Journal of Oral Biology and Craniofacial Research 10 (2020) 690–697

Contents lists available at ScienceDirect

Journal of Oral Biology and Craniofacial Research

journal homepage: www.elsevier.com/locate/jobcr

Efficacy of lycopene in management of Oral Submucous Fibrosis– A systematic review and meta-analysis

Neha Gupta[a,*], Ashita Kalaskar[b], Ritesh Kalaskar[c]

[a] Department of Oral Medicine and Radiology, Post-graduate Student, Government Dental College and Hospital, Nagpur, India
[b] Department of Oral Medicine and Radiology, Associate Professor, Government Dental College and Hospital, Nagpur, India
[c] Department of Pediatric Dentistry, Professor, Government Dental College and Hospital, Nagpur, India

ARTICLE INFO

Keywords:
Burning pain
Clinical trials
Lycopene
Oral submucous fibrosis
Trismus

ABSTRACT

Purpose: To evaluate the efficacy of lycopene in the management of Oral Submucous Fibrosis (OSMF).
Study design: A comprehensive search was done in MEDLINE via PubMed, Cochrane, EBSCO-host and Google scholar from July 31st, 1999 to July 31st, 2019 to identify OSMF related clinical trials (Randomized and Non-randomized) involving lycopene as one of the intervention.
Results: 16 randomized control trials and 3 non-randomized control trials comprising 1181 subjects were included. The results of meta-analysis showed non-significant differences between lycopene and other interventions used in the treatment of OSMF.
Conclusion: The present review suggests that lycopene is a safe and equally effective therapeutic modality as compared to other interventions for patients with OSMF. Further well-designed clinical trials are required to accurately assess the effectiveness of lycopene as compared to other medicinal treatments in the management of OSMF.

1. Introduction

Oral Submucous Fibrosis (OSMF) is a chronic insidious disease associated with a significantly increased risk of cancer.[1] Initially the disease is characterized by blanching and burning pain of oral mucosa, which is aggravated by consuming hot and spicy food. There is submucosal fibrosis that affects most parts of the oral cavity, pharynx and upper third of the esophagus leading to trismus and dysphagia respectively.

Eventhough Schwartz (1952) was the first to report a case of "atrophica idiopathica tropica mucosa oris" occurring in Indians in East Africa,[2] Lal and Joshi (1953) were the first to describe it in India. Also the term "Oral Submucous Fibrosis" was coined by Joshi.[3] The first pathologic definition of OSMF was given by Jens J. Pindborg[4] and the clinical definition was given by More and Rao.[5]

There is substantial evidence present indicating the role of areca nuts in the etiology of OSMF.[6,7] The constituents of areca – nut, mainly coline has the capacity to modulate metabolism of collagen, which leads to an increased fibrosis pointing towards a definite dose – dependent relation between areca – nut and causation of the disease.[8]

The malignant potential in Oral Submucous Fibrosis has been documented by Pindborg and Sirsat (1996) with the malignant transformation rate being in the range of 7–13%.[4,9] The various factors that could affect the malignant transformation are younger age group (15–30 years), habit of betel nut chewing, and association with other premalignant lesions like leukoplakia, erythroplakia.[10]

A wide range of therapeutic approaches have been proposed for OSMF, including cessation of betel quid chewing, physiotherapy, medical interventions and surgical intervention.[11] Inspite of these many treatment options tried in OSMF patients, complete relief of symptoms has not been identified till date.[12] OSMF being a chronic disease and a highly prevalent premalignant condition in Indian adult population (prevalence of 0.03%–6.42%) and in children and adolescents, an alternative, effective and safe therapy should be explored and studied further.[2,13]

Lycopene, an effective anti-oxidant from tomato extract has been proved to be the most potent radical scavenger in various in-vivo and in-vitro studies. Apart from its use in other health related conditions, its antioxidant properties have also been evaluated in the management of OSMF. But due to lack of systematic evidence in this regard, a systematic review and meta-analysis was planned to evaluate the role of lycopene in OSMF.

* Corresponding author. Department of Oral Medicine and Radiology Government Dental College and Hospital, Medical Square – 440012, Nagpur, India.
E-mail addresses: nehagupta616001@gmail.com, nehagupta616001@gmail.com (N. Gupta), kalaskarashita@gmail.com (A. Kalaskar), riteshpedo@gmail.com (R. Kalaskar).

https://doi.org/10.1016/j.jobcr.2020.09.004
Received 29 July 2020; Received in revised form 7 September 2020; Accepted 14 September 2020
Available online 17 September 2020

Table 1
Shows the eligibility criteria for inclusion of the studies in regards to Participants, Intervention, Comparator & Outcomes (PICO).

INCLUSION	EXCLUSION
❖Participants (P): •Individuals in any age group diagnosed clinically and/or histopathologically with OSMF. •No evidence of dysplasia and malignancy •No history of prior treatment for the same. ❖Intervention (I): Lycopene in any form ❖Comparator (C): Any medicinal intervention and/or placebo and/or standard treatment ❖Outcomes (O): Main outcomes- •Improvements in maximal interincisal mouth opening •Reduction in burning sensation Additional outcomes- •Side effects of intervention •Quality of life/interference in daily activity/improvement index ❖Study design (S): Clinical trials (Randomized and non- Randomized).	•Patients with systemic disease. •Patients with trismus due to other reason (pericornitis, abscess). •Pregnant and lactating mother •Presence of other premalignant lesion - leukoplakia, oral lichen planus •History of hypersensitivity to lycopene •Case report, case series, animal studies, in vitro studies, review paper, editorials letters to the editor and monographs were excluded.

