

Therapeutic effectiveness of alternative medications in oral lichen planus: A systematic review

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Abstract

Lichen planus is a chronic inflammatory condition affecting the skin and mucosa. The etiology is unknown but the pathogenesis appears to be an immune-mediated reaction. The mainstay drugs used in the treatment are immunomodulators. The aim of this paper is to report on the therapeutic effectiveness of the alternate medications used in the management of oral lichen planus (OLP). A systematic search of PubMed, Web of Science and Cochrane Controlled Clinical trials were done for all the papers published until December 2019. The search resulted in a total of 20 studies that were found suitable for the review. The results showed that the reduction in pain, treatment effectiveness was comparable between the steroids and alternative medications. However, the 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. There is definitely a therapeutic potential in the usage of alternative medications in the management of OLP. In terms of therapeutic effectiveness, they are on par with the immunomodulators. These alternative medications offer us a new therapeutic option in the management of OLP without any adverse effects.

Keywords: Alternative medications, immunomodulators, oral lichen planus, steroids, therapeutic effectiveness

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INTRODUCTION

Lichen planus is a chronic inflammatory condition that affects the skin and mucosa with a global prevalence of 0.1%–4%. This mucocutaneous disorder predominantly affects middle-aged women.^[1] The lesion commonly affects the epithelium of the oral cavity, skin mucosa, genitals, nasal mucosa and nails. The uncommon sites are the larynx and esophagus.^[1,2] Lichen planus affecting the oral cavity,

is referred to as oral lichen planus (OLP). The etiology of OLP is poorly understood with stress being cited as a main factor. However, the etiopathogenesis of the disease has been clearly elucidated.^[1,2]

OLP clinically presents as reticular, papular, plaque-like, atrophic, bullous and erosive lesions.^[2] Some of the commonly occurring variants of OLP are reticular and erosive variants in

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gingiva referred to as desquamative gingivitis are summarized in Figure 1. OLP tends to affect the quality of life by causing pain and burning sensation. The oral symptoms with OLP are predominantly associated with the erosive, ulcerative and atrophic variants.^[3] The main aims of the treatment are to alleviate the pain and discomfort by healing the lesions, preventing recurrences, provide sustained remission phases and prevent the malignant transformation from erosive OLP. Being an immune-mediated disorder, the current mainstay options of treatment would be to use steroids and other immunomodulatory drugs along with drugs to alleviate the pain.^[4] Topical steroids is the preferred mode of drug delivery prior to commencement of systemic steroids.^[4] There has been a lot of attention in developing an alternative therapy to steroids to achieve a complete cure without relapse and to avoid the adverse effects of steroids such as weight gain, alteration of blood sugar levels, osteoporosis and immunosuppression.^[4] In India, where diabetes is very commonly seen, the usage of systemic steroids is best avoided to prevent alteration of blood sugar levels.

As alternative medications such as Aloe vera, Bacillus Calmette Guerin–Polysaccharide nucleic acid (BCG-PSN), curcumin hyaluronic acid, ignatia and purslane extract^[3] have been used in OLP patients. Although there are several randomized control trials with aforementioned agents, systematic reviews have been done only with curcumin and Aloe vera in the management of OLP.^[5,6] However, both the reviews pointed that steroids had better therapeutic effectiveness.^[5,6] Therefore, the aim of this review is to comprehensively enlist all the alternative medications used in the management of OLP. The objectives were to find if there an alternative drug that could bring about a cure, reduce relapse, avoiding the adverse effects of conventional drug therapy for OLP.

METHODOLOGY

The guidelines of transparent reporting of systematic reviews and meta-analyses (PRISMA statement) were used in the preparation of this systematic review. The primary objective of this systematic review was the following PICO question:

- Population – All clinical variants of OLP
- Intervention – Use of alternative medications namely Aloe vera, curcumin, curcuminoids, Glycyrrhiza, Purslane, Lycopene, Raspberry extracts, BCG, hyaluronic acid, and ignatia
- Control – Corticosteroids or placebo
- Intervention – therapeutic effectiveness. The therapeutic effectiveness was assessed in terms of pain reduction and reduction in the size of the lesion.

