Review Article

Turmeric in the management of oral submucous fibrosis: A systematic review and meta-analysis

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ABSTRACT

Turmeric exhibits a big promise as a therapeutic agent in the management of oral submucous fibrosis (OSMF). The primary aim of our study is to synthesize the evidence of the use of turmeric/curcumin in the management of OSMF. The secondary goal of this study is to assess the limitations of previous studies to identify gaps in evidence for future research and give an evidence-based recommendation regarding the usage of turmeric/curcumin for OSMF patients and outline the direction of research. A comprehensive search of PubMed, Web of Science, Scopus, Cochrane Library database, Google Scholar, clinical trial registries, and hand searching was conducted from inception until December 2018. This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (guidelines). In this review, 11 articles were selected for qualitative analysis and 3 out of 11 were selected for meta-analysis. Of these 11 studies, involving 428 patients, 7 were randomized control trials (RCTs), 1 was a nonrandomized trial, and 3 were observational studies. Turmeric was found to be effective in reducing signs and symptoms of OSMF in all 11 studies. All the studies included in this review have reported improvement in mouth opening after treatment with turmeric formulations. This could also be concluded from the meta-analysis of three RCTs. Similar improvement in tongue protrusion, burning sensation, and cheek flexibility has been reported. The lack of reliable evidence for the effectiveness of turmeric for the management of OSMF is illustrated by the paucity and poor methodological quality of studies retrieved for this review. We recommend that RCTs are needed using larger sample size with longer duration follow-up with special attention to the recurrence of signs and symptoms.

KEY WORDS: Curcumin, meta-analysis, oral submucous fibrosis, systematic review, turmeric

INTRODUCTION

Oral submucous fibrosis (OSMF) is a potentially malignant disorder of oral cavity primarily caused by areca nut chewing.[1] OSMF occurs predominantly in people of South Asia.[2] It is a major health issue affecting an estimated 14 million Indian population in 2010 and having a prevalence rate of 6.42 per 1000.[3,4] Although no recent data are available, the prevalence of OSMF in Taiwan was reported as 17.6%.[5] Younger population is more affected.[4] Studies from Gujarat and Allahabad have reported as high as 85% and 46% of the OSMF patients belonging to the third decade of life.[6,7] The malignant transformation rate of OSMF ranges from 2.3% to 7.6%.[8,9] More recently, two large cohort studies from Taiwan reported 9.13% and 10% malignant transformation rates for OSMF.[10,11] Oral cancer is 19.1 times more likely to occur in OSMF patients.[12]

OSMF is characterized by burning sensation on having hot and spicy food and stiffness and blanching of the oral mucosa leading to restricted mouth opening. The standard of care for OSMF encompasses cessation of habit, drugs to alleviate symptoms of burning sensation, nutritional supplement (multivitamins), surgery, and physiotherapy for improvement in mouth opening along with oral cancer surveillance.[13] Medicinal therapy like corticosteroids, antioxidants, peripheral vasodilators; surgical therapy including lasers and physiotherapy have been previously used for the management of OSMF, but the treatment remains empirical and symptomatic.[14] It is a challenge for the dentist who manages OSMF since signs and symptoms of the disease have a tendency to advance

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regardless of treatment modality. Pathological changes, i.e., tissue-level changes, remain permanent even after cessation of the habit. The analytical framework of OSMF is detailed in Figure 1.

