

## Effect of *Curcuma longa* and its derivatives, curcumin and curcuminoids on treatment of oral lichen planus: A systematic review of clinical evidence

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### ABSTRACT

Oral lichen planus (OLP) have become a serious problem for health system. *Curcuma longa* (*C. longa*) is recognized as a medicinal plant with numerous biological properties. Hence, this study was conducted to review the effect of *C. longa* and its derivatives, curcumin and curcuminoids in treatment of OLP. This study followed systematic review design. We used the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statements. To perform this study, we searched Scopus, PubMed/Medline, Web of Science and Google Scholar tools using appropriate keywords including “oral lichen planus”, ” turmeric”, ” *Curcuma longa*”, “curcumin” and “curcuminoids”. The search was limited to English articles. In this study, all studies published until May 2023 were used. Of 76 identified articles from searching, 16 studies including 10 randomized controlled trials (RCTs), two case-controls and one case report were included in this systematic review. The sample size in these studies was 570 patients. Furthermore, most of these studies was done in India, Iran and USA. Taking together, turmeric and its derivatives curcumin and curcuminoids play important role in treatment of OLP. Indeed, its antioxidant and anti-inflammatory characteristics are probably responsible for therapeutic effects of turmeric and its derivatives. However, further studies are recommended for explaining therapeutic mechanisms of these compounds.

**Keywords:** Oral Lichen Planus, *Curcuma longa*, Turmeric, Curcumin, Curcuminoids.

**Article type:** Review Article.

### INTRODUCTION

Oral lichen planus (OLP) is recognized as a chronic inflammatory disorder that lead to the involvement of the oral mucous membranes. OLP is characterized by abnormal keratinization of the mucous membranes inside the mouth (Alrashdan *et al.* 2016; Motahari *et al.* 2023; Manouchehri *et al.* 2023). Presence of reticular, erosive, or plaque-type lesions are the most common clinical features of OLP (Munde *et al.* 2013). The causes of OLP are still unknown, although several risk factors such as autoimmunity, using certain medications, infection, oral injuries, and allergy caused by dental materials play important roles in development of OLP (Nogueira *et al.* 2015). A considerable amount of literature has shown that female gender, smoking, alcohol and drug addiction are possible risk factors for OLP. Furthermore, a strong relationship between OLP and systemic diseases including diabetes mellitus, thyroid dysfunction, hepatitis C, and graft-versus-host disease has been reported in the literature (Abe *et al.* 2022). Globally, prevalence of OLP found as 1.01% (Nogueira *et al.* 2015). A primary concern of OLP is malignancy. However, it is estimated that 1.2% of patients with OLP represent malignancy (González-Moles *et al.* 2021). There are several pieces of evidence about the role of corticosteroids, photodynamic therapy, and their combination as therapeutic options for treatment of OLP (Sufiawati *et al.* 2022). Corticosteroids are the most potent anti-OLP agents known. The side effects

of corticosteroids have been extensively studied in recent years. Over the years, an enormous amount of studies have been carried out in an attempt to introduce alternative agents to reduce side effects caused by corticosteroids treatment (Han *et al.* 2017). Data from several studies have identified the role of inflammation and oxidative stress in development of OLP (Agha-Hosseini *et al.* 2012). Numerous studies have suggested that natural compounds represent therapeutic properties on various diseases (Ghuman *et al.* 2019). In recent years, there has been an increasing interest in the application of natural compounds such as medicinal plants and their active phytochemical constituents to treat OLP. An increased interest in the employment of turmeric as a therapeutic agent against various diseases has emerged in recent years (Amalraj *et al.* 2017). *Curcuma longa* (*C. longa*) also known as turmeric is an edible plant with medicinal properties. A key aspect of turmeric is its numerous therapeutic properties. Antioxidant, anti-microbial, anti-inflammatory, and anticancer are reported as its most widely-investigated therapeutic effects (Beiranvand & Alizadeh 2019; Amiri *et al.* 2023). Curcumin and curcuminoids are well known components of *C. longa*. Quite recently, considerable attention has been paid to plentiful biological effects of curcumin and curcuminoids (Kocaadam *et al.* 2017). Ample evidence exists to support the hypothesis that *C. longa*, curcumin and curcuminoids represent therapeutic effect on OLP (Chainani-Wu *et al.* 2012). The purpose of this systematic review paper is to review recent studies about the effects of turmeric and its derivatives, curcumin and curcuminoids in treatment of OLP.

