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REVIEW

EFFECTIVENESS OF STEROID AND NON-STEROID MOUTHWASHES FOR ORAL LICHEN PLANUS: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: *Definitive management of Oral Lichen Planus (OLP) remains challenging due to its intractable nature and unclear cause. Steroid and non-steroid mouthwash preparations are recommended for OLP, especially for diffuse or difficult-to-access lesions.* ***Aim:*** *This review aims to evaluate the efficacy of available steroid and non-steroid anti-inflammatory mouthwashes in managing OLP focusing on pain reduction, lesion size reduction, and possible side effects.* ***Methods:*** *A systematic literature search from 2012- 2022 was conducted using Scopus, PubMed, and ScienceDirect, following PRISMA guidelines.* ***Results:*** *Nine RCTs included with steroid mouthwashes (dexamethasone, triamcinolone) show promise as effective treatment options for reducing pain and lesion size in OLP, while non-steroid mouthwash (cyclosporine) demonstrates better long-term remission. Natural adjuvant therapies, like nanocurcumin gel, quercetin capsules, and SE-ACE tablets can support the use of steroid mouthwashes. Additionally, fluconazole capsule, itraconazole capsule, and nystatin suspension can be used as adjuvant therapy to prevent secondary candidiasis infection caused by steroid mouthwashes. The risk assessment of bias using the Joanna Briggs Institute (JBI) Critical Appraisal Tools showed seven articles with a low risk of bias and two with a moderate risk.* ***Conclusion:*** *Heterogeneity in the type, dose, trial duration, and outcome measures limit direct comparisons of treatment effectiveness.*

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INTRODUCTION

One of the major chronic inflammatory diseases with manifestations in the oral mucosa is *Oral lichen planus* (OLP).[1,2] And with the inflammatory exacerbation, the oral mucosa has white lesions accompanied by a variety of damage, such as hyperemia, erosion, and even ulceration. Ulcerations are characterized by the loss of all epithelial layers due to secondary lesions. These ulcers can be accompanied by oedema or tissue proliferation, leading to swelling in the surrounding area (inflammation), and causing symptoms such as pain or a burning sensation.[1,3] Various studies have been conducted to determine the best treatment for

OLP. The unpredictable periods of remission and exacerbation, as well as the risk of malignancy, are crucial considerations in determining definitive treatment, especially for controlling OLP lesions.[4,5]

Topical therapy is a preferred treatment option for OLP due to its easy frequency and duration of treatment for patients, with minimal systemic side effects.[6] At present, there are only a limited number of specialized topical formulations designed specifically for oral mucosal diseases. The majority of topical medications used for oral conditions are adapted from those originally intended for skin conditions, and they may have certain limitations in their effectiveness for oral use.[7] Topical steroid medication is highly effective in managing the inflammation of OLP. It can provide several benefits, including pain relief, preservation of mucosal cell membrane integrity, reduction of oedema (swelling), prevention of excessive swelling, and control of the disease with different effects on lymphocytes.[8,9] Although commonly used as a first-line treatment for OLP lesions, prolonged use of topical steroid medication may lead to secondary infections candidiasis, mucosal atrophy, and occasional discomfort or a burning sensation.[10] In light of these concerns, researchers are actively exploring alternative treatments for OLP to mitigate these side effects and prevent secondary infections caused by topical steroid medications.[11]

Non-steroid topical medications, such as *tacrolimus*, *pimecrolimus*, and *cyclosporine* (*calcineurin* inhibitors), have shown comparable effectiveness to topical steroids in managing OLP, as evidenced by a systematic review conducted by Sun et al.[12] in 2019. According to systematic reviews by Lodi et al.[6] and Chamani et al.,[13] tacrolimus appears to be more effective than topical steroids (specifically clobetasol) in the short term for OLP patients who are susceptible to secondary infections candidiasis, and resistant to other topical or systemic therapies. However, it is important to note that tacrolimus has a higher statistically significant incidence of local side effects, such as temporary burning or tingling sensations, when compared to topical steroids.[12] Other alternative non-steroidal medications, such as aloe vera and curcumin, show promise as new treatment options for OLP with fewer side effects.[14] Chlorhexidine mouthwash and nystatin suspension can be prescribed as adjuvant therapy alongside topical steroids to prevent secondary infections.[15,16]

