

## **Efficacy of topical curcumin in the management of oral lichen planus: A randomized controlled-trial**

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### **Abstract**

Lichen planus is a chronic inflammatory, autoimmune, mucocutaneous condition which commonly involves the oral mucosa. Management of oral lichen planus (OLP) is important as it is an oral potentially malignant disorder. Corticosteroids have been the mainstay of treatment; however, their usage is associated with potential side effects. Phytochemicals, such as curcumin, have been used extensively for centuries, owing to its numerous therapeutic properties.

**Aim:** To evaluate the efficacy and safety of topical curcumin in the management of OLP.

**Materials and Methods:** The research group consisted of 27 adult OLP patients, who were randomly divided into two groups. The control group ( $n = 12$ ) was treated with triamcinolone acetonide 0.1% and the study group ( $n = 15$ ) with commercially available topical curcumin ointment each to be applied thrice daily for 2 weeks. The patients were reviewed every week.

**Statistical analysis:** Descriptive statistics, independent samples *t*-test, paired samples *t*-test, and repeated measure ANOVA were performed.

**Results:** The research groups showed a significant reduction in all the parameters measured. The comparison showed significant improvement in the erythema ( $P = 0.002$ ), but non-significant reduction in pain ( $P = 0.697$ ), and ulceration ( $P = 0.291$ ) in the study group as compared to the control group.

**Conclusion:** Curcumin fared better in reducing pain, erythema, and ulceration. Thus, curcumin can be used as an alternative to steroid in the management of signs and symptoms of OLP with minimal side effects as compared to steroids with similar efficacy.

**Keywords:** Curcumin, Oral, Lichen Planus, Treatment, Steroid

## Introduction

Lichen planus is a chronic inflammatory, immune-mediated, mucocutaneous, potentially malignant disorder. It commonly involves the oral mucosa, which may be the only affected site. Oral lichen planus (OLP) can cause oral discomfort, and is characterized by white reticular changes, erythema, and ulcers. OLP lesions may be disabling enough to create a negative impact on the quality of life; hence, it is essential for the health care provider to provide adequate treatment to the patient.<sup>1</sup>

Corticosteroids, either topical or systemic or both are the mainstay of treatment because of their profound anti-inflammatory properties. However, these potent medications should be used cautiously, considering the drug benefits against potential side effects.<sup>2</sup> Curcumin, a constituent of turmeric has been used extensively in Ayurvedic medicine for centuries, as it is non-toxic and has a variety of therapeutic properties including antioxidant, analgesic, anti-inflammatory, antiseptic activity, and anticarcinogenic activity. These properties have prompted investigators to check its efficacy on oral diseases namely, lichen planus, oral submucous fibrosis (OSMF), leukoplakia, recurrent aphthous stomatitis, etc. Previous studies have indicated that use of topical curcumin has a chemo preventive effect in oral potentially malignant disorders such as OSMF and leukoplakia.<sup>3,4</sup>

In this backdrop, this study was designed to evaluate the efficacy of topical curcumin in the management of OLP and to further strengthen the previously obtained results.

## Materials and Methods

The present study was conducted from May to July in the Department of Oral Medicine and Radiology, Rama Dental College and Research Centre, Kanpur. Ethical approval was obtained from Institutional Review Board following which 27 patients with symptomatic (atrophic/erosive) OLP were selected. The subjects were randomly divided into study group and control groups consisting of 15 and 12 patients, respectively.

## Inclusion criteria

Adult patients who were diagnosed with the atrophic/erosive form of OLP and who consented to be a part of the study were included.

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- Patients, who had not used systemic or topical glucocorticosteroids (GC) for at least past 2 weeks or any other medication such as analgesics and anesthetics in either topical/ systemic form during the study.

### **Exclusion criteria**

- Patients with lichenoid lesions thought to arise as a hypersensitivity reaction to drugs and dental materials or those on long-term GC therapy were not included. Pregnant and lactating female patients were also excluded.

The patients were informed about the study parameters and signed informed consent was taken. The study group subjects were prescribed topical curcumin (commercially available as Curenext Oral gel-Abbott Pharmaceuticals, India) and the control group was given topical triamcinolone acetonide 0.1% (commercially available as Kenacortoralpaste 0.1% - Abbott Pharmaceuticals) to be applied thrice daily for 15 days.

Symptom score for OLP was considered at baseline using numerical rating scale (NRS) ranging from: 0 (no oral discomfort) to 10 (worst imaginable oral discomfort).

