

An overview of effect of lycopene and curcumin in oral leukoplakia and oral submucous fibrosis

ABSTRACT

The purpose of the current article was to evaluate the recently published researches on the use of lycopene and curcumin in oral leukoplakia (OL) and oral submucous fibrosis (OSF). A comprehensive review of the current researches enveloping PubMed, Ovid, and Cochrane was made using the keywords [(Lycopene) OR (Curcumin) AND (Leukoplakia OR OL OR OSF OR OSMF OR OSF OR Submucous Fibrosis)]. We included only randomized control trials and in the English language. The search covers the data from 1994 to August 2020. Six studies (2 of OL and 4 of OSF) finally qualified are included in the study for the qualitative analysis of the result. Out of these six studies, four were found having high risk, one with unclear risk and one with low risk. Only one study came out as finally suitable for the quantitative analysis of the result. A total of 90 participants were included in this review, with a mean age of 32 with a range of 17–60 years. Out of 90 participants, 70 were male and 20 were female. It is evident from the result of this study that the use of oral curcumin and lycopene has significant improvement in the mouth opening, burning sensation, and cheek flexibility in comparison to the placebo. The use of oral curcumin and lycopene appears to be effective and safe in the treatment of OL and OSF but to read the result of use of oral curcumin and lycopene in OL caution should be taken because of bias.

Keywords: Curcumin, lycopene, oral leukoplakia, oral mucosal lesions, oral mucositis, oral potentially malignant disorders, oral submucous fibrosis, oral ulcers, premalignant lesion

INTRODUCTION

Oral potentially malignant disorders (OPMDs) are the lesions of the oral cavity having higher chances of transformation into the malignancy in comparison to the normal mucosa. Oral leukoplakia (OL) is the most common OPMD of the oral cavity usually associated with tobacco chewing and smoking. Malignant potential of OL was hinted by Sugar and Banoczy in 1957.^[1]

Oral submucous fibrosis (OSF) is also one of the most prominent OPMDs. According to Pindborg and Sirsat 1966, OSF, a chronic condition that affect oral cavity and occasionally the pharynx. Sometimes foreshadowed or combine with the evolution of vesicle, it is invariably accompanying the juxta-epithelial inflammatory reaction succeeded by fibroelastic transformation of the lamina propria with epithelial atrophy that causing the rigidity of the oral mucosa. OSF is commonly correlated with areca nut chewing. The malignant transformation rate of OSF is ranging from 3% to 19%.^[2,3] Tobacco smoke contains

carcinogenic free radical, nitric oxide. Areca nut also contains carcinogenic product such as arecoline, an alkaloids, seems to be the primary etiologic factors.

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Received: 19 February 2021, **Revised:** 29 March 2021, **Accepted:** 26 April 2021, **Published:** 13 December 2021

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How to cite this article: Ahmad T, Khan I, Rizvi MM, Saalim M, Manzoor N, Sultana A. An overview of effect of lycopene and curcumin in oral leukoplakia and oral submucous fibrosis. *Natl J Maxillofac Surg* 2021;12:316-23.

Access this article online	
Website: www.njms.in	Quick Response Code 
DOI: 10.4103/njms.njms_324_21	

The treatment of both the diseases should be focus on the free radical scavenging property of the therapeutic agent. Hence, that these agents may prevent the formation, remission, or conversion of OPMDs into the malignancy. There is no treatment reported in the literature that prevents the progression of the OPMDs into malignancy. Surgical excision of leukoplakia has significant morbidity with a relapse rate of 26%–35%.^[4,5] Although chemoprevention by retinoids has a clinical response rate of up to 67%,^[6,7] high toxicities and relapse following cessation of therapy have prevented its clinical use.^[8] All subsequent chemoprevention trials, with various agents so far, have been ineffective.^[9] The main problem with other chemoprevention is the recurrence of the lesion after cessation of the therapy and it is different for different agents as reported 50% with topical bleomycin^[10] 54%–64% with Vitamin A and beta carotene^[11] and 56% with retinoid.^[7]