The secondary objectives of the systematic review:

- Any reduction in the treatment time when using alternative medications?
- Any reduction in the adverse effects when using alternative medications?
- Any reduction in the relapse rate when using alternative medications?

Search strategy

A systematic search was done in the databases of MEDLINE-PubMed, Web of Science and Cochrane Central Register of Controlled Clinical Trials for all the papers published till December 2019. The sample search used in PubMed is enclosed as shown in Figure 2. In addition to the above sources, we had also searched the references of the selected papers for relevant papers.

Eligibility criteria

The inclusion criteria followed for the search were:

- Randomized control trials
- Controlled clinical trials
- Papers authored in English
- Human studies

The exclusion criteria that was adopted was:

- Observational studies
- Case reports/case series reports
- Studies without control groups.

Screening and selection

The titles from across the databases were searched and collated to include the keywords. At the next stage, the

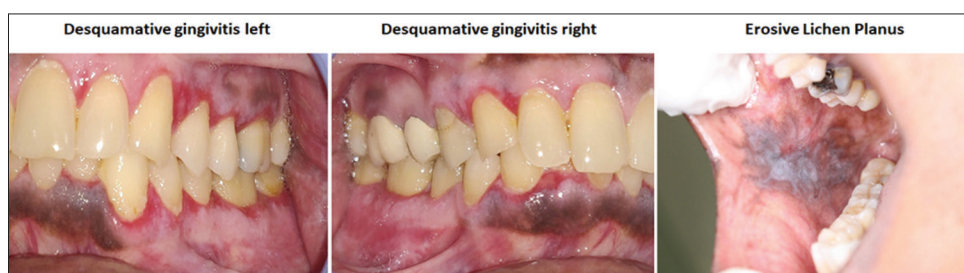


Figure 1: Clinical variants of oral lichen planus

abstracts were analyzed to ensure that they comply with the eligibility criteria mentioned above. The authors discussed whenever there was any disagreement. Meticulous care taken to avoid overlapping studies from the various databases and a final list of eligible studies were made. From this list, the full-text articles were collected and taken up for data extraction.

Assessment of heterogeneity

The heterogeneity across the papers was assessed on the following criteria of study design, formulation of the alternative medication, control drug, dosage of use, clinical parameters evaluated and the follow-up periods.

Quality assessment

The methodology of the eligible studies was mentioned with any variations in the methods pointed out. For the assessment of bias, the following parameters were assessed: Sequence generation, allocation concealment, blinding, outcome data, reporting of the data and source of funding. If a citation matched all the six criteria they were considered to be having a low risk of bias if any of the one criterion was missing they were considered to be having a moderate risk of bias, and when two or more criteria were not reported they were considered to have a high risk of bias

Data extraction

The selected studies were subject to a data extraction mainly to see the therapeutic effectiveness of the drug in comparison to the established therapies or placebo, assessment of quality and heterogeneity.

RESULTS

Search and selection

A thorough search of the databases mentioned above resulted in a total number of 22 studies from PubMed, 40 studies from the Web of Science and 19 studies from the

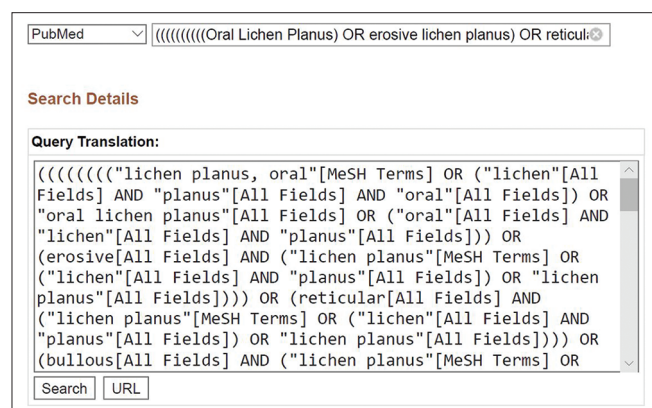


Figure 2: Search string used in PubMed

Cochrane Central Register for Controlled Clinical Trials. The PubMed search string is shown in Figure 2. After eliminating the overlapping studies, a cumulative number of 37 studies were found to be relevant. At the second level the abstracts were analyzed and 24 studies were subjected to full text analysis. During the abstract screening process a total of 13 studies were excluded as they were case or case series reports. At the final stage, 20 studies were found suitable for the systematic review. During the full text screening, those studies which had unequal sample sizes and those where the preparation of the alternative medications which were not clearly mentioned were excluded. The entire selection process as the PRISMA flowchart is given in Figure 3.