The clinical signs of OLP were measured at baseline using a semi-quantitative scale, modified oral mucositis index, validated for measurement of clinical signs of OLP.

An oral examination was conducted, and atrophic and erosive changes were quantified based on severity and the number of sites involved. An intensity score for erythema (E) ranging from 0 to 3 was used:

0 = Normal

1 = Mild erythema

2 = Moderate erythema

3 = Severe erythema.

The score for ulcerations (U) was based on area of ulceration

0 = No ulcerations

1 = Between 0 and 0.25 cm<sup>2</sup>

2 = Between 0.25 and 1 cm<sup>2</sup>

3 =  $\geq 1$  cm<sup>2</sup>.

The patients were followed up after 7 and 15 days. Readings for all clinical parameters for each patient from baseline to subsequent visits were recorded. The patients were enquired for side effects if any. assessment of the grades was performed by a single calibrated examiner in order to reduce intra examiner variability

### **Statistical analysis**

The data was tabulated and subjected to the following statistical analysis. Descriptive statistical procedures including means, Standard deviation, medians minimum, maximum, and percentages were used to summarize all variables. At baseline, all the parameters were tested for randomization between two groups using independent samples *t*-test and all the obtained *t*-values revealed non-significant differences between study and control groups for pain, erythema, and ulceration scores. Pairwise comparison using paired sample *t*-test was done for all the tests. Repeated measures ANOVA was applied to verify the differential changes between study and control groups from baseline to second follow-up. The results were obtained and analyzed using the SPSS software for windows (version 16.0).

### **Results**

27 symptomatic (atrophic/erosive) OLP patients selected using purposive sampling were included in the study and divided into study and control groups. Table 1 shows the demographic data of the study subjects. The study ( $n = 15$ ) and control ( $n = 12$ ) groups were given topical curcumin and triamcinolone acetonide 0.1%, respectively, to be applied thrice daily for 15 days duration. The patients were followed up at 7 and 15 days.

The patients in both the study and control groups showed statistically significant reduction ( $P = 0.005$  for the study group and  $P = 0.016$  for the control group) in pain scores from baseline to the second follow-up visit. However, on a comparison of the reduction in pain scores between the two groups, the difference was found to be statistically insignificant ( $P = 0.697$ ).

The patients in the study group showed a highly statistically significant reduction in erythema ( $P = 0.000$ ). The control group patients also showed an overall statistically significant reduction ( $P = 0.007$ ). Comparison of the mean erythema scores of the study and control groups showed that the improvement in erythema was highly statistically significant in the study group ( $P = 0.002$ ).

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The study group patients showed statistically significant ( $P = 0.041$ ) reduction in the ulceration scores from baseline to second follow-up visit, whereas the control group did not show significant ( $P = 0.674$ ) reduction in the ulceration scores. However, comparison of the mean ulceration scores of the study and control groups yielded statistically ( $P = 0.291$ ) insignificant results .

Table 1: Demographic data of the study subjects and patient characteristics

Patient Characteristics	Curcumin	Triamcinolone acetonide
	Study groups (n=15).	0.1% control group (n-12)
Age	25-50 years (mean 44.46years)	25-50 years (mean 44.46 years)
Gender(%)		
Males	8(53.34)	8(66.67)
Females	7(46.66)	4(33.34)
Type of OLP(%)		
Atropic	9(60.0)	8(66.67)
Erosive	6(40.0)	4(33.33)

OLP-oral lichen planus

**Table 2:** Mean baseline, first and second follow-up values for pain, erythema, and ulceration of the study and control groups and results of repeated measures ANOVA

Variable	Group	Mean	SD.	First follow up	Second follow up.	Change	Statics
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N (pain)	Test	3.28	2.64.	1.86.	1.81	1.13	1.64	2.15	F= 0.365
	Control	5.00.	1.69.	3.79.	2.31.	2.58.	2.66.	2.42	p=0.697
	Total	4.04.	2.39.	2.49.	2.60.	1.77.	2.23.	2.27	
E(erythema).	Test	2.27.	0.88.	1.33.	0.62.	0.60	0.82.	1.67	F=7.048
	Control.	1.50.	0.67.	1.33.	0.77.	1.00.	0.60.	0.50	P=0.002
	Total.	1.92.	0.87.	1.33.	0.67.	0.77.	0.75.	1.15	
U(Ulcer).	Test.	0.93.	1.27.	0.73.	1.09.	0.40.	0.63.	0.55.	F=1.27
	Control.	0.50.	0.79.	0.75.	0.86.	0.41.	0.66	0.09	P=0.291
	Total.	0.74.	1.09.	0.74.	0.98.	0.40.	0.63.	0.34	