Mouthwash formulations are recommended as topical forms for both steroid and non-steroidal medications compared to gels, ointments, and pastes, particularly for lesions located in difficult-to-access areas like the soft palate and movable tissues such as the tongue. The advantages of using mouthwash formulations are well-suited for the challenging nature of OLP lesions, which are often found in bilateral buccal mucosa and lateral tongue.[2,17] In a study conducted by Park et al.[18] in 2018, *dexamethasone* mouthwash and ointment demonstrated similar effectiveness, whether used together or separately, resulting in improvement

in over 60% of OLP patients. Furthermore, ensuring adequate contact time (3-5 minutes) with the oral mucosa is essential for both steroid and non-steroidal mouthwash, regardless of the size or location of the lesion.[9,19]

Finding safer and more effective therapies remains an important area of investigation to improve the management of OLP. Considering the advantages and disadvantages of topical anti-inflammatory steroid and non-steroid medications in mouthwash formulations, this review aims to evaluate the efficacy of available steroid and non-steroid anti-inflammatory mouthwashes in managing OLP. The results of this study are expected to provide information and knowledge, serving as a reference for further research.

METHODS

This study was a systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[20] and the Joanna Briggs Institute (JBI) method for Systematic Reviews.[21] This review protocol was registered on PROSPERO (registration number: CRD42023444996).

The research framework is centered around the research question "is there a difference in the effectiveness of steroid and non-steroid anti-inflammatory mouthwashes for the management of oral lichen planus?" and follows the PICO (Population, Intervention, Comparison, Outcome) format, which is as follows: (1) Population: OLP patients; (2) Intervention: steroid anti-inflammatory mouthwashes; (3) Comparison: other steroid/non-steroid mouthwashes, different concentrations of the same type of steroid mouthwash, or the same type of steroid mouthwash plus adjuvant therapy; (4) Outcome: healing of oral lichen planus in terms of pain reduction (subjective assessment), lesion size reduction (objective assessment), and possible side effects (follow-up on participants' complaints).

In this study, the electronic databases utilized were PubMed, Scopus, and ScienceDirect. The literature selection process began with a search using the following keywords: ("Oral Lichen Planus") AND ((steroid) OR (Dexamethasone) OR ("Triamcinolone acetonide") OR (“Non-Steroidal Anti-inflammatory Agents”) OR (“Calcineurin Inhibitors”)) AND ((mouthwash) OR ("mouth rinse")). Furthermore, additional literature searches were conducted manually through hand-searching to identify relevant and eligible studies for inclusion in this review.

The inclusion criteria used in this study were articles published within a 10-year timeframe (2012-2022), including randomized clinical trials, cohort studies, and case series related to the PICO of this review. The articles had to be available in English and Indonesian languages and accessible in full-text format. The exclusion criteria for this research were to review articles and studies with subjects other than humans.

A literature review was carried out by three reviewers (L.A.P.; N.N.; D.Z.) from

databases using the specified combination of specific keywords. After saving the articles from the results page, the obtained articles were stored in the Rayyan AI website (https://www.rayyan.ai/). First screening was made automatically with Rayyan AI to identify duplicate articles and the languages of the articles. Screening was continued manually based on the inclusion and exclusion criteria according to the PRISMA guidelines. Subsequently, a number of articles will undergo a study quality assessment before being analyzed and synthesized into tabular form to address the research questions. The article's quality assessment is performed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools. (22,23). The final stage of study selection involves discussing the review findings with experts (D.Z. and N.N.). The selected articles were stored in the Zotero reference manager software. If any discrepancies arise during this stage, researchers will discuss to resolve them.

Data extraction was carried out independently. Information extracted from each article included: (Table 1) the study sample characteristics (author's name, publication year, title, country of origin, and study design) and research subject characteristics (criteria, number of participants, gender, and age of participants); (Table 2) research object characteristics (formulation type, concentration, frequency, duration of administration, and follow-up duration); and (Table 3) therapy effect assessment (pain reduction, lesion size changes, and side effects). Evaluation of study quality assessment using the JBI critical appraisal tools will be seen in Table 4. If any discrepancies arise during this stage, researchers will discuss to resolve them.

RESULTS

Based on the search results, a total of 150 articles were obtained. The article selection process can be seen in Figure 1. 9 selected articles were obtained for further analysis and review. All articles were randomized clinical trials (RCTs), seven had a parallel two-arm design, one had a parallel three-arm design, and one had a crossover trial design. Detailed characteristics of each study included in this review can be found in Table 1.

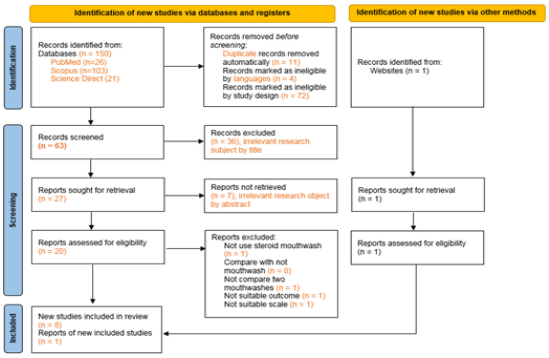

Figure 1. PRISMA 2020 flowchart for study selection results.