A brief summary of the studies is shown in Tables 1 and 2. From the collected data, we had six papers on curcumin/curcuminoids,^[7-12] four on Aloe vera,^[13-15] three on hyaluronic acid,^[16-18] two on topical BCG-PSN extract injections,^[21,22] one each on lycopene,^[20] propolis,^[23] quercetin,^[24] purslane,^[25] and ignatia^[26] as the test drug.

Study design

Among the 20 selected papers, all the papers were randomized control trials (RCTs) of the parallel design.^[7-26]

Characteristics of the participants

The summary of the study participants is listed in Table 2. All the included studies had 20–126 participants. One study^[18] had a maximum of 120 participants. However, none of the studies had mentioned the method of sample calculation, and hence, we assumed it to be based on convenience sampling. All papers except one^[11] had used customized formulations duly approved by the ethical committees.

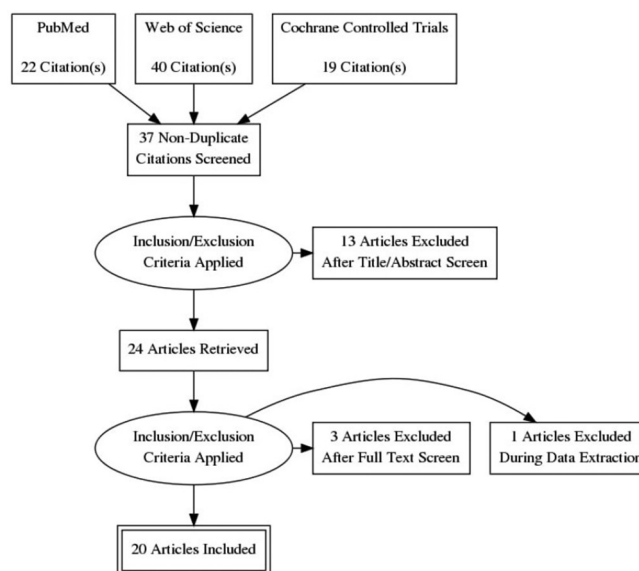


Figure 3: PRISMA flowchart

Table 1: Summary of the individual studies in PICO format

Study	Patient group	Intervention	Control	Outcome
Chainani-Wu <i>et al.</i> ^[7]	100 OLP patients divided into 2 groups	2000 mg of in two divided doses daily for 7 weeks	Placebo	No significant difference in pain intensity. But an increase of burning sensation noted in the curcumin group ($P>0.05$). Increase in the incidence of diarrhea
Chainani-Wu <i>et al.</i> ^[8]	20 OLP patients divided into 2 groups	6000 mg of curcumin in three divided daily doses for 2 weeks	Placebo	No significant difference in pain and symptoms intensity
Kia <i>et al.</i> ^[9]	50 patients divided equally between the study and the control groups	25 patients treated with 5% curcumin thrice daily for 4 weeks	25 patients treated with 0.1% triamcinolone acetonide	No significant difference in the efficacy in the treatment with the two modalities ($P>0.05$)
Amirchaghmaghi <i>et al.</i> ^[10]	20 OLP patients divided into two groups	2000 mg/day of curcumin for 4 weeks	Placebo	No significant difference in the efficacy in the treatment with the two modalities ($P>0.05$)
Thomas <i>et al.</i> ^[11]	75 patients divided into 2 study group and 1 control group equally	One group treated with 1% curcumin thrice daily and the other group treated with 1% curcumin 6 times daily. Both groups used it for 12 weeks	25 patients treated with 0.1% triamcinolone acetonide thrice a day for 12 weeks.	The group treated with 1% curcumin for three times a day showed poor response when compared to the control group. ($P<0.05$) The group treated with curcumin 6 times a day showed no significant difference to the controls ($P>0.05$)
Nosratzahi <i>et al.</i> ^[12]	40 patients equally divided between the study and the control groups	20 patients treated with topical curcumin thrice a day for 12 weeks	20 patients treated with 0.1% triamcinolone acetonide thrice a day for 12 weeks.	No significant difference in the efficacy in the treatment with the two modalities ($P>0.05$)
Choonhakarn <i>et al.</i> ^[13]	54 patients divided between the study and control groups	27 patients were treated with topical aloe vera twice daily for 8 weeks	27 patients were treated with placebo twice daily for 8 weeks	Remarkably good response seen in the patients treated with aloe vera ($P<0.05$)
