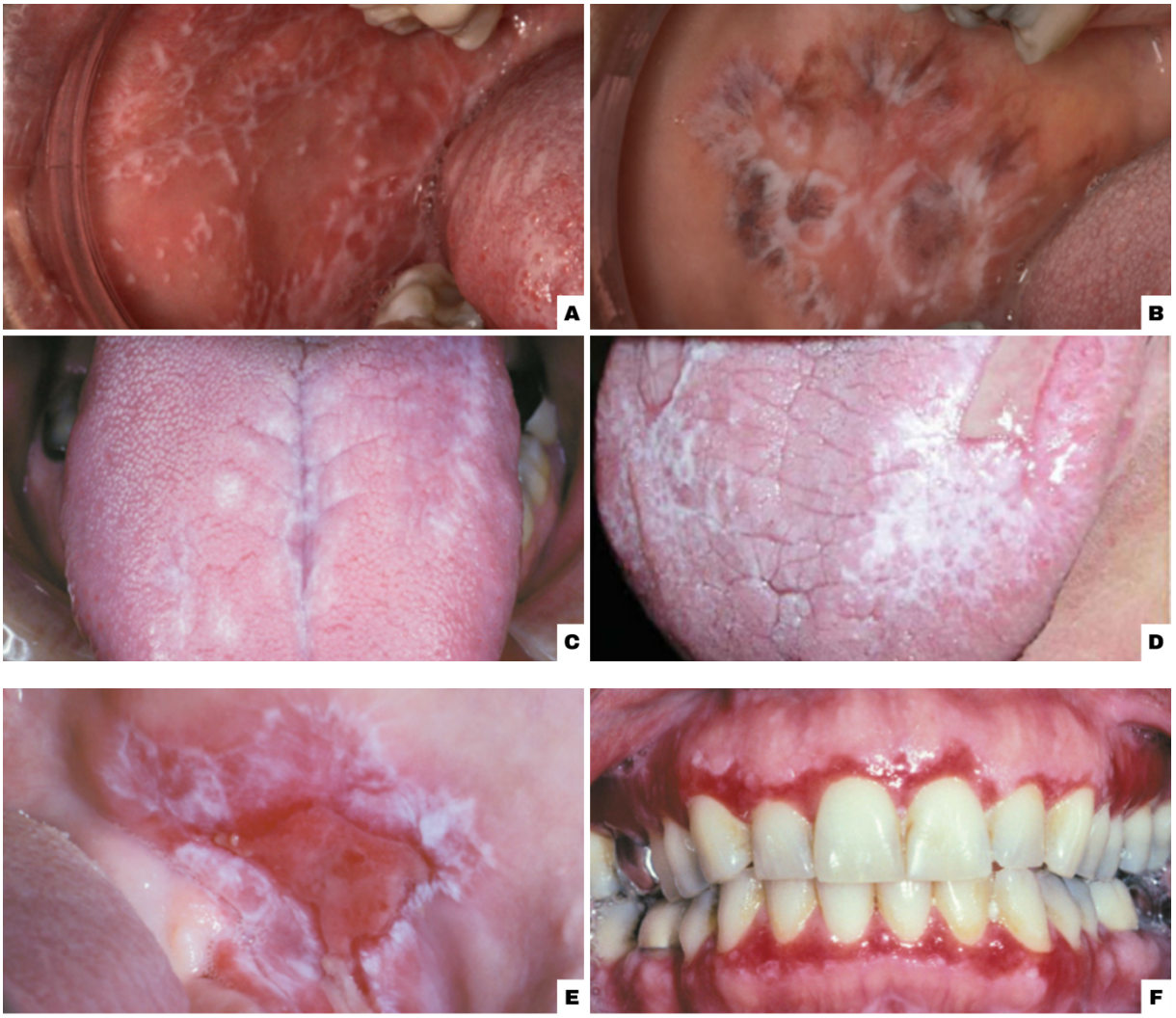
### 1.3 Características clínicas

O LP possui 17 diferentes apresentações clínicas. As principais manifestações vistas em pele são pápulas poligonais, frequentemente cobertas por linhas brancas sutis (estrias de Wickham), arroxeadas e pruriginosas, localizadas principalmente nas regiões flexoras como punhos e tornozelos. O LP pode resultar em descamação nas unhas, em alopecia, e na mucosa genital pode resultar na presença de lesões semelhantes às descritas em pele e mucosa oral (FARHI; DUPIN, 2010; SCULLY, 2009).

Já o LPO pode ser classificado em seis diferentes subtipos de acordo com suas características clínicas. Estes subtipos podem apresentar-se individualmente ou em combinação com os outros. São eles: reticular, papular, tipo placa (semelhante à leucoplasia), erosivo, atrófico e bolhoso (ELENBAAS; ENCISO; AL-ERYANI, 2022; FARHI & DUPIN, 2010).

Dentre estas manifestações clínicas do LPO, a variante reticular é a mais reconhecida e característica. Apresenta-se como estrias brancas simétricas (estrias de

Wickham), assintomáticas, geralmente acometendo porção posterior de mucosas jugais bilaterais (ALRASHDAN et al., 2016; CANTO et al., 2010). O subtipo papular é raro em cavidade oral, porém, quando presente, caracteriza-se por pequenas pápulas esbranquiçadas circundadas com finas estrias na sua periferia (CANTO et al., 2010; PARASHAR, 2011). Já a variante do tipo placa, apresenta placas brancas homogêneas, podendo ser mais rugosas e múltiplas, acometendo principalmente dorso de língua e mucosa jugal (CANTO et al., 2010). Estes subtipos geralmente são assintomáticos e não requerem tratamento, apenas acompanhamento periódico. Além disso, foi relatado na literatura que 46% dos pacientes apresentaram LPO exclusivamente reticular e 44% apresentaram a doença na forma erosiva ou atrófica, podendo influenciar o grau de sintomatologia dos pacientes e consequentemente o tratamento (GONZÁLEZ-MOLES et al., 2020).




Fonte: NEVILLE, 2016 (A, B, C, E, F). CANTO et al., 2010 (D).

**Figura 1**: **manifestações clínicas de LPO.** A) Subtipo reticular em sítio de acometimento mais comum, mucosa jugal. B) Subtipo reticular associado à pigmentação pós-inflamatória. C) Variante do tipo placa, sendo mais comumente vista como placas brancas homogêneas em dorso de língua. D) LPO erosivo associado a placas brancas em dorso de língua. E) LPO erosivo em mucosa jugal, com área de ulceração central e estrias esbranquiçadas na periferia. F) Gengivite descamativa.

Quanto às demais variantes do LPO, o subtipo erosivo apresenta-se como ulcerações cobertas ou não por membrana fibrinopurulenta, dolorosas, circundadas por halo esbranquiçado, podendo ser múltiplas e extensas (ALRASHDAN et al., 2016; CANTO et al., 2010). O subtipo atrófico apresenta áreas de eritema e estrias brancas reticulares, com atrofia do epitélio causando desconforto e sintomatologia dolorosa (ALRASHDAN et al., 2016; CANTO et al., 2010). O subtipo mais incomum de ser observado em cavidade bucal é o bolhoso, que leva a formação de bolhas que podem coalescer e romper, deixando a superfície ulcerada e dolorida (ALRASHDAN et al., 2016; CANTO et al., 2010; PARASHAR, 2011).

O sítio bucal mais acometido é a mucosa jugal (67,15%), seguido da língua (10,47%), enquanto região retromolar e assoalho bucal são os sítios com menor acometimento (0,25% e 0,13%, respectivamente). Quando as lesões acometem a região gengival, o termo conhecido é gengivite descamativa. Porém, a gengivite descamativa não é uma manifestação exclusiva do LPO, sendo necessário diferenciar o LPO de outras doenças com manifestações gengivais semelhantes, como penfigoide, pênfigo vulgar, doença do IgA linear (CANTO et al., 2010; SURESH; NEIDERS, 2012). A presença de LPO confinado a apenas manifestações gengivais está presente em cerca de 10% dos pacientes (ALRASHDAN et al., 2016).

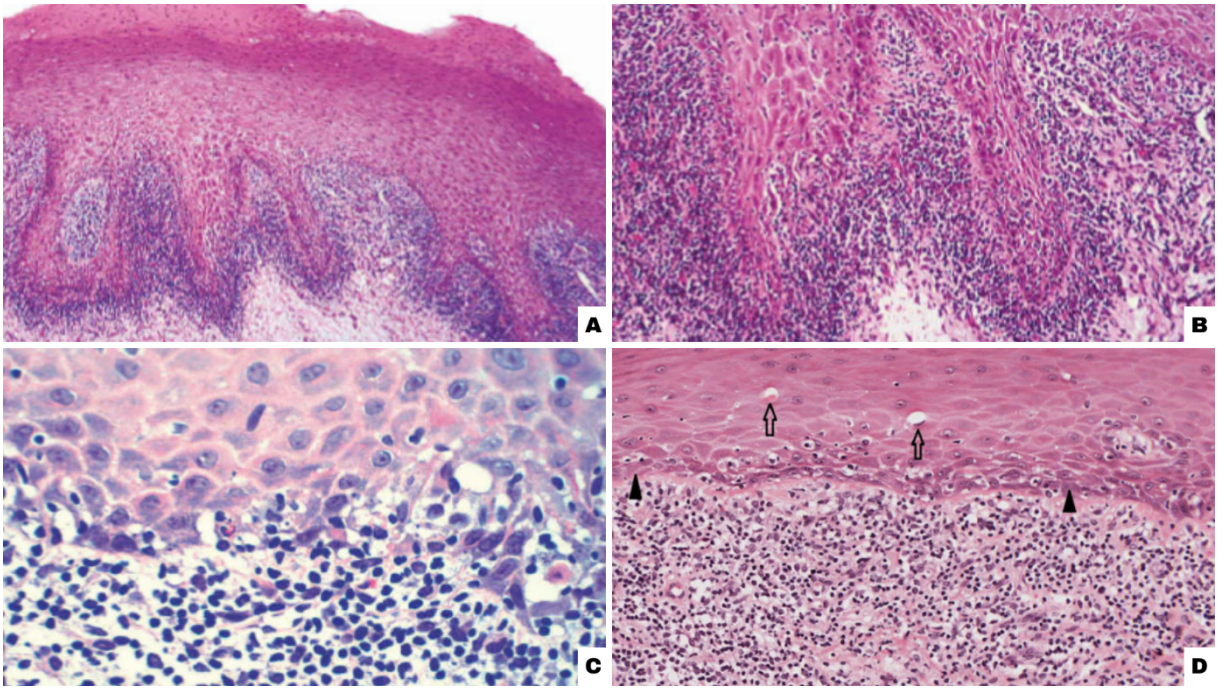
## 1.4 Diagnóstico

O LPO clássico, caracterizado por estrias esbranquiçadas em mucosa jugal bilateral, é considerado por alguns autores sinal patognomônico da doença sem necessidade de submeter a amostra à biópsia e análise histopatológica (NEVILLE, 2016). Porém, algumas apresentações clínicas podem assemelhar-se com outras doenças imunologicamente mediadas como pênfigo vulgar, penfigoide benigno de membranas mucosas, doença do enxerto-contra-hospedeiro, estomatite crônica ulcerativa, lúpus

eritematoso oral e reação liquenoide, além de assemelhar-se com lesões brancas como candidíase hiperplásica e leucoplasia, sendo necessárias manobras para realizar o diagnóstico diferencial (WARNAKULASURIYA et al, 2020). A biópsia seguida da análise histopatológica é indicada para realização do diagnóstico definitivo e para excluir a possibilidade de malignidade e displasia (GUPTA; JAWANDA, 2015). Em casos de gengivite descamativa, o diagnóstico geralmente é mais complexo, necessitando de realização de biópsia perilesional seguida de análise de imunofluorescência direta, para excluir outras lesões vesicobolhosas citadas anteriormente (ALRASHDAN et al., 2016; SURESH; NEIDERS, 2012).

## 1.5 Histopatologia

Os principais aspectos observados na análise histopatológica de uma amostra de LP são o infiltrado predominantemente linfocitário disposto em banda subepitelial com perda de definição dos limites entre epitélio e tecido conjuntivo. Além disso, há presença de hiperceratose, hiperplasia e áreas de acantose no epitélio de revestimento, apresentando cristas epiteliais pontiagudas ou em formato de “dentes de serra”, degeneração hidrópica das células da camada basal e presença de células apoptóticas (corpos de Civatte). As características histopatológicas do LPO são típicas e normalmente definem o diagnóstico (ALMEIDA, 2016; GUPTA; JAWANDA, 2015; NEVILLE, 2016).




Fonte: NEVILLE, 2016 (A, B, C). ALRASHDAN et al., 2016 (D).

**Figura 2**: **características histológicas do LPO.** A) Observa-se presença de epitélio com hiperceratose, projeções epiteliais em formato de "dentes de serra" e infiltrado inflamatório linfocitário. B) Imagem de maior aumento detalhando a degeneração das células da camada basal. C) Degeneração da camada basal do epitélio, com presença de infiltrado linfocitário na camada superficial da lâmina própria. F) Presença de Corpos de Civatte indicados nas setas.

## 1.6 Tratamento

O LP reticular geralmente é assintomático e não necessita de tratamento. Já as lesões sintomáticas requerem tratamento, geralmente com o emprego de corticoides tópicos como primeira escolha, visto que apresentam boa eficácia com menos efeitos adversos relacionados a esta classe terapêutica (ALRASHDAN et al., 2016; GUPTA et al., 2017). Podem ser utilizados corticoides tópicos como o propionato de clobetasol, dexametasona, triancinolona, hidrocortisona, betametasona, tanto em solução oral quanto gel, creme, orabase ou aerossol (GONZÁLEZ-MOLES et al., 2010). Em casos severos ou com envolvimento mucocutâneo da doença, em que o tratamento tópico não resultou em controle das lesões dolorosas, pode ser necessário o uso de corticoides sistêmicos com cautela visto que apresentam efeitos adversos importantes, como

retenção de líquidos, hipertensão, diabetes, úlceras gástricas, candidíase, alterações visuais, entre outras (AL-HASHIMI et al, 2007; ANDABAK-ROGULJ et al., 2023).

Outras modalidades terapêuticas têm sido amplamente estudadas na literatura com vistas principalmente ao manejo de lesões de LPO refratárias, que acabam representando um desafio tanto ao profissional da saúde quanto ao paciente. Dentre essas modalidades de tratamento, podem ser citados os inibidores de calcineurina, imunossupressores sistêmicos, fitoterápicos, retinoides, fotobiomodulação com laser de baixa potência, terapia fotodinâmica, fototerapia ultravioleta, crioterapia e remoção cirúrgica (ELENBAAS; ENCISO; AL-ERYANI, 2022; LAJEVARDI et al., 2016).

Os inibidores de calcineurina, como tacrolimo e pimecrolimo, usados de forma tópica têm demonstrado boa eficácia no manejo de lesões refratárias à corticoterapia. Porém, devido ao seu potencial efeito carcinogênico relatado em alguns estudos, não é tão amplamente prescrito como tratamento de primeira linha (DIDONA et al., 2022).

Em lesões recalcitrantes, os imunossupressores e imunomoduladores sistêmicos como a azatioprina, o metotrexato, o micofenolato mofetil, além do antimalárico hidroxicloroquina, têm sido empregados nestes casos visando reduzir a resposta inflamatória do organismo. Porém, carecem de evidência científica forte que supere os riscos relacionados aos efeitos adversos da administração destas medicações, que podem incluir retinopatia, aplasia de medula óssea, hiperpigmentação cutânea, náuseas, mialgia, entre outros (AL-HASHIMI et al, 2007; ANDABAK-ROGULJ et al., 2023; DIDONA et al., 2022).