A total of 269 participants, ranging in age from 18 to 85 years, were included in this systematic review. All participants met the Clinical and histopathological diagnosis criteria for OLP. Other criteria for participants included specific systemic conditions. The most common exclusion criteria were participants who were pregnant, with nine articles, and participants who were breastfeeding, with six articles. Detailed characteristics of each study and its participants included in this review can be found in Table 1.

Table 1. Study Sample Characteristics and Research Subject Characteristics in included studies

No	Author(s) (Years)	Title	Country	Study Design	Participants Criteria	Participants Demography		
						Group	Total number (F/M)	Mean Age/Range (years)
1.	Ahadian et al (2012)[25]	Comparison of two corticosteroids mouthwashes in treatment of symptomatic oral lichen planus.	Iran	Randomized clinical trial	1) Clinical and/or histological diagnosis of OLP. 2) Not pregnant or have systemic diseases.	Study Control	22 (14/8) 22 (13/9)	19-65 22-65
2.	Sanatkhani et al (2014)[27]	Effect of Cedar Honey in the Treatment of Oral Lichen Planus	Iran	Randomized clinical trial	1) Clinical and/or histological diagnosis of OLP. 2) Not pregnant, have kidney disease, hepar disease, or diabetics.	Study Control	15 (13/2) 15 (15/0)	46.53±10.75 / 18-75 46.8±8.9 / 18-75
3.	Amirchaghmaghi et al (2015)[28]	A Randomized Placebo-controlled Double Blind Clinical Trial of Quercetin for Treatment of Oral Lichen Planus	Iran	Randomized clinical trial	1) Clinical and/or histological diagnosis of OLP. 2) Not pregnant/breastfeeding, or have systemic diseases.	Study Control	15 (10/5) 15 (12/3).	44.6±10.22 / 18-72 48.26±16.28 / 18-72
4.	Belal (2015)[29]	Management of symptomatic erosive-ulcerative lesions of oral lichen planus in an adult Egyptian population using Selenium-ACE combined with topical corticosteroids plus antifungal agent	Egypt	Randomized clinical trial	1) Clinical and/or histological diagnosis of OLP. 2) Not pregnant/breastfeeding or or have systemic diseases.	Study Control 1 Control 2	10 (N/A) 10 (N/A) 10 (N/A)	N/A N/A N/A
5.	Amirchaghmaghi et al (2016)[30]	Evaluation of the Efficacy of Curcumin in the Treatment of Oral Lichen Planus: A Randomized Controlled Trial	Iran	Randomized clinical trial	1) Clinical and/or histological diagnosis of OLP. 2) Not pregnant/breastfeeding, gastric ulcers, duodenal ulcers, gallstones, or hepatic diseases history, or use anticoagulant/ antiplatelet agents.	Study Control	8 (3/5) 12 (10/2)	52.75± 9.43 49.42± 11.22
6.	Hambly et al (2017)[26]	Comparison between self-formulation and compounded-formulation dexamethasone mouth rinse for oral lichen planus: a pilot, randomized, cross-over trial	Australia	Randomized clinical trial	1) Clinical and/or histological diagnosis of OLP. 2) Not pregnant/breastfeeding.	Study Control	9 (7/2)	27-78
7.	Bakhshi et al (2020)[31]	Combination Therapy with 1% Nanocurcumin Gel and 0.1% Triamcinolone Acetonide Mouth Rinse for Oral Lichen Planus: A Randomized Double-Blind Placebo Controlled Clinical Trial	Iran	Randomized clinical trial	1) Clinical and/or histological diagnosis of OLP. 2) Not pregnant.	Study Control	17 (13/4) 14 (11/3)	48 ±12.71 /25-67 59 ±15.12 /42-85
8.	Georgaki et al (2022)[24]	A randomized clinical trial of topical dexamethasone vs. cyclosporine treatment for oral lichen planus	Greece	Randomized clinical trial	1) Clinical and/or histological diagnosis of OLP. 2) Not pregnant/breastfeeding, candidiasis, have hypertension, or kidney diseases.	Study Control	18 (14/4) 14 (9/5)	61.8 ±12.7 /33-82 59.6 ±13.9/ 44-81
9.	Zhang et al (2022)[32]	Clinical Evaluation of Dexamethasone Plus Gentamycin Mouthwash Use in Combination with Total Glucosides of Paeony for Treatment of Oral Lichen Planus without Fungal Infection: A Comparative Study with Long-Term Follow-Up	China	Randomized clinical trial	1) Clinical and/or histological diagnosis of OLP. 2) Not pregnant/breastfeeding, candidiasis, systemic diseases, such as heart, lungs, hepar, kidney, or have tumor.	Study Control	21 (15/6) 22 (14/8)	50.29 ±18.8 49.32 ±16.63

OLP=Oral lichen planus, N/A=not applicable.