Salazar <i>et al.</i> ^[14]	64 patients divided into two equal groups	32 patients were treated with topical aloe vera thrice daily for 12 weeks	32 patients were treated with placebo thrice daily for 12 weeks	No significant difference between the groups ($P>0.05$)
Mansourian <i>et al.</i> ^[15]	56 patients divided into two groups equally	23 patients used topical aloe vera mouth wash 4 times daily for 4 weeks	23 patients used topical triamcinolone acetonide 4 times daily for 4 weeks	No significant difference in VAS, Thongprasom scale ($P>0.05$)
Reddy <i>et al.</i> ^[16]	40 patients divided into two equal groups	20 patients used topical aloe vera gel	20 patients used placebo	Significant difference in pain intensity reduction ($P<0.05$)
Hashem <i>et al.</i> ^[17]	40 patients divided equally into two groups	20 patients received 0.2% topical hyaluronic acid three times a day for 4 weeks	20 patients received 0.1% topical triamcinolone acetonide three times a day for 4 weeks	No significant difference based on VAS, Size of the lesion ($P>0.05$)
Shetty <i>et al.</i> ^[18]	50 patients divided equally between the two groups	25 patients used 0.2% hyaluronic acid three times a day for 4 weeks	25 patients used placebo	Highly significant improvement with use of hyaluronic acid in terms of VAS, size of the lesion ($P<0.05$)
Nolan <i>et al.</i> ^[19]	120 patients divided equally	60 patients treated with 0.2% hyaluronic acid 4 times daily for 4 weeks	60 patients treated with placebo.	Highly significant difference noted with hyaluronic acid in terms of VAS ($P<0.05$) But no change in size of the lesion
Saawarn <i>et al.</i> ^[20]	30 patients divided into two equal groups	15 patients treated with lycopene 8 mg/day for 8 weeks	15 patients treated with placebo for 8 weeks.	Highly significant difference noted in the reduction of pain and disease improvement ($P<0.05$)
Metwalli <i>et al.</i> ^[21]	26 patients divided into two equal groups	13 patients had been treated with 0.5 ml of BCG injection every other day for 2 weeks	13 patients had been treated with triamcinolone acetonide twice a week for 2 weeks	No significant difference in both the treatment options ($P<0.05$)
Xiong <i>et al.</i> ^[22]	56 patients divided into two groups	31 out of 56 patients were treated with BCG-PSN every other day for 2 weeks	25 out of 56 patients received 10 mg of triamcinolone acetonide for 2 weeks.	No significant difference in both the treatment options ($P<0.05$)
Joshy <i>et al.</i> ^[23]	27 OLP patients with 12 patients in study group and 15 patients in the other group	Study group treated with 5% propolis thrice a day for 2 weeks	Control group treated with 0.1% triamcinolone acetonide thrice a day for 2 weeks	No significant difference in the efficacy in the treatment with the two modalities ($P>0.05$)
Amirchaghmaghi <i>et al.</i> ^[24]	30 patients were divided into two equal groups	15 patients received 250 mg of quercetin BD for 4 weeks. 0.5 mg of dexamethasone as mouthwash with 1000 U of nystatin four times a day for 4 weeks.	15 patients received identical placebo tablets with lactose. 0.5 mg of dexamethasone as mouthwash with 1000 U of nystatin four times a day for 4 weeks.	No significant difference in the efficacy in the treatment with the two modalities ($P>0.05$)

Contd...