Tendo em vista estes efeitos colaterais severos, opções de tratamento menos invasivas e com o mínimo de efeitos adversos têm sido amplamente pesquisadas. O uso de lasers através da fotobiomodulação é capaz de acelerar o reparo tecidual, reduzir a inflamação e promover analgesia (FERRI et al., 2020). Além disso, o uso tópico ou sistêmico de agentes naturais – como curcuminoides, aloe vera, camomila - tem sido estudado como alternativas terapêuticas (DHARMAN et al., 2020; LEONG et al., 2023; ZENG et al., 2022). Apesar disso, ainda carecem de evidências científicas, com estudos clínicos randomizados e com tempo suficiente de acompanhamento (LODI et al., 2012).

## 1.7 Prognóstico

O LPO é uma doença que raramente apresenta cura, mas que o tratamento consiste no controle da sintomatologia dolorosa nos períodos de exacerbação das lesões (SCULLY, 2009).

O potencial de transformação maligna do LPO ainda é contraditório, com alguns autores relatando relação das lesões bucais com transformação em carcinoma espinocelular (FITZPATRICK; HIRSCH; GORDON, 2014; WARNAKULASURIYA et al., 2020), e outros refutando essa associação na população brasileira (MIGLIARI; SUGAYA; HIROTA, 2022). Como esse risco de transformação maligna ainda não é totalmente esclarecido, é recomendado manter o acompanhamento semestral desses pacientes (MARCUCCI, 2016; VAN DER MEIJ; SCHEPMAN; VAN DER WAAL, 2003).

# 2 ARTIGO CIENTÍFICO

## Assessing oral lichen planus treatment options: an Overview of systematic reviews

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**Abstract**

Background: Oral lichen planus (OLP) is defined as an immunologic-mediated mucocutaneous disease that affects 0.89% of the world population, and it can lead to intense painful symptoms in these patients. The aim of this study was to summarize the available evidence of OLP treatment modalities and suggest a clinical protocol for the clinician.

Methods: An overview of systematic reviews was conducted based on the 2020 PRISMA statement. Four databases were assessed to find articles published regarding oral lichen planus and therapeutic modalities. Risk of bias was evaluated using AMSTAR 2 tool.

Results: In the qualitative analysis, 74 full articles were included encompassing natural agents (n=35), calcineurin inhibitors (n=26), corticosteroids (n=21), photodynamic therapy (n=15), retinoids (n=12), other immunosuppressants (n=10), photobiomodulation (n=9), UV phototherapy (n=8), and other treatment modalities (n=13). Based on our findings, it is recommended the use of topical corticosteroids as first-line therapy. There are no corticosteroids more efficacious than another. On refractory OLP lesions, it is recommended the use of topical calcineurin inhibitors. For multiple mucocutaneous lesions, it can be used for systemic corticosteroids for less time as possible to avoid systemic side effects. Natural agents, topical retinoids, and lasers can be used as an adjuvant to first-line therapy. UV radiation is not recommended due to its oncogenic potential. Surgical removal and CO2 laser ablation are considered only for persistent, small and localized lesions, not indicated as a routine treatment.

Conclusion: Despite the significant heterogeneity in the literature regarding treatment protocols and doses, we present a suggested protocol for clinicians. This protocol aims to offer a structured, evidence-based framework for effectively managing OLP, particularly focusing on cases resistant to conventional treatments.

**Keywords**: Oral Lichen Planus. Therapeutics. Systematic review. Laser Therapy. Corticosteroids. Calcineurin inhibitors.

## Introduction

Lichen planus is a chronic inflammatory disease that affects the squamous epithelium of the skin, genital, and oral mucosa, and exhibits periods of remission and exacerbation of lesion Although the immune-mediated mechanisms involved in this disease are well-established, the etiology of lichen planus is not fully elucidated[1]. Various intrinsic or extrinsic antigens, such as hepatitis virus infection, psychological factors, various drugs, mechanical trauma, and changes in microbiota, can trigger an inflammatory response in susceptible individuals[2].

On the skin, lichen planus can manifest as polygonal papules, purplish, pruriginous, usually covered by subtle white striae, localized especially at flexor regions of the body such as wrists and ankles[1]. Oral manifestations of this condition can be categorized into six different types based on their clinical characteristics: reticular, papular, plaque-like (resembling leukoplakia), erosive, atrophic, and bullous[3]. Oral lichen planus (OLP) is estimated to affect 0.89% of the world's population, most prevalent in ages above 40 years old, and women[4]. The oral site most affected is buccal mucosa, tongue, gingiva, lips, and less prevalent in the floor of the mouth and palate[5].

OLP usually is asymptomatic and does not require treatment. Nevertheless, two-thirds of patients with this chronic disease experience symptoms that can significantly interfere with their quality of life[6]. Current treatments aim to reduce pain and promote lesion healing. The first-line management for symptomatic OLP is based on the use of corticosteroids[7]. More literature has emerged about different treatment modalities, including phytotherapy, retinoids, photobiomodulation (PBM), photodynamic therapy (PDT), and cryotherapy, among other[3,8]. While there is a substantial body of studies regarding the therapeutic management of OLP, an increasing number of novel treatment modalities are described in the literature, warranting exploration. Moreover, managing refractory lesions poses a significant challenge for both patients and clinicians, necessitating a different approach. Therefore, the objective of this study is to summarize the existing evidence on OLP treatment modalities and propose a treatment protocol to aid dental practitioners in its management.

## Materials and Methods

### Study design and eligibility criteria

This overview assessed systematic reviews and meta-analysis that evaluated the clinical effects and pain relief of diverse treatment modalities for symptomatic OLP. The acronym PICOS (Population, Intervention, Comparison, Outcomes, and Studies) was structured as follows: (P) individuals with OLP; (I) treatment modalities; (C) other treatment or placebo; (O) treatment effectiveness. (S) systematic reviews and meta-analyses.

Publications were restricted to English language and no publication time restriction was set.

### Exclusion criteria

Studies that did not evaluate OLP, or where data extraction of OLP could not be clearly segregated from other lesions, were excluded from this overview. Similarly, publications that did not analyze treatment effects on OLP and those not written in English were excluded. As well as other study types that were not systematic reviews.

### Search strategy

Electronic search was performed in four databases: PubMed (National Library of Medicine), Scopus (Elsevier), Embase (Elsevier) and Web of Science (Thomson Reuters), using the MeSH and free terms (**Supplementary File 1**). Duplicated references were removed by a reference manager software (EndNote®, Thompson Reuters, Philadelphia, PA). A gray literature search was performed on Google Scholar and ProQuest Dissertations & Theses Global. Furthermore, the reference list of included articles was searched in order to identify potential studies that meet the inclusion criteria.

### Study selection and data collection

The titles and abstracts of the studies found at the databases were independently screened by two authors (L.D.M and A.A.D). Then, the studies were read fully and those that meet the inclusion criteria were included in this overview. Divergences among authors were solved by discussion with a third author (L.F.S.). For each study, the following data were collected: author’s

name, year and country of publication, presence of meta-analysis, number and type of included studies, sample size, gender and mean age of patients include, oral manifestation of oral lichen planus, intervention, control, outcome evaluation, response, follow-up, recurrence and conclusions. Collected data of systematic reviews were described at **Supplementary File 2**. When treatment involved laser therapy, the following parameters were included at **Supplementary File 3**: laser type wavelength, power, spot size, power density, irradiation duration, energy density, photosensitizer and number of sessions.

Risk of bias in individual studies

The risk of bias (RoB) of included studies was assessed through the Measurement Tool to Assess the Methodological Quality of Systematic Reviews 2 (AMSTAR 2) by two authors (L.D.M and A.A.D)[9]. The calculation was done considering yes = 1, partial yes = 0.5 and no = 0. When meta-analysis was not available, it was considered as thirteen the total of questions. Risk of bias was categorized as high when the study reached up to 49% score “yes,” moderate when the study reached 50 to 69% score “yes,” and low when the study reached more than 70% score “yes”. Disagreements between authors were solved by discussion with a third author (L.F.S.).

Data analysis

Data were tabulated with Microsoft Office Word 2019 (Microsoft®software, Redmond, WA, USA) and analyzed qualitatively.

Other information

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The study protocol was registered at International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42023412260[10].

## Results

Study selection

At phase I of the study selection process, 428 articles were identified after searching at four databases, and after removal of duplicates, it remained

170 articles. In phase II, the titles and abstracts were read applying the inclusion and exclusion criteria, remaining 103 studies to access full text. After the full-text reading, 64 articles met the inclusion criteria. There were 6 more articles identified in gray literature and 4 identified by search at reference lists. Finally, 74 full-text articles were included in the qualitative analysis in this overview[11-84]. A flowchart detailing the process of identification, screening, and inclusion of studies is presented in **Supplementary File 4.**

Characteristics of included studies

The qualitative analysis included 74 articles, enrolling a total sample number of 36,402, with a mean of 543.31 individuals per study, ranging from 53 to 2831. The studies were published between 1999 and 2023. In the past recent years, it was published more systematic reviews about treatment modalities for OLP. The year with more publications about this topic was 2022 (n=17 / 22.97%), followed by 2020 (n = 9/ 12.16%) and 2021 (n=8/10.81%).

The articles included in this overview were published in 22 different countries. The main countries with the highest number of published articles were India (n=17/22.97%) and China (n=11/14.86%).

The majority of the systematic reviews analyzed OLP only, but some studies broadened the investigations to oral potentially malignant disorders[16,22,27,31,42], oral lichenoid lesions[13], autoimmune diseases[30,74,83], oral ulcers[23], chronic skin diseases[28,67], and other mucosal conditions[33,34,51,61,80]. If it was possible to extract the results of OLP individually in order to analyze it, the articles were included.

Systematic reviews mainly included randomized clinical trials (RCTs). However, it also comprehended other primary study designs such as non-RCTs, case reports, case series, split mouth design, and pilot studies. It was conducted meta-analysis in 28 studies (37.83%). The information regarding all of these details is described in **Supplementary File 2**.

Treatment modalities

*Corticosteroids*

Twenty-one systematic reviews evaluated the efficacy of corticosteroids for OLP treatment, comparing their use with placebo and other treatment

modalities. Out of these, seven studies performed a meta-analysis (33.33%). The majority of the studies analyzed only topical corticosteroids (66.66%)[24,25,26,44,45,46,52,60,64,65,72,73,75,76], followed by a combination of topical, intralesional, or systemic treatments (23.8%)[13,35,37,58,82]. A smaller percentage focused solely on intralesional treatments (4.76%)[19], while others concentrated on systemic treatments (4.76%)[40].

Regarding the use of topical corticosteroids, nine studies demonstrated the efficacy of this treatment modality over other treatments and placebo, suggesting the use of topical corticosteroids as first-line treatment[13,35,37,52,58,60,75,76,82]. However, six studies reported only weak evidence for the superiority of corticosteroids for pain and clinical scores over other treatments[25,26,44,64,65,73]. Regarding which corticosteroid is the most efficacious, five studies demonstrated that there is no topical corticosteroid superior to another[35,44,45,52,65], and that doses of 0.05% or 0.025% of clobetasol have the same efficacy[35,37]. In contrast, one study suggest the superiority of clobetasol over other corticosteroids[13].

The use of topical intralesional injections for the treatment of OLP lesions was described in three studies comparing different intralesional injections, to oral health side, and to topical corticosteroids[19,35,37]. All of the studies demonstrated its efficacy, showing a reduction in pain (85%), erythema, and ulceration (78 to 80%) after two weeks of using triamcinolone acetonide injection[19]. It has been proposed the intralesional injection of triamcinolone acetonide (8 to 40mg), dexamethasone (1.4mg), and betamethasone (1.4mg), with the latter presenting more efficacy than triamcinolone acetonide injection with fewer recurrences[35,37]. The relapse rate ranged from 14.8% (betamethasone) to 58% (triamcinolone acetonide) within a mean period of two to twelve months. The subregional administration of corticosteroids for erosive OLP lesions is supported, with potential weekly reapplication, as indicated by two systematic reviews[19,35].

There are few systematic reviews regarding the use of systemic corticosteroids for OLP management, but it has been reported as effective as topical corticosteroids[13]. An initial dose of 40 to 80 mg of prednisone was suggested by Carrozzo and Gandolfo (1999), with most patients showing a 50 to 75% reduction in lesion size within two weeks. After this period, the dose

should be reduced to 30 to 50 mg per day. A different recommendation is indicated by Al-Hashimi et al. (2007), which is the administration of 0.5 to 1 mg per patient's weight daily until a satisfactory therapeutic response has been achieved.

*Calcineurin inhibitors*

Twenty-six studies evaluated the efficacy of calcineurin inhibitors - which includes tacrolimus, pimecrolimus, and cyclosporin - in the treatment of OLP lesions, and twelve of these performed meta-analyses. The comparison group mainly used placebo or corticosteroids, but some articles compared different treatment modalities.

Regarding the outcomes of tacrolimus on OLP management, three studies demonstrated superior efficacy of tacrolimus when compared to topical corticosteroids[24,33,35]. A similar efficacy between tacrolimus and topical corticosteroids on pain relief was described in nine studies[29,36,37,44,57,62,63,76,84,] and on clinical scores were described in seven[29,44,57,62,63,75,76,84]. Although there is solid evidence supporting the efficacy of tacrolimus on OLP management, some studies reported inconclusive findings[52,64,78].

Regarding the application of pimecrolimus, when compared to placebo, three studies demonstrated superior effectiveness in terms of clinical signs[29,57,60] and symptoms[33,60]. In contrast to three studies[44,64,65], who reported no evidence that pimecrolimus is more effective than placebo. When comparing this drug to topical corticosteroids, the results are controversial. A similar efficacy between these two treatment modalities was described in four studies[29,37,63,76], superiority of pimecrolimus in one[35], and inferiority in one[33].

When comparing cyclosporine to placebo, superiority of this drug was reported in two systematic reviews[33,60] with a level of evidence at 3b/grade of recommendation B. When comparing to topical corticosteroids, cyclosporine showed similar efficacy in two studies[13,63], and inferiority in two studies[29,33]. This lack of strong evidence is corroborated by other eight systematic reviews[25,40,44,64,65,73,82,83].

The follow-up period ranged from none to ten years. This aspect was not reported in three studies[33,44,65]. Recurrence of OLP lesions was shown within 3 weeks to 6 months after discontinuation of tacrolimus[37,63,83] and in 1 month after

ceasing pimecrolimus[26]. When compared to topical corticosteroids, two studies[29,78] demonstrated that tacrolimus showed less recurrence at follow-up. According to one systematic review[62], the relapse rate was similar between these two treatment modalities.

*Other immunosuppressants*

Ten studies evaluated the effects of other immunosuppressants on OLP lesions. Most studies were regarding Azathioprine (60%) and Thalidomide (60%), followed by Mycophenolate mofetil (50%), Dapsone (40%), Rapamycin (30%) and Methotrexate (20%). The evidence supporting the use of these drugs in OLP management is weak and there is a lack of randomized clinical trials.

Among all these immunosuppressants, azathioprine appeared to be the most effective, with complete resolution in 75% of patients[40]. Additionally, four studies[26,37,40,82] reported the efficacy of Azathioprine on OLP management, with an excellent response in 77.8% of the patients using 50 mg twice a day within 4 to 6 weeks of therapy.

The use of thalidomide resulted in the complete resolution of lesions in 50% of patients[40]. Two studies[29,46] reported thalidomide with similar efficacy to topical steroids. One study[29] reported that rapamycin presented a similar clinical response to topical steroids but less efficacy in terms of symptoms. In addition, when compared to placebo, they reported that mycophenolate mofetil 2% mucoadhesive does not present superior effects.

Moreover, some systematic reviews state that there is insufficient evidence supporting the use of mycophenolate mofetil, thalidomide, dapsone, MTX, or rapamycin[13,26,34,37,65,78].

*Photobiomodulation*

Nine studies evaluated the efficacy of PBM on the management of OLP lesions[11,14,30,35,37,41,53,54,70]. Eight studies compared the effects of PBM with corticosteroids, and one study did not report information about the control group[53].

Regarding the efficacy of PBM, four studies found it to be superior to corticosteroids, with a treatment response rate of 61.9% compared to 28.6% in the control group[11,14,35,53]. However, two studies reported that PBM is less

effective than dexamethasone and triamcinolone[37,54] but it was superior only to 0.05% clobetasol propionate at long-term treatment (between days 60-90)[35,37]. Two meta-analyses indicated a significant difference between PBM and topical corticosteroids in terms of severity, favoring the control group, but no difference was observed in terms of signs (TSS) and pain scores (VAS)[30,41]. In addition, a systematic review with meta-analysis found no differences in pain and severity scores between PBM and corticosteroids[70].