Various treatments can be categorized as invasive and conservative have been tried to improve sign and symptoms of OSF. Invasive treatments included intralesional injections of steroids, fibrinolytic agents, placentex, and surgical elimination of fibrous bands. Invasive treatments are traumatic and provided variable and unsatisfactory results.^[12]

Conservative treatments included antioxidants and iron supplements. Conservative treatment agents are safe, painless, giving promising results, and proven to be easily acceptable.^[13]

In the past decade, there has been a growing interest in natural remedies for the management of many diseases including OL and OSF. These have the advantage of antioxidant properties, safety, tolerability, low toxicity, and general acceptance by the patients. Lycopene is an antioxidant primarily found in tomatoes. It is an acyclic isomer of β -carotene. It has been claimed by many authors that lycopene is effective in relieving the symptoms of OL and OSF.^[14,15] Curcumin is a yellow color plant derivative obtained from the root of *Curcuma longa* (Turmeric) which belongs to the ginger family.^[16] Anti-inflammatory, antifibrotic, antioxidant, and anticarcinogenic property of curcumin made it useful for the medicinal purpose.^[17,18] Clinicians show a great interest in recent years for the use of curcumin in OL, OSF, and other OPMDs.^[17,19-21]

The literature is devoid of data on the effectiveness of interventional management of OL and OSF. Many medicinal agents have been tried for the treatment of OL and OSF.

The main target of the treatment should be improvement in oral function and prevention of malignant transformation of

OL and OSF. OL and OSF are more prevalent in population with low socioeconomic status may be because of stress or unawareness these people develops habit and then disease. Considering lower socioeconomic status, the treatment should be cost-effective for the patients. As OSMF is chronic and progressive in nature, treatment compliance toward aggressive therapies is unsatisfactory. Bio-nutraceuticals with an antioxidant property such as curcumin and carotenoids have been the emerging treatment modality with almost no side effects. Such potential therapeutic agents, therefore, need to be further researched upon extensively. Taking above considerations into the account, we have decided to critically appraised literature on curcumin and lycopene in OL and OSF.

METHODOLOGY

This study conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis.

Eligibility criteria

Inclusion criteria

- Randomized control trial (RCT) on the use of lycopene in OL
- RCT on the use of curcumin in OL
- RCT on the use of lycopene in OSF
- RCT on the use of curcumin in OSF
- RCTs should include histopathologically proven OL and OSF participants and only in the English language.

Exclusion criteria

Case report, case series, prospective observational studies, case–control studies, systematic reviews, meta-analysis, letter to editor, and non-English research were excluded from the study.

Sources of information and search

The persisting published work in PubMed, Ovid, and Cochrane was explored by using the keywords [(Lycopene) OR (Curcumin) AND (Leukoplakia OR OL OR OSF OR OSMF OR OSF OR Submucous Fibrosis)]. We had consider the work with randomized control trials in the English language only. The exploration screens the data from 1994 to August 2020.

Selection of studies

An exhaustive survey of every single article for titles and abstracts by the two authors (MS and TA) from identified databases was done. The authors remained totally oblivious of the individual decision regarding all the articles. Any conflict that arose after primary search was resolved by their collective opinion regarding the issue. Opinion of the third author (IK) was sought in case the conflict could not get sorted out by the two authors consensually.

After the screening of the articles was done on the basis of titles and abstracts, full text of all the selected articles was narrated for the final selection as per the eligibility criteria and subsequently assessed for quality.

Data collection and data items

Data were extracted by two authors from the studies that were finally included using a specially designed form. Characteristics of trial participants, interventions, and outcomes for the included trials were present in the tables.

Quality of assessment

Both the authors (MS and TS) independently and thoroughly assessed for the risk of any bias in each the study included. Controversies for any issues were settled by unanimous decision and the third author (IK) was reached out for final agreement in case the two failed to arrive a common point.