Table 2. Research Object Characteristics in included studies

No	Author (s) (years)		Drugs Name	Formulations	Concentrations	Frequency	Duration of Treatments (Week)	Duration of Follow-Up (Week)
1.	*Ahadian et al (2012)*[25]	S	*a) Dexamethasone*	Mouthwash	0.1%	QID 5ml coll oris	4	0, 1, 2, 4
		C	*a) Triamcinolone acetonide*	Mouthwash	0.2%	QID 5ml coll oris	4	0, 1, 2, 4
2.	*Sanatkhani et al (2014)*[27]	S	*a) Dexamethasone*	Mouthwash	0.5 mg	QID coll oris	4	0, 4
			b) Fluconazole	Capsule (*adjuvant*)	100 mg	QD po		
		C	*a) Dexamethasone*	Mouthwash	0.5 mg	QID coll oris	4	0, 4
			b) *Fluconazole*	Capsule (*adjuvant*)	100 mg	QD po		
			c) Cedar honey	Liquid (*adjuvant*)	20 ml	TID lit oris		
3.	*Amirchaghmaghi et al (2015)*[28]	S	a) *Dexamethasone*	Mouthwash	0.5 mg	QID coll oris	4	0, 1, 2, 3, 4
			b) *Nystatin*	Suspension (*adjuvant*)	100.000 unit	QID po		
			c) Placebo (lactose)	Capsule (*adjuvant*)	N/A	BID po		
		C	a) *Dexamethasone*	Mouthwash	0.5 mg	QID coll oris	4	0, 1, 2, 3, 4
			b) *Nystatin*	Suspension (*adjuvant*)	100.000 unit	QID po		
			c) Quercetin hydrate	Capsule(*adjuvant*)	250 mg	BID po		
4.	*Belal (2015)*[29]	S	a) *Dexamethasone*	Mouthwash	0.75 mg	QID 7.5ml coll oris	6	0, 2, 4, 6
		C1	a) *Dexamethasone*	Mouthwash	0.75 mg	QID 7.5ml coll oris	6	0, 2, 4, 6
			b) *Itraconazole*	Capsule (*adjuvant*)	100 mg	QD po	4	
		C2	*a) Dexamethasone*	Mouthwash	0.75 mg	QID 7.5 ml coll oris	6	0, 2, 4, 6
			b) Itraconazole	Capsule (*adjuvant*)	100 mg	QD po	4	
			c) SE-ACE	Tablet (*adjuvant*)	100% natural	QD po	6	
5.	*Amirchaghmaghi et al (2016)*[30]	S	*a) Dexamethasone*	Mouthwash	0.5 mg	TID coll oris	4	0, 2, 4
			b) Nystatin	Suspension (*adjuvant*)	100.000 unit	TID po		
			c) Placebo (lactose)	Capsule (*adjuvant*)	N/A	BID po		
		C	*a) Dexamethasone*	Mouthwash	0.5 mg	TID coll oris	4	0, 2, 4
			b) Nystatin	Suspension (*adjuvant*)	100.000 unit	TID po		
			c) Curcumin	Capsule (*adjuvant*)	500 mg	BID po		
6.	*Hambly et al (2017)*[26]	S	*a) Dexamethasone*	Mouthwash	0.5 mg/2ml	TID coll oris	3	0, 3, 4, 7
		C	*b) Dexamethasone*	Larutan kumur	0.5 mg/20ml	TID coll oris	3	0, 3, 4, 7
7.	*Bakhshi et al (2020)*[31]	S	a) *Triamcinolone*	Mouthwash	0.1%	TID coll oris	4	0, 2, 4
			b) *Placebo*	Gel (*adjuvant*)	N/A	TID lit oris		
		C	a) *Triamcinolone*	Mouthwash	0.1%	TID coll oris	4	0, 2, 4
			b) Nanocurcumin	Gel (*adjuvant*)	1%	TID lit oris		
8.	*Georgaki et al* (2022)[24]	S	*a) Dexamethasone*	Mouthwash	2 mg/ 5 ml	TID 15ml coll oris	4	0, 1, 2, 3, 4, 24
		C	a) *Cyclosporine*	Mouthwash	100 mg/ml	TID 15ml coll oris	4	0, 1, 2, 3, 4, 24
9.	*Zhang et al (2022)*[32]	S	*a) Dexamethasone*	Mouthwash	5 mg/ml	BID 5ml coll oris	3	0, 2, 4, 12, 24
			b) Gentamycin sulfate		80 mg/2ml			
		C	*a) Dexamethasone*	Mouthwash	5 mg/ml	BID 5ml coll oris	3	0, 2, 4, 12, 24
			b) Gentamycin sulfate		80 mg/2ml			
			c) TGP	Capsule (*adjuvant*)	0.3 mg	TID2 po		