## Discussion

The oral mucosa is commonly affected by lichen planus, a mucocutaneous, immune-mediated, chronic inflammatory condition.<sup>5</sup> The most common reticular regions are white ones, which are typically asymptomatic and don't need to be treated. The disease affects quality of life because OLP lesions are chronic, rarely go into spontaneous remission, may be precancerous, and frequently a source of morbidity, especially when erythematous or erosive lesions are present. Other forms of the disease may manifest as erythematous or erosive areas.<sup>6,7</sup>



**Figure 1:** (a) Patient with atrophic lichen planus at baseline visit included in the study group, (b) Shows reduction in severity of erythema following treatment with curcumin at first follow-up visit, (c) Shows further reduction in erythema at the second follow-up visit, (d) patient with atrophic lichen planus at baseline visit included in the control group, (e) first follow-up visit photograph following treatment with triamcinolone acetonide 0.1%, (f) second follow-up photograph after 15 days of treatment did not show much improvement in erythema.

The lesions run a long clinical course with frequent remissions and exacerbations in a somewhat unpredictable fashion. The primary goal of therapy is palliative since the exact etiology is unknown.<sup>7</sup> Corticosteroid therapy is the treatment of choice. However, several side effects may be encountered with the usage of steroids, namely, candidiasis, burning or stinging sensation, mucosal atrophy, bad taste, nausea, sore throat, dry and swollen mouth. Systemic absorption and adrenal suppression from the superpotent topical steroids and systemic steroids have also been reported, especially when used for long-term in the management of diseases which are chronic in nature such as OLP.<sup>8,9</sup>



**Figure 2:** (a) Patient with erosive lichen planus at baseline visit included in the study group, (b) shows reduction in severity of ulceration following treatment with curcumin at the first follow-up visit, (c) shows further reduction in ulceration at the second follow-up visit, (d) patient with erosive lichen planus at baseline visit, (e) first follow-up photograph after 7 days after treatment with triamcinolone acetonide 0.1%, (f) second follow-up photograph after 15 days of treatment.

Various alternative remedies, such as aloe vera, tacrolimus, pimecrolimus, oral curcuminoids, amlexanox, thalidomide to name a few, have been described in literature for the management of OLP which appear to be promising. However, most of the alternate modalities are still in their nascent stage of research and require large scale studies in order to establish their efficacy.<sup>10</sup>

When evaluating the cost-effectiveness of any treatment modality, it is important to take into account the recalcitrant nature of OLP, the patients' medical history with particular regard to comorbidities such as liver diseases and diabetes, psychological state, occupation, lifestyle, and treatment compliance, as well as possible drug interactions.<sup>11</sup>

Among phytochemicals, curcumin has been used extensively over centuries for its numerous therapeutic properties namely anti-inflammatory, antitumoral, antimicrobial, and analgesic action. Extensive *in vitro* and *in vivo* data have paved the way for curcumin to become the

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subject of clinical trials. Early- phase trials have ascertained pharmacological properties and consistently demonstrate it to be safe and well-tolerated.<sup>12</sup>

Previous studies have indicated the use of curcumin in the management of other potentially malignant disorders such as oral sub mucous fibrosis and leukoplakia.<sup>13</sup>

Chainani-Wu *et al.*<sup>14</sup> performed a randomized controlled- trial on OLP patients comparing high doses of curcuminoids (6000 mg/day for 7 weeks) and prednisolone (60 mg/day for 1 week) with prednisolone alone and achieved some benefit with the curcuminoids at the follow-up visit. However, use of systemic curcuminoids can cause adverse side effects such as nausea and diarrhoea in up to 40% of the patients, including liver dysfunction.<sup>15</sup>

With this background, the present study was conducted to evaluate the efficacy of topical curcumin in the management of OLP in an effort to find an alternative drug with greater or similar efficacy as compared to steroids and minimum side effects to achieve a better prognosis.<sup>16</sup>

In the present study, a total of 27 symptomatic OLP patients were included. They were in the age range of 25-50 years with a mean age of 44.46 years.

OLP can affect either sex; however, a female predominance has been reported, On the other hand, Munde *et al.* in 2013 reported an M: F ratio of 1.61:1.<sup>17</sup> In the present study also a slight male predilection was noted with a male:female ratio of 1.45:1.