Higgins *et al.* 2011 approach was opted for assessing risk of bias. This particular approach was used for assessing risk of bias of studies in Cochrane reviews and addresses the following seven specific domains:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias.

The tool has two main components. Each of the seven domains in the tool includes one or more specific entries in a “Risk of bias” table. The first part of the tool within each entry has a comprehensive description about what was reported to have happened in the study to support any inference about risk of bias. The second part of the tool provides with a discernment related to the risk of bias for that entry- “low risk,” “high risk” or “unclear risk.” After taking into account, the additional information provided by trial authors, the risk of bias in included studies were summarized and enlisted as follows.

- Low risk of bias: low risk of bias for all key domains
- Unclear risk of bias: unclear risk of bias for one or more key domains
- High risk of bias: high risk of bias for one or more key domains.

RESULTS

A total of 52 studies were found relevant on searching. All of those were screened for title and abstract after which

14 studies were recorded. Four additional records were added from references, and therefore, a total of 18 full text studies were assessed for eligibility. Out of 18 recorded studies, 12 records were not fulfilling inclusion criteria and therefore were excluded. Reasons for exclusion are depicted in Figure 1 and Table 1. Six studies finally qualified are included in the study for the qualitative analysis of the result. Out of these six studies, four were found having high risk, one with unclear risk and one with low risk. Only one study came out as finally suitable for the quantitative analysis of the result.

Leukoplakia

Out of the six included studies, two studies were found on leukoplakia, one with unclear risk and one with high risk. Kuriakose *et al.* 2016 reported significant better response with oral administration of 3.6 gram/day curcumin (both clinical and histological response) when compared to the placebo. Singh *et al.* 2004 reported that Lycopene 8 mg/day and 4 mg/day shows significant resolution of the leukoplakic lesion when compared to the placebo arm over 3 months treatment.

Oral submucous fibrosis

Out of total six, four studies were found with OSF, three were with high risk and one with low risk. Data of low risk study were taken for the quantitative synthesis of the result [Table 2]. A total of 90 participants were included with a mean age of 32 years (age range 17–60). Out of 90 participants, 70 were male and 20 were female. Patients were divided in three parallel arms of 30 participants each. Participants in the first group received 600 mg Curcumin daily in two divided doses while in the second group, participants were given Lycopene capsules (8 mg) twice daily and third group received placebo once every day. The duration of the treatment was 6 months, and the follow-up period was 9 months. After 6 months, the treatment was stopped. Recurrence was not commented in the included study but there was no malignant transformation during follow-up. Efficacy assessment of the test drugs/placebo was made on the parameters of mouth opening, burning sensation, and cheek flexibility. The overall statistically significant improvement in these parameters was seen with curcumin and lycopene arms when compared to the placebo arm, whereas no significant difference was found between curcumin and lycopene group.

Random sequence generation bias (selection bias) found to be the most common bias in the excluded study followed by allocation concealment, performance, detection, and attrition bias [Figure 2].