S=study, C=control, SE-ACE=Selenium with vit. A, C, & E, TGP=total glucosides of paeony, QD= once daily, BID= twice daily, TID=three times daily, QID= four times daily, coll oris=collutio oris (used as a mouthwash), lit oris=liquor oris (applied topically in the mouth), po= per oral (taken by mouth, orally).

Table 3. Research results characteristics in included studies.

No	Author (years)	Parameters of Pain Reduction		Parameters of Change in Lesion Size		Side Effects	Efficacy Comparison	Risk of Bias Assessment
		Scale	Results	Scale	Results			
1.	*Ahadian et al (2012)*[25]	10-*cm* VAS	- Study **significant** (p=0.0001[1]). - Control **significant** (p=0.0001[1]). - Study: control **not significant** (p>0.05[2]).	*Size of lesion* (mm^2)	- Study: control **not significant** at W1-2 (p>0.05[2]), but **significant** at W4 (p=0.02[2]).	None.	Study > control	Moderate.
2.	*Sanatkhani et al (2014)* [27]	5-*point* Thongprasom	- Study **Significant** (p<0.001[3]). - Control **Significant** (p<0.001[3]). - Study: control **not significant** (p=0.775[3,4]).	*Size of lesion* (mm^2)	- Study **not significant** (p=0.133[3]). - Control **not significant** (p=0.231[3]). - Study: control **not significant,** better study (p=0.85[3,4]).	Control: burning sensation.	Study = Control.	Low.
3.	*Amirchaghmaghi et al (2015)*[28]	5-*point Pain Index* (PI) *Improvement*, 10-cm VAS	- Study **not significant** (p=0.086[1] VAS). - Control **significant** (p=0.01[5] PI). - Study: control **not significant** (p>0,05[4] VAS).	5-*point Severity Index* (SI) *Improvement*	- Study **not significant** (p=0.26[1]). - Control **significant** (p = 0.00[5]). - Study: control **not significant** (p>0,05[4]).	None.	Study < Control.	Low.
4.	*Belal (2015)* [29]	*4-point Clinical improvement and patient satisfaction*	- Study **significant** (p=0.010[3] W2-4, p=0.000[3]W2-6, p=0.005[3] W4-6). - Control I **significant** (p=0.037[3] W2-4, p=0.000[3] W2-6, p=0.010[3] W4-6). - Control II **significant** (p=0.000[3] W2-4, p=0.000[3] W2-6, p=0.000[3] W4-6). - Study: control I **not significant** (p=0.007[4]). - Study: control II **significant** (p=0.005[4]). - Control I: control II **significant** (p=0.002[4]).	*4-point Clinical improvement and patient satisfaction*	- Study **significant** (p=0.005[3] W2-4, p=0.000[3] W2-6, p=0.001[3] W4-6). - Control I **significant** (p=0.008[3] W2-4, p=0.000[3] W2-6, p=0.004[3] W4-6). - Control II **significant** (p=0.000[3] W2-4, p=0.000[3] W2-6, p=0.004[3] W4-6). - Study: control I **not significant** (p=0.011[4]). - Study: control II **significant** (p=0.001[4]). - Control I: control II **significant** (p=0.003[4]).	None.	Control II > Study > Control I.	Moderate.
5.	*Amirchaghmaghi et al (2016)*[30]	10-cm VAS	- Study **significant** (p=0.027[2] W2, p=0.026[2] W4). - Control **significant** (p=0.046[2] W2, p=0.002[2] W4). - Study: control **significant** (p<0.05[2]).	5-*point* Thongprasom	- Study **significant** (p=0.002[2] W2, p=0.006[2] W4). - Control **significant** (p=0.005[2] W2, p=0.002[2] W4). - Study: Control **not significant** (p=0.77[2]).	None.	Study = control.	Low.
6.	*Hambly et al (2017)*[26]	10-cm VAS	- Study effective (4.11) - Control effective (3.78) - Study: control not statistically measured because of the small sample.	N/A	N/A	None.	Study = Control	Low.
7.	*Bakhshi et al (2020)*[31]	N/A	N/A	REU, *Efficacy index*	- Control **significant** (p<0.001[4]). - Study: control **significant** (p<0.001[4]).	None.	Study < control.	Low.
8.	*Georgaki et al* (2022)[24]	10-*cm* VAS	- Study **significant** at W0-W4 (p=0.000[2]) but **not significant** at W4-M5. - Control **significant** at W0-W4 (p=0.02[2]), but **not significant** at W4-M5. - Study: control **not significant** (p=0.249[2] W0-4, p=0.052[2] W4-M5).	Sign Score, 5-*point* Thongprasom	- Study **significant** (p<0.025[1] W0-4, p=0.02[1] W0-M5). - Control **significant** (p=0.034[1] W0-4, p=0.017[1] W0-M5). - Study: control **significant** at W0-4 (p=0.001[1]), but **not significant** at W0-M5 (p=0.345[1]).	Study: Candidiasis. Control: Candidiasis. (p=0.031[6])	Study > control.	Low.
9.	*Zhang et al (2022)*[32]	10-*cm* VAS	Study: control **significant** at M3 (p=0.009[3]) and M6 (p=0.001[3]), but **not significant** at W2 (p=0.745[3]) and W4 (p=0.281[3]).	Sign Score	Study: control **significant** at M3 (p=0.003[3]) and M6 (p<0.001[3]) but **not significant** at W2 (p=0.795[3]) and W4 (p=0.838[3]).	Study*:* candidiasis Control: candidiasis, dysgeusia, nausea, diarrhea, abnormal liver function.	Study < control.	Low.