Several complementary and alternative medicines have been evaluated in OSMF patients such as turmeric,[15] *Aloe vera*,[16] spirulina,[17,18] allicin,[19] and papain.[20] Antioxidants such as lycopene obtained from tomato extract and herbal antioxidants such as oxitard have been tried with variable response.[21,22]

Turmeric – the Indian golden spice – has been widely researched for its pharmaceutical properties. Turmeric has been widely used in India since ancient times and is well accepted by the masses. Turmeric, or its active ingredient curcumin, exhibits a big promise as a therapeutic agent in the management of OSMF due to its antioxidant, anti-inflammatory, anticarcinogenic activity, chemopreventive, chemotherapeutic activity, and anti-fibrotic potential. Zhang *et al*. in their *in vitro* study demonstrated anti-fibrotic activity of curcumin in transforming growth factor-β1-induced myofibroblasts.[23] It has fibrinolytic action in liver and lung fibrosis and is used as a fibrinolytic agent in Chinese medicine.[24] Curcumin also suppresses bleomycin-induced pulmonary fibrosis in rats.[25]

Turmeric was first used for OSMF patients by Hastak *et al*. in 1998.[26] Since then, several studies have evaluated the role of turmeric or curcumin in the management of OSMF. Although all these studies have supported the effectiveness of turmeric/curcumin in OSMF treatment, the research is not focused. Evidence from these scattered studies with varying study design has not been synthesized previously. There is ambiguity in research design, small study sample size, variability in different forms of turmeric administration, and duration of treatment. Therefore, there is a need to review all the studies together and generate evidence for the use of turmeric in the management of OSMF in clinical settings. The primary aim of our study is to synthesize the evidence of the use of turmeric/curcumin in the management of OSMF. The secondary goal of this study is to assess the limitations of previous studies to identify gaps in evidence for future research and give an evidence-based recommendation regarding the usage of turmeric/curcumin for OSMF patients and outline the direction of research.

Research question

The PICO principle was considered for framing the research question of this study.[27]

- P: Patients of OSMF, all ages, both sexes, all ethnicities, and all nationalities
- I: Turmeric or curcumin in topical, oral, or systemic form
- C: Placebo, or no intervention, or any medical intervention
- O: Clinical, biochemical, and histopathological.

On the basis of PICO, we reframed the question as: "Among OSMF patients, compared with all other medicinal approaches, what is the effectiveness of turmeric for relief of OSMF signs and symptoms?"

METHODOLOGY

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (guidelines).[27] The corresponding checklist is provided as Supplementary 1. The review protocol has been registered at PROSPERO (Registration number – PROSPERO 2017 CRD42017081651. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID = CRD42017081651).