The follow-up period for these studies ranged from none to ten years of evaluation, and recurrence rates were only reported in one study, showing a 4.8% recurrence rate in the PBM group compared to 47.6% in the corticosteroid group during a follow-up period of 4 to 48 weeks[11].

In terms of laser parameters for PBM (**Supplementary Table 3)**, the diode laser was the most commonly used type, with wavelengths ranging between 308 nm to 1064 nm. Power levels mainly ranged from 10 to 3000 mW, spot sizes varied from 0.04 to 1 $cm^2$, power density ranged from 10 to 1500 $mW/cm^2$, irradiation times varied from 3.73 to 480 seconds, and energy density ranged from 0.1 to 19.23 $J/cm^2$. The number of sessions administered varied between 4 to 30.

*Photodynamic therapy*

Fifteen studies evaluated the effect of PDT on OLP lesions[12,15,22,27,35,37,39,41,42,52,53,60,69,70,75]. Among them, six studies performed meta-analysis[39,41,42,60,69,70,75]. Control groups were primarily treated with corticosteroids in nine of these studies, although PDT was also compared to other therapeutic modalities and placebo.

Regarding the outcomes, PDT was less effective than corticosteroids in two studies[12,35]. In the latter study when PDT was compared to clobetasol, it demonstrated superior results in clinical sign scores, but less efficacy when compared to dexamethasone and triamcinolone acetonide. Similar efficacy of PDT to corticosteroids was reported in five systematic reviews with[39,41,69,70] or without[37] meta-analysis.

When compared to placebo, PDT exhibited superior results in three systematic reviews with meta-analyses[42,60,75]. Beneficial effects in 81% of OLP cases were reported, but it did not mention a control group[53]. In four studies

results were reported to be controversial[15,22,27,52]. Consequently, it was not possible to draw any definitive conclusions from them.

Analyzing the laser parameters for PDT (**Supplementary Table 3**), the laser type most used was the diode laser, with wavelengths ranging between 420 nm to 670 nm, power mainly ranged between 10 to 3000 mW, spot sizes ranged from 0.04 to 1 $cm^2$, power density varied from 10 to 1500 $mW/cm^2$, irradiation times ranged from 3.73 to 480 seconds, and energy density varied from 0.1 to 19.23 $J/cm^2$. Number of sessions administered varied between 4 to 30. The most used photosensitizing was both methylene blue and toluidine blue in seven systematic reviews, followed by 5-aminolevulinic acid (5-ALA) in four studies, methyl 5-aminolevulinate in three, chlorin-e6 derivative in two and Photodithazine in one. Seven articles did not specify the photosensitizer used. One study showed that the use of 20% 5-ALA was more effective than other photosensitizers[42]. Additionally, other study concluded through meta-analysis that the topical use of 5% ALA could be the optimal photosensitizer[39].

The follow-up period ranged from none to ten years. Only two studies reported a recurrence rate[22,27]. One reported no relapse in 81.4% of OLP patients compared to 74.1% in the PBM group and 99.5% in the corticosteroids group in one-year follow-up[22]. The other reported a recurrence of one case in the third month of follow-up and a relapse of two cases in the fourth month[27].

*CO2 laser*

Four systematic reviews were conducted using CO2 lasers for the management of symptomatic OLP lesions[30,49,53,80]. The CO2 laser surgery and ablation were found to be less effective than corticosteroids in one study, although there was a reduction in lesion size and VAS scale after the procedure compared to the baseline[49]. When compared to FBM, CO2 laser surgery showed less efficacy in two studies[30,80]. Furthermore, one study evaluated the removal of OLP lesions using CO2 laser ablation and reported it to be a fast and easy technique, with no need for suturing[53].

Regarding the CO2 laser parameters (**Supplementary Table 3**), the wavelengths ranged between 810 to 10600 nm, power mainly ranged between 1000 to 20000 mW, power density varied from 2.12 to 228 $mW/cm^2$, irradiation times ranged from 80 μsec (super pulse mode) to 5 seconds, and energy

density varied from 0.3 to 0.5 J/cm$^2$. Number of sessions administered was described as a single session. None of the systematic reviews provide information on spot sizes.

The follow-up period ranged from 2 to 480 weeks. It was reported an improvement of 85 to 100% at the third and sixth months (short-term follow-up), as well as 33.4 to 62% at long-term follow-up. Only two studies reported recurrence rate evaluation, which ranged from 9.1% to 38.2%[49,80].

*Photochemotherapy (PUVA)*

Eight studies evaluated the efficacy of photochemotherapy for OLP lesions[13,25,37,44,53,65,73,82]. Among these, four performed meta-analyses[25,44,65,73].

There is weak evidence to support the employment of UV light irradiation for OLP management. When compared to the other side of the mouth without intervention (split-mouth design study), clinical improvement of OLP lesions was reported in 50% to 86% of patients in the intervention group, using UV light irradiation associated with psoralen. The pain score was not evaluated. All systematic reviews had similar results, and the PUVA for OLP treatment was not recommended[13,53].

Adverse effects were documented in 77.77% of patients, with milder neurological side effects such as nausea, dizziness, ocular symptoms, paresthesia, and headache. Furthermore, severe nausea after oral administration of the photosensitizer psoralen led to withdrawals.

*Retinoids*

Ten studies evaluated the efficacy of retinoids on OLP lesions[13,25,34,35,37,40,60,64,73,82]. Three of them performed meta-analyses[25,60,73]. Nine studies compared retinoids to placebo. In studies with comparison of retinoids to other types of treatments, the first-line therapy and the most used drugs were corticosteroids[40,60,64]. Among the retinoid agents, topical retinoids were the most commonly used in six studies, followed by systemic retinoids in five studies, and topical isotretinoin, retinoic acid, and vitamin A in one study.

When compared to placebo, one study reported that retinoids are more effective, particularly topical isotretinoin in the concentration of 0.18%[34]. However, the results of two other studies delineated that the evidence to

support the superiority of retinoids over placebo for palliation of symptomatic OLP is circumstantial and weak, requiring more trials to determine that[25,73].

One study suggested retinoic acid as the prime option for unresponsive cases to steroids[37]. Additionally, two studies demonstrated that combining retinoids with corticosteroids, may improve the efficacy and reduce OLP's clinical signs compared to only retinoids[35,82]. In contrast, one study did not recommend systemic retinoids and proposed retinoids only as second-line therapy[13].

Follow-up time was between none to 10 years, with one study not reporting follow-up time[34]. Recurrence was specified in one study which described no recurrence at all[37].

*Natural agents*

Thirty-five studies evaluated the efficacy of natural agents in treating OLP, including various herbal agents[31,43,47,59,60,61,68,76], curcuminoids[21,28,31,32,37,48,67,71,74], aloe vera[18,21,44,50,51,65,75,76], hyaluronic acid[21,23,37,65,77,81], and one study each of lycopene[16], vitamin D[55], antioxidants[21], ayurvedic[38], while eleven studies focused on multiple natural agents[20,26,35,37,44,52,56,64-66,75]. Meta-analysis was conducted in nine of them[16,18,21,44,47,60,65,68,75].

Lycopene, purslane, antioxidants, ayurvedic, chamomile and supplementation with vitamin D showed positive results. However, there is weak evidence supporting the use of these agents[16,21,38,55,65,75,76]. More robust evidence of efficacy on OLP management was found using aloe vera, hyaluronic acid, and curcuminoids, being suggested as an adjuvant to first-line therapy or as an alternative therapy[32,48,56,61,66].

Aloe vera 70% gel or mouthwash applied three times a day is an effective natural agent[65,75], showing complete or partial reduction of OLP lesions without side effects in four studies[18,50,51,76]. However, when compared to corticosteroids, aloe vera showed inconsistent results with short follow-ups[21,44].

Hyaluronic acid 0.2% three to five times a day showed positive outcomes when compared to placebo in six studies[21,23,37,65] and similar effects as corticosteroids in two[77,81].

Curcuminoids showed results similar to corticosteroids in two studies[32,74], and superior results in lesion reduction in one[21]. When compared to placebo, curcumin improved pain symptoms and exhibited complete remission of lesions in 75% of patients, without signs of toxicity[32,48,67]. When compared to tulsi, another natural agent, turmeric demonstrated more success in decreasing burning sensation and pain, improving healing in one study[31]. The concentration found to be efficacious for curcumin was an oral intake of 6000 mg/day instead of 2000 mg/day[37,67], as well as topical use of 5% curcumin paste[37].

Follow-up time ranged between none to ten years and no recurrence was reported when treating OLP lesions with natural agents in five studies[23,26,37,66,81]. In one study the use of herbal agents led to a reduced rate of recurrence[47].

*Other treatment modalities*

Nine studies reported non-usual treatments for OLP. Four studies investigated intralesional Bacille Calmette-Guerin Polysaccharide Nucleic Acid (BCG-PSN)[34,37,40,66], two excision surgery[37,52], two amlexanox[37,75], two cryotherapy[37,52], two hydroxychloroquine[13,52], two ozone[37,52], two mesalazine[26,37], one plaque control[17], one levamisole[37], one inhibitor of neo-angiogenesis[52], and one pallet-rich plasma[79]. Meta-analysis was conducted in almost 23% of them[17,75].

Plaque control, BCG-PSN, cryotherapy, ozone, hydroxychloroquine, mesalazine, injections of bevacizumab (inhibitor of neo-angiogenesis), and Pallet-Rich Plasma showed positive outcomes in OLP management[13,17,26,34,37,40,66,52,79]. In contrast, amlexanox showed poor outcomes, with less efficacy than purslane, and levamisole showed inconclusive results[37,75]. More studies are necessary regarding the use of all these treatment modalities.

Concerning the use of BCG-PSN, it demonstrated similar results to corticosteroids[34,66], and presented an overall quality of evidence of 2.42[40]. One study showed similar outcomes between intralesional pallet-rich plasma and intralesional triamcinolone acetonide. No difference was found between clobetasol and mesalazine[26,37]. Cryotherapy performed under local anesthesia showed similar results to TA paste[37,52].

Furthermore, ozone showed better results than placebo and PBM and comparable results to corticosteroids[52]. Levamisole associated with low-dose prednisolone showed inconclusive findings, with over 80% improvement in 12 patients and 11 patients showed no response[37]. Surgical therapy is indicated when the lesion is circumscribed or is small and isolated, not being employed as a routine treatment[37,52].

The follow-up time was between none to ten years. In one study the follow-up was not informed[34]. Recurrence was reported in 33.33% of studies. In two studies no recurrence was presented[26,37]. Furthermore, in one study controversial results were shown, with a mean of relapses in the three-month follow-up[79].

Risk of bias assessment

Risk of bias of the systematic reviews included in this overview was categorized as low in 43 studies (58.1%), moderate in 15 studies (20.27%), and high in 16 studies studies (21.62%). **Supplementary File 5** shows the summary of the RoB analysis.

## Discussion

The management of OLP has been the subject of extensive research and poses a significant challenge for both healthcare professionals and patients. This is primarily due to the autoimmune and chronic nature of this disease. In an attempt to summarize the evidence regarding the management of patients diagnosed with OLP, the present Overview analyzed 74 systematic reviews. Our findings showed that corticosteroids represent the primary drug used, with more promising results. On the other hand, significant therapeutic modalities such as calcineurin inhibitors, which have also shown effectiveness, can serve as alternatives in the management of OLP.

Corticosteroids are employed in the management of OLP, promoting pain relief and tissue healing due to their anti-inflammatory, immunosuppressive, and metabolic effects[85]. The topical use of corticosteroids is considered to be the first line therapy[13,18,35,37,52,58-60,71,75,76,82]. The most recommended topical corticosteroids were triamcinolone acetonide 0.1%, clobetasol propionate 0,05%, dexamethasone 0,05%, and betamethasone, which use is

recommended due to more robust clinical trials using these drugs showing its efficacy and safety[52,72].

Dexamethasone, considered the safest among these options, shows no significant superiority in efficacy compared to other corticosteroids[35,44,45,52,65]. Studies demonstrate comparable efficacy between different concentrations of clobetasol propionate (0.05% and 0.025%)[35,37]. The choice between adhesive vehicles or mouthwashes for application remains inconclusive, with mouthwashes potentially causing more adverse effects, while adhesive vehicles may be preferable for specific lesions[13,37,82]. Additionally, it was also suggested that fluocinolone acetonide 1% gel is more efficacious than the orabase formulation.

Intralesional injection of corticosteroids also represents an effective treatment modality, which has the advantage of delivering a high concentration of the drug in the injured area, and the active agent can remain longer in the tissues due to its insolubility[19]. The locally adverse effects of this application were candidiasis, swelling of the mucosa, burning, pain, tingling sensation, and the possibility of developing atrophy of the epithelium at the site of application[37,86]. Although it has been supported the use of intralesional corticosteroid injection even as first-choice therapy for OLP by one study[35], more randomized clinical trials are necessary.

Systemic corticosteroids, although effective, are not recommended as a first-choice treatment due to the diverse and dose-dependent adverse effects, especially when used for more than two weeks[13,40,82]. These adverse effects include sodium and water retention (Cushing's syndrome), obesity, diabetes mellitus, peptic ulcers, hypertension, secondary candidiasis, and visual alterations such as glaucoma and cataracts, among others[13,86]. Since that has not been proven a difference in outcomes between topical and systemic corticosteroids[13], and adverse effects are more likely to occur in systemic administration it should be indicated for severe recalcitrant erosive OLP or diffuse mucocutaneous involvement[13,40,82].

For recalcitrant lesions to corticosteroids, they could be associated with different treatment modalities, such as lasers, topical retinoids, and natural agents to reduce symptoms and severity of OLP lesions. Regarding the efficacy of PBM on OLP management, the majority of studies showed superior or similar

efficacy than corticosteroids[11,14,30,35,41,53,70]. Regarding PDT, it was more effective than placebo[42,60,75] but when compared to corticosteroids, it showed similar efficacy in most studies[37,39,41,70,77] and inferior results in two[12,35]. However, it is not possible to draw any solid conclusions based on these systematic reviews using lasers due to several factors, including a high risk of bias, considerable heterogeneity in both data and laser parameters, and limited sample sizes. It is recommended more randomized clinical trials, and it is suggested PBM and PDT as adjunctive therapy to first line treatment[27,52,69]. For PDT, 5-ALA was defined as the optimal photosensitizer at concentrations of 5% to 20%[39,42].

Although there is weak evidence supporting the treatment with retinoids alone[25,73], three studies[35,37,82] reported that the efficacy of corticosteroids can be potentialized when associated with vitamin A mouthwash or oral intake of vitamin A plus selenium. However, systemic retinoids should be prescribed with caution due to deranged transaminase levels and liver damage, cheilitis, alopecia, dystrophic nail formation and its teratogenic effects[13,86]. Concerning natural agents, they present a wide range of treatment options with an absence of adverse effects, being less toxic and cost-effective, reducing clinical signs of OLP[18,48,67]. Currently, there is insufficient data to determine the superiority of any of them against each other[20,26,43,52,60,64]. More robust evidence of efficacy on OLP management was found using aloe vera, hyaluronic acid, and curcuminoids, however, larger and high-quality RCTs and more studies were essential[28,48,61,71]. Consequently, they have been suggested as adjuvants to corticosteroids to improve their action[21,32,35,37,47,48,52,56,61,66,76], and not being indicated as therapy alone by one study[68].