VAS=Visual Analog Score, REU=Reticular-erosive-ulcerative, W0=Baseline, W1-2=Week 1-Week 2, W2=Week 2, W2-4=Week 2–week 4, W0-4=Baseline-week4, W4=Week 4, W2-6=Week 2-week 6, W4-6=Week4-week6, W0-M5=Baseline-5 month, M3=3 month, M6=6 month, N/A=Not applicable, 1Wilcoxon test, 2Mann-Whitney test, 3ANOVA test, 4T-test, 5Friedman test, 6McNemar test.

Table 4. JBI Critical Appraisal Tools for Randomized Clinical Trials

No	JBI assessment indicators[22]	Ahadian et al (2012)[25]	Sanatkhani et al (2014)[27]	Amirchagh maghi et al (2015)[28]	Belal (2015)[29]	Amirchagh maghi et al (2016)[30]	Hambly et al (2017)[26]	Bakhshi et al (2020)[31]	Georgaki et al (2022)[24]	Zhang et al (2022)[32]
1	Was true randomization used for assignment of participants to treatment groups?	✓	✓	✓	✓	✓	✓	✓	✓	✓
2	Was allocation to treatment groups concealed?	✓	✓	✓	?	✓	✓	✓	✓	?
3	Were treatment groups similar at the baseline?	✗	✓	✓	✓	✓	✓	✓	✓	✓
4	Were participants blind to treatment assignment?	✓	?	✓	?	✓	✓	✓	✓	✓
5	Were those delivering the treatment blind to treatment assignment?	✗	✓	✗	?	✓	✗	✓	✓	✗
6	Were treatment groups treated identically other than the intervention of interest?	✓	✓	✓	✓	✓	✓	✓	✓	✓
7	Were outcome assessors blind to treatment assignment?	✗	✓	✓	?	✓	✗	✓	✓	✗
8	Were outcomes measured in the same way for treatment groups?	✓	✓	✓	✓	✓	✓	✓	✓	✓
9	Were outcomes measured in a reliable way?	✓	✓	✓	✓	✓	✓	✓	✓	✓
10	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	✓	✓	✓	✓	✓	✓	✓	✓	✓
11	Were participants analysed in the groups to which they were randomized?	✓	✓	✓	✓	✓	✓	✓	✓	✓
12	Was appropriate statistical analysis used?	?	✓	✓	✓	✓	✗	✓	✓	✓
13	Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Total score	69.2%	92.3%	92.3%	69.2%	100%	76.9%	100%	100%	76.9%
	Risk of Bias	Moderate	Low	Low	Moderate	Low	Low	Low	Low	Low