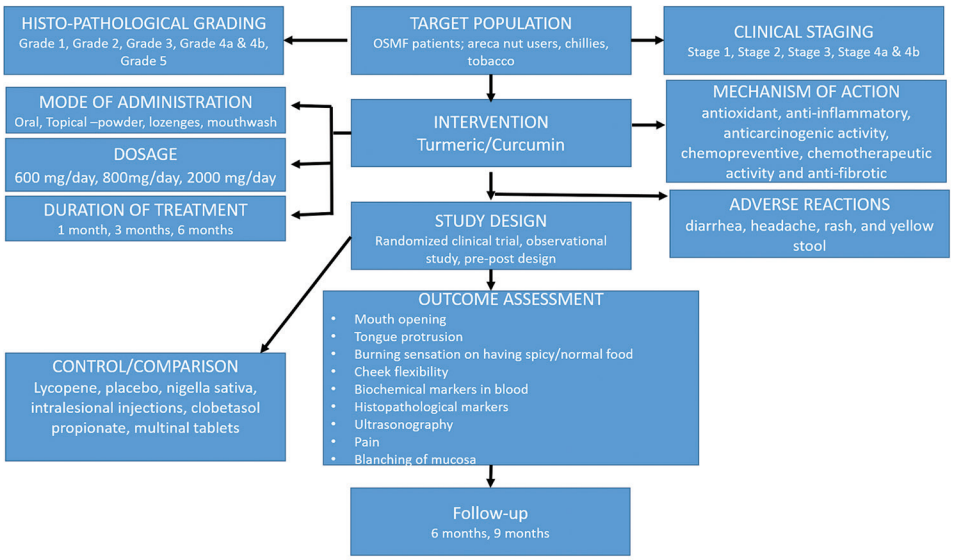

Figure 1: Analytical framework of oral submucous fibrosis

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Search strategy

A comprehensive search of electronic databases – PubMed, Web of Science, Scopus, and Cochrane Library – was conducted from inception until December 2018. The clinical trial registries such as CTRI and ISRCTN were searched. The key words used were (oral submucous fibrosis or OSMF or OSF or submucous fibrosis) AND (turmeric or curcumin). No language restrictions were placed. The search was augmented using the "related articles" link to articles recovered with PubMed. In addition, the reference lists of the selected studies and reviews were scanned manually. The Google Scholar and Google Search engines were also used to do an all-inclusive search of the World Wide Web.

Two investigators independently evaluated the results by reviewing titles and abstracts. Articles in English language which reported the use of turmeric/curcumin in OSMF patients (*in vivo* studies on humans) were included in this review. No articles were found in any other language. Animal studies, studies done on cell lines, or studies that did not state/discuss clinical outcome assessment were excluded [Figure 2]. In case of disagreement between the investigators, full-length articles were reviewed and discussed for the suitability of this review by three investigators.

Data extraction

The following parameters were extracted from each of the selected studies: (1) reference list including first author and year of publication; (2) study design; (3) number, age, and gender of participants included in the study; (4) baseline characteristics of the study population – OSMF staging, adverse habits, and dietary deficiencies; (5) clinical sites of involvement; (6) mode of administration; (7) treatment dosage; (8) treatment duration; (9) use of other treatment modalities; (10) objective improvement in signs – interincisal mouth opening, tongue protrusion, and cheek flexibility; (11) subjective improvement in symptoms – burning sensation; (12) biochemical/histopathological or any other outcome assessment; (13) time period for outcome assessment; (14) follow-up period; (15) subgroup analysis based on severity; (16) data on habit cessation; (17) prognostic information; and (18) adverse reaction.

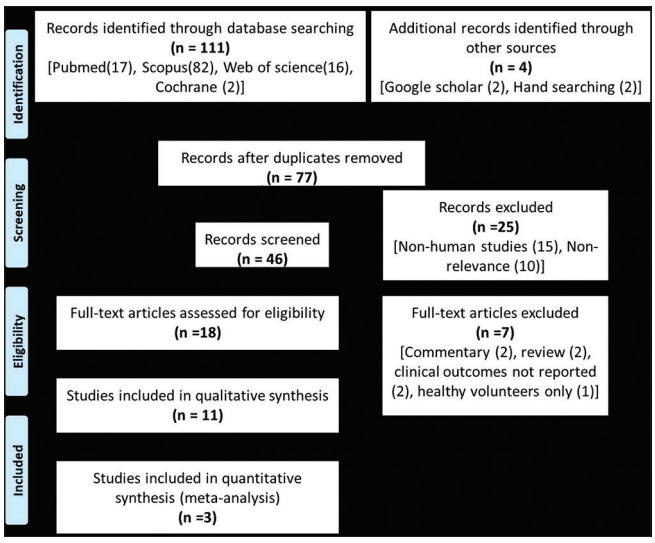

Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart showing the result of the search strategy

Statistical analysis

For the purpose of qualitative analysis, all prospective study designs – randomized, nonrandomized trials and observational studies – were included. For meta-analysis, only randomized control trials (RCTs) were considered.

RESULTS

Literature search

The search strategy resulted in the retrieval of 111 articles from the databases. In addition, 393 results were obtained from Google Scholar which were screened for relevance and two articles were selected for closed review. The search in ISRCTN yielded two results which were excluded on the basis of nonrelevance. Several studies were found at CTRI (CTRI/2015/07/006001, CTRI/2017/09/009674, CTRI/2017/09/009671, CTRI/2017/09/009666, and CTRI/2017/01/007732). Of these, one published article has been included in the review. A total of 77 articles were obtained after removing duplicates and 18 underwent full-text screening. The rest were excluded for reasons given in Figure 2.