Table 1: Contd...

Study	Patient Group	Intervention	Control	Outcome
Agha-Hosseini et al. ^[25]	37 patients of OLP divided into two groups	20 patients received purslane 250 mg once	17 patients received placebo	Clinical and symptomatic relief seen in purslane group ($P < 0.05$)
Mousavi et al. ^[26]	30 patients of OLP divided into two equal groups	15 patients received ignatia	15 patients received placebo	Significant difference in the treatment outcome of the two modalities ($P < 0.05$)

VAS: Visual analog scale, OLP: Oral lichen planus, BCG-PSN: Bacillus Calmette Guerin- polysaccharide nucleic acid, PICO: Population intervention control outcome

Table 2: Characteristics of the study participants and study characteristics

Medication	Number of studies	Number of participants	Average age range	Proportion of females	Follow up period (weeks)	Adverse effects	Relapse rates
Curcumin	6	238	38.4-60.81	46.64	2-12	2	0
Aloe Vera	4	164	47.2-62.19	68.32	8-12	0	0
Hyaluronic acid	3	214	54.34-56.3	69.62	2-4	0	0
Lycopene	1	30	32-45	36.67	8	0	0
BCG-PSN	2	82	50.8-53.7	67.0	2	0	1
Propolis	1	27	41.5	48.14	2	0	0
Quercetin	1	30	48.26	48.14	8	0	0
Purslane	1	37	25-70	61.76	12		
Ignatia	1	30	Not specified	50	12		

BCG-PSN: Bacillus Calmette Guerin- polysaccharide nucleic acid

Type of control

A total of three papers based on curcumin had adopted placebo as a control; incidentally.^[7,8,10] Three papers had used 0.1% topical triamcinolone acetonide as the controls.^[9,11,12] All three papers based on Aloe vera^[13-15] had used 0.1% topical triamcinolone acetonide as the controls. Among three papers based on hyaluronic acid, two had adopted placebo as controls^[17,18] and one paper had used topical triamcinolone acetonide.^[16] The papers on lycopene, quercetin, purslane and ignatia had used placebo as a control.^[19,20,24,25] Both the papers, on BCG-PSN had used intralesional triamcinolone acetonide as controls.^[21,22] The paper on propolis had used triamcinolone acetonide as controls.^[23] To summarize among the 20 studies nine had used placebo as controls. A total of 2 studies^[7,8] had employed a 2 weeks' washout period in which patients were using steroids before enrolling the participants into the study.

Clinical parameters

All the papers had included the different clinical varieties of OLP; however, a majority of participants belonged to erosive/ulcerative OLP. The clinical parameters were assessed based on the patient's response to the alleviation of symptoms such as pain or burning sensation. The signs used were the area of the lesion are enumerated in Table 3. For the assessment of pain, either the numerical rating scale (NRS)^[8,11,23,24] or visual analog scale^[7,9,10,13-22,25,26] or pain index^[12] was used. For the size of the lesion, modified oral mucositis index (MOMI)^[7,8,11,17,23] or severity index was used.^[12,24] The size of the lesion in square millimeters was assessed.^[13,18,19] To assess the response to treatment Thongaprasom scoring^[9,10,13-15]

and Tel Aviv-San Francisco scale^[16,20] was used. Both the papers on BCG-PSN had accounted for the adverse effects and recurrence potential of the lesion over 6 months.^[21,22]

Follow-up period

The follow-up period of all the studies was in the range of 2–24 weeks, with the longest reported study on ignatia.^[26] The follow-up periods of various studies are presented as summarized in Table 2.

Quality assessment

All the papers had a moderate risk of bias except for two papers^[25,26] which had a high risk of bias.

