

CURCUMIN TOPICAL APPLICATION FOR SYMPTOMATIC TREATMENT OF ORAL LICHEN PLANUS: A SYSTEMATIC REVIEW OF EVIDENCE

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ABSTRACT

Objective: The aim of this systematic review was to assess the clinical effectiveness of topical curcumin, compared to topical corticosteroids for the management of symptomatic oral lichen planus.

Material & Methods: Three databases were searched including MEDLINE-PubMed, Cochrane-Central & LILACS as well as Grey literature & hand-searching till September 2018. Randomized and non-randomized controlled clinical trials relevant to our topic were comprised.

Results: Four studies met our eligibility criteria and were included in this systematic review; 2 randomized and 2 non-randomized controlled trials. All included studies reported clinical improvement of oral lichen planus, in terms of pain alleviation as well as reduction in erythema and ulceration, with the topical use of curcumin. No statistical significant differences were found when comparing the effectiveness of topical curcumin to topical corticosteroids.

Conclusion: Topical curcumin application shows promising effects, comparable to topical corticosteroids for the symptomatic treatment of OLP, with no adverse effects.

KEYWORDS: Curcumin, Turmeric, Oral lichen planus, systematic review.

INTRODUCTION

Medicinal plants have been used in the past decades for the treatment of several human diseases throughout the world ¹. In some developing countries, these medicinal plants are still used as the main medications. As reported by the

World Health Organization (WHO), nearly 80% of people in developing nations depend mainly on traditional herbal medicines for their primary healthcare ². Even in developed countries as United Kingdom, United States, Australia & Canada, the use of herbal medicines have been growingly established ³⁻⁶. Curcumin is among the most

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powerful well-recognized & widely studied medicinal herb. Curcumin is an extract from Turmeric which is derived from rhizome of the plant "Curcuma Longa"⁷. Over the last decade, numerous studies have delineated the efficacy & safety of this magical Curcumin & have provided a solid basis for investigating its effectiveness in human clinical trials⁸. In fact, Curcumin has been progressively studied for its pleiotropic therapeutic properties such as anti-inflammatory, antioxidant, antimicrobial, antiviral & anti-carcinogenic properties⁹.

Oral lichen planus (OLP) is a chronic inflammatory & immunologically mediated disorder, described firstly in 1869 by Wilson¹⁰. OLP affects most commonly females & has a prevalence of 2% among the general population. Clinically, OLP is characterized by usually bilateral mucosal lesions affecting mainly the buccal mucosa, tongue, gingiva & rarely the palate¹¹. OLP may present in different clinical forms including papular, reticular, plaque-like, atrophic or erythematous as well as ulcerative or erosive forms^{12, 13}. Contemporary treatment modalities of OLP are primarily symptomatic aiming to reduce pain, erythema & ulceration. Steroids are still the mainstay gold standard for palliative symptomatic treatment of OLP^{14, 15}. Depending on disease severity, steroids are administered topically, systemically or intra-lesional¹⁵. Topical steroids application is the preferred one in the management of mild to moderate OLP lesions owing to their fewer side effects¹⁶. However, prolonged use of topical steroids may lead to secondary candidiasis & mucosal atrophy¹⁷. Recently, herbal medicines have been introduced for symptomatic treatment of OLP. Specifically, Curcumin is one of the nutraceuticals that has received a great attention nowadays. Fortunately, Curcumin has been proved to be a safe, non-toxic & effective alternative for many traditional drugs due to its various therapeutic properties^{18, 19}. The objective of this systematic review was to elucidate the existing evidence of the efficacy of topical curcumin application

for alleviating the symptoms of OLP. Up to our knowledge, this systematic review is the first to explore the efficacy of topical curcumin in OLP.

MATERIALS AND METHODS

The systematic search & review process was carried out according to the guidelines of Preferred Reporting Items for Systematic Reviews & Meta-Analysis (PRISMA)²⁰. This review had been registered in the International Prospective Register of Systematic Reviews (PROSPERO), Center for Reviews and Dissemination, University of York on October 25, 2018. The registration number is CRD42018111210.

Focused Question

Is curcumin topical application effective in alleviating pain & clinical improvement of symptomatic oral lichen planus patients?