Characteristics of studies included

A total of 11 studies, spanning over 20 years, involving 428 patients, were included in this review. All the studies have been published in India.[28-35] Of these, 7 are RCTs,[28-34] 1 is a nonrandomized trial,[26] and 3 were observational studies.[35-37] The age of patients ranged between 15 and 60 years. All studies reported a strong male predominance for OSMF. A minimum of 25 participants and maximum of 90 were enrolled in various studies. Baseline clinical staging was done in four studies,[31,33-35] but different staging methods were used by the authors. In two studies, the inclusion criteria resulted in the enrollment of patients in specific mouth opening range.[30,32] Only four studies recorded baseline adverse habits of their participants,[28-30,33] and gutkha chewing was the most commonly associated areca/tobacco habit reported. Two studies provided some information regarding the involvement of clinical sites by OSMF, in which buccal mucosa was invariably affected in all the patients.[33,35]

Intervention summary

The summary of interventions in 11 studies included in the qualitative synthesis of this review is given in Table 1. The most common form of turmeric administered in eight studies was oral form.[26,28-31,33,35,37] Tablets of *Curcuma longa* 300 mg with 5 mg piperine were given in four studies.[28,29,33,35] Other forms of oral turmeric administration included *C. longa* 400 mg tablets,[30] capsules of 400 mg turmeric

Table 1: The details of different turmeric formulations in the included studies

Reference	Design	*n*	Age (years)	M: F	Turmeric formulation	Mode	Dosage	Comparator	Duration
Piyush 2018	RCT	90	17-60 (mean 32)	07:02	Tablets of turmix (C.Longa 300 mg with 5 mg piperine)	oral	300mg twice daily	Two arms ->lycopene capsule (8mg) BD for 6 months > placebo capsules OD for 6 months	6 months
Saran 2018	RCT	60	27.9±8.66	14:01	Turmix tablet (C.Longa 300 mg with 5 mg piperine)	oral	300mg thrice daily	lycopene capsules (lycopene 4mg zinc 7.5mg Selenium 35mcg)	3 months
Kopuri 2016	RCT	30	>15 yrs	not known	Haridra tablet (C.longa 400mg)	oral	400mg twice daily	lycored capsule (lycopene 2000mcg zinc 7.5mg Selenium 35mcg)	3 months
Pipalia 2016	RCT	46 (40)	Gr I 29.60±7.58 GR II 26.80±6.36	only males	capsules of 400 mg turmeric with 100 mg black pepper	oral	2 CAPSULES TID	capsules of 500 mg nigella sativa - 2 cap tid for 3 months	3 months
Hazarey 2015	RCT	33 (30)	18-50	30:3	Longvida lozenges (400 mg lozenges)	topical	2 g/DAY	topical clobetasol propionate - TenovateTM	3months
Srivastava 2015	observational	41	17-56 (mean 31.93±10.92)	34:7	1gm tulsi powder mixed with 1 gm turmeric powder in glycerine	topical -paste	4-5 times/ day	NA	3 months
Yadav 2014	RCT	40	20-40 (mean 32)	31:9	Tablets of turmix (C.Longa 300 mg with 5 mg piperine)	oral	2 tablets once/day	sumucosal intralesional injections	3 months
Agarwal 2014	Observational	30	35.1±11.4 years	2.3:1	Tablets of turmix (C.Longa 300 mg with 5 mg piperine)	oral	1TAB TID	NA	3 months
Das D 2010	RCT	48	NR	NR	GROUP I - 250 gm CURCUMIN capsules GROUP II TURMERIC OIL -25 mg/drop	Oral + topical	Group I -2 cap bd Group II - 12 drops bd	Multinal tablets	3 months
Rai 2010	observational	25	17-50 years	11:14	Curcumin 1 g caplets (900 mg curcumin, 80 mg desmethoxycurcumin, and 20 mg bisdesmethoxycurcumin)	oral	NR	NA	Clinical cure
Hastak 1998	non-randomized trial	60	18-40 years	NR	Group I -capsules OF 100 MG TURMERIC OIL (TO)+ 500MG TURMERIC EXTRACT (TE) Group II - capsules of 120 mg Turmeric oleoresin (TOR) + 600 mg TE Group III - tablets of 500mg TE	oral	Group 600 TO and 3g TE Group 600 mg TOR and 3g TE group III 3g TE	NA	3 months