Calcineurin inhibitors, particularly tacrolimus, exhibit strong evidence for treating OLP. However, evidence for pimecrolimus and cyclosporine is disputable, necessitating more randomized clinical trials. Adverse effects of these inhibitors include temporary local sensations like burning, dry mouth, reflux, mucosal staining, and taste alteration[29,83]. Although tacrolimus is recognized for its efficacy in OLP treatment, it's typically recommended as a secondary option for lesions unresponsive to corticosteroids[13,52,58,62,63,76,82,83]. The preferred initial choice is typically topical 0.1% tacrolimus applied several times daily for 6 to 8 weeks, followed by considering 1% pimecrolimus if the lesions persist unresponsive. Although no significant difference in efficacy between

these two drugs was found[35], tacrolimus holds stronger evidence in treating OLP. The idea of an increased risk of oral squamous cell carcinoma post-immunosuppressant use lacks solid evidence[83], with reported cases lacking conclusive links[57].

Some treatments are not being recommended as a first-line due to a lack of strong evidence supporting their use. For instance, the use of azathioprine appeared to be the most effective of other immunosuppressants, but it is not recommended due to its severe adverse effects, which include bone marrow aplasia, pancytopenia, and liver dysfunction[13,86]. Additionally, there is insufficient evidence supporting the use of this drug, as well as, mycophenolate mofetil, thalidomide, dapsone, MTX, or rapamycin[13,26,34,37,65,78]. For natural agents, there is insufficient evidence to support the use of Lycopene, antioxidants, ayurvedic, and supplementation with vitamin D[16,21,38,55] due to lack of RCTs with bigger sample sizes.

Surgical management, which includes conventional excision with a blade, cryosurgery, and the use of free soft tissue grafts is not suitable for the erosive and atrophic types[37,52]. Since OLP is an inflammatory condition, lesions can recur even after excision, and trauma by surgical procedure may induce new lesions at these sites by the Koebner phenomenon[53,87]. For CO2 laser excision, it was reported a good postoperative, with minimal pain, bleeding, or scar formation[53]. Other advantages were instant relief of symptoms and prevention of malignant transformation[53]. However, its efficacy was proven to be inferior to corticosteroids and PBM[30,49,80]. Additionally, the laser removal makes it difficult for histopathological analysis and it is considered an invasive procedure[53], being recommended only for small, localized and persistent lesions.

Regarding the therapies that are not recommended for the management of OLP, the use of UV irradiation is one of them[13,53]. This is attributed to the oncogenic potential associated with this light source[53,88,89]. Adverse effects were documented in 77.77% of patients, with milder neurological side effects such as nausea, dizziness, ocular symptoms, paresthesia, and headache[53,86,90]. Furthermore, severe nausea after oral administration of the photosensitizer psoralen led to withdrawals in the studies mentioned above.

It is important to emphasize the potential impact of a strict plaque control regimen in ameliorating the clinical severity of OLP lesions, especially those manifesting as desquamative gingivitis[17]. It also underscores the preventive role against other oral conditions like gingivitis and dental caries[91]. Considering these aspects, offering dental hygiene guidance should be a fundamental aspect of caring for patients with OLP.

This Overview has some limitations. The findings of this study should be interpreted with caution since the systematic reviews included presented a high heterogeneity regarding study designs, treatment protocols, doses used, and laser parameters, making it difficult to compare the results. Consequently, the description of variations of what each article informed can be found in our supplementary material and it was not possible to perform a meta-analysis. Another limitation is the lack of sample data, such as gender, mean age and information about the clinical manifestation of OLP between all six types of OLP that present variable characteristics and symptoms. Lastly, another concern is the length of follow-up, which in one systematic review was ten years, but some cases did not even evaluate the follow-up. A long observation period would facilitate a more informed selection of the treatment modality, considering that OLP is a chronic disease characterized by periods of remission and exacerbation. The fewer the recurrences with a particular treatment, the more grounded the recommendation for its use will be.

**Conclusion**

The first-line treatment for OLP management is topical corticosteroids. However, for recalcitrant OLP lesions, there is a wide range of alternative treatment modalities that were explored in this study. The following protocol was suggested to present the best results found in this overview:

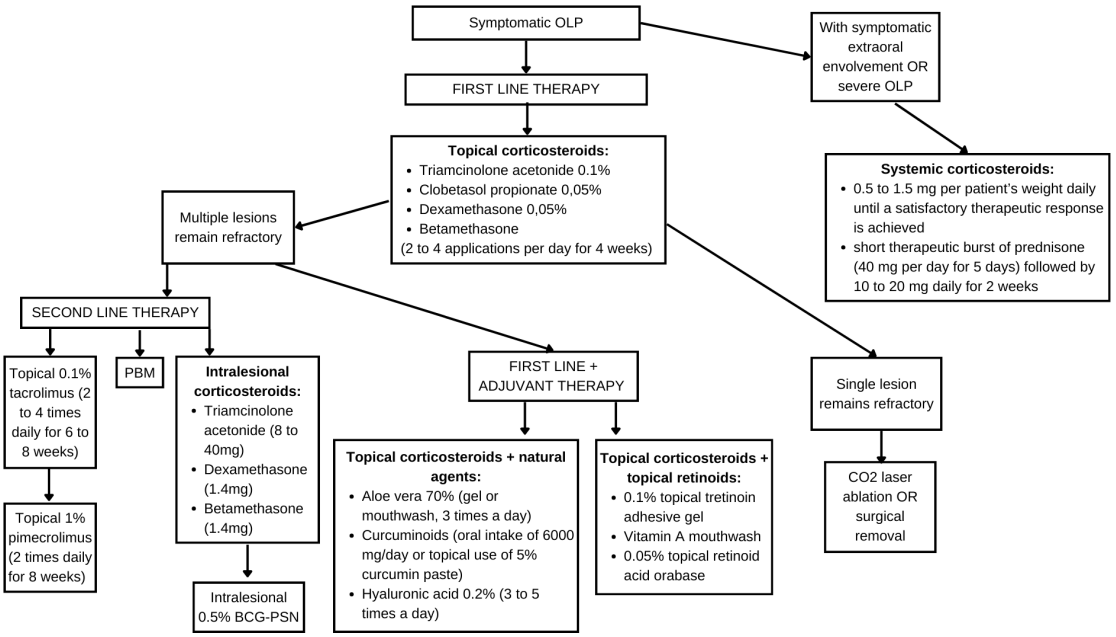


**Figure 1**. Flowchart of suggested clinical management of symptomatic OLP based on the findings of this overview.

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## Supplementary Files

**Supplementary File 1.** Search strategy used to identify articles in electronic databases

| Databases | Search Strategy |
|---|---|
| PubMed | (("Lichen Planus, Oral" OR "oral lichen planus" OR "mouth lichen planus") AND (Therapeutics OR Therapeutic OR Therapy OR Therapies OR Treatment OR Treatments)) AND ("systematic review" OR "meta-analysis") |
| Web of Science | ((ALL=("Lichen Planus, Oral" OR "oral lichen planus" OR "mouth lichen planus")) AND ALL=("Therapeutics" OR "Therapeutic" OR "Therapy" OR "Therapies" OR "Treatment" OR "Treatments")) AND ALL=("systematic review" OR "meta-analysis") |
| Scopus | ( TITLE-ABS-KEY ( "Lichen Planus, Oral" OR "oral lichen planus" OR "mouth lichen planus" ) AND TITLE-ABS-KEY ( "Therapeutics" OR "Therapeutic" OR "Therapy" OR "Therapies" OR "Treatment" OR "Treatments" ) AND TITLE-ABS-KEY ( "systematic review" OR "meta-analysis" ) ) |
| Embase | ('lichen planus, oral':ti,ab,kw OR 'oral lichen planus':ti,ab,kw OR 'mouth lichen planus':ti,ab,kw) AND ('therapeutics':ti,ab,kw OR 'therapeutic':ti,ab,kw OR 'therapy':ti,ab,kw OR 'therapies':ti,ab,kw OR 'treatment':ti,ab,kw OR 'treatments':ti,ab,kw) AND ('systematic review':ti,ab,kw OR 'meta-analysis':ti,ab,kw) |
| Google Scholar | ("Lichen Planus, Oral" OR "oral lichen planus" OR "mouth lichen planus") AND ("Therapeutics" OR "Therapeutic" OR "Therapy" OR "Therapies" OR "Treatment" OR "Treatments") AND ("systematic review" OR "meta-analysis") |
| ProQuest | ("Lichen Planus, Oral" OR "oral lichen planus" OR "mouth lichen planus") AND ("Therapeutics" OR "Therapeutic" OR "Therapy" OR "Therapies" OR "Treatment" OR "Treatments") AND ("systematic review" OR "meta-analysis") |

**Supplementary File 2**. Summarized data of the systematic reviews included in this overview.

| Author(s), year of publications (country) | Meta-analysis | Number of studies included (type) | Sample size | Gender | | Mean age | Oral manifestations | Intervention | Control treatment | Outcome evaluation | Response | Follow-up (weeks) | Recurrence | |
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| | | | | M | F | | | | | | | | | |
| Akram et al., 2018 a (Pakistan) | No | 5 (3 RCTs and 2 non-RCT) | 240 | NA | NA | NA | Erosive-atrophic OLP | PBM | Topical corticosteroids | VAS, CS, FS, TSS, EI, ERA | PBM: 61.9%<br>Control: 28.6% | 4 to 48 | - PBM: 4.8%<br>- Steroid group: 47.6% | It ren<br>PB<br>compa<br>th |
| Akram et al., 2018 b (Pakistan) | No | 6 (2 RCT and 4 non-RCT) | 131 | 38 | 93 | NA | Erosive-atrophic and reticular OLP | PDT | Topical corticosteroids | VAS, TSS, EI, lesion size and RAE | PDT did not show significant improvement when compared with steroid therapy | 4 to 48 | NA | PDT ap<br>in the<br>OLP. H |
| Al-Hashimi et al., 2007 (USA) | No | 25 (9 RCT and 16 non-RCT) | 565 | NA | NA | NA | NA | - Topical and systemic corticosteroids<br>- Topical and systemic retinoids<br>- Immunossupressants (azathiprine and calcineurin inhib)<br>- Ultraviolet (UV) phototherapy<br>-Hydroxychloroquine | Placebo | VAS, TSS | Corticosteroids are effective in the management of OLP, being clobetasol probably more effective. | 4 to 24 | NA | Cortic<br>the<br>ret<br>inhibit<br><br>line th<br>are no<br>U<br>bec<br><br>Lack<br><br>of va |

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| Al Johani et al., 2009 (UK) | No | 46 | 808 | NA | NA | NA | NA | Calcineurin inhibitors | -Placebo<br>-Corticosteroids | NA | - there remains little strong evidence demonstrating that **tacrolimus** is notably superior to topical corticosteroids for the treatment of OLP. However, tacrolimus can be considered effective in controlling the extent of mucosal lesions and the related symptoms of OLP. It has few adverse side effects but relapses may arise after discontinuation of therapy.<br>- **Pimecrolimus**: results are not consistent. Transient burning sensation and relapse reported.<br>- Results of different | 2 to 36 | NA | Curre<br><br>demon<br><br>topic<br>tre<br>how<br>co<br>co<br>mucos |

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| | | | | | | | | | | | trials investigating the effectiveness of **topical cyclosporine** are not consistent. | | | |
| Al-Maweri, et al., 2017 (Saudi Arabia) | No | 6 (4 RCTs and 2 controlled trials) | 268 | NA | NA | NA | Erosive-atrophic and reticular | PBM | - Topical corticosteroids<br>- Ozone<br>- CO2 laser surgery<br>- Placebo | VAS, TSS, RAE, recurrence rate and levels of anxiety, serum proinflammatory mediators | All studies reported PBM to be effective in reducing signs and symptoms of OLP | 8 to 48 | NA | PBM is of sym use cortic |
| Al-Maweri et al., 2018 (Saudi Arabia) | No | 5 (3 RCT and 2 non-RCT) | 91 | NA | NA | NA | Erosive-atrophic OLP | PDT | - Topical corticosteroids<br>- Systemic corticosteroids | VAS, TSS, EI | PDT is more effective than corticosteroids in 1 study, less effective in 2 and as effective as costicosteroids in 2 | 4 to 12 | NA | PDT optio OLP. trials w a |
| Al-Maweri et al., 2023 (Qatar) | Yes | 5 RCT | 218 | 83 | 135 | 37.7 to 52.1 | Reticular, atrophic, plaque, erosive, papular, bullous, ulcerative | Systemic Lycopene | - Prednisolone<br>- Levamisole<br>- Placebo | VAS, Tel Aviv - San Francisco Scale, Escudier Score, 8-isoprostane levels and malondialdehyde | Lycopene showed significant improvement in overall treatment clinical response, with comparable efficacy to controls | 8 | NA | Good reducin OL |
| Albaghli et al., 2021 (UK) | Yes | 3 | 228 | NA | NA | 18-87 | Desquamative gingivitis | | Normal oral hygiene regimen | PI (Silness and Loe, 1964, | Significant improvements in the OLP lesions in the | 4 to 72 | NA | Plaque effecti clinica |

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| | | | | | | | | Plaque control | | Escudier Index, VAS, OHIP-49 | test rather than control groups | | | and ora life |
| Ali et al., 2016 (Egypt) | Yes | 7 (4 RCT, 1 'split mouth design' and 2 case reports) | 217 | 80 | 137 | NA | Erosive-atrophic, papular and reticular OLP | Aloe vera | -Placebo gel<br>- Topical corticosteroid | VAS, TSS, treatment response by Carrozzo & Gandolfo criteria, OHIP-49, HAD Scale, lesion size | AV is inferior to the control. AV was effective in managing OLP in the AV groups, not inferior when compared to placebo groups | 4-36 | NA | Althou the g pro |
| Alsubhi et al., 2020 (Saudi Arabia) | No | 7 (4 RCT, 1 quasi-experimental study, 2 case series) | NA | NA | NA | NA | Erosive | TA intralesional injections alone OR in addition to oral prednisolone | - Topical corticosteroid<br>- Betamethasone or BCG-PSN intralesional injection<br>- Oral healthy side | VAS, OHIP-14, Escudier et al. scoring (measure ulcer size) | Reduction in pain (85%), erythema and ulceration (78-80%). were noted after 2 weeks of the TA injection. Complete resolution of erythematous sites (88.9%) and ulcerations (84.4%) in 4 weeks | 2 to 96 | 14.8% betamethasone, 45% - 58% for the TA injection. Combined with oral prednisolone, recurrence happened between | Th appl cortic manag randor |

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| | | | | | | | | | | | | | 3 - 24 months | |
| Azab et al., 2020 (Egypt) | No | 12 RCT | 675 | NA | NA | NA | NA | Natural agents | Topical corticosteroids | VAS, TSS | Aloe vera and licorice: inferior when compared to control. Curcumin: superior to TA in lesion reduction. Tripterygium: comparable to Dexamethasone. Hyaluronic acid: improve pain score. Glucosamine, Selenium-ACE, vitamin A, honey, quercitin: showed better results only when associated with corticosteroids. | 2 to 24 | NA | There suppor the in metho |
| Bao et al., 2022 (China) | Yes | 19 RCT | 723 | 221 | 502 | NA | NA | Antioxidants | - Placebo<br>- Topical and systemic corticosteroids | VAS, NRS, TSS, salivary total antioxidant capacity; pain/clinical resolution; REU, MOMI, CRP and IL-6 levels, | The antioxidants and placebo groups had similar clinical resolution rates, compared with the conventional treatment, the conventional treatment + | 2 to 24 | NA | Treat could metho and clinica |

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| | | | | | | | | | | bleeding index, salivary total oxidative capacity, OHIP-49, HAD | antioxidants had a higher clinical resolution rate | | | |
| Binnal et al, 2022 (India) | No | 16 (5 RCTs) | 349 | 92 | 249 | 50,38 | Reticular, atrophic, keratotic, ulcerative | PDT | - Topical corticosteroids<br>- Placebo | TSS, EI, SI, REU, pain VAS score, effectiveness, clinical response | Efficacy, signs and pain symptoms showed controversial results between studies | 4 to 240 | No relapse in PDT (81.4%), LLLT (74.1%) and corticosteroid (99.5%) groups in 1 year follow up. | Hete<br>s<br>Mor |
| Casale et al., 2017 (Italy) | No | 2 | 174 | NA | NA | NA | Erosive | Hyaluronic acid | Placebo | VAS, lesion area, degree of erythema | HA showed a highly reduction on soreness and degree of erythema than placebo group | 1 to 6 | NA | Mor |