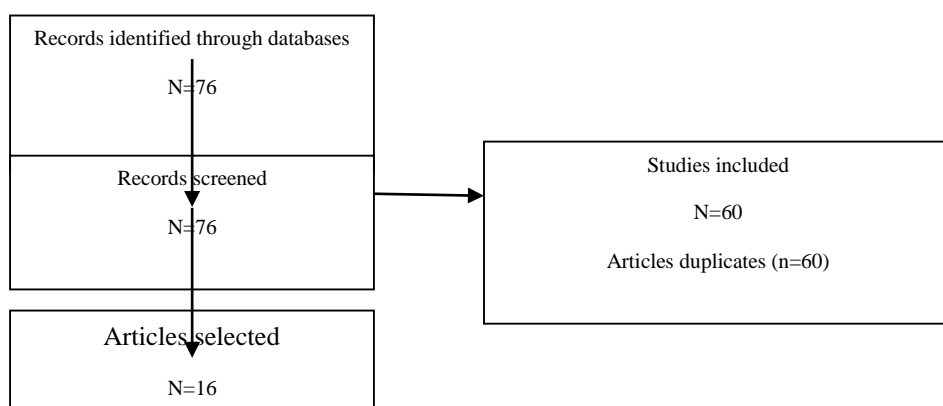
## MATERIALS AND METHODS

### Database and search strategies

This study followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statements. To conduct this systematic review, literature search was carried out through Scopus, PubMed/Medline, Web of Science and Google Scholar tools. First of all, appropriate keywords were selected as follow: “oral lichen planus”, “turmeric”, “*Curcuma longa*”, “curcumin” and “curcuminoids”. The systematic search was performed in English documents. In this study, all studies published until May 2023 were used. Our search was limited to studies with clinical evidence such as randomized clinical trial, Case-control, cohort studies, and case report (Fig. 1).

### Data extraction

We extracted data as follow: type of treatment, authors, publication year, study design, sample size, group design, gender of patients, dose of treatment, preparation method, form of administration, duration of follow up, and outcomes (Amiri *et al.* 2023).



**Fig. 1.** Flowchart of study selection.

## RESULTS

Our search leads to extraction of 76 articles from databases. After removing duplicates, the results of 16 studies were extracted. As shown in Table 1, a total of 570 patients were studied in these articles. We found that 10 studies were clinical trials (Chainani-Wu *et al.* 2012; Singh *et al.* 2013; Kia *et al.* 2015; Kia SJ *et al.* 2015; Bakhshi *et al.* 2020;

Khaitan *et al.* 2022; Ghobadi *et al.* 2022), two were case-controls (Nosratzahi *et al.* 2018; Naik *et al.* 2021) and one was case report (Prasad *et al.* 2014). The results showed that 7 studies were conducted in India (Singh *et al.* 2013; Thomas *et al.* 2017; Naik *et al.* 2019), 7 in Iran (Chainani-Wu *et al.* 2012; Kia SJ *et al.* 2015; Kia *et al.* 2015; Bakhshi *et al.* 2020; Khaitan *et al.* 2022; Ghobadi *et al.* 2022) and 2 in USA (Chainani-Wu *et al.* 2007). Our findings revealed that most of studies used turmeric, Curcumin and Curcuminoids in the form of oral (n = 9) and other studies administered treatment in the form of topical (n = 7).