with 100 mg black pepper,[31] curcumin 1 g caplets,[37] and capsules of turmeric oil, turmeric oleoresin, and turmeric extract.[26] In two studies, topical forms of turmeric were used 2 g Longvida lozenges and 1 g tulsi powder mixed with 1 g turmeric powder in glycerine.[32,36] In the study by Das *et al*., oral and topical turmeric in two arms were used, respectively.[34] A lot of variation was reported in the dosage of turmeric. The tablets of *C. longa* 300 mg with 5 mg piperine given in four studies were administered as two tablets once a day[28,33] or thrice daily.[29,35] *C. longa* 400 mg tablets were given twice daily,[30] whereas capsules of 400 mg turmeric with 100 mg black pepper were prescribed to be taken as two capsules three times a day, making a total dose of 2400 mg turmeric/day.[31] In most of the studies, the duration of treatment was 3 months. Piyush *et al*. (2019) administered curcumin tablets for 6 months,[28] whereas in the study by Rai *et al*., treatment was continued till clinical cure was achieved.[37]

In two studies, comparison was made between the turmeric formulations and lycopene,[29,30] whereas two studies compared turmeric with steroids in the form of intralesional injections and topical ointment.[32,33] Pipalia *et al*. compared the efficacy of turmeric with *Nigella sativa*.[31] Piyush *et al*.[28] used lycopene as well as placebo for comparison, and multinal tablets were used as the comparator by Das *et al*.[34]

Only in one study, physiotherapy by mouth exercise device in addition to turmeric lozenges was recommended to the patients.[32]

Outcome summary

The objective outcomes assessed by various studies were interincisal mouth opening, tongue protrusion, and cheek flexibility. The subjective outcomes assessed were burning sensation of oral cavity and pain control. The biochemical outcomes were assessed in three studies, whereas one study assessed histopathological

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Table 2: The main outcomes assessed in the included studies

Reference	Mouth opening before	Mouth opening after	Tongue protrusion before	Tongue protrusion after	Cheek flexibility before	Cheek flexibility after	Burning sensation before	Burning sensation after	Biochemical outcomes	Hp outcomes	Any other outcome	Time period
Piyush 2018	values not given	3.9±4.9 mm	values not given	5.07±7.2mm	values not given	0.36±0.71mm	values not given	4.8±2.6mm	NR	NR	NR	30 days
Saran 2018	33.2±0.07 mm	35.2±0.08 mm	NR	NR	NR	NR	62.33±5.22%	0	NR	NR	NR	15 days
Kopuri 2016	26.07±2.66 mm	29±2.27 mm	NR	NR	NR	NR	grading	Grading	NR	NR	USG, blanching fibrous bands	30 days
Pipalia 2016	26.8	30.6	38.85	41.95	1.55	2	6.2	0.75	SOD levels	NR	NR	15 days
Hazarey 2015	21.13±4.54 mm	27.06±4.80 mm	NR	NR	NR	NR	NORMAL FOOD 64 (42-73), SPICY FOOD 77 (70.5-82)	NORMAL FOOD 7 (3-24), SPICY FOOD 23 (4.5-34)	NR	NR	NR	30 days
Srivastava 2015	24.46±4.0 mm	27.85±3.39 mm	NR	NR	NR	NR	6.07±1.75	2.22±1.41	NR	NR	NR	30 days
Yadav 2014	24.5 mm	Mean increase 1.25 mm	18.7mm	mean increase 0.38mm	NR	NR	100%	0%	NR	NR	NR	7 days
Agarwal 2014	GRAPH ONLY	GRAPH ONLY	NR	NR	NR	NR	GRAPH ONLY	GRAPH ONLY	NR	NR	NR	30 days
Das D 2010	GRAPH ONLY	GRAPH ONLY	Results not described	Results not described	NR	NR	GRAPH ONLY	GRAPH ONLY	NR	YES	PAIN	15 DAYS
Rai 2010	24.64 mm (3.2)	39.4mm (3)	NR	NR	NR	NR	NR	NR	MDA, 8-OHdG, VIT E AND C	NR	PAIN, HEALING OF LESION	NR
Hastak 1998	Mean values not reported	Mean values not reported	Nr	Nr	Nr	Nr	Semi-quantitative	Semi-quantitative	LFT, KFT	NR	NR	NR