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| Chamani et al., 2015 (Iran) | Yes | 10 RCT | 385 | NA | NA | 34.7 - 66 | NA | - Clobetasol 0.025 or 0.05%<br>- Tacrolimus 0.1% | - Topical and systemic corticosteroids<br>- Cyclosporine<br>- Mesalazine | Clinical improvement, treatment stability | Tacrolimus was more effective than triamcinolone acetonide and clobetasol, with appropriate stability | 4 to 8 | NA | Tacrol than c for sl susce and fo |
| Chan et al., 1999 (Singapore) | Yes | 9 RCT | 192 | NA | NA | NA | NA | - Topical corticosteroids<br>- Topical and systemic retinoids<br>- Cyclosporine<br>- Psoralen Ultraviolet A (PUVA) | Placebo | VAS and clinical improvement: degree of erosion, erythema and reticulation on ordinal scale (0 to 3) | Topical cyclosporine OR = 33.91 (symptoms) and OR = 28.93 (signs); retinoids OR = 8.32 (combined symptoms-signs); steroids OR = 6.60 and OR = 4.76 (symptoms) and OR = 7.17 (signs); PUVA OR= zero | 2 to 48 | NA | The re evide the as placeb Larger |
| Cheng et al., 2012 (UK) | No | 15 RCT | 473 | NA | NA | NA | Erosive | - Topical and systemic corticosteroids<br>- Immunossupressants | - Placebo<br>- Clobetasol propionate<br>- Triamcinolone acetonide | VAS, Physician Global Assessment and Participant global self-assessment | Greater pain reduction in cyclosporin group compared to topical corticosteroids. No difference between 0.025% vs 0.05% clobetasol. Pimecrolimus vs vehicle: 7x more | 4 to 24 | In one study comparing pimecrolimus to placebo for 4 weeks | The eviden single |

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| | | | | | | | | - Natural agents<br>- Mesalazine | | | likely to result in a strong improvement | | all participants who improved during treatment relapsed within 1 month of ceasing treatment. | |
| Choudhary et al., 2022 (India) | No | 8 | 95 | NA | NA | NA | Erosive-atrophic | PDT | Corticosteroids | NA | Aghahosseini et al.: 2 CR, 2 PR, 1 NR. Umber et al: 1 CR. Koty Naik et al.: 2 CR, 8 PR, 2 NR. Fatemeh et al.: PDT more effective than control until 4th week. Mirza Sana et al: PDT is effective, less than control but showing better results than PBM. | 2 to 192 | Recurrence occurred after three months in 1 case and four months in 2 cases. The other | PDT c<br>thera<br>topica |

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| | | | | | | | | | | | Rakesh et al and Shivani et al: good results with 1 session of ALA-PDT. Sadaksharam et al.: 3 cases with no improvement, moderate in 9, marked in 6 an CR in 2 | | studies did not show recurrence in follow-up. | |
| Da Mata et al., 2020 (Brazil) | No | 2 RCTs | 53 | 17 | 36 | 44 to 70 | NA | Curcumin C3 complex alone OR with Prednisone | - Placebo alone or with Prednisone | MOMI | Greater reduction in symptoms and signs on curcumin group | 7 to 12 | NA | Mor |
| Da Silva et al., 2021 (Brazil) | Yes | 28 RCTs | 1114 | NA | NA | NA | Atrophic, erosive, or ulcerative | Topical non-steroid immunomodulators | - Placebo<br>- Corticosteroids | VAS, modified clinical score by Setterfield et al., Kaliakatsou et al., Raj et al. score, TSS, Farzaneh Agha Hosseini et al. score, NCS, modified version proposal by Piboonniyom et al., serum IL-6 and IL-8 levels, complete resolution of | Pimecrolimus vs placebo: superior efficacy in clinical signs. Cyclosporine vs placebo: superior in signs and symptoms. Cyclosporine and corticosteroids: the latter showed better efficacy of clinical response. Thalidomide vs dexamethasone: both decreased signs and | 1 to 48 | Tacrolimus showed better performance preventing symptom relapse when compared to corticosteroids, | T<br>pimec<br>and<br>sho<br>topic<br>show<br>preve<br>c |

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| | | | | | | | | | | signs, lesion size, Corrocher et al. score, OHIP, IGA, Asian Lichen planus Group criterion | symptoms, with no difference between them. MM 4 weeks vs baseline: reduction in signs and symptoms. | | as well as pimecrolimus in signs and symptoms. | |
| De Carvalho et al., 2022 (Brazil) | Yes | 6 | 100 | 25 | 65 | 56.65 | NA | - PBM<br>- CO2 laser | - Topical corticosteroids<br>- CO2 laser | VAS, TSS, EI, FS, RAE, Profile of Mood States (POMS) | 3 studies showed that all gingival cases were successfully treated with PBM, while 2 studies reported unsatisfactory response to the laser. Remaining 12 showed general results, without differentiating the outcomes according to the lesion site. | 4 to 104 | NA | PBM h<br>reduc<br>clinica<br>differ<br>topica<br>limited<br>th<br>autoi |
| Dhanvanth et al., 2022 (India) | No | 2 | NA | N A | N A | NA | NA | Topical herbal therapeutic | - Topical corticoid<br>- Between herbal therapeutics | VAS, Burning sensation, Redness, Ulceration, Striae | Turmeric is more effective compared to tulsi in reducing burning sensation, pain and healing | 12 to 16 | NA | This r<br>conclu<br>and tu<br>t |
| Dharman et al., 2020 (India) | No | 12 (7 RCT, 5 non-RCT) | 325 | 91 | 19 4 | NA | Atrophic-erosive | | - Topical corticosteroides<br>- Placebo | VAS, NRS, TSS, MOMI | Studies showed reduction in pain in curcumin group, | 2 to 12 | NA | Cur<br>mainte<br>afte |

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| | | | | | | | | Curcumin | | | with no difference between TA group. Complete remission of lesions in 75% of curcumin group compared to 62.5% of control group. | | | cortico insuffi the ef ov |
| Elad et al., 2010 (Israel) | No | 15 RCTs | 463 | N A | N A | NA | NA | Calcineurin inhibitors | - Placebo - Topical corticosteroids | VAS, TSS, lesion Asian Lichen Planus Group Scale, OHIP | **Cyclosporine:** effective in 3 studies, not effective in 2, as good as control in 3 **Tacrolimus:** effective in 2 studies an as good as control in 1 **Pimecrolimus:** effective in 1 study, parcial results in 2 studies and as good as control in 1. | NA | NA | **Cyc** placel gra B). Top (1b, E clobeta mo (2b, C sympto but r local long |
| Elad et al., 2011 (Israel) | No | 4 RCTs and 2 non-RCT | 237 | N A | N A | NA | NA | Miscellanous agents | - Placebo - Topical corticosteroids | Clinical appearance, pain | Improvement of symptoms of erosive OLP in 1 patient using topical **tetracycline** solution in 1 week. **Retinoids**: effective | NA | NA | **Tetr** repor e rec recomm |

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| | | | | | | | | | | | in 3 studies and partial in 1. **BCG**: effective in 1 study | | | **Retin** pla is 0.1 **BC** effect i **Sirolin** |
| García-Pola et al., 2017 (Spain) | No | 55 RCTs | 1073 | N A | N A | NA | Reticular, ketatotic, atrophic, erosive | -Corticosteroids - Calcineurin inhibitors - Retinoids | - Between treatments | VAS, Raij et al., Tel Aviv-San Francisco scale, TSS, Farzaneh Agha-Hosseini et al., Kaliakatsouet al., Ungphaibon et al., Piboonniyom et al., Corrocher et al., Escud-ier et al. | No evidence that one glucocorticoid is more effective than another. **TA 0,1%** 2-4x/day, more effective with nanoliposomals particles added to orabase**. TA + vit A** is more effective than TA alone. **Oral betamethasone** at low doses is faster than 0.1% TA in reduction of signs. **Intralesional betamethasone** presents fewer | 2 to 60 | NA | As a f the s betam dose is form being wer clobet 0.05% 0,4%) for fre progre Next tacro mainta |

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| | | | | | | | | - Natural agents<br>- PBM<br>-PDT | | | recurrences than TA injection. TA / Dexamethasone > diode laser > Clobetasol in signs. **Clobetasol** 0,05% = clobetasol 0,025%. Higher effectiveness of **dexamethasone** with cedar honey /selenium/ vitamins are added. Fluocinolone acetonide 0,1% > retinoic acid 0,05%. **PDT**: worse results than 0.1% triamcinolone acetonide and dexamethasone. Paradoxically, however, 660 nm diode laser offered a better response on OLP signs than clobetasol propionate. | | | pimecr<br>for<br>lesion<br>mg/kg<br>las<br>thera |
| Guo et al., 2015 (China) | Yes | 9 RCTs | 459 | 183 | 276 | NA | Erosive | | - Placebo<br>- Topical corticosteroids | REU, VAS, NCS, erosive area, severity of | Neither study showed any statistical significant | 2 to 60 | NA | No e<br>topi<br>e |

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| | | | | | | | | - Tacrolimus | | lesion, percentage of patients attaining clinical improvement | difference between groups. The pooled odds ratio (OR) of clinical improvement was 1.19. Subgroup analyses regarding 0.1% and 0.03% tacrolimus were performed OR = 1.87 and 1.47 respectively | | | cort could r to be t prese |
| Gupta et al., 2017 (India) | No | 70 RCTs | NA | N A | N A | NA | NA | - Topical and systemic corticosteroids<br>- Immunossupressants<br>- Retinoids<br>- Natural agents<br>- Levamisole<br>- Excision with Bioresorbable membrane<br>- Photochemotherapy<br>- Amlexanox<br>- Thalidomide<br>- BCG-PSN<br>- Cryotherapy<br>- Mesalazine<br>- Ozone | - Placebo<br>- Between treatments | VAS and clinical resolution of erythema, ulceration, erosion and reticulation. | - Topical steroids: first-line treatment<br>- Systemic steroids: used in unresponsive cases to topical treatment.<br>- Tacrolimus and pimecrolimus were equally efficacious as steroids but relapses with tacrolimus.<br>- Intralesional betamethasone > TA injection<br>- Clobetasol 0.025 and 0.05% = efficacy | None to 10 years | Relapses have been reported with tacrolimus within 3-9 weeks of therapy and need for treatment with topical steroids. | No trea be supe first manage treatme tacrolir retinoic advoca first l unrespo System or imm be re lesions with i sites conside Surgica |

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| | | | | | | | | - PDT<br>- PBM | | | - Steroid mouthwash = gel/paste (but more adverse effects)<br>- Fluiconolone acetonide 0.1% in gel > orabase<br>- Steroid + vitamin A and selenium > steroid alone<br>- Steroids > Tazarotene > Placebo<br>- Isotretinoin: 35% response in high concentration and 13% in low.<br>- TA + vit A (mouthwash) > TA alone<br>- Retinoids: second line treatment<br>- MMF: complete remission in 60% cases and partial remission in 30%<br>- Azathioprine: 77.8% excellent response | | | employ<br>lesions<br>therapy<br>There i<br>few RC<br>use of<br>no conc |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | - Levamisole + prednisolone: 80% improvement<br>- Steroids similar to AV.<br>- Purslane: 83% partial to complete clinical improvement<br>- Ignatia > placebo<br>- Curcumin at dose of 6000mg/day is efficacious, also 5% curcumin paste.<br>- EA: reduces pain and size of lesions<br>- HA: reduction in erythema and size of lesions<br>- FBM < steroids<br>- FBM > carbon dioxide laser | | | |
| Gupta et al., 2022 (India) | No | 9 (8 RCTs and 1 pilot-study) | 232 | NA | NA | NA | All types of OLP | Ayurvedics | NA | Score scale for erythema, pain burning, | Ayurvedic treatments showed efficacy in OLP signs and symptoms | NA | NA | Ayurve in trea are nec |
| He et al., 2020 (China) | Yes | 16 | 503 | NA | NA | NA | Reticular and erosive | | Topical corticosteroids | VAS, TSS | Lesion size decreased by 1.53 cm2, partial | 4-192 | NA | The ov and the could b as |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | PDT | | | response (PR) was 0.77, VAS decreased by 3.82 and TSS decreased by 1.33 after PDT. Subgroup analysis: 5-ALA was more effective than MB. In VAS, diode laser showed a better clinical PR in the treatment of OLP. In lesion size, the efficacy of semiconductor laser was higher than the diode laser. PDT had a similar efficacy to topical steroids. | | | cortico OLP ar resistar when contrai |
| Ho et al, 2012 (USA) | No | 47 | 384 | N A | N A | 54.82 | Erosive | Systemic treatments | Placebo | NA | Overall quality of evidence: BCG (2.42), Corticosteroid (1.39), Retinoid (1.04), immunosuppressant (0.64), antihelminth (0.51), thrombolytic (0.38), | 0-480 | NA | System treatme medica most approac survey Calmet highest stemmi and sou |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | ECP (0.27), antibacterial (0.18), antifungal (0.18), anticancer (0.16), biologics (0.13), antileprotic (0.06), antimalarial (0.01), colchicine (0.01), antihistamine | | | |
| Jajarm et al., 2018 (Iran) | Yes | 13 | NA | NA | NA | NA | NA | PBM and PDT | Topical corticosteroids | TSS, VAS, size and severity of lesions | No difference between intervention and control in TSS and VAS. In severity of lesions control > intervention. | NA | NA | PBM i without failed t signific signs o |
| Kalaskar et al., 2020 (India) | No | 8 RCTs | 354 | 117 | 237 | 18-75 | Mixed, erosive, atrophic and reticular | Herbals | - Topical and systemic corticosteroids<br>- Placebo | VAS, NRS, pain index, TSS, MOMI, severity index/ improvement | Statistically nonsignificant difference between the two groups | 4-24 | NA | Insuffic most therapi necessa |
| Leong et al., 2023 (Malaysia) | Yes | 37 RCTs | 1573 | NA | NA | NA | Erosive, atrophic, reticular, ulcerative, hyperkeratotic, papular, bullous, plaque, combined | - Amlexanox paste<br>- PDT<br>- Natural agents<br>- Corticosteroids topical and systemic | - Placebo<br>- Between treatments | TSS, clinical score | Purslane, topical calcineurin, PDT and aloe vera showed clinical improvement vs placebo. Purslane > AML paste. Purslane the mlos effective and safe. | 1-24 | NA | Purslan most e small perform evidenc effectiv howeve PDT is for pai |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | - Calcineurin inhibitors | | | | | | scores. necessa |
| Lodi et al., 2012 (Italy) | Yes | 28 RCTs | 1204 | N A | N A | NA | NA | - Topical corticosteroids<br>- Topical calcineurin inhibitors<br>- Natural agents<br>- Photochemotherapy | - Placebo<br>- Topical corticosteroids<br>- No treatment | VAS, TSS, MOMI, OHIP,OHQoL, clinical response, HAD | No difference between TCSs and TCIs in pain and clinical signs. No evidence that one steroid treatment is better or worse than another; weak evidence that aloe vera and ciclosporin reduce pain and clinical signs; no evidence that topical pimecrolimus is more effective than placebo. | NA | NA | More s |
| Lodi et al., 2020 (Italy) | Yes | 35 | 1474 | N A | N A | NA | NA | | - Placebo<br>- Calcineurin inhibitor<br>- Another corticosteroid<br>- Corticosteroid + extra treatment<br>- Other treatments | VAS, TSS, MOMI, clinical rating scale, complete resolution | Pain resolution was more common in topical corticosteroids group than placebo, with no difference in clinical scores. Pain resolution and clinical resolution were significantly more frequent | 3-9 | NA | Low cortic c low-c calcin may cortico No con stero |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Topical or systemic corticosteroid | | | among topical tacrolimus group compared with clobetasol propionate. No corticosteroid or formulation has proven to be superior, but single trials suggest that PBM, cryotherapy and PDT may be superior to topical corticosteroids | | | |
| Lukaszewska-Kuska et al., 2021 (Poland) | No | 8 RCTs | 263 | NA | NA | NA | NA | Topical forms of dexamethasone | - PDT<br>- PBM<br>- Amlexanox<br>- Clobetasol + ketoconazole + amitriptyline<br>- Thalidomide | VAS, COMDQ, TSS, REU, SI, EI, Piboonniyom clinical data scale, erosive area size, severity of the lesion. TSQM-9, recurrence rates | Pain reduction and EI was greater in Dexamethasone group in comparison with the **PDT** and **PBM**. **Clobetasol/ Ketoconazole / Amitriptyline group:** greater improvement of pain and lesions, less time to complete resolution, more patient satisfaction, lower | 4-12 | Lower relapse risk for corticosteroids group in comparison with PDT | Dexam<br>more e<br>compa<br>except<br>keto<br>mouth<br>limite |