✓ = yes; ✗ = no; ? = unclear

The systematic review included several studies that compared the effectiveness of different mouthwash treatments for OLP. One study compared steroid (dexamethasone) mouthwashes to non-steroidal (cyclosporine) mouthwashes.[24] Two studies compared two steroid mouthwashes or the same steroid mouthwash at different concentrations. One study compared dexamethasone mouthwash with triamcinolone mouthwash[25] and one study compared ready-to-use dexamethasone mouthwash with self-contained dexamethasone mouthwash.[26] Six studies tested adjuvant therapy to steroid mouthwash with both trial groups receiving the same steroid mouthwash. The adjuvant therapies that were tested for their effectiveness are cedar-honey,[27] quercetin hydrate,[28] Selenium with vit. A, C, & E (SE-ACE),[29] curcumin,[30,31] and Total Glucosides of Paeony (TGP).[32] Information regarding concentration, frequency, duration of treatment, and duration of follow-up is listed in Table 3. The range of treatment duration was 3-6 weeks and the range of follow-up duration was 0-24 weeks.

Eight articles measured the parameters of pain reduction using the various methods, including VAS (Visual Analog Scale),[24–26,28,30,32] the Thongprasom scoring system,[27] PI (pain index) improvement,[28] and clinical improvement and patient satisfaction.[29] Eight articles measured the parameters of change in lesion size using the Thongprasom scoring system,[24,30] size of lesion (mm^2),[25,27] sign score,[24,32] SI (severity index) improvement[28], REU (reticulation, erosion, ulceration) score,[31] and clinical improvement and patient satisfaction[29]. Nine articles listed possible side effects, with three articles reporting local side effects[24,27,32] and one article reporting systemic side effects.[32] Most of the studies showed statistically significant results ($p<0.05$) supporting the effectiveness of each intervention can be seen in Table 3.

The quality of the articles' study was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools. Based on the research results, seven randomized clinical trial articles were categorized as having a low risk of bias, and two articles were categorized as having a moderate risk of bias. The complete assessment results can be seen in Table 4.

OLP is associated with immune system disturbances and its exact cause is unknown, but it occurs more frequently in women than men.[34] It mainly affects adults and the elderly, with an average age of 53 years. OLP is rarely found in children and does not show hereditary tendencies.[2] Park et al.[18] found that treatment outcomes of OLP were significantly influenced by age, history of malignancy, menopausal status, and the site of the OLP lesion. Stress can trigger OLP exacerbations, as there is a correlation between lesion exacerbation and anxiety and psychological stress according to Krupaa et al.[35] research in 2015. However, this review did not

specifically examine the effectiveness of mouthwashes on subjects with systemic and stress-related conditions.

The comparison between steroid and non-steroid mouthwashes in this review found that the use of steroid mouthwashes (dexamethasone) provided stable clinical responses (reduction in pain) during the treatment period, with long-term effects gradually declining during the follow-up period. On the other hand, non-steroidal mouthwashes (cyclosporine) worked relatively slower and were less effective during the treatment period, but resulted in better long-term remission (reduction in lesion size) even during the follow-up period. The findings are in line with the review's aims of identifying the differences in effectiveness between the two types of mouthwashes, where both had significant direct effects on healing chronic oral mucosal ulcerations with minimal local side effects. There were no major complications reported, but candidiasis was observed in both groups and was more common in the dexamethasone group. Ge et al.[36] found that steroids, particularly dexamethasone, and cyclosporine can inhibit the pathogenesis of OLP by suppressing the production of inflammatory cytokines (such as Tumor-Necrosis-Factor-α and Interleukin-6) and chemokines through negative regulation of Toll-Like-Receptor-4 expression and Nuclear-Factor-κB signaling. Additionally, cyclosporine can induce apoptosis, which inhibits the proliferation of human keratinocyte cells.[36]

In this review, the use of steroid mouthwash (dexamethasone, triamcinolone) showed effectiveness in healing OLP, aligning with the aims of this research.[24–30,32] Dexamethasone mouthwash provided a more stable effect on reducing pain and lesion size with a concentration of 0.5 mg three times a day for 4 weeks or 0.75 mg four times a day for 6 weeks. Dexamethasone mouthwash did not show a significant effect on pain reduction and lesion size when used at a concentration of 0.5 mg four times a day for 4 weeks. After the fourth week of treatment, dexamethasone mouthwash demonstrated better lesion size improvement compared to triamcinolone acetonide mouthwash. No side effects were reported. Dexamethasone is a potent steroid, while triamcinolone acetonide is a moderately to highly potent steroid with a lower level of complications compared to other steroids, making dexamethasone mouthwash more effective.[9] The treatment of moderate OLP according to the British Association of Dermatologists (BAD) guidelines involves the use of topical steroids available in the form of mouthwash, spray, paste, and orally soluble tablets.[13,37] Although not designed for the oral environment, mouthwash preparations made from systemic medications, such as crushed dexamethasone tablets, have shown clinical effectiveness in treating OLP.[26] A combination of prednisone 5mg mouthwash

with Aquadest 10ml twice a day remains the first-line treatment for OLP, as reported in the Nelonda et al[38] case-report study, due to the limited availability of highly potent topical steroid mouthwashes in the management of oral diseases in Indonesia. However, the study by Hambly et al.[26] indicated that ready-to-use mouthwash formulations developed by pharmacists may contribute to better clinical outcomes for OLP patients.