Search strategy

The authors (G.M. & A.A.) had searched three electronic databases including MEDLINE-PubMed, Cochrane-Central & LILACS. In addition, hand-searching & searching in Grey literature was carried out. The search was done in May 2018 & updated in September 2018. Search terms used in databases were ["Curcumin" OR "Curcuma Longa" OR "Turmeric" OR "Curcuminoids"] AND ["Oral lichen planus" OR "OLP" OR "Erythematous oral lichen planus" OR "Atrophic oral lichen planus" OR "Erosive oral lichen planus" OR "Ulcerative oral lichen planus"].

Eligibility criteria

Inclusion criteria included: (1) randomized controlled clinical trials (RCTs) & non-randomized controlled clinical trials (NRCT); (2) articles written in English; (3) population: symptomatic OLP patients; (4) intervention: Curcumin topical application; (5) Control/comparator: corticosteroids topical application; (6) primary outcome: alleviation

of pain whereas secondary outcome: clinical improvement of OLP in terms of reduction of erythema & ulceration.

Exclusion criteria were: (1) animal studies; (2) in-vitro studies; (3) narrative reviews; (4) case reports.

Studies Selection

Initial screening of the title & abstract of studies was performed by the two reviewers G.M. & A.A. separately. Full-text screening was then carried out by the same reviewers & any disagreement between them was solved by discussion. Studies fulfilling the eligibility criteria were included.

Quality Assessment

Assessment of the methodological quality of selected studies was performed by the authors G.M. & S.H. independently. Assessment of risk of bias was accomplished utilizing the Cochrane Risk of Bias tool as clarified in the Cochrane handbook for RCTs²¹. For assessment of risk of bias for non-randomized studies of interventions, Cochrane ROBINS-I tool was used²². Domains assessed for every included study encompassed sequence generation; allocation concealment; blinding of participants, personnel & outcome assessors; incomplete outcome data; selective outcome reporting and other source of bias. When all these domains are fulfilled, the study is categorized as being a study with low risk of bias. If one domain is missing, the study will have a moderate risk of bias. Two or more missing domains categorize the study as having a high risk of bias²¹.

Data Extraction

Selected articles were processed for data extraction. Data extracted from selected papers included: the study design & duration of the study; sample size; demographic characteristics of included patients; OLP forms; curcumin formulations & applications; the control or comparator used; clinical parameters assessed & the authors' conclusions.

Extracted data were then tabulated. (Table 1)

In fact, data extracted from included studies showed substantial heterogeneity in several aspects, thus, we couldn't perform a meta-analysis. Hence, extracted data from selected studies were abridged & exhibited in an illustrative method.

RESULTS

After our initial search & removal of duplicates, 18 papers were discovered. Screening the titles & abstracts resulted in exclusion of 4 papers & 14 papers were then selected. Following full-text reading, 10 papers were excluded as one paper¹⁷ was a Narrative Review, two papers^{23,24} were Pilot studies with only one OLP group & no control or comparator group, one paper²⁵ was a case report, one retrospective cohort study²⁶, four papers²⁷⁻³⁰ used systemic administration of Curcumin & one paper³¹ used a different comparator that did not match our eligibility criteria. Only 4 articles met the eligibility criteria³²⁻³⁵. The number of papers recognized at different stages of reviewing is shown in the PRISMA flowchart (Figure 1).

Among the 4 included studies, 2 studies were randomized controlled trials; Keshari et al.,³² and Kia et al.,³³ and the other 2 studies were non-randomized controlled trials; Thomas et al.,³⁴ and Nosratzahi et al.,³⁵. In the 4 included studies, total number of participating subjects was 192 (130 females & 62 males) with age ranges from 20-78 years. All participating subjects were suffering from symptomatic OLP. In their studies, Keshari et al.,³² and Kia et al.,³³ as well as Nosratzahi et al.,³⁵ enrolled patients with atrophic and/or erosive OLP types. Thomas et al.,³⁴ enrolled only patients with erosive OLP.