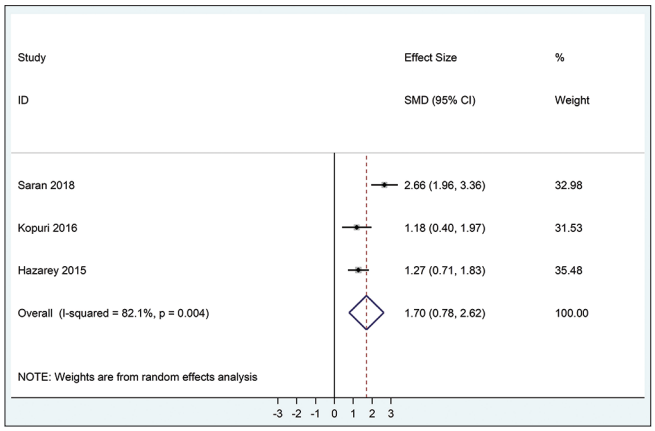

Figure 3: Forest plot graph of the studies included in the meta-analysis

outcomes. The study by Kopuri *et al*. (2016) assessed the presence/absence of blanching and fibrous bands along with the submucosal layer thickness on ultrasonography.[30] Rai *et al*. (2010) additionally assessed the size of the lesion in their study. The frequency of assessment of outcomes ranged from every 7th day to every 30th day.[37] The summary of outcomes assessed by various studies is given in Table 2.

Interincisal mouth opening was assessed by all the studies, and the mean difference in the mouth opening before and after the treatment was reported in millimeters. Two studies reported this outcome only graphically,[34,35] whereas in one study, mean values were not calculated.[26] In six studies, Vernier calipers were used,[26,29,31-33,35] one used scale,[28] whereas the method of recording has not been reported by four others.[30,34,36,37] All the studies reported improvement in mouth opening after treatment with turmeric formulations.

Tongue protrusion was assessed by four studies, of which[28,31,33,34] three have described the method of its assessment using either Vernier caliper or scale.[28,31,33] The mean increase in tongue protrusion was reported as 0.38 mm in one study[33] and 3.1 mm in another study at the end of 3 months of treatment.[31] However, Piyush *et al*. (2019) have reported a mean increase of 5.07 ± 7.2 mm in tongue protrusion at the end of 6 months of therapy.[28] Das *et al*. (2010) have reported that improvement in tongue protrusion was recorded more in the topical application group than the systemic turmeric group, both of which were more effective than multinal tablets.[34]

Cheek flexibility was been assessed by Piyush *et al*.[28] and Pipalia *et al*.[31] Both of them have used the same method of its measurement[38] and reported the results in millimeter. Piyush *et al*.[28] have reported a mean improvement of 0.36 ± 0.71 mm in cheek flexibility after 6 months of therapy, and Pipalia *et al*.[31] have found a 0.45 mm improvement after 3 months, respectively.