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| | | | | | | | | | | | probability of the disease persisting | | | |
| Luo et al., 2020 (China) | Yes | 18 RCTs | 1339 | N A | N A | NA | NA | Tripterygium wilfordii Hook. f. (TG) alone or in combination to conventional therapy | -Corticosteroids<br>-Immuno modulators<br>- Natural agents | SSRI, VAS, RER, effectiveness rate | Total effectiveness of TG alone was lower than that of immunomodulators. SSRI values were higher when TGs were combined with corticosteroids. | 4-48 | Combination of TGs with topical corticosteroids could significantly reduce the recurrence rate | TGs may regime effe shou neede |
| Lv et al., 2019 (China) | No | 9 (6 RCTs) | 259 | N A | N A | NA | NA | Curcuminoids | -Corticosteroids<br>- Baseline | VAS, NRS, TSS, MOMI | Improved pain symptoms when compared to placebo. No side effects. | 1-12 | NA | High treatm adju cortico |
| Mozaffari et al., 2017 (Iran) | No | 7 (1 RCT) | 425 | N A | N A | NA | NA | Co2 laser | -Corticosteroids<br>- Analgesics<br>- Other types of laser<br>- Baseline | VAS, EI, physician's overall assessment of signs, lesion size | Reduction of lesion size and pain VAS compared with the baseline.<br>VAS and lesion size in CO2 group < corticosteroids group. | 12-480 | 38.2% of patients showed recurrence. Short-term studies | The signi and comp groups |

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| | | | | | | | | | | | 3 patients with defocused continuous laser developed OSCC. | | indicated success of 100 and 85%. However, in long-term studies were 33.4-62%. It seems that laser therapy is effective in medium-term and recurrence of OLP is predictable in | |

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| | | | | | | | | | | | | | long-term follow-ups. | |
| Muthusamy et al., 2016 (India) | No | 5 RCTs | 224 | NA | NA | NA | NA | Aloe vera | - Placebo<br>- Topical corticosteroids | VAS, TSS, Carrozzo and Gandolfo score | Aloe vera showed complete or partial remission in most patients, but percentages vary between studies and do not differ much from placebo | NA | NA | Th<br>eviden<br>effecti<br>for |
| Nair et al., 2016 (India) | No | 5 | 254 | NA | NA | NA | NA | Aloe vera | - Topical corticosteroids | VAS, healing of lesions, lesion size, TSS, OHIP-49 | Aloe Vera reduced VAS /pain/ burning sensation in all studies. Aloe vera group: 74 % of patients and triamcinolone acetonide group 78% of patients showed degrees of healing. In 1 study, aloe vera was found more effective than 0.1 % TA. | NA | NA | Clinica<br>aloe<br>treati<br>most b<br>but is<br>vera i<br>0.1% f |
| Oberti et al., 2019 (Italy) | No | 25 RCTs | 1060 | 30 – | 60 – | 40 – 60 | Atrophic-erosive or reticular | | - Placebo<br>- Between treatments | VAS, NRS, TSS, MOMI, histological | There is not the most effective topical | 4-48 | NA | Topi<br>treatm |

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| | | | | 40 % | 70 % | | | - Topical corticosteroids<br>- PDT<br>- Calcineurin inhibitors<br>- Natural agents<br>- Ozone therapy<br>- Cryotherapy<br>- Excisional surgery<br>- Inhibitors of neo-angiogenesis<br>- Tocopherol<br>- Hydroxychloroquine | | changes, plasma IL-6 and IL-8 levels, OHIP-14, functional alteration scale of Lilleby, HAD scale | corticosteroid. Treatment with pimecrolimus tends to guarantee more stable results over time, with a lower risk of relapse. There is not consensus in the studies about efficiency of other treatment modalities. | | | are TA<br>and<br>None c<br>been<br>topic<br><br>In<br>refrac<br>thera<br>calc<br>topica<br>PDT<br><br>circ<br>surg<br>i |
| Pavlic et al., 2014 (Bosnia and Herzegovin) | No | 15 | 338 | N A | N A | NA | NA | - UV phototherapy<br>- PBM<br>CO2 laser<br>-PDT | NA | VAS, TSS | **PBM/UV radiation:** overall improvement in signs and symptoms. **PDT:** reduction ins igns and symptoms, including in a 4 years follow-up; showed beneficial effect in 81% of OLP cases in 1 study. | 2 to 192 | NA | More<br><br>follow-<br>solid re |

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| Pinto et al., 2023 (India) | Yes | 11 RCTs | 404 | NA | NA | NA | NA | Tacrolimus | - Topical corticosteroids<br>- Retinoids<br>- Calcineurin inhibitors<br>- Placebo | TSS, modified version of Piboonniyom et al. scale, ordinal and four point scale, staging given by Farzaneh Agha - Hosseini et almodified clinical score by Setterfield et al., lesion size, VAS, pain and burning sensation according to Raj et al., | **1, 2, 4, 7-**Topical tacrolimus 0.1% was significantly more effective than triamcinolone acetonide 0.1% and clobetasol propionate 0.05% ointment.<br>**3-** Clobetasol = Tacrolimus.<br>**5, 6-**Tacrolimus and Pimecrolimus are both effective, but Pimecrolimus is more effective in providing long-term resolution of signs and symptoms.<br>**8-**Clobetasol>TA 0.1% ointment > tacrolimus ointment 0.03%.<br>**9-**Oral dapsone > all. Topical triamcinolone acetonide= topical tacrolimus= topical retinoid. | 1 to 24 | Clobetasol propionate group showed more recurrence at follow-up than Tacrolimus | There to p bette dru |

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| | | | | | | | | | | | 10- . Tacrolimus= Triamcinolone acetonide Tacrolimus and TA> Placebo. 11-Tacrolimus 0.1% is better than Isotretinoin 0.1% gel. | | | |
| Ruiz Roca et al., 2022 (Spain) | No | 7 | 300 | NA | NA | NA | Atrophic and erosive | PBM | Drugs or laser off | VAS, EI, TSS | **PBM**: clinical improvement in 59.3% of the lesions and complete remission in 37.3% of the cases. | 1 to 48 | NA | Cor effecti PBM term. b met ar ef |
| Saeed et al., 2022 (India) | No | 5 (3 RCTs and 2 observational studies) | 714 | NA | NA | NA | NA | Vitamin D supplementation | - Placebo<br>- Steroids<br>- Psychological counseling | VAS, size of lesion | Patients treated with vitamin D supplementation reported a statistically significant amelioration in subjective symptoms and lesion appearance | 2 to 15 | NA | conclu in C |
| Samycia et al., 2012 (Canada) | No | 30 (4 RCTs) | 392 | NA | NA | NA | Erosive, ulcerative | Topical calcineurin inhibitors | - Placebo | NA | Double-blind studies have shown | 1 to 240 | NA | These the u |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | - Topical corticosteroids | | that **tacrolimus** is at least as effective as clobetasol propionate 0.05% ointment, and open studies have shown favorable results. **Pimecrolimus** 1% cream was superior to placebo in three double-blind studies and equal to triamcinolone acetonide 0.1% paste in another. | | | inhi<br><br>Two ca<br>carcin<br>tacrol<br><br>but fu<br>to c |
| Serafini et al., 2023 (Italy) | No | 15 RCTs | 1074 | N A | N A | NA | NA | Topical treatments | - Placebo<br>- Between treatments | VAS, clinical resolution | Ozone and corticosteroid are more effective than PBM. PBM has small number of studies with discordant results. Cryotherapy can be considered an alternative or adjuvant therapy with the same efficacy than TCS. Chamomile showed | 1 to 480 | NA | TCSs<br>treatme<br>sympto<br>cost-be<br>similar<br>used f<br>OLP,<br>patients<br>candidi<br>cortico<br>effects<br>must<br>includi<br>with |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | improvement after 4 weeks of treatment. Beneficial effects of TAC 0.1% and pimecrolimus 1% in comparison to TCSs. Dexamethasone, TA, and betamethasone as equally recommendable with respect to efficacy and safety. | | | isotreti therapy adjuva with fi |
| Sotoodian et al., 2015 (Canada) | No | 33 (9 RCTs) | 453 | N A | N A | NA | Erosive, ulcerative | Topical calcineurin inhibitors | - Topical corticosteroids - Placebo | NA | In numerous studies, there is strong evidence to suggest that the use of tacrolimus 0.1% ointment and pimecrolimus 1% cream is superior or equally efficacious as traditional therapies. Both are well tolerated, and there were no clinically significant adverse effects. But | 2 to 240 | NA | There suggest tacroli pimecr is supe as trad Topical well to signific effects. |

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| | | | | | | | | | | | results are still inconsistents. | | | |
| Sriram et al, 2023 (USA) | No | 5 (1 RCT) | 94 | 25 | 69 | 24-74 | Reticular, plaque, erosive | Platelet-Rich Plasma (PRP) | - Corticosteroids injection<br>- Cyclosporin<br>- 0.05% retinoic acid | REU, NRS, pain reduction and clinical scores | The efficacy of intralesional PRP therapy was found to be similar to that of intralesional TA. It ameliorates signs and symptoms in steroid-resistant OLP. However, intralesional PRP therapy was associated with more adverse effects (especially pain) and a higher relapse of OLP lesions after a 3-month follow-up. | 2 to 16 | Controv ersial results. | PRP h potenti Howev larger s to corro |
| Zakrzewska et al., 2005 (UK) | Yes | 11 | 223 | N A | N A | NA | OLP | - Topical immunosupressant<br>- Topical or systemic retinoids<br>- Topical steroids<br>-PUVA | Placebo | OR, ITT, ordinal scale | No therapy was replicated exactly. Trials recording the same outcomes in each therapeutic class were pooled. The largest number of pooled trials was four. Small odds ratios with very | 2 to 16 | NA | This circun sup interv the pa OLP. placel ca standar |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | wide confidence intervals indicating statistically significant but imprecisely known treatment benefits were seen in all but one trial. Only systemic agents were associated with treatment toxicities; all other side-effects were mild and mainly local | | | |
| Suresh et al., 2016 (India) | No | 35 | 1521 | NA | NA | NA | OLP | - Topical steroid<br>- Calcineurin inhibitors<br>- Retinoids<br>-Natural agents | - Placebo<br>-Topical steroid<br>- Retinoids<br>-Natural agents | VAS, Physician Global Assessment, Ordinal & Nominal scales of self-assessment, Oral Mucositis Assessment Scale. | No strong evidence suggesting superiority of any specific intervention in reducing pain and clinical signs of OLP were shown by the RCTs included here | 1 to 24 | NA | Top<br>calci<br>most<br>treatm<br>from th<br>eviden<br>of eit<br>clinica |
| Vaughn et al., 2016 (USA) | No | 3 | 153 (dois não diferencia m gênero0 | 10 | 23 | NA | OLP | | Placebo | NRS, MOMI | The severity of OLP was lower in the curcuminoid group versus | 7 | NA | Over<br>6000<br>for OL<br>ap |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Herbal agents (curcumin) | | | placebo, and no signs of toxicity were found. There was no significant difference between the treatment and placebo groups, and the study was ended early. | | | |
| Sun et al., 2019 (China) | Yes | 21 | 965 | 418 | 547 | 32-67.95 | Symptomatic OLP | Topical calcineurin inhibitors | Topical corticosteroids | Improvement of clinical signs and/or symptoms, relapse, blood levels of TCI, and adverse events; VAS | TCI were similar to TCS in efficacy. TCS resulted in similar outcomes with relapse. Blood levels of TCI were usually undetectable to low level. In addition, tacrolimus showed a statistically higher incidence of local adverse events than TCS for short term treatment. A few systematic adverse events occurred in the tacrolimus and cyclosporine groups, but they were not serious | 2 to 24 | Yes (3 weeks to 6 months). TCS (RR 1.02; 95% CI 0.38-2.72; $I^2$=68%) | The ev TC approa res prot should in T treatm Furthe warra term e |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| White et al., 2019 (USA) | No | 7 | 248 | NA | NA | NA | OLP | Topical or oral curcumin | - Topical corticosteroids<br>- Placebo | VAS, NRS, Thongprasom classification, MOMI | Topical curcumin provided reductions in pain, burning, and 'clinical manifestations of OLP versus baseline, effects similar or inferior to topical corticosteroids. In oral curcumin trials, there were no significant benefits of curcumin therapy versus placebo but there were some potential benefits and reasonable safety in an observational extension study. | 2 to 12 | NA | It is whethe is a via pla curcu promi would corti of cl |
| Vadivel et al., 2020 (India) | No | 20 | 852 | 349 | 503 | 48.14 | Erosive, ulcerative and atrophic OLP | Alternative medications (natural agents) | – Corticosteroids<br>- Placebo | MOMI, Thongprasom scale, VAS | The results showed that the reduction in pain, treatment effectiveness was comparable between the steroids and alternative medications. However, the | 2 to 12 | BCG-PSN (1.22%) | There po altern manag therap imm alterna a new |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | alternative medications had a therapeutic advantage in studies that had used placebo as controls and the results were statistically significant (P < 0.05). No major adverse effects were reported with the usage of alternative medications | | | mana a |
| Sridharan and Sivaramakrishnan, 2021 (Bahrein) | Yes | 55 | 2831 | NA | NA | 45.41 | OLP | Corticosteroids<br>Calcineurin inhibitors<br>Retinoids<br>Photodynamic therapy<br>Hyaluronic acid<br>1, 25 (OH)2D3<br>Herbal drugs | Placebo | Odds ratio (OR) with (95% CI), Weighted mean difference (WMD) | Corticosteroids (OR: 13.6; 95% CI: 1.2, 155.4), pimecrolimus (OR: 14.7; 95% CI: 1.7, 125), purslane (OR: 18.4; 95% CI: 3.5, 97), and ozonized water/corticosteroids (OR: 52; 95% CI: 1.4, 1882.6) had better rates of clinical resolution compared to placebo. | 2 to 24 | NA | Topica most trea Topic be trea Althou and cy signifi |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Corticosteroids (OR: 3.18; 95% CI: 1.2, 8.43), ozonized water/corticosteroids (OR: 9.9; 95% CI: 2.7, 36.2), aloe vera (OR: 13; 95%: 1.5, 111.8), pimecrolimus (OR: 18.8; 95% CI: 2, 177.4) and hyaluronic acid (OR: 24.8; 95% CI: 1.3, 457.6) were significantly associated withsuperior rates of pain resolution compared to placebo. Pimecrolimus and cyclosporine were associated with significantly higher risk of adverse effects than placebo. | | | |
| Su et al., 2021 (China) | Yes | 9 | 335 | 119 | 216 | 31.75 | Symptomatic OLP | | Topical corticosteroids | Clinical Response (extension, severity, | The results indicated that clinical resolution, pain resolution, and | 3 to 24 | Yes | This me the si tacr |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Tacrolimus | | resolution); Pain; CS | relapse were not significantly different among patients treated with tacrolimus and corticosteroids. However, tacrolimus may be more likely to cause mild adverse effects. | | | reg resis system the adv were m not aff |
| Sahoo et al., 2022 (India) | No | 59 (11 RCT and 48 clinical reports) | NA | N A | N A | NA | OLP | Natural agents | Topical corticosteroids Placebo | NA | Results showed that all formulations were effective in reducing the signs and symptoms of OLP (lesion size, burning sensation, redness, pain, and ulceration) within four to twelve weeks. | 4 to 16 | NA | ev ethn could them a and le comp towa |
| Sandhu et al., 2022 (USA) | No | 70 (RCT) | 2612 | N A | N A | NA | OLP | Topical steroids and non-steroids | - PDT - Placebo - Topical corticosterois - Immunossupressan t - Aloe-vera gel | VAS (57%), Thongprasom scoring system (27%), Modified Oral Mucositis Index, the Tel Aviv-San Francisco scale, | Most studies (57%) showed statistically significant results ($p < 0.05$) supporting the effectiveness of their respective interventions | 4 to 200 | NA | Topic be econ treatm topic (first sta meta- |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | RAE score, RPAE score, REU score. | | | | assess therape |
| Santo et al., 2022 (Indonesia) | No | 7 | 220 | NA | NA | NA | OLP | Herbal mouthwash | Synthetic mouthwash | NA | Synthetic mouthwash made from dexamethasone reduced the ulcer size by 38.6% and pain by 46.4% compared to other mouthwashes in 2 w. However, the therapy caused a side effect, candidiasis, in 7 of 18 patients. On the other hand, herbal mouthwash made from henna reduced ulcer size by 17.9% and pain by 32.7% in 2w without causing side effects. | 1 to 12 | NA | The made the therapy an mou he eff mou |
| Sterniczuk et al., 2022 (USA) | No | 6 | 295 (um dos estudos | 113 | 114 | 48.68 | OLP | | - Systemic corticoids - Placebo - Curcumin gel | VAS, Modified VAS | Systemic curcumin showed a similar efficacy to systemic corticoids in the treatment of OLP. | 3 to 12 | NA | Curc alte therap the O limitati |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | não separa gêneros) | | | | | Herbal agents (Curcumin) | | | Topical curcumin with prednisolone is significantly more effective in reducing pain compared to topical curcumin alone in the treatment of OLP. | | | afore high-c |
| Vychaktami et al., 2022 (Indonesia) | Yes | 6 | 212 | 51 | 16 1 | 52.04 | Erosive, reticular and atrophic OLP | Herbal agents | - Placebo - Topical corticosteroids | VAS, OHIP-49, HAD, Thongprasom scale, Individual severity index | Improvement in quality of life or OLP severity was recorded in the intervention group treated with purslane, curcumin and lycopene (P<0.05) but not in the control group. The total effect of herbal medicine in reducing pain severity (measured with the Visual Analogue Scale [VAS]) in OLP patients was not significant (mean difference 0.13; | 1 to 12 | NA | Herbal as a sin seve recomm desig pro me |