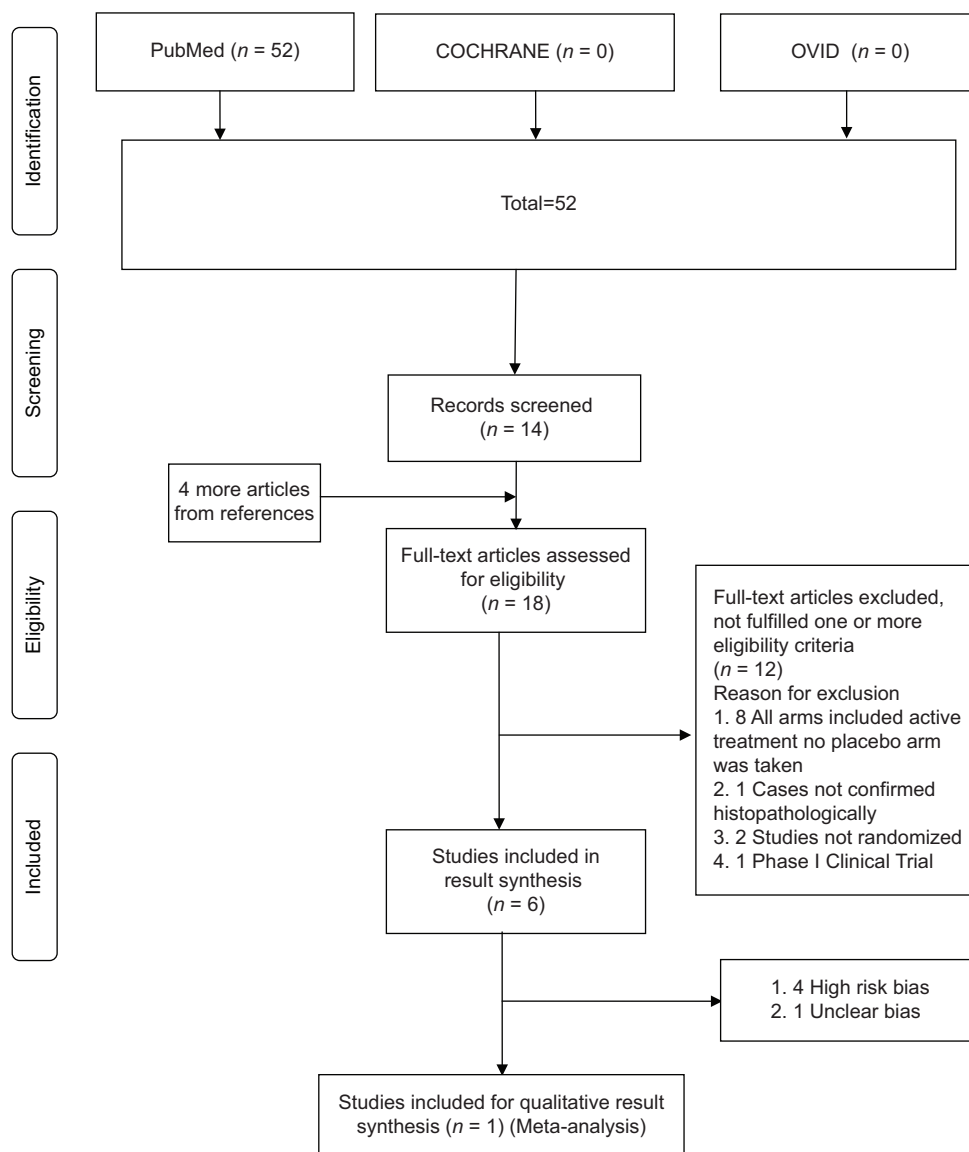


Figure 1: Flow chart diagram

DISCUSSION

Leukoplakia

Rigorous and conscious attempts are being continuously made to develop safe and effective chemopreventive agent for the treatment of leukoplakia. First description for the use of chemopreventive agents for leukoplakia dates back around 25 years ago.^[7] Due to frequent relapse (with topical bleomycin, Vitamin A, beta carotene, and retinoid) and adverse effects coupled with inconsistent effects of these therapeutic agents has caused these drugs to fall out of favors and has led to the necessity of a promising option with adequate safety profile. Vitamin A is the most investigated chemopreventive agent for leukoplakia.^[8] Out of the total six RCTs included, only two RCTs were found on leukoplakia. One study was based on the use of curcumin and the other

was done with lycopene.^[15,30] Both studies were included for the qualitative synthesis of the results. Out of two studies, one study of Singh *et al.*^[15] revealed significant difference between dose-dependent lycopene arms when compared to the placebo group. Both arm of lycopene (8mg/day and 4 mg/day) showed same clinical significance in terms of resolution of the leukoplakic lesions when compared to the placebo group. The arm which was given 8 mg/day had highly significant histological improvement (reversal of dysplastic changes) in comparison to low dose arm as well as placebo; however, the arm (4 mg/day) shows significant histological improvement only in comparison with placebo. It signifies the histological improvement to be dose dependent. There is a sequence of normal tissue to transform into the malignancy through OPMDs. As in the study of Singh *et al.*,^[15] it was found that lycopene helps reversing the dysplastic changes