Burning sensation of oral cavity has been assessed by all but one author.[26,28-36] The most common method of recording this subjective sign was Visual Analog Scale (VAS). Only four authors have described the usage method of this scale in their study.[28,29,31,32] Hazarey *et al*. have used VAS for spicy food and normal food separately in their study.[32] There is no consensus on the range of the scale, which varied from 0–10 in three studies[28,31,32] to 0–100 in four others.[29,33,35,36] Kopuri *et al*.[30] have graded the patients as having mild, moderate, and severe based on the burning sensation, Hastak *et al*.[26] have used a semi-quantitative method for its estimation, whereas Das *et al*.[34] and Agarwal *et al*. have shown the results graphically only.[35] While two studies have reported elimination of burning sensation after treatment with turmeric,[29,32] others have shown a reduction in burning sensation.[28,30,31,33-35]

Biochemical outcomes have been assessed by Pipalia *et al*.[31] and Rai *et al*.[37] Pipalia *et al*. have measured serum superoxide dismutase as a marker of oxidative stress before and after 3 months of treatment and reported + 0.62 U/ml increase after treatment with turmeric.[31] In their study, Rai *et al*. measured serum and salivary oxidative markers such as malondialdehyde (MDA), 8-hydroxydeoxyguanosine (8-HOdG), and Vitamins C and E at baseline, after 1 week of treatment, and following clinical cure of OSMF.[37] A statistically significant increase in Vitamins C and E and a decrease in MDA and 8-HOdG were observed after turmeric intake. Hastak *et al*. also reported biochemical tests for organ dysfunction such as liver function tests and kidney function tests and found them to be within the normal range, indicating that turmeric formulations used in their study were safe.[26]

Meta-analysis

Of the seven RCTs included in this review, studies which reported the outcomes at 3 months were considered for meta-analysis. A study by Das *et al*. was excluded due to only graphical representation of outcomes. Two RCTs did not report standard deviation in their results.[31,33] Only one outcome – interincisal mouth opening – has been assessed by all the RCTs. Therefore, meta-analysis for three studies, i.e., Saran 2018, Kopuri 2016, and Hazarey 2015, was performed for interincisal mouth opening.[29,30,32] The pooled estimate is 1.70 (0.78–2.62) by applying the random-effects model, standardized mean difference (SMD) = 1.70 along with 95% confidence interval (0.78–2.62). There is an increase of 1.70 from baseline to giving the treatment (I squared = 82.1%, P = 0.004). Figure 3 shows the forest plot graph of meta-analysis done in the present review.

DISCUSSION

OSMF is an irreversible and incurable disease affecting 14 million Indians and has a high potential for malignant transformation.[3] The available drugs do not provide a complete cure and may have adverse effects, and clinical signs and symptoms may recur after cessation of therapy. Therefore, there is an urgent need to look for an effective and safe remedy for the management of OSMF.

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Turmeric and its active ingredient curcumin have been used for its medicinal value in diseases such as cancer, Alzheimer's disease, and diabetes by traditional systems which are considered incurable in the modern system of medicine.[39-43] This has attracted the attention of modern medical researchers. The present systematic review and meta-analysis looked at the available evidence on the effectiveness of turmeric or curcumin in the treatment of OSMF.

Although there are a large number of studies using turmeric as intervention, most of them have explored mechanism of pharmacological action, molecular targets, safety through animal studies, and *in vitro* studies of human tissues.[43-47] Only 11 studies were found to be suitable to answer our research question.

Turmeric was found to be effective in reducing signs and symptoms of OSMF in all 11 studies. All the studies included in this review have reported improvement in moth opening. This could also be concluded from the meta-analysis of three RCTs. Similar improvement in tongue protrusion, burning sensation, and cheek flexibility has been reported.

However, because of the marked heterogeneity among these studies, the results of this review should be interpreted with caution. Several limitations were noted.