The presence or absence of symptoms depends on the form of the lesion. Reticular form which is asymptomatic is the most commonly occurring form and is often identified on routine clinical oral examination. Erosive lichen planus is the second most commonly occurring form observed amongst the various subtypes.<sup>18</sup>

Erosive, atrophic, and bullous forms are usually associated with symptoms ranging from mild discomfort to severe burning sensation which could be attributed to acute inflammatory exacerbations associated with these forms.<sup>19</sup> This can also be explained by the fact that the patients with erosive forms report more to their physicians seeking treatment owing to the discomfort experienced by them. In the present study, however, 16 (59.26%) of the total 27 patients presented with the atrophic form of OLP while 11 patients (40.74%) suffered from

the erosive form. This finding is not in accordance with the previously published data. This could be explained by the fact that the sample included in this study was small in number, whereas previous studies have included a large number of cases.

OLP frequently occurs bilaterally. The buccal mucosa is typically involved in 80-90% of OLP cases. The Koebner phenomenon is present in both cutaneous and OLP. Eisen suggested that the mechanical trauma of dental procedures, cigarette smoking, mucosal trauma from sharp cusps, and oral habits such as lip chewing are koebnerogenic factors that can exacerbate OLP.<sup>20</sup> The gingiva is affected in more than 50% of the cases, and the tongue lesions are seen in about 40% patients.

No treatment modality has proved curative for OLP; switching on to the alternative agents used in the management of OLP suggests the inadequacy of any one agent to provide relief to the patient.

Corticosteroids have been in regular clinical usage for a range of inflammatory and immune-mediated conditions. In conditions such as LP, the effects of GC both as anti-inflammatory agents and immunosuppressives can be exploited. Although GC may improve some components of the local tissue lesion in a case of LP, however, the underlying and persistent immune mechanisms remain active. Therefore, treatment is not directed against the primary disease mechanisms.<sup>19,20</sup>

Although considered as the mainstay of treatment, topical corticosteroids do not alleviate the pain or heal ulcerations in all patients.

In fact, in a study performed by Vincent *et al.* in 1990, 23 of 33 patients treated with topical or systemic corticosteroids reported no symptomatic change and 8 reported only slight improvement. Although these results seem excessively incompatible with other published studies, they suggest that topical corticosteroids are not universally effective. Even clobetasol propionate, the most potent of all topical corticosteroids, failed to produce any benefit in two of nine patients treated for OLP. It is unclear why the response to topical corticosteroid therapy is so variable.<sup>20,21</sup>

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It is essential to remember that corticosteroids do not attend to the primary disease mechanisms. They are used in the minimization of both disease activity and clinical morbidity. Furthermore, corticosteroids are associated with a significant number of side effects.

This suggests the need for an alternative drug which would probably address the underlying mechanism of the disease process and provide effective treatment to the patient with minimum side effects.

Curcumin, a phytochemical has been used as a dietary supplement as well as a therapeutic agent. Curcumin displays a wide range of pharmacological properties against various human disorders. Curcumin exhibits strong anti-inflammatory, analgesic, antioxidant, anti-aging, chemopreventive, antitumoral, anti-angiogenic, anti-metastatic, radio sensitizing, and chemosensitizing effects in cancer. Of therapeutic interest, studies have indicated that curcumin as a lone therapeutic agent is safe and exhibits no major toxicity.<sup>22</sup>

Owing to the above-mentioned therapeutic actions of curcumin, we hypothesized that curcumin due to its anti-inflammatory effect could possibly help minimize the underlying inflammatory process in case of OLP which would prevent the destruction of the basement membrane by the lymphocytes thereby reducing the disease severity by addressing the underlying mechanism. Reduced or absent apoptotic rate in inflammatory cells in OLP have been thought to contribute to the development of OLP.<sup>19</sup> It is possible that curcumin could induce apoptosis in such cells thereby enhancing the healing process. Curcumin inhibits MMP-9 expression via inhibition of nuclear factor-kappa B assembly.<sup>20</sup> This could probably be utilized to prevent the proteolytic degradation of the connective tissue matrix of the oral mucous membrane thereby maintaining its integrity. Curcumin also has antitumoral effects which might prevent the malignant transformation of OLP lesions. To establish this hypothesis, further studies are warranted at a molecular level with a larger sample size that would take into account the underlying disease mechanism and the role of curcumin in the healing of the same.<sup>22</sup>

Curcumin also shows antifungal effects which would thus prevent the development of candida infection over the OLP lesions which is a well-known side effect of topical corticosteroid therapy.