Table 1: Excluded studies with reason

Authors name and year	Title of the study	Reason for exclusion
Lanjekar <i>et al.</i> , 2020 ^[22]	Comparison of efficacy of topical curcumin gel with triamcinolone-hyaluronidase gel individually and in combination in the treatment of oral submucous fibrosis	All the three arms of the study employed active treatments, i.e. no placebo (or no treatment) group was included in the study
Johny J <i>et al.</i> , 2020 ^[23]	Comparison of efficacy of lycopene and lycopene-hyaluronidase combination in the treatment of oral submucous fibrosis	The study was not randomized
Arakeri <i>et al.</i> , 2020 ^[24]	Long-term effectiveness of lycopene in the management of OSMF: A 3 years follow-up study	Subjects included in the study were clinically diagnosed
Tp <i>et al.</i> , 2019 ^[25]	Evaluation of therapeutic efficacy of different treatment modalities in oral submucous fibrosis: A comparative study	All the three arms of the study employed active treatments, i.e. no placebo (or no treatment) group was included in the study
Rai <i>et al.</i> , 2019 ^[26]	Comparative evaluation of curcumin and antioxidants in the management of oral submucous fibrosis	All the three arms of the study employed active treatments, i.e. no placebo (or no treatment) group was included in the study
Saran <i>et al.</i> , 2018 ^[21]	A comparative study to evaluate the efficacy of lycopene and curcumin in oral submucous fibrosis patients: A randomized clinical trial	Both arms of the study employed active treatments, i.e. no placebo (or no treatment) group was included in the study
Kopuri <i>et al.</i> , 2016 ^[20]	A comparative study of the clinical efficacy of lycopene and curcumin in the treatment of oral submucous fibrosis using ultrasonography	Both arms of the study employed active treatments, i.e. no placebo (or no treatment) group was included in the study
Hazarey <i>et al.</i> , 2015 ^[16]	Efficacy of curcumin in the treatment for oral submucous fibrosis-a randomized clinical trial	The study was not randomized, and both arms of the study employed active treatments, i.e. no placebo (or no treatment) group was included in the study
Yadav <i>et al.</i> , 2014 ^[27]	Comparison of curcumin with intralesional steroid injections in oral submucous fibrosis-a randomized, open-label interventional study	Both arms of the study employed active treatments, i.e. no placebo (or no treatment) group was included in the study
Rai <i>et al.</i> , 2010 ^[19]	Possible action mechanism for curcumin in precancerous lesions based on serum and salivary markers of oxidative stress	The study was not randomised
Deepa <i>et al.</i> , 2010 ^[28]	Comparative study of the efficacy of curcumin and turmeric oil as chemopreventive agents in oral submucous fibrosis: A clinical and histopathological evaluation	All the three arms of the study employed active treatments, i.e. no placebo (or no treatment) group was included in the study
Cheng <i>et al.</i> , 2001 ^[29]	Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or premalignant lesions	Phase I clinical trial