## DISCUSSION

This study provides an overview of therapeutic effects of turmeric and its derivatives curcumin and curcuminoids on OLP. Numerous scholars found evidence that turmeric and its derivatives such as curcumin and curcuminoids play important roles in treatment of OLP (Singh *et al.* 2013; Bakhshi *et al.* 2020). The results of this systematic review revealed that *C. longa* as a promising medicinal plant in traditional medicine has a great therapeutic effect on OLP. There are several pieces of evidence about numerous therapeutic effects of *C. longa* on various diseases (Razavi *et al.* 2021; Tang *et al.* 2021; Jyotirmayee *et al.* 2022). It is generally accepted wisdom that *C. longa* is an effective agent for treatment of oral diseases (Umapathy *et al.* 2022). Several studies have examined the effect of *C. longa* in treatment of OLP (Singh *et al.* 2013). For instance, in a study conducted by Kia SJ *et al.* (2015) the results demonstrated that treatment with *C. longa* through oral administration of ethanolic extract of root can induce reduction in VAS score, pain and thongprasom score. The authors also observed that complete remission occurred in some of patients. In another similar study, Singh and colleagues reported that treatment of OLP patients with extract of turmeric in form of topical improved clinical symptoms such as burning sensation, redness, ulceration and decreased thongprasom sign score and VAS score (Singh *et al.* 2013). It has been accepted that OLP is an oral disease that is characterized by T-cell mediated inflammatory responses and imbalance between oxidative stress and endogenous antioxidants (Abe *et al.* 2022). *C. longa* is a medicinal plant with several biological properties such as antioxidant and anti-inflammatory effects. A growing body of evidence has demonstrated that *C. longa* is recognized as a rich source of active phytochemical constituents with potent antioxidant and anti-inflammatory effects including curcumin and curcuminoids (Sabir *et al.* 2020). It is possible that phytochemical compounds in *C. longa* neutralize inflammatory response and oxidative status in OLP patients through their antioxidant and anti-inflammatory effects (Khaitan *et al.* 2022). Curcumin is an active ingredient with numerous therapeutic effects. It has been suggested that curcumin could alleviate symptoms caused by OLP. Ghobadi *et al.* (2022) reported that oral capsule contain nanocurcumin could use for pain relief and decreasing appearance of lesions and burning sensation. Another similar study conducted by Khaitan T *et al.* (2022) revealed that using oral gel contain 10 mg g<sup>-1</sup> curcumin in form of topical paste treated OLP patients through reduction in pain, burning sensation score through VAS scoring. They also concluded that curcumin treatment decreased the size and severity of the lesions (Khaitan *et al.* 2022). Curcumin is a well-known antioxidant compound that is recognized by its free radical scavenging property. Since the imbalance between oxidative stress and antioxidants plays an important role in the occurrence of lesions caused by OLP, using antioxidants such as curcumin plays an important role in improving the damage caused by OLP (Meng *et al.* 2013). On the other hand, inflammation and inflammatory responses are the most effective mechanisms for the development of lesions in OLP patients. Therefore, the administration of anti-inflammatory compounds with natural origin such as curcumin works well in eliminating these lesions (Meng *et al.* 2013). Curcuminoids constitute an important part of the chemical compounds in *C. longa*. Demethoxycurcumin and bisdemethoxycurcumin are most studied curcuminoids present in *C. longa*. Numerous biological properties are the prominent features of these compounds (Amalraj *et al.* 2017). The application of demethoxycurcumin and bisdemethoxycurcumin in the treatment of oral diseases including OLP is one of the other functions of these compounds. In a randomized, placebo-controlled, double-blind clinical trial conducted by Chainani Wu *et al.* (2007) the results highlighted that oral consumption of curcuminoids including demethoxycurcumin and bisdemethoxycurcumin could treat OLP through decreasing erythema scores, ulceration scores, VAS scores, and NRS scores.

**Table 1.** Summary of available literature on the effect of turmeric, Curcumin and Curcuminoids in Treatment of OLP.

Treatm ent	Author s and publica tion year (Ref)	Co untry	Study Design	N	Group Design	Dosage	Preparat ion	Form of applic ation	Follow up	Key Findings
<i>C. longa</i>	Kia <i>et al.</i> (2015)	Iran	A Random ized, Controll ed Clinical Trial	50 patients (36 females and 14 males)	Group 1 (intervention group): received curcumin once a day (n = 25) Group 2 (control group): received 0.1% triamcinolone (n = 25)	5%	Ethanol ic extract of root	Oral	four weeks	Treatment with <i>C. longa</i> decreased VAS score, pain and Thongprasom score. Complete remission was also observed in some of patients.
	Singh <i>et al.</i> 2013	Indi a	A pilot study	10 patients	Group 1: Treatment group	-	Extract of turmeric	Local applica tion in the ointme nt form	3 months (1 <sup>st</sup> week, 2 <sup>nd</sup> week 4 <sup>th</sup> week, and 3 <sup>rd</sup> month)	Turmeric extract improved clinical symptoms of 9 patients completely. All of symptoms of OLP including burning sensation, redness, and ulceration were removed in the 3 <sup>rd</sup> month of treatment. Treatment with <i>C. longa</i> extract reduced thongprasom sign score (0-1) in patients after 3 months. Furthermore, VAS decreased in treated patients with turmeric after 3 months.