In all included studies³²⁻³⁵ topical application of curcumin was compared to topical corticosteroids application for symptomatic treatment of OLP. However, different formulations & concentrations of both curcumin as well as corticosteroids were

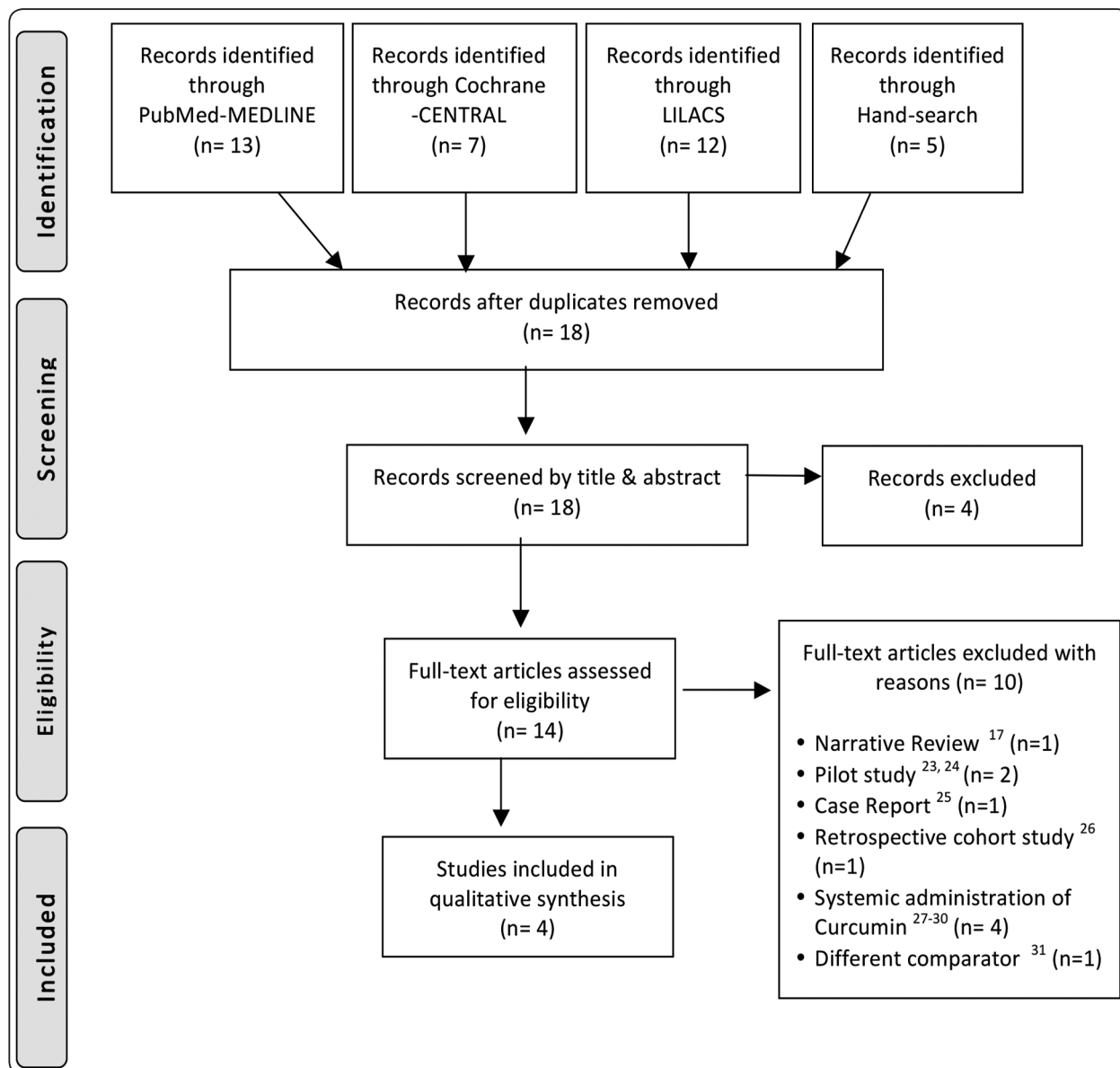


Fig. (1) Preferred Reporting Items for Systematic Reviews & Meta-analysis (PRISMA) flow Diagram showing number of studies

applied. Specifically, Keshari et al.,³² and Thomas et al.,³⁴ used commercially available curcumin 1% oral gel (Curenex oral gel) whereas Kia et al.,³³ used curcumin 5% oral paste. Nosratzahi et al.,³⁵ used curcumin mucoadhesive paste prepared in the faculty of Pharmaceutics, Tabriz University of Medical Sciences in Iran and the authors didn't report the exact concentration of curcumin. Curcumin was applied three times daily after meals in all included

studies. Topical corticosteroids application was used as comparator in the form of triamcinolone acetonide oral paste 0.1% in Keshari et al.,³² Kia et al.,³³ and Thomas et al.,³⁴ studies unlike Nosratzahi et al.,³⁵ who used Betamethasone 0.1% local steroid lotion. Topical corticosteroids were applied three times daily in all included studies. The duration of the intervention varied between included studies; two weeks in Keshari et al.³² study, four weeks in

Kia et al.,³³ study and three months in both Thomas et al.,³⁴ and Nosratzahi et al.,³⁵ studies.