- There is remarkable heterogeneity in the 11 studies selected for this systematic review
- The major methodological weakness noted was the highly variable study design. Therefore, data could not be submitted for meta-analysis. We could do meta-analysis for only one outcome, interincisal mouth opening, using only three RCTs
- Among patient population characteristics, major differences in baseline patient characteristics were noted. No uniformity in grading and staging of disease or age groups was observed in the included studies. Histological confirmation of diagnosis was not available in many studies, and OSMF scoring was not done in all of the included studies. Those who did scoring did not follow a standardized method of scoring
- Majority of the studies had small sample size with inequal distribution of patients in different clinical stages. None of the included studies reported subgroup analysis, though patients of all subgroups were included in each study
- Marked heterogeneity in curcumin preparations, dosages, and mode of administration was observed which can affect the bioavailability of active ingredient and therefore can affect the outcome. Co-interventions such as piperine or tulsi could also confound the outcomes
- There was a lot of variability in the comparator arm. Different studies compared the turmeric formulation with different comparators such as lycopene, steroids, *N. sativa*, and multinal tablets. Only a single study uses placebo for comparison of effectiveness of turmeric[32]
- Several issues regarding outcome assessment were noted. The measurements were insufficient and were done at a highly variable frequency. Both objective and subjective measurements were included in different studies. Furthermore, the method of assessment of each outcome was variable. A noteworthy point not addressed in the included studies was bias, as no blinding was reported among patients or outcome assessor. Correlation with biochemical parameters or histological changes was not done
- Sufficient time frame to see an effect was also not available, and evaluation of dose–response gradient was not done
- The follow-up period was inadequate and was different in different studies. In addition, relapse was not studied or reported
- There are several limitations to this systematic review. Ayurveda and Unani literature databases were not looked into as they were not accessible through commonly available search engines. We included articles available in only English literature in our study. Moreover, all available studies are from India and not from any other country of Southeast Asia where OSMF is highly prevalent. There may be a possibility that some studies of those countries are published in their local journals and not available in databases that were looked here leading to publication bias.

CONCLUSION

The evidence synthesized from this systematic review and meta-analysis regarding the use of turmeric or curcumin in OSMF suggests turmeric as a potentially effective treatment choice for the management of patients with OSMF. There is marked heterogeneity among the studies reviewed; therefore, the results of this review should be interpreted with caution. The recommendations for future studies evaluating the role of turmeric/curcumin in OSMF must follow the recommendations made by Kerr *et al.*[14] for studying medical interventions in OSMF. A double-blinded RCT having sufficient sample size in respective arms taking into account power calculations would be ideal. A multi-arm parallel-group design should be considered. The subpopulations of patients grouped by disease severity/stage should be studied separately, and minimization should be considered to achieve balance among groups in terms of participants' baseline characteristics. There is a scope of comparing the effects of different curcumin dosages and formulations using dose-comparison concurrent control design to make evidence-based recommendations for its use in OSMF. Calibration of investigators for outcome assessment is necessary, and measurements should be made by investigators blinded to the intervention and with intra- and inter-rater reliability assessments. Both treatment period and follow-up after stopping the treatment should be sufficient to assess the recurrence of signs and symptoms.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary 1: PRISMA 2009 Checklist (Adapted for KIN 4400)

Section/topic	#	Checklist item	Reported on page #
		TITLE	
Title	1	Identify the report as a literature review.	1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings;	1
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known about your topic.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
		METHODS	
Eligibility criteria	5	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	6	Describe all information sources (e.g., databases with dates of coverage) in the search and date last searched.	3,4
Search	7	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3,4
Study selection	8	State the process for selecting studies (i.e., screening, eligibility).	3,4
Risk of bias in individual studies	9	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level).	
Risk of bias across studies	10	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
		RESULTS	
Study selection	11	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	12	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Synthesis of results of individual studies	13	For all outcomes considered (benefits or harms), present, for each study: (a) summary of results and (b) relationship to other studies under review (e.g. agreements or disagreements in methods, sampling, data collection or findings).	5-8
		DISCUSSION	
Summary of evidence	14	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	15	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
		CONCLUSION	
Conclusions	16	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9

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