Assessment of heterogeneity

When the studies were assessed for heterogeneity as per the aforementioned criteria they were highly heterogeneous, as even studies which had used the same alternative medication differed in their drug delivery mode or the preparation of the drug or the sample size.

Study outcomes

Pain assessment

A total of 15 studies had used VAS as pain assessment scale.^[7,9,10,13-22,25,26] Among them studies which had used placebo as control report a significant intergroup difference. A total of four studies^[7,8,11,23] had also used the NRS for pain assessment without any significant intergroup difference ($P > 0.05$). Two studies^[12,24] had used the pain index for the assessment of pain without any significant difference ($P > 0.05$). There was difference only when placebo was used in the control.

Table 3: Clinical parameters assessed one study had used two pain indices for measurement

Variable	Mode of assessment	Number of studies	Results
Pain	VAS	15 ^[7,9,10,13-22,25,26]	6 studies ^[7,9,10,17,21,22] reported no difference between test and control drug
Pain	NRS	4 ^[7,8,11,23]	No significant difference
Pain	Pain index	2* ^[12,24]	No significant difference
Clinical outcome	MOMI	5 ^[7,8,11,17,23]	1 study reported a difference ^[8]
Clinical outcome	Thongprasom score	7 ^[9,10,12,13,15,19,25]	1 study reported a difference ^[25]
Lesion size	Metric measurement (mm)	5 ^[15,16,18,19,26]	2 studies ^[18,26] reported a difference

*Significance ($P < 0.05$). NRS: Numerical Rating Scale, MOMI: Modified Oral Mucositis Index, VAS: Visual analog scale

Clinical outcome score

A total of 5 studies^[7,8,11,17,23] had used MOMI to assess the clinical outcome with only one study^[8] reporting a significant difference between the test and control drug. A total of six out of seven studies^[9,10,12,13,15,19,25] did not report any significant difference in the clinical outcome measures using the Thongprasom scale between the groups except for the study by Agha-Hosseini *et al.*^[25] which had used placebo.

Size of the lesion

A total of 5 studies^[15,16,18,19,26] had assessed the lesion size in square millimeter and only two studies^[18,26] which had used placebo as controls showed ($P < 0.05$) statistically significant intergroup difference.

Adverse effects

The adverse effects were monitored in a total of three studies.^[7,9,13] The study by Chainani-Wu *et al.*^[7] had reported a significant increase in the proportion of diarrhea during the systemic administration of curcumin ($P < 0.05$). The study by Kia *et al.*^[9] had reported yellow staining of the gums. The study by Choonhakarn *et al.*^[13] had reported a mild burning sensation on the application of hyaluronic acid [Table 2].

Relapse rates

One paper by Xiong *et al.*^[22] had assessed the relapse or recurrence rate of the disease. The paper reported that in the BCG-PSN group, there was an early recurrence compared to topical triamcinolone acetonide. However, there was no significant difference in the relapse rate after 3 months when both the groups were compared ($P > 0.05$) [Table 2].

Other parameters

The study by Chainani-Wu *et al.*^[7] had used a customized change in symptom score without providing detailed statistical analysis for the same. Another study by Chainani-Wu *et al.*^[8] had also assessed the C-reactive protein, interleukin-6 (IL-6), sulcular bleeding at baseline and 2-week intervals. The study by Salazar-Sánchez *et al.*^[14] also assessed the Hospital Anxiety-Depression Scale. The study by Saawarn *et al.*^[20] had used the Tel Aviv-San Francisco scale to assess the treatment outcome.

DISCUSSION

OLP being a mucocutaneous disorder of immune origin has attracted a wide variety of immunomodulators in its management. As the etiology of OLP remains unclear, we have been giving therapeutics that mainly correct the immune dysregulation and bring the lesion under control.^[16] The clinical symptoms of OLP range from a burning sensation to severe pain that, at times, interferes with the normal speaking, mastication functions of the individual.^[27] Due to the adverse effects associated with immunomodulators, there have been several drugs; plant products have been evaluated in the management of OLP.