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| | | | | | | | | | | | 95% CI -0.202 to 0.463; p=0.442). | | | |
| Waingade et al., 2022 (India) | Yes | 5 (RCT) | 126 (2 estudos não informam gênero) | 20 | 50 | 53.86 | Symptomatic OLP | PDT | Corticosteroids therapy | VAS, Thongprasom sign scores, lesion size, response to treatment, and exacerbation of lesions after therapy | All parameters of VAS score, Thongprasom sign score, lesion size, and response to treatment were statistically non-significant. Our results indicate that both MB-PDT and corticosteroid therapy are effective for the management of OLP | 2 to 12 | No | MI alterna OLP con conclu asc heterog |
| Waingade et al. 2022b (India) | No | 7 RCTs | 319 | NA | NA | 55.56 | Reticular, atrophic, erosive, desquamative gengivitis, ulcerative, plaque | Hyaluronic acid | - Placebo<br>- Corticoids<br>- Other interventions | VAS, TSS, clinical severity, size of lesions, degree of erythema | Topical application of HA 0.2% appears to be significantly more effective in the control of the symptoms of OLP when compared to topically applied corticosteroid in 1 study. Others did not show significant improvement. | 4 to 12 | NA | Similar degree and sig HA, co co alter Mor |
| Zeng et al., 2022 (China) | No | 6 | 225 | NA | NA | 53.84 | OLP | | Corticosteroids (Prednisolone) | TSS | Found that Curcumin | 2 to 12 | NA | The s |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Herbal agents (Curcumin) | | | may decrease Modified oral mucositis index (P<0.05). However, (68) found no significant difference in efficacy between Curcumin and Prednisolone. The heterogeneity test showed low heterogeneity (I2 = 0%, P=0.78), so the fixed-effects model was used | | | contr curc (WM |
| Thongprasom et al, 2011 (Thailand) | Yes | 28 RCTs | 1204 | N A | N A | NA | OLP | Any intervention | Placebo Between treatments | VAS, clinical parameters (extension and severity) | Pain reduction in aloe vera, purslane and cyclosporin groups vs placebo (weak evidence).. AV, cyclosporin, fluocinonide, PUVA and HA showed reduction in clinical scores (weak evidence). | NA | NA | There is bett The sugg reduce lichen to pla un cyclosp |

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| | | | | | | | | | | | | | | sig<br>evide<br><br>Alth<br>incl<br>rev<br>interv<br>there i<br>suppor |
| Jin et al., 2019 (China) | Yes | 6 | NA | NA | NA | NA | OLP | PDT | Placebo | CR, PS | Subgroup analyses revealed that the lesion response (CR: 0.21 [95% CI: 0.12–0.33]) of oral lichen planus was worse than that of other disease entities | 1 to 20 | NA | PDT<br>modal<br>OPMI<br>which<br>factors<br>20<br>approa<br>and ver<br>not re |
| Wang et al., 2021 (China) | Yes | 9 | 344 | 102 | 170 | 52.07 | Erosive and atrophic OLP | PBM and PDT | Topical corticosteroid therapy | VAS, Thongspran sign scoring, ERA, EI, CS, FS, CR, RR, BAI, SI, REU | PBM: No significant diferences for pain scores and severity therapy. For PDT, No significant diferences for sign scores and pain scores | 4 to 48 | No | PBI<br>reliab<br>cortist<br>less s |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Condor et al., 2021 (Romania) | No | 3 | 215 | NA | NA | NA | Erosive OLP | CO2 laser | LLT | NRS | The clinical response showed 100% partial to complete improvement in the case of LLLT, and 85% in the case of CO2 laser surgery. The study demonstrated that some factors (such as symptomatic analgesic treatment in the case of erosive OLP) have significantly higher risk associated with the occurrence of malignant transformation. The numerical rating score (NRS) decreased at all 11 sites (100%) and 10 sites (90.9%) at 1 year after irradiation, compared to pre-irradiation scores | 12 to 48 | No | After e<br>the<br>rev<br>statem<br>that C<br>op<br>consid<br>oral<br>compar<br>used in<br>laser s<br>advant<br>that L |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Al-Maweri et al., 2021 (Qatar) | No | 4 | 234 | NA | NA | 17-56.46 | Erosive OLP | Topical hyaluronic acid | - Topical corticosteroids<br><br>- Placebo | VAS, lesion size, healing signs | Overall, topical hyaluronic acid showed good efficacy in alleviating the signs and symptoms of OLP. Two studies found hyaluronic acid significantly more effective in reducing pain and improving clinical signs of OLP compared to placebo. Compared to topical corticosteroids, one study<br><br>reported comparable results; and one study found hyaluronic acid to be superior to triamcinolone in reducing pain but inferior to triamcinolone in improving the healing time. | 4 to 12 | No | The li<br>sugg<br>may h<br>mana<br>well<br>adequ<br>h |
| Carrozzo and Gandolfo, 1999 (Italy) | No | 12 | 295 | NA | NA | NA | OLP | | Placebo | NA | Mainly highpotency topical corticosteroids in an adhesive médium appear at present the | 2 to 48 | NA | At p<br>concer<br>of trea<br>C |

Visual analogue scale (VAS), clinical scores (CS), functional scores (FS), Clinical severity index (SI), Thongprasom sign scoring (TSS), efficacy indices of the treatment (EI), and reticular-atrophic-erosive scores (RAE), symptom score reducing index (SSRI), recurrence rates (RERs), Oral

Health Impact Profile-49 (OHIP-49), Hospital Anxiety–Depression Scale (HAD), Numerical rating score (NRS), Modified Oral Mucositis Index (MOMI), IGA (Investigators Global Assessment), Chronic Oral Mucosal Diseases Questionnaire (COMDQ), Reticulation/erythema/ulcer score (REU), Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9), OR (Odds Ratio), Bacillus Calmette–Guérin polysaccharide nucleic acid (BCG-PSN), Net Clinical Score (NCS), Topical corticosteroids (tcs), Topical calcineurin inhibitors (TCI), Hyaluronic acid (HA).

**Supplementary File 3**. Laser parameters

| Author(s), year of publications (country) | Intervention | Laser type | Laser wavelength (nm) | Power (mW) | Spot size ($cm^2$) | Power density ($mW/cm^2$) | Irradiation duration (sec) | Energy density ($J/cm^2$) | Photosensitizer | Number of sessions |
|---|---|---|---|---|---|---|---|---|---|---|
| Akram et al., 2018 (Pakistan) | PBM | Diode (n=3) and In:Ga:Al:P (n=2) | 630–970 | 10 –3000 | 0.2 -1.0 | NA | 6–480 | NA | - | NA |
| Akram et al., 2018 b (Pakistan) | PDT | Diode (n=3), GaAlAs laser (n=1), semiconductor (n=1) and xenon arc lamp (n=1) | 630-660 | NA | NA | 130 | 70-150 | 120 | Methylene blue (n=4) and toluidine blue (n=2) | 4-10 |
| Al-Hashimi et al., 2007 (USA) | Photochemotherapy | Ultraviolet (UV) phototherapy | NA | NA | NA | NA | NA | 16.5 | 0.6 mg/kg methoxypsoralen | 12 |
| Al-Maweri, et al., 2017 (Saudi Arabia) | PBM | Diode | 630–970 | 10 –3000 | 0.04 to 1 | 10-1000 | 5-480 | 0.3-6 | - | 4-10 |
| Al-Maweri et al., 2018 (Saudi Arabia) | PDT | Diode laser (n=1), LED red (n=2), LED blue (n=1), GaAlAs (n=1) | 420-660 | NI | 0.5-1 | 10-500 | 30-600 | 1.5-15.6 | Methylene blue 5% (n=3), toluidine blue (n=1), 5-aminolevulinic acid (n=1) for 5-30 minutes | NI |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Binnal et al, 2022 (India) | PDT | Blue diode laser, LED, GaAlAs, InGaAlP, Xenon arc lamp, metal halide lamp, custom-made diode lamp, laser Alod-01, semiconductor laser | 420 -670 | 25 | 0.78 - 1 | 100- >500 | 600 | 1.5–280 | 5% methylene blue , topical 1 mg/ml toluidine blue for 10 min, topical 5% ALA, topical MAL cream (Metvix), Photodithazine, Chlorin-e6-Photolon® (20 % chlorin e6 and 10 % dimethyl Sulfoxide) | 1-10 |
| Carrozzo and Gandolfo, 1999 (Italy) | Photochemotherapy | Psoralen Ultraviolet A (PUVA) | NA | NA | NA | NA | NA | 11.6 to 16.5 | Methoxsoralen 0.6 mg kg−1 taken 2 hours prior to UVA irradiation | NA |
| Chan et al., 1999 (Singapore) | Photochemotherapy | Psoralen Ultraviolet A (PUVA) | 320-400 | NA | NA | 17.5 | NA | 16.5 | 8-methoxypsoralen 0.6 mg/ kg orally 2 hours before irradiation | 12 |
| Choudhary et al., 2022 (India) | PDT | Diode laser, xenon arch lamp, LED, GaAIAs | 480-670 | 8W | 320nm-3cm2 | 100 - >500 | 1200 | 75-120 | 5% MB, MAL, 98% 5 ALA, ALA gel 4%, Toluidine Blue 50 µl | 1-12 |
| Condor et al., 2021 | - | CO2 laser | NA | 3000 (continuous wave mode) | NA | NA | NA | NA | NA | NA |

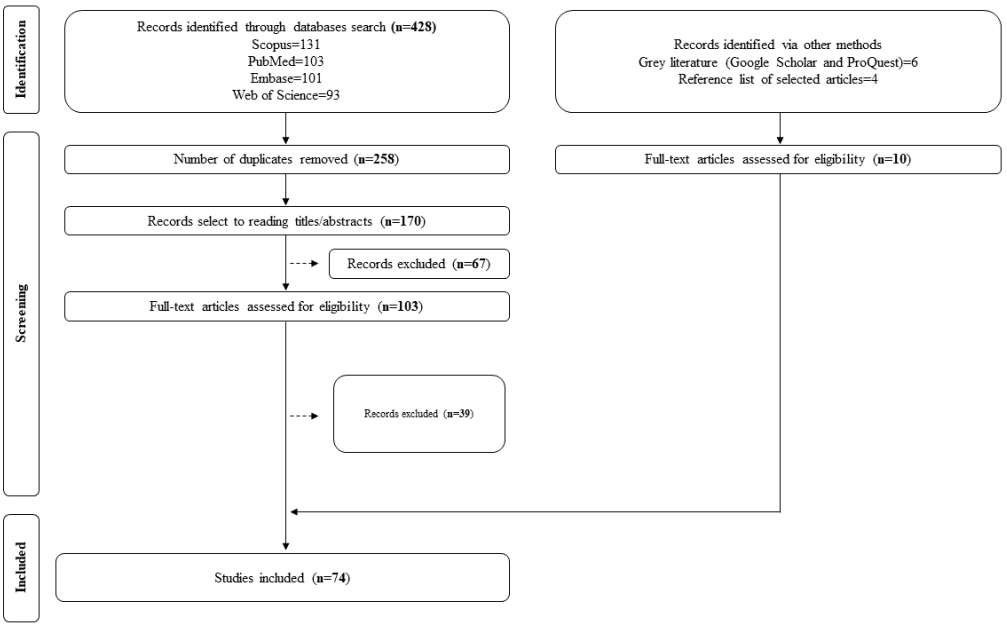
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| De Carvalho et al., 2022 (Brazil) | PBM | Excimer, diode, CO2 laser, Neodymium | 308-980 | 7-3000 | 0.28-1 | 200-1500 | 3.73-60 | 0.1-6 | - | 6-30 |
| García-Pola et al., 2017 (Spain) | PBM and PDT | Diode laser | 633 - 890 | NA | NA | NA | NA | NA | When PDT: NA | 10-12 |
| Gupta et al., 2017 (India) | PBM, PDT and Photochemotherapy | Diode laser, UV irradiation | NA | NA | NA | NA | NA | NA | When PDT: Toluidine blue. When PCT: 0.6 mg/kg 8-methoxypsoralen | NA |
| He et al., 2020 (China) | PDT | Diode laser, xenon lamp, semiconductor laser, metal halide lamp, LED, red light, focal red light, GaAlAs | 630–660 | NA | NA | NA | 120 - 600 | 80–150 | 5-ALA, MB, MAL,TB, chlorin e6 derivative (5–120 minutes) | 1-10 |
| Jajarm et al., 2018 (Iran) | PBM and PDT | Helium-neon and diode | NA | NA | NA | NA | NA | NA | When PDT: NA | NA |
| Jin et al., 2019 (China) | PDT | NA | 420-660 | NA | NA | NA | 120-1000 | 8-210 | NA | 1-10 |
| Leong et al. 2023 (Malaysia) | PDT | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Lodi et al., 2012 (Italy) | Photochemotherapy | UVA irradiation | NA | NA | NA | NA | NA | 0.75 increased by 0.25 per session | methoxsalen (0.6 mg/kg) | 12 |
| Mozaffari et al., 2017 (Iran) | - | CO2 laser | 633-10600 | 2000-20000 W | NA | 2.12 – 228 W/cm-2 | 80 µsec (super pulse mode). Others NA | 0.3-0.5 | - | NA |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Oberti et al., (Italy) | PDT | LED | 630 - 970 | NA | NA | NA | 120-150 | NA | Toluidine blue, methylene blue | 1-3/week for 2 months |
| Pavlic et al., 2014 (Bosnia and Herzegovin) | PBM, PDT, Photochemotherapy | UVA, UVB, CO2 laser, Nd:YAG, Ga-As diode, Ga-Al-As diode, Xenon arc lamp, diode laser | 308 - 10600 | NA | NA | NA | NA | 4- 120 | PDT: NA. PCT: 8-methoxypsoralen | NA |
| Ruiz Roca et al., 2022 (Spain) | PBM | Diode laser, neodymium, red light helium–neon | 630 - 1064 | 0.1 - 3000 / 400 and 10 mW | 0.5 - 1 | NA | 10 – 150 | 1.2 - 1415 (red light helium-neon) | - | 8 - 21 |
| Sridharan and Sivaramakrishnan, 2021 (Bahrein) | PDT | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Thongprasom et al., 2011 | Photochemotherapy | PUVA | NA | NA | NA | NA | NA | NA | methoxsalen (0.6 mg/kg) | NA |
| Wang et al., 2021 (China) | PBM and PDT | Diode laser | 630-970 | 10-3000 | 0.04-1 | 10-1000 | 150-480 | 1.5-6 | NA | 10-12 |
| Waingade et al., 2022a (India) | PDT | Diode lasers | 630–660 | NA | 0.8 | 100 - 1034 | 30 - 227 | 7.2 - 120 | 5% Methylene Blue (5-10 min) | 3 - 8 (every 2–3 days for 8–9 days or once weekly for 1 month to 2 months) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Zakrzewska et al., 2005 (UK) | Photochemotherapy | PUVA | NA | NA | NA | NA | NA | NA | NA | NA |