<b>Curcumin</b>	Khaitan <i>et al.</i> (2022)	India	A non-randomized controlled trial	40 patients (14 males and 26 females)	Group A (intervention group): patients who received curcumin oral gel and a multivitamin capsule containing zinc (n = 20) Group B (control group): patients who received multivitamin containing zinc only (n = 20)	Curenex oral gel containing 10 mg g <sup>-1</sup> curcumin	-	Topical paste	First follow-up: after 4 weeks Second follow-up: after 12 weeks	Curcumin played potential role in the treatment of OLP. Curcumin could reduce pain burning sensation score through VAS scoring. Treatment with curcumin significantly decreased REU score. Furthermore, the size and severity of the lesion decreased after 4 weeks and 12 weeks.
	Ghobadi <i>et al.</i> (2022)	Iran	A Single Blind Randomized Controlled Clinical Trial	28 patients (15 females and 13 males)	Group A (intervention group): patients who received nanocurcumin (n=29) Group B (placebo group): patients who received Prednisolone 10mg (n=28)	Nanocurcumin (80 mg)	Nano-Micellar Soft gel capsule	Oral capsule	1 month	Treatment with nanocurcumin decreased pain severity, appearance of lesions and burning.
	Naik <i>et al.</i> (2021)	India	-	68 patients	Group I: received Curenex oral gel was prescribed for 15 minutes, three times a day (n=34) Group II: received prednisone and curenex oral gel for 15 minutes, three times a day (n = 34)	-	Curenex oral gel	Topical application	First follow-up: after 10 days Second follow-up: after 20 days	Curcumin show effectiveness on treatment of OLP especially in combination to prednisone. Indeed, curcumin particularly in combination to prednisone decreased reticulation score, erosion score, and VAS score.

Kia <i>et al.</i> (2020)	Iran	A randomized double-blinded clinical trial	57 (48 females and 9 males)	Group A (trial group): patients who received nanocurcumin (n = 29) Group B (control group): patients who received Prednisolone 10 mg (n = 28)	Nanocurcumin 80mg	Nano-Micellar Soft gel capsule	Oral capsule	1 month	Administration of nanocurcumin decreased pain severity and burning sensation through VAS score. The results of Thongprasom scale scoring showed that treatment with nanocurcumin decreased OLP lesions.
Naik <i>et al.</i> (2020)	India	A Case Controlled Comparative Study	60 patients (29 females and 31 males)	Group 1: received curenext gel for 15 mins, three times a day (n=30) Group 2: received prednisone and curenext oral gel for 15 minutes, three times a day (n = 30)	-	Curenxt oral gel	Topical application	First follow-up: after 10 days Second follow-up: after 20 days	Combined treatment with curenext gel and prednisone play role in reduction of pain reticulation, and erosion caused by OLP.
Bakhshi <i>et al.</i> (2020)	Iran	Randomized Double-Blind Placebo Controlled Clinical Trial	31 patients (24 females and 7 males)	Group 1: received 0.1% triamcinolone mouth rinse + %1 nanocurcumin gel (n=14) Group 2: received 0.1% triamcinolone mouth rinse + placebo gel (n = 17)	1%	Nanomicelle	Topical application	1 month	Mean REU score significantly decreased in patients treated with nanocurcumin.
Nosratzahi <i>et al.</i> (2018)	Iran	Case-control study	40 patients (26 females and 14 males)	Group 1 (case group): received curcumin mucoadhesive paste thrice daily after meals (n = 20)	-	Mucoadhesive paste	Topical	3 months	Curcumin showed therapeutic effect on OLP via decreasing lesion size and pain severity.