Regarding clinical parameters assessed, Keshari et al.,³² used pain score³⁶ in the form of numerical rating scale ranging from 0 to 10 and erythema score³⁶ ranging from 0 to 3 where 0 = Normal; 1 = Mild erythema; 2 = Moderate erythema; 3 = Severe erythema, as well as ulceration score³⁶ where 0 = No ulcerations; 1 = between 0 and 0.25 cm²; 2 = between 0.25 and 1 cm²; 3 = ≥ 1 cm². On the other hand, Kia et al.,³³ assessed the severity of pain using visual analog scale³⁷ ranging from 0 to 10 as well as size of the lesions using Thongprasom score³⁸ where 0= No lesion; 1= Mild white striae, no erythematous area; 2= White striae with atrophic area less than 1cm²; 3= White striae with atrophic area more than 1cm²; 4= White striae with ulcerative area less than 1cm²; 5= White striae with ulcerative area more than 1cm². Thomas et al.,³⁴ assessed burning sensation by means of numerical rating scale from 0 to 10³⁹ and they evaluated clinical signs using Modified Oral Mucositis Index developed by Schubert et al.,⁴⁰. Nosratzahi et al.,³⁵ evaluated the size of lesions using Thongprasom score³⁸, severity of pain and burning sensation using a 10 cm visual analog scale⁴¹ and they also assessed severity index & pain index⁴².

Concerning pain reduction which is the primary outcome assessed in all included studies, Keshari et al.,³² reported statistically significant reduction in pain scores from baseline to follow-up in both curcumin study group and triamcinolone control group (P=0.005 and P=0.016 respectively). However, when comparing the difference in decrease of pain scores between the two studied groups, insignificant statistical difference was observed (P=0.697). Similarly, Kia et al.,³³ reported significant pain reduction in both curcumin & triamcinolone groups. The authors revealed that complete remission was observed in 36% & 32% of the cases respectively; good response in 16% & 32% respectively; poor

response in 24% & 16% respectively and no response to treatment in 24% & 20% respectively. No statistical significant difference was detected between the two studied groups (P=0.17 at baseline; P=0.3 at 2 weeks; P=0.46 at 4 weeks follow up). Similar results were reported by Nosratzahi et al.,³⁵ who showed statistically significant decrease in pain severity in both studied groups from baseline to 12 weeks follow up (p<0.05). However, no statistical difference was found between the curcumin & corticosteroid groups (P>0.05). Thomas et al.,³⁴ showed in their study results significant reduction in burning sensation among their three studied groups from baseline to three months follow up; triamcinolone (77.39%); curcumin applied 3 times daily (54.4%) and curcumin applied 6 times daily (64.99%). Triamcinolone group showed the highest reduction in burning sensation followed by curcumin application 6 times daily. The authors reported that reduction in burning sensation among the triamcinolone group & curcumin application 6 times daily group was almost comparable.

Clinical improvement of OLP in terms of reduction of erythema & ulceration was reported in all included studies. In fact, Keshari et al.,³² demonstrated statistically significant reduction in erythema in both curcumin and triamcinolone acetamide groups (P=0.000 and P=0.007 respectively). Moreover, the authors reported a statistically significant improvement in erythema among the curcumin group when comparing the mean erythema scores of curcumin and triamcinolone acetamide groups (P=0.002). In addition, a statistically significant reduction in the ulceration scores was shown among the curcumin group from baseline to follow up (P= 0.041), while the ulceration scores in the triamcinolone acetamide group did not show significant reduction (P=0.674). Though, comparing the mean ulceration scores of both studied groups revealed statistically insignificant results (P=0.291).