A study by Vilar-Villanueva *et al.*^[28] showed that patients with OLP had higher scores in Hospital Anxiety Depression Scale (HADS) and Oral Health Impact Profile (OHIP-14) than normal individuals. HADS is a scale that was developed by Zigmond and Snaith,^[29] which is a validated psychological test used to assess anxiety and depression. Specifically, the authors had noted that the scores were higher in erosive/ulcerative variants of OLP than the reticular variants of OLP. A study by Parlatescu *et al.*^[30] showed that patients with erosive OLP had shown that poor scores were noted in OHIP. All these point to the fact that the burning sensation impacts the quality of life.

The commonly used immunomodulators were steroids, wherein triamcinolone acetonide in orabase, betamethasone, fluticasone, and hydrocortisone.^[2] These were topically used to prevent the adverse effects of steroids such as suppression of hypothalamic-pituitary axis, weight gain and altered glycemic control from naming a few, and other minor side effects such as insomnia, mood swings, and fatigue.^[2,4] Although topical steroids gave a good remission of the disease, the literature does not mention a single dosing regimen that suits most or all patients.^[4] For each patient, the dose had to be adjusted and modified. Several studies had pointed that systemic absorption from the topical drug delivery is negligible.^[2,4] The shortcoming of steroids is that they are not curative of the diseases without any side effects but help in controlling the symptoms of the disease.^[2,4] Further, in cases where there was no response to topical steroids, it was switched to systemic

steroid medications. When using systemic steroids, there was a tendency to tachyphylaxis, which reduces the effect of drugs on repeated use.^[31] When patients were prescribed systemic steroids, the drug dosage had to be tapered progressively to prevent side effects.

There have been several alternatives to steroid therapy in the management of OLP.^[13] Curcuminoids derived from turmeric has been the most extensively studied in the management of OLP. Apart from this, Aloe vera, lycopene, hyaluronic acid and BCG-PSN have been assessed for efficacy in the management of OLP. Propolis, a derivative of beeswax, purslane, a herb, ignatia, a homeopathic medication and quercetin, have shown promise in the management of OLP.

Three studies based on Aloe vera^[13-15] compared the effectiveness Aloe vera with placebo, wherein two studies reported a significant difference in pain improvement between the test and control group. Two studies compared the effectiveness of hyaluronic acid with placebo^[16,17] with significant improvement in the hyaluronic acid treatment group. One study based on lycopene^[20] with placebo as control also showed a significant reduction in pain intensity and symptom improvement. There was one study, each evaluating purslane^[25] and homeopathic drug ignatia^[26] with placebo, which reported significant improvement. All the above studies had used placebo as controls.

On analyzing the studies evaluating the alternate medications to steroids and immunomodulators, we find that there is heterogeneity in the individual studies. About the results, we find that the studies using placebo as controls have reported a positive outcome wherein the alternative medications were giving statistically significant cure rates. Those studies which had taken steroids as control drug did not report any significant improvement in the cure rate compared to alternative medications. This implies that OLP responds to steroids due to immunomodulatory effects and the alternative medications also have an immunomodulatory role which is not very clearly stated in the literature. Furthermore, in terms of adverse effects, no significant reaction has been reported by the individual studies based on alternative medications. However, we observed a few shortcomings in the studies. All the studies had a variable follow-up period and had involved more cases erosive/ulcerative OLP compared to other variants.

Therefore, studies need to be undertaken on a multicentric basis to evaluate the efficacy with a scientifically standardized protocol with a follow-up of at least 8 weeks. Further, the studies must also evaluate the recurrence of the lesion over 12 months.

CONCLUSION

This extensive systematic review following the PRISMA guidelines sheds light on a path which has been taken by several researchers worldwide to look for an alternative medication for OLP to the risk prone steroids and immunomodulators. However, uniformly some shortcomings were noted in terms of follow-up periods. Moreover, most of these alternative medications are plant product based which is believed to be more biocompatible and with limited adverse effects. Among the alternative medications, curcumin, Aloe vera, lycopene have been found to have a therapeutic potential and we would suggest of having a multicentric trial with a uniform protocol which may give us a promising alternative to steroids and other immunomodulators.

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Conflicts of interest

There are no conflicts of interest.

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