Some studies in this review included natural adjuvant therapies alongside steroid mouthwashes. The combination of dexamethasone mouthwash with cedar honey liquid or curcumin capsules showed similar effectiveness to using dexamethasone mouthwash alone. However, the addition of cedar honey liquid did not significantly reduce lesion size and caused a mild burning sensation as a local side effect. The combination of dexamethasone mouthwash with SE-ACE tablets, quercetin hydrate capsules, or TGP (total glucosides of paeony) capsules showed better results. The addition of TGP capsules was effective after 3-6 months of treatment but also led to some systemic side effects, such as diarrhea and abnormal liver function. The use of natural alternative medicine in combination with topical steroids is always preferred over the combination of two chemical drugs, in line with the findings of this review[32]. Honey is rich in polyphenols (anti-inflammatory compounds) and antibacterial substances that promote wound healing and ulcerative lesion healing in OLP.[39,40] Curcumin contains polyphenols (antioxidants comparable to vitamin C and vitamin E) and also has antifungal effects, preventing candidiasis (a common complication of steroid use). Quercetin is an herbal medicine belonging to the flavonoid group with antioxidant properties and is used in the management of various systemic conditions such as cancer, hypertension, cardiovascular diseases, and some oral conditions like aphthous ulcers.[41–43] SE-ACE provides effective nutrition to support the healing of chronic mucosal ulcers. SE is considered an essential component of the endogenous antioxidant enzyme called glutathione peroxidase (GSH-Px). Vitamin A and E inhibit lipid peroxidation in cell membranes, while Vitamin C acts as a cofactor for enzymes that stabilize collagen structure and also helps in the recycling of Vitamin E for mucosal tissue regeneration.[44] TGP is extracted from the dried root of Paeonia lactiflora Pallas, a traditional Chinese medicine that has been used for over 1000 years to treat inflammation, pain, and immune system control.[45] In OLP, there is a decrease in the body's antioxidant and cortisol levels, so using steroid mouthwash with the addition of substances containing antioxidants can enhance the effectiveness of treatment.[34] Fluconazole capsules, itraconazole capsules, and nystatin suspension were used as other adjuvant therapies to prevent secondary

candidiasis infections resulting from the use of dexamethasone mouthwash. According to the national survey conducted by Piñas et al.,[46] 30% of dentists and 10.49% of maxillofacial surgeons in Spain reported combining treatment with other drugs along with nystatin (100,000 IU per millimeter) was the most frequent approach, accounting for 80% of the cases.

This study has several limitations, including heterogeneity in the inclusion criteria of the research subjects and outcome measurement parameters from each article reviewed in this systematic review. The research subjects included comparisons of steroid and non-steroid mouthwashes, two types of steroid mouthwashes, as well as adjuvant therapy with steroid mouthwash with different dosages and trial durations in each article reviewed. The small sample size of the research subjects also limited the statistical comparison of treatment effectiveness. This heterogeneity highlights the need for further development in the treatment of OLP using steroid and non-steroid anti-inflammatory mouthwashes to reduce study bias and enable meta-analyses.

CONCLUSION

Over the past ten years, various therapies have been employed in the treatment of Oral Lichen Planus (OLP). In this systematic review, topical steroid mouthwashes (dexamethasone, triamcinolone) were identified as potentially the most effective treatment option for reducing pain and lesion size in OLP ulcerations, followed by non-steroidal mouthwash (cyclosporine) with better long-term remission rates. Natural adjuvant therapies, such as nanocurcumin gel, quercetin hydrate capsules, and SE-ACE tablets, can be used to complement the use of topical steroid mouthwashes based on individual patient conditions.

Additionally, other adjuvant therapies like fluconazole capsules, itraconazole capsules, and nystatin suspension can be administered to prevent secondary candidiasis infections resulting from the use of topical steroid mouthwashes. However, further research in the form of randomized controlled trials (RCTs) and meta-analyses is needed to assess the effectiveness of these additional therapies in the future.

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