Table 1: Data extraction for included studies

Authors	Sample Size	Study Design & Duration	Patients Sex & Age in years (range)	OLP Type	Curcumin application & instructions	Control/Comparator	Clinical parameters assessed	Authors' conclusion
Keshari et al., 2015 ³²	N= 27	RCT 2 weeks	11 Females 16 Males 28-78 years	Atrophic Erosive	Ointment (Curenxt Oral gel-Abbott Pharmaceuticals, India) Thrice daily	Triamcinolone acetonide (0.1%Kenacort oralpaste 0.1% - Abbott Pharmaceuticals) Thrice daily	Pain score Erythema score Ulceration score	Curcumin is efficient in the control of pain, erythema & ulceration associated with OLP.
Kia et al., 2015 ³³	N= 50	RCT 4 weeks	36 Females 14 Males 38-73 years	Atrophic Ulcerative	Curcumin oral paste 5% Three times daily applied after eating & brushing.	Triamcinolone oral paste 0.1% Three times daily after eating & brushing	Pain severity (visual analogue scale) Size of lesion (Thongprasom score)	Curcumin is suggested for OLP treatment due to its beneficial anti-inflammatory effects.
Thomas et al., 2017 ³⁴	N= 75	NRCT 3 months	74.6 % Females 25.4% Males 20- 70 years	Erosive	Curcumin gel 1% (Curenxt Oral Gel) Group 1: Three times daily Group 2: Six times daily	Triamcinolone acetonide oral paste 0.1% thrice daily	Burning sensation (Numerical Rating Scale) Clinical signs (Modified Oral Mucositis Index)	Curcumin results in clinical improvement of OLP but can't be used alone. It can be used as an adjunct after initial corticosteroids treatment.
Nosratzahi et al., 2018 ³⁵	N= 40	NRCT 3 months	26 Females 14 Males 28-60 years	Atrophic Erosive	Curcumin muco-adhesive paste Three times a day after meals.	Betamethasone 0.1% local steroid lotion & nystatin suspension three times daily	Thongprasom score Severity index Pain index Visual analogue scores	Curcumin is effective in OLP treatment as it results in reduction of lesion size, pain & burning sensation with no complications.

RCT: Randomized controlled trial; NRCT: Non-Randomized controlled trial; N: Number of patients

Kia et al.,³³ reported decreased mean Thongprasom score in curcumin group from 3.88 ± 0.78 at baseline, to 2.64 ± 1.29 at final follow up. In triamcinolone group, mean Thongprasom score decreased from 3.95 ± 1.07 at baseline, to 2.95 ± 0.97 at final follow up. However, the authors reported no significant difference between the two groups³³.

Thomas et al.,³⁴ showed in their results a significant decrease in erythema & ulceration among curcumin & triamcinolone acetonide studied groups using the Modified Oral Mucositis Index ($p < 0.001$). They clarified that this reduction was the highest among triamcinolone group (67.8%) followed by curcumin applied six times daily group (58.36%). The lowest reduction was observed in curcumin applied three times daily group (46.6%).

Nosratzahi et al.,³⁵ observed significant decrease in OLP lesion sizes within both curcumin & corticosteroid groups along all follow up visits (2.45 ± 1.1 to 0.75 ± 0.34 and 2.61 ± 1.2 to 0.91 ± 0.46 respectively) ($p < 0.05$). Yet, intergroup comparison revealed no significant difference observed between curcumin and corticosteroid groups ($P > 0.05$). In addition, based on Thongprasom classification, the authors reported improvement in the two studied groups along follow-up visits. No statistical difference was reported between the two groups. The authors stated that curcumin had a comparable effect to corticosteroids³⁵.

Assessment of risk of bias of all included studies revealed that only Kia et al.,³³ study had moderate risk of bias while Keshari et al.,³² and Thomas et al.,³⁴ as well as Nosratzahi et al.,³⁵ studies had high risk of bias.