OSMF: Oral submucous fibrosis

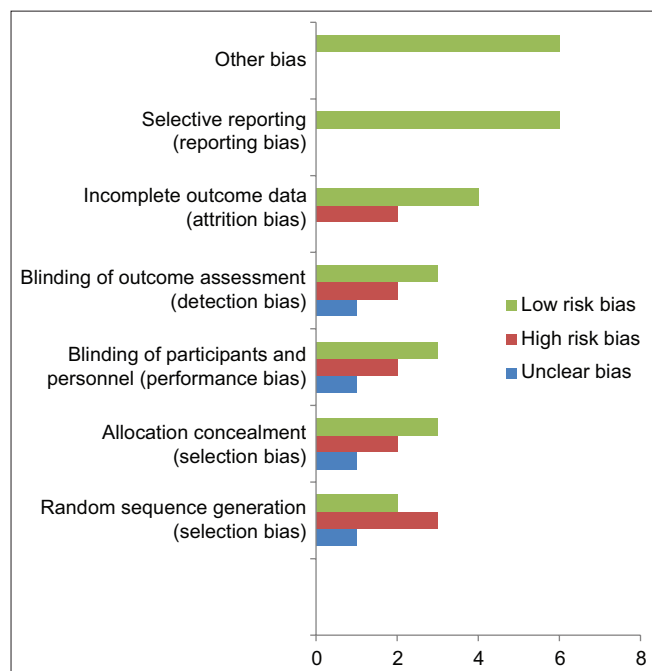


Figure 2: Showing individual Bias wise distribution of the studies

hence potentially prevents carcinogenesis. Bhuvaneshwari *et al.*^[34] checked the efficacy of lycopene in the buccal pouch

carcinogenesis in the hamster and found that lycopene is effective in the prevention of neoplasia.

In second study of Kuriakose *et al.*, it was found that oral administration of curcumin (3.6 g/day) gave both clinical and histopathological response in leukoplakia when compared to the placebo arm. In this study, investigators found very low relapse rate in leukoplakic lesions after the use of curcumin (7.7 and 7.3% for clinical and histopathological, respectively) when compared to the considerable relapse (50%–64%) with various other chemopreventive agents.^[7,10,11] Subgroup analysis shows that curcumin has significantly enhanced improvement rate in smokeless tobacco users, alcohol users, and in those who continuously uses tobacco or alcohol during the trial when compared to the placebo. This result strengthens the claims of the previous hypothesis that curcumin prevents tobacco or alcohol induced carcinogenesis by altering the nuclear factor-kappa B cyclooxygenase-2 and AKT/mammalian target of rapamycin pathway.^[35] The investigators of this study further appreciated that curcumin results noticeable improvement in the initial 6 months followed by minimal effects. However, further studies on more comprehensive protocols are required to know the actual mechanism of resistance after 6 months to

yield sustained and optimal efficacy of curcumin. The result of this review clearly suggests that lycopene and curcumin may be used as effective and safe chemopreventive agents for oral leukoplakia. Results are required to be read cautiously because both studies carrying the risk of bias and have not taken for the quantitative synthesis of the result because of the high risk and unclear risk of bias.

Oral submucous fibrosis

Four studies of OSF finally surveyed in this review out of which only one study of Piyush *et al.*^[33] could have been included for the quantitative synthesis because of low risk bias [Table 3].

A total of 90 participants were included in this review, with a mean age of 32 years with a range of 17–60 years which is in firmness with the recent study of Saalim *et al.*^[36] Out of 90 participants, 70 were male and 20 were female with a male to female ratio of 3.5:1. This ratio is lower than that found (6.07:1) by Saalim *et al.*^[36] OSF is has predominance in male as this may be attributed to the fact that males seek medical care earlier than females due to social reasons because and since male population is still the main breadwinner in countries in India which further makes them more exposed and vulnerable to community influences such as various addictions including tobacco chewing in

comparison to the females. Many treatments have been tried to relieve-related symptoms and for enhanced function status in OSF patients ranging from conservative treatments such as steroids, hyaluronidase, placental extracts, collagenase and nutrients supplements to surgical excision of fibrotic bands, and grafting and bilateral coranoidectomy. The main objective of the treatment of OSF remains to downscale the severity in terms of morbidity and to intercept its malignant transformation. In the study included for the quantitative synthesis, OSF patients were not classified into the groups on the basis of mouth opening. OSMF patients were included in RCT with mouth opening ranging from 15–35 mm and were randomized into three parallel arms. As in our study, we have found that we have all the grades of OSF in the range of 15–35 mm of maximum mouth opening. So here we can state that lycopene and curcumin may be useful in all the patients of OSF irrespective of the grades, but it is should be confirmed by a large sample size study and with the division of the patients in grades of the OSF. This is a suggestion for future studies to be done on the use of these medicines in OSF to clearly divide the patients into groups and to see any difference in response for these medicines or not.