GaAlAs: Gallium-Aluminum-Arsenide; LED: light emitting diode; TB: toluidine blue; 5-ALA: 5 aminolevulinic acid; MB: Methylene Blue ; MAL: Methyl 5-aminolevulinate;

**Supplementary File 4**. Flowchart of the literature search and study selection.



**Supplementary File 5**. Risk of bias assessed by A Measurement Tool to Assess the Methodological Quality of Systematic Reviews (AMSTAR) critical appraisal tools.

| Author(s), year of publication | 1. Did the research questions and inclusion criteria for the review include the components of PICO? | 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | 3. Did the review authors explain their selection of the study designs for inclusion in the review? | 4. Did the review authors use a comprehensive literature search strategy? | 5. Did the review authors perform study selection in duplicate? | 6. Did the review authors perform data extraction in duplicate? | 7. Did the review authors provide a list of excluded studies and justify the exclusions? | 8. Did the review authors describe the included studies in adequate detail? | 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | 10. Did the review authors report on the sources of funding for the studies included in the review? | 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? | 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | 13. Did the review authors account for RoB in primary studies when interpreting/ discussing the results of the review? | 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | % Yes Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Akram et al., 2018 a (Pakistan) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Partial yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 76.92 |
| Akram et al., 2018 b (Pakistan) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Partial yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 76.92 |
| Al-Hashimi et al., 2007 (USA) | No | No | No | No | No | No | No | No | No | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | No | 15.38 |
| Al Johani et al., 2009 (UK) | No | No | No | Partial yes | No | No | No | Partial yes | No | No | No meta-analysis conducted | No meta-analysis conducted | Yes | No | No meta-analysis conducted | Yes | 23.07 |
| Al-Maweri, et al., 2017 (Saudi Arabia) | Yes | Partial yes | Yes | Partial yes | Yes | Yes | Yes | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 84.61 |
| Al-Maweri, et al., 2018 (Saudi Arabia) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 80.76 |
| Al-Maweri, et al., 2023 (Qatar) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | 78.12 |
| Albaghli et al., 2021 (UK) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | 81.25 |

| Author(s), year of publication | 1. Did the research questions and inclusion criteria for the review include the components of PICO? | 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | 3. Did the review authors explain their selection of the study designs for inclusion in the review? | 4. Did the review authors use a comprehensive literature search strategy? | 5. Did the review authors perform study selection in duplicate? | 6. Did the review authors perform data extraction in duplicate? | 7. Did the review authors provide a list of excluded studies and justify the exclusions? | 8. Did the review authors describe the included studies in adequate detail? | 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | 10. Did the review authors report on the sources of funding for the studies included in the review? | 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? | 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | 13. Did the review authors account for RoB in primary studies when interpreting/ discussing the results of the review? | 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | % Yes Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ali et al., 2016 (Egypt) | Yes | Yes | Yes | Partial yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No | No | No | No | Yes | 65.62 |
| Alsubhi et al., 2020 (Saudi Arabia) | No | No | No | No | No | No | No | Partial yes | No | No | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | Yes | 19.23 |
| Azab et al., 2020 (Egypt) | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 92.30 |
| Bao et al., 2022 (China) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 84.37 |
| Binnal et al, 2022 (India) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | No | No | No | Yes | 65.62 |
| Casale et al., 2017 (Italy) | No | No | Yes | Partial yes | Yes | No | No | Partial yes | No | No | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 30.76 |
| Chamani et al., 2015 (Iran) | Yes | No | No | Partial yes | Yes | Yes | Yes | Yes | No | No | Yes | No | No | Yes | No | Yes | 53.12 |
| Chan et al., 1999 (Singapore) | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Partial yes | No | Yes | Yes | Yes | No | Yes | Yes | 78.12 |
| Cheng et al., 2012 (UK) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 92.30 |
| Choudhary et al., 2022 (India) | Yes | No | Yes | Partial yes | Yes | No | No | No | No | No | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 34.61 |
| Da Mata et al., 2020 (Brazil) | Yes | Yes | Yes | Partial yes | Yes | No | No | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 73.07 |
| Da Silva et al., 2021 (Brazil) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 84.37 |
| De Carvalho et al., 2022 (Brazil) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Yes | Yes | No | Yes | No | No | No | No | Yes | 59.37 |
| Dhanvanth et al., 2022 (India) | Yes | Yes | Yes | No | No | No | No | No | Yes | No | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 38.46 |

| Author(s), year of publication | 1. Did the research questions and inclusion criteria for the review include the components of PICO? | 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | 3. Did the review authors explain their selection of the study designs for inclusion in the review? | 4. Did the review authors use a comprehensive literature search strategy? | 5. Did the review authors perform study selection in duplicate? | 6. Did the review authors perform data extraction in duplicate? | 7. Did the review authors provide a list of excluded studies and justify the exclusions? | 8. Did the review authors describe the included studies in adequate detail? | 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | 10. Did the review authors report on the sources of funding for the studies included in the review? | 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? | 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | 13. Did the review authors account for RoB in primary studies when interpreting/ discussing the results of the review? | 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | % Yes Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dharman et al., 2020 (India) | Yes | Yes | Yes | Partial yes | No | No | No | Yes | Partial yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 61.53 |
| Elad et al., 2010 (Israel) | No | No | Yes | No | No | No | No | Partial yes | No | No | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | Yes | 26.92 |
| Elad et al., 2011 (Israel) | No | No | Yes | No | No | No | No | Partial yes | No | No | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | Yes | 26.92 |
| García-Pola et al., 2017 (Spain) | Yes | Yes | Yes | Partial yes | No | No | No | Yes | No | No | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | Yes | 50 |
| Guo et al., 2015 (China) | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | 75 |
| Gupta et al., 2017 (India) | Yes | Yes | Yes | Partial yes | Yes | No | No | Yes | No | No | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | Yes | 57.69 |
| Gupta et al., 2022 (India) | No | No | Yes | Partial yes | No | No | No | Yes | No | No | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 26.92 |
| He et al., 2020 (China) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Partial yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 81.25 |
| Ho et al, 2012 (USA) | No | No | Yes | Partial yes | No | No | No | Partial yes | No | No | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | Yes | 30.76 |
| Jajarm et al., 2018 (Iran) | Yes | No | Yes | Partial yes | Yes | Yes | Yes | No | Yes | No | Yes | No | No | No | No | No | 46.87 |
| Jin et al., 2019 (China) | No | No | No | Partial yes | Yes | Yes | Yes | Partial yes | No | No | Yes | No | No | Yes | Yes | Yes | 50 |
| Kalaskar et al., 2020 (India) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 84.61 |
| Leong et al., 2023 (Malaysia) | Yes | Yes | Yes | Partial yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 90.62 |
| Lodi et al., 2012 (Italy) | Yes | Yes | Yes | Yes | Yes | Yes | No | Partial yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | 84.37 |
| Lodi et al., 2020 (Italy) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 100 |

| Author(s), year of publication | 1. Did the research questions and inclusion criteria for the review include the components of PICO? | 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | 3. Did the review authors explain their selection of the study designs for inclusion in the review? | 4. Did the review authors use a comprehensive literature search strategy? | 5. Did the review authors perform study selection in duplicate? | 6. Did the review authors perform data extraction in duplicate? | 7. Did the review authors provide a list of excluded studies and justify the exclusions? | 8. Did the review authors describe the included studies in adequate detail? | 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | 10. Did the review authors report on the sources of funding for the studies included in the review? | 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? | 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | 13. Did the review authors account for RoB in primary studies when interpreting/ discussing the results of the review? | 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | % Yes Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lukaszewska-Kuska et al., 2021 (Poland) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Partial yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 76.92 |
| Luo et al., 2020 (China) | Yes | Yes | No | Partial yes | Yes | Yes | Partial yes | Partial yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | 71.87 |
| Lv et al., 2019 (China) | Yes | Partial yes | No | Partial yes | Yes | Yes | Partial yes | Partial yes | No | Yes | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | Yes | 61.54 |
| Mozaffari et al., 2017 (Iran) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Partial yes | No | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | Yes | 73.08 |
| Muthusamy et al., 2016 (India) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | No | 69.23 |
| Nair et al., 2016 (India) | Yes | Yes | Yes | Partial yes | Yes | Yes | Partial yes | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 84.62 |
| Oberti et al., 2019 (Italy) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 76.92 |
| Pavlic et al., 2014 (Bosnia and Herzegovin) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | No | 69.23 |
| Pinto et al., 2023 (India) | Yes | Partial yes | No | Partial yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 87.50 |
| Ruiz Roca et al., 2022 (Spain) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Partial yes | Yes | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 96.15 |
| Saeed et al., 2022 (India) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 100 |

| Author(s), year of publication | 1. Did the research questions and inclusion criteria for the review include the components of PICO? | 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | 3. Did the review authors explain their selection of the study designs for inclusion in the review? | 4. Did the review authors use a comprehensive literature search strategy? | 5. Did the review authors perform study selection in duplicate? | 6. Did the review authors perform data extraction in duplicate? | 7. Did the review authors provide a list of excluded studies and justify the exclusions? | 8. Did the review authors describe the included studies in adequate detail? | 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | 10. Did the review authors report on the sources of funding for the studies included in the review? | 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? | 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | 13. Did the review authors account for RoB in primary studies when interpreting/ discussing the results of the review? | 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | % Yes Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Samycia et al., 2012 (Canada) | No | No | No | Partial yes | No | No | No | Partial yes | No | Yes | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 23.08 |
| Serafini et al., 2023 (Italy) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 100 |
| Sotoodian et al., 2015 (Canada) | No | No | Yes | Partial yes | No | No | No | No | No | Yes | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 26.92 |
| Sriram et al., 2023 (USA) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 100 |
| Zakrzewska et al., 2005 (UK) | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | 68.75 |
| Suresh et al., 2016 (India) | Yes | Yes | Yes | Partial yes | Yes | Yes | Partial yes | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | No | 76.92 |
| Vaughn et al., 2016 (USA) | Yes | Partial yes | Yes | Partial yes | Yes | Yes | Partial yes | Yes | Yes | No | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 88.46 |
| Sun et al., 2019 (China) | Yes | Yes | Yes | Partial yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | 71.87 |
| White et al., 2019 (USA) | Yes | No | Yes | Partial yes | No | No | No | Partial yes | No | No | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | No | 30.77 |
| Vadivel et al., 2020 (India) | Yes | Yes | Yes | Yes | Yes | Yes | Partial yes | Partial yes | No | Yes | No meta-analysis conducted | No meta-analysis conducted | No | Yes | No meta-analysis conducted | Yes | 76.92 |
| Sridharan and Sivaramakri | Yes | Yes | Yes | Partial yes | Yes | Yes | Yes | Partial yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | 81.25 |

| Author(s), year of publication | 1. Did the research questions and inclusion criteria for the review include the components of PICO? | 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | 3. Did the review authors explain their selection of the study designs for inclusion in the review? | 4. Did the review authors use a comprehensive literature search strategy? | 5. Did the review authors perform study selection in duplicate? | 6. Did the review authors perform data extraction in duplicate? | 7. Did the review authors provide a list of excluded studies and justify the exclusions? | 8. Did the review authors describe the included studies in adequate detail? | 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | 10. Did the review authors report on the sources of funding for the studies included in the review? | 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? | 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | 13. Did the review authors account for RoB in primary studies when interpreting/ discussing the results of the review? | 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | % Yes Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| shnan, 2021 (Bahrein) | | | | | | | | | | | | | | | | | |
| Su et al., 2021 (China) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 100 |
| Sahoo et al., 2022 (India) | Yes | No | No | Partial yes | No | No | No | Partial yes | No | Yes | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 30.77 |
| Sandhu et al., 2022 (India) | Yes | Partial yes | Yes | Partial yes | Yes | Yes | Yes | Yes | Yes | Yes | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 76.92 |
| Santo et al., 2022 (Indonesia) | Yes | Partial yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 73.08 |
| Sterniczuk et al., 2022 (USA) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 100 |
| Vychaktami et al., 2022 (Indonesia) | Yes | Yes | Yes | Partial yes | No | Yes | Partial yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | 81.25 |
| Waingade et al., 2022 (India) | Yes | Yes | Yes | Partial yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | 84.37 |
| Waingade et al., 2022b (India) | Yes | Yes | Yes | Partial yes | Yes | Yes | Partial yes | Yes | Yes | No | No | Yes | No | Yes | No | Yes | 68.75 |
| Zeng et al., 2022 (China) | Yes | Yes | No | Partial yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | 65.62 |
| Thongprasom et al., 2011 (Thailand) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 84.62 |
| Wang et al., 2021 (China) | Yes | Yes | Yes | Partial yes | Yes | Yes | Partial yes | Partial yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | 84.37 |

| Author(s), year of publication | 1. Did the research questions and inclusion criteria for the review include the components of PICO? | 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | 3. Did the review authors explain their selection of the study designs for inclusion in the review? | 4. Did the review authors use a comprehensive literature search strategy? | 5. Did the review authors perform study selection in duplicate? | 6. Did the review authors perform data extraction in duplicate? | 7. Did the review authors provide a list of excluded studies and justify the exclusions? | 8. Did the review authors describe the included studies in adequate detail? | 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | 10. Did the review authors report on the sources of funding for the studies included in the review? | 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? | 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | 13. Did the review authors account for RoB in primary studies when interpreting/ discussing the results of the review? | 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | % Yes Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Condor etano., 2021 (Romania) | Yes | Partial yes | No | Partial yes | Yes | Yes | No | Yes | No | Yes | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | Yes | 53.85 |
| Al-Maweri et al., 2021 (Qatar) | Yes | Partial yes | Yes | Yes | Yes | Yes | Partial yes | Yes | Yes | Yes | No meta-analysis conducted | No meta-analysis conducted | Yes | Yes | No meta-analysis conducted | Yes | 92.31 |
| Carrozzo and Gandolfo, 2008 (Italy) | No | No | Yes | No | No | No | No | No | Partial yes | No | No meta-analysis conducted | No meta-analysis conducted | No | No | No meta-analysis conducted | No | 11.54 |
| Yuan et al., 2022 (China) | No | Yes | Yes | Partial yes | Yes | Yes | Yes | Partial yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | 81.25 |

# 3 CONSIDERAÇÕES FINAIS

Tendo em vista a ampla gama de modalidades terapêuticas para LPO disponíveis na literatura, este trabalho foi conduzido para agrupar as evidências científicas relacionadas a este tema de forma sistemática. Além disso, foi proposto um protocolo clínico que visa auxiliar o cirurgião-dentista no manejo de lesões de LPO – especialmente as refratárias, em que o tratamento é mais desafiador - durante a sua prática clínica.

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