In the present study, only 2 of the 12 patients in the triamcinolone acetonide group reported complete pain relief at the second follow-up visit, whereas 7 patients reported a mild decrease in pain intensity. Two patients did not report any change in pain intensity while one patient reported an increase in symptoms. An overall significant improvement in the pain scores was found from baseline to second follow-up visit.<sup>22</sup>

The curcumin group showed 5 (33.33%) patients with complete relief of symptoms and 8 (53.33%) patients reported a reduction in the intensity of pain. 2 (13.33%) patients showed mild increase in the pain scores. The curcumin group showed marked improvement in the pain scores which was found to be highly statistically significant. However, on a comparison of the reduction in pain scores among the two groups, the difference was found to be statistically insignificant. This finding indicates that although both the groups showed improvement in the pain scores; However, better response was observed with curcumin.

In the triamcinolone acetonide group, complete resolution of the erythematous area was noted in 2 (16.67%) patients. 4 (33.33%) patients showed a significant decrease in the erythema scores from baseline to second follow-up visit, whereas 6 (50%) patients did not show any change in the severity of erythema. An overall improvement was found in the erythema scores in the control group patients from baseline to second follow-up visit.

When compared to the control group, in the curcumin group, 8 (53.33%) of the 15 patients exhibited complete resolution of erythema. A reduction in the erythema scores was observed in 5 (33.33%) patients while 2 (13.33%) patients did not show any change in the severity of erythema. There was an overall improvement in the erythema scores which was highly statistically significant .

Comparison of the mean erythema scores of the study and control groups showed that the improvement in severity of erythema was highly statistically significant in the study group.

The decrease in the erythema scores in the triamcinolone acetonide group was gradual, whereas the curcumin group exhibited a rapid decrease in erythema scores . This finding shows that curcumin played a better role in reducing the severity of erythema in OLP patients as compared to triamcinolone acetonide.

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In the triamcinolone acetonide group, of the 4 patients who had presented with ulceration at the baseline, 1 (25%) showed complete healing of the lesion while 3 (75%) did not show any change. There were two patients who had developed ulceration during the course of study. Of the 2 patients who had developed ulceration at the time of first follow-up, 1 patient showed complete healing, while 1 patient did not show any change. An overall non-significant difference was found in the ulceration scores in the control group patients from baseline to second follow-up visit.

In the curcumin group, of the 6 patients who had presented with ulceration at baseline, 2 patients (33.33%) showed complete healing of the lesion, and 4 patients (66.67%) showed a significant reduction in the ulcerated area at the second follow-up. One patient who had developed ulceration during the course of treatment also showed a decrease in the size of ulcer at second follow-up. An overall statistically significant reduction in the ulceration scores was found from baseline to second follow-up visit .

The ulceration scores in the triamcinolone acetonide group significantly increased from baseline to first follow-up visit, whereas curcumin group showed a constant decrease in the area of ulceration. However, the improvement in the size of ulcers was almost similar from the first follow-up to second follow-up visit in both the groups. The study group patients showed statistically significant reduction in the ulceration scores from baseline to second follow-up visit, whereas the control group did not show a significant reduction in the ulceration scores . However, comparison of the mean ulceration scores of the study and control groups yielded statistically insignificant results. This finding also suggests a better role of curcumin in the healing of ulcers as compared to triamcinolone acetonide.

Three (25%) of the 12 patients in the triamcinolone acetonide group developed superadded candida infection, whereas none (0%) in the curcumin group showed any side effect. This could be attributed to the antifungal effect of curcumin.

This observation also shows that curcumin fared better than triamcinolone acetonide in minimizing the side effects that OLP patients often develop during the course of treatment with triamcinolone acetonide.

## Conclusions

The following inferences can be drawn from this study:

1. Topical curcumin was found to be efficacious in controlling the signs and symptoms of OLP. All the parameters studied namely pain, erythema, and ulceration associated with OLP showed statistically significant improvement with topical curcumin therapy.<sup>19</sup>
2. Topical curcumin was found to be safe at the prescribed dose, i.e. 99% curcumin in gel base. No adverse effects were reported with the use of curcumin as compared to patients treated with triamcinolone acetonide 0.1%, who developed superadded candida infection as a side effect.<sup>22</sup>
3. The results of the present study indicate that topical curcumin could be used as an alternative to the standard corticosteroid therapy in the management of OLP and thus alleviate the need for drugs with more serious adversities including corticosteroids.

To conclude, favourable results were obtained with the use of topical curcumin in the management of OLP in this study. Nevertheless, further studies with larger sample size and evaluation of histological parameters pre and post-treatment, are warranted to establish the efficacy of topical curcumin in the management of OLP at a cellular level.

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