It is evident from the result of this study that the use of oral curcumin 300 mg twice daily has significant improvement in

Table 2: Study included for quantitative synthesis of result

Author	Study groups (number of participants)	Age mean/ range	Gender	Duration (months)	Follow-up months	Variables evaluated
Piyush <i>et al.</i> (India) ^[16]	Group A: Curcumin tablet 300 mg twice daily (n=30) Group B: Lycopene cap 8 mg twice daily (n=30) Group C: Placebo cap (n=30)	32 (17-60)	M: 70 F: 20	6	3	Burning sensation, mouth opening, cheek flexibility, tongueprotrusion
Intergroup comparison of groups						
		P value for difference VAS		P value for difference MO		P value for difference CF
Group A and Group B		0.82		0.56		0.17
Group A and Group C		0.0001		0.023		0.03
Group B and Group C		0.0001		0.003		0.0001

VAS: Visual Analog Scale, MO: Mouth opening, CF: Cheek flexibility

Table 3: Quality assessment of included studies

Lesion	Included studies	Item for risk of bias							Overall bias
		Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	
OL	Singh <i>et al.</i> , 2004 ^[15]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear
	Kuriakose <i>et al.</i> , 2016 ^[30]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High
OSF	Kumar <i>et al.</i> , 2007 ^[31]	High risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High
	Karemore and Motwani 2012 ^[13]	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	High
	Goel and Ahmed 2015 ^[32]	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	High
	Piyush <i>et al.</i> , 2019 ^[33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low

OL: Oral leukoplakia, OSF: Oral submucous fibrosis

the mouth opening, burning sensation, and cheek flexibility in comparison to the placebo. This result is also found to be in firmness with the result of previous study of Deepa *et al.*^[30] where the author used 250 mg curcumin capsule in OSF subjects and observed considerable clinical improvement. This clinical efficacy with curcumin can be explained due to its antifibrotic, anti-inflammatory, antioxidant, and anticarcinogenic^[17,18] activities. These properties render curcumin promising in the management of OSF. Lycopene is a known powerful antioxidant and its role as an antioxidant is well established and studied through various mechanisms. Lycopene inhibits carcinogen, induces angiogenesis, and favors cell cycle growth. Lycopene acts as an anti-inflammatory agent and has also been documented by increased number of target lymphocytes and it also inhibits fibrosis in rats.^[16] These properties of lycopene make it helpful in the treatment of OSF. In this review as well, use of oral lycopene 8 mg twice daily has shown significant improvement in the mouth opening, burning sensation, and cheek flexibility parameters when compared to the placebo. This result is in accordance with the result of previous studies of Kumar *et al.*^[31] and Goel and Ahmed.^[32]

Other medicinal treatment has limited effect in the OSF patents and leukoplakia as well. As per literature, many moderate and advanced OSF patients with mouth opening less than 30 mm have shown less effect with chemoprevention with lycopene or curcumin, but in our result, we have found that the patients of OSF with mouth opening ranging from 15 to 35 mm those had taken lycopene or curcumin had significant improvement in burning, mouth opening, and cheek flexibility. This review suggested that lycopene and curcumin may be efficacious for all the patients of OSF.

As we know that OSMF has a list of etiological factors among them one is autoimmunity. By taking autoimmunity into consideration, the response of the individuals with the use of lycopene and curcumin in OSF may be varies for the same treatment.

As far as the nature of bias is concerned, random sequence generation bias was found to be the most common bias in the included study for the qualitative synthesis of the result. Hence, it is suggested to make attempts to nullify these bias in the future RCT's by conducting in accordance with the proper CONSORT guidelines. Large sample size and long-duration follow-up to reach on firm conclusion will also help in minimizing such type of biases.

CONCLUSION

It can therefore be inferred and advocated that the use of oral curcumin and lycopene appears to be effective, safe,

and economical options in the treatment of OL and OSF; however, great caution need to be employed while drawing any conclusion from results regarding oral use of curcumin to avoid biases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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