DISCUSSION

Although topical corticosteroids remain the backbone for symptomatic treatment of OLP, alternative treatment modalities are greatly considered nowadays, owing to the deficiency of

robust evidence regarding existing therapeutic modalities⁴³⁻⁴⁵. In fact, Thongprasom et al., (2011)⁴³, Cheng et al., (2012)⁴⁴ and Lodi et al., (2012)⁴⁵ conducted three systematic reviews to assess the effectiveness of existing treatment modalities for symptomatic OLP. Unfortunately, they all reported insufficient evidence supporting the efficacy of existing treatment modalities when compared to placebo or even when comparing two active interventions, including steroids. Indeed, management of OLP represents a great challenge as, till now, there is no treatment that leads to complete cure of the disease. Only symptomatic treatments alleviating pain, reducing erythema and ulcerations are available¹⁴. New therapeutic modalities including topical pimecrolimus⁴⁶, tacrolimus⁴⁷, thalidomide⁴⁸, amlexanox⁴⁹, aloe vera⁵⁰ and curcumin^{24, 32-35} have been suggested. Curcumin is among the new therapeutic modalities for managing OLP with great promising results^{14, 17}. The universal approval and usage of herbal medicines keep on assuming an exponential rise nowadays. Therefore, the aim of this systematic review was to assess the standing evidence regarding the effectiveness of topical curcumin as a new alternative for symptomatic treatment of OLP.

This systematic review comprised four clinical trials; 2 randomized controlled trials (Keshari et al., 32 & Kia et al., 33) and 2 non-randomized controlled trials (Thomas et al., 34 & Nosratzahi et al., 35). The four trials investigated the efficacy of topical application of curcumin, compared to topical corticosteroids, for the symptomatic treatment of patients with OLP. The total number of included patients is 192 and the duration of intervention ranged from 2 weeks to 3 months. The included studies showed considerable heterogeneity regarding study design, curcumin formulation and dosage, type and dose of corticosteroid comparator as well as the duration of treatment, thus we couldn't perform meta-analysis. Interestingly, results of all included studies 32-35 revealed improvement

of OLP symptoms, in terms of pain alleviation as well as reduction in erythema and ulceration, with the use of topical curcumin. Precisely, Keshari et al.,³² concluded that curcumin can be used as an alternative to corticosteroids in OLP management. However, the authors recommended further trials to evaluate, pre- and post-treatment, histological parameters to determine the effectiveness of topical curcumin at the cellular level. Likewise, Kia et al.,³³ and Nosratzahi et al.,³⁵ suggested topical curcumin application for OLP management owing to its fortunate anti-inflammatory properties.

Although Thomas et al.,³⁴ reported clinical improvement of OLP with topical curcumin oral gel; they concluded that curcumin cannot be utilized as a substitute for corticosteroids. They proposed the use of curcumin after an initial regimen of topical steroids. It is imperative here to highlight the potential association between the different doses/formulations of curcumin used and its therapeutic effects in the included clinical trials. For instance, Thomas et al.,³⁴ used 1% curcumin oral gel whereas Kia et al.,³³ used 5% curcumin oral paste. This may explain the different conclusions reported by the two studies. In addition, it may be suggested that higher concentration of curcumin produces superior favorable therapeutic results. Fortunately, all included studies did not report any adverse effects associated with the application of curcumin topically. In fact, this represents the major advantage of curcumin compared to corticosteroids. Corticosteroids have considerable adverse effects, even when applied topically. Actually, prolonged use of topical corticosteroids may lead to mucosal atrophy and oral candidal infection^{16, 17}. Given the chronic nature of OLP and the need for long treatment periods, curcumin seems to be more advantageous and safer compared to steroids³³.

To our knowledge, this is the first systematic review evaluating the available clinical evidence concerning the therapeutic use of topical curcumin

for the management of symptomatic OLP. Assessment of risk of bias revealed that among the included four studies, only Kia et al.,³³ had moderate risk of bias. Keshari et al.,³² Thomas et al.,³⁴ and Nosratzahi et al.,³⁵ studies had high risk of bias. Thus, although we found clinical evidence in the literature that topical curcumin is as effective as topical corticosteroids in managing symptomatic OLP, yet the existing body of evidence is weak.

The main limitation that encountered us in this systematic review was the little number of conducted randomized controlled trials. Other limitations comprised small sample sizes, different formulations and concentrations of curcumin as well as the outcome assessment measures. Moreover, we only included studies in English. Hence, we may have overlooked other studies published in different languages.

CONCLUSION

Based upon the existing evidence, the authors concluded that topical curcumin application shows promising effects comparable to topical corticosteroids for the symptomatic treatment of OLP with no adverse effects. We advocate more randomized controlled trials to be conducted with large sample sizes and standardized curcumin topical preparations and dosage, to increase the body of evidence concerning the effectiveness of curcumin in OLP.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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