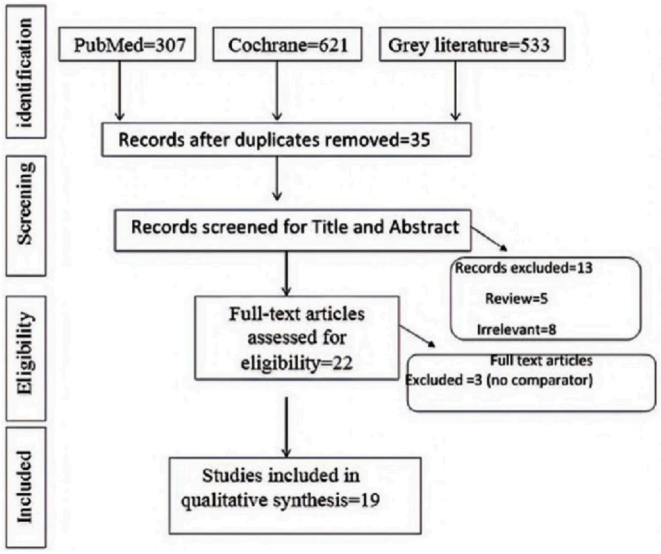

Fig. 1. Flow chart of methodology according to PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines.

2. Methods

2.1. Protocol and registration

The protocol of the present systematic review was designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines 2009 and was registered in PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42019144926).[14]

2.2. Eligibility criteria

Eligibility criteria for inclusion of the studies in regards to Participants, Intervention, Comparator and Outcomes (PICO) is as shown in Table 1.

2.3. Search

Databases (MEDLINE via PubMed, Cochrane, EBSCO-host, Google scholar), relevant journals, books, bibliographies, reviews and conference proceeding were searched from July 31st, 1999 to July 31st, 2019. The following MeSH terms and keywords were searched with Boolean operators OR within the same category and between the disease & intervention category.

For Disease category – Oral Submucous Fibrosis, idiopathic scleroderma of the mouth, juxtaepithelial fibrosis, asian sideropenic dysphagia, OSF.

For Intervention category – Lycopene, tomato extract, carotenoid, all trans lycopene, all cis lycopene.

All the articles available in the English language were included.

2.4. Study selection

The titles and abstracts of all retrieved articles were screened by 2 independent reviewers, and irrelevant studies were excluded. Full text of the eligible studies were obtained and thoroughly assessed by the 2 reviewers for inclusion. Disagreements were resolved by the 3rd reviewer. For the unreported data or additional details, concerned study authors were communicated.

2.5. Data collection process

Data collection was performed using a customized data extraction form, which included following contents: Title of the study, Author's name, duration of study, year of publication, study setting, study design, study population, method of randomization used (if any), types of intervention, types of comparator, characteristic of participants (age and gender), inclusion and exclusion criteria, indicators of acceptability of users, times of measurement, outcomes (primary and secondary), and concluding remarks.

2.6. Risk of bias in individual studies

To evaluate the risk of bias in individual studies, different tools were used for randomized controlled trials (RCTs) and non-randomized controlled trials. Cochrane collaboration's risk of bias tool[15] was used for RCTs and Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)[16] was used for non –randomized controlled trials.

2.7. Synthesis of results

Narrative synthesis was planned to provide the findings obtained from the studies, which was mainly focused on the intervention details (form, dose etc), characteristics of participants (gender, age, stages of Oral Submucous Fibrosis) and outcome assessment (primary, secondary, side effects etc). Summaries of intervention effects for each study were provided by calculating risk ratio (for dichotomous outcomes) or standardized mean difference (for continuous outcomes). Heterogeneity of the previously mentioned characterstics were assessed by using chi^2 test (significance:0.1) and I^2 statistics.

Table 2
Showing details of population, study groups and outcome (PICO) of included randomized controlled trials.

S.no	Author, year, country	Population details		Variables evaluate	Main outcomes
		No/Age	Study groups (intervention and control group)		
1	Kumar A et al.[11] 2007, India	No- 58 Age - 18 to 70 years	Groups(G) G1-n = 21 Lycopene G2-n = 19 Lycopene and Betamethasone G3-n = 18 placebo	MO,BS, TS,FB	G1 & G2 (MO & BS) – SSD G3 (MO & BS) –SNSD
2	Chole RH et al.[12] 2011, India	**No** – 90 **Age-** mean age G1-27 G2-26 G3-29	**Groups(G)** G1-n = 27 lycopene G2-n = 33 lycopene and triamcinolone acetonide G3-n = 25 placebo	MO,BS,BL,UL	MO & BS-SSD in G1 & G2 SNSD in G3
3	Karemore T. et al.[13] 2012, India	**No** - 92 **Age** - 17–57 years	**Groups** – According to Khanna and Andrade staging G1-n = 46 lycopene G2-n = 46 Placebo	MO,BS,UL	MO & BS – SSD
4	Selvam et al.[14] 2013, India	**No** - 45 **Age** –age range 18–50 yrs,	**Groups**-G1- 15 lycopene intralesional steroids and hyaluronidase G2 – 15 antioxidant capsules intralesional steroids and hyaluronidase Gr 3–15 intralesional steroids and hyaluronidase alone	MO,BS	MO: Intragroup – SSD Intergroup –A vs C B vs C Overall p value - <0.0001 BS: All group – SSD
5	Subramaniam AV et al.[15] 2014, Iindia	**No** - 30 **Age** – not mention	G1 –n = 15 lycopene G2-n = 15 Ultrasound therapy	MO,BS, TP	MO - better in group 2 as compared to group 1. However, the difference is not statistically significant BS - better in group 1 