					Group 2 (control group): received 0.1% beta-methasone local steroid lotion (n = 20)					
<i>Kia et al.</i> (2017)	Iran	A pilot clinical trial intervention study	10 patients (9 females and 1 males)	Treatment group received curcumin capsules 80 mg once a day	80 mg	Curcumin capsules	Oral capsule	4 weeks	After treatment with curcumin, pain and lesions were improved in most of the patients.	
<i>Thomas et al.</i> (2017)	India	An intervention study	75 patients (74.6% were females and 25.4% were males)	Group 1: received 0.1% triamcinolone acetonide Group 2: received curcumin three times a day Group 3: received curcumin six times a day	10 mg	Curenxt oral gel	oral gel	3 months	It has been observed that curcumin treatment play significant role in reduction in erythema, ulceration, and burning sensation in patients with OLP.	
<i>Amirchaghmaghi et al.</i> (2016)	Iran	A Randomized Controlled Trial	20 patients (13 females and 7 males)	Group 1 (intervention group): received curcumin (n = 12) Group 2 (control group): received placebo (n = 8)	2000 mg day <sup>-1</sup>	Tablets	Oral	Four weeks	Atrophic and erosive lesions improved following curcumin treatment. Furthermore, a significant reduction was observed in the VAS score and the Thongprasom score after treatment with curcumin.	
<i>Keshari et al.</i> (2015)	India	A randomized controlled-trial	27 patients (16 males and 11	Group 1 (study group): received curcumin ointment thrice daily (n = 15)	-	Commercially available	topical curcumin ointment	First follow-up: after 7 days	Treatment with curcumin ointment significantly decreased pain, erythema, and ulceration scores.	

				females )	Group 2 (control group): received triamcinolone acetonide 0.1% (n = 12)				Second follow-up: after 15 days	
	Prasad <i>et al.</i> (2014)	India	Case report	1 patient (22-year-old and male)	-	Patient received 500 mg two times a day for a month. After three weeks, patient received 500 mg once a day curcumin capsule for 2 weeks 250 mg curcumin for the last two weeks	Capsule	Oral	3 months	OLP response to curcumin completely.
Curcuminoid (demethoxycurcumin, bisdemethoxycurcumin)	Chainani Wu <i>et al.</i> (2012)	USA	A randomized double-blind, placebo-controlled	20 patients (13 females and 7 males)	Group 1 (intervention group): received curcuminoids (n=10) Group 2 (control group): received placebo (n = 10)	6000 mg day <sup>-1</sup>	Tablets	Oral	2 weeks	Curcuminoids play important role in improvement of OLP signs. Treatment with curcuminoids could decrease erythema and ulceration through decreasing NRS and MOMI scores.



			clinical trial							
	Chainan i Wu <i>et al.</i> (2007)	US A	A randomized, placebo-controlled, double-blind clinical trial	33	Group 1 (intervention group): received prednisone (60 mg day <sup>-1</sup> ) + curcuminoids (n = 16) Group 2 (control group): received prednisone (60 mg day <sup>-1</sup> ) + placebo (n = 17)	2000 mg day <sup>-1</sup>	Capsules	Oral	7 weeks	Administration of curcuminoids showed a better outcomes. Treatment with curcuminoids dropped erythema scores, ulceration scores, VAS scores, and NRS scores.

Note: VAS: Visual analogue scale; REU: reticulation/keratosis, erythema, and ulceration; NRS: Numerical Rating Scale; MOMI: Modified Oral Mucositis Index

It has been observed that curcuminoids exert their therapeutic effects on OLP through antioxidant and anti-inflammatory properties. A number of limitations may influence the results. Some of these limitations in our systematic review are as follows: the quality of included study and different patient populations.

## CONCLUSION

Based on the results of mentioned studies, treatment of OLP patients by turmeric and its derivatives curcumin and curcuminoids can reduce signs and symptoms caused by OLP including, severity of pain, the size and appearance of lesions and burning sensations. Furthermore, findings revealed that *C. longa* and its derivatives curcumin and curcuminoids in combination with corticosteroids such as prednisolone could exert better therapeutic function against OLP. Indeed, the numerous biological properties of turmeric and its derivatives curcumin and curcuminoids such as antioxidant and anti-inflammatory effects have raised this compound as an effective factor in the treatment of OLP. However, more studies with higher accuracy can confirm this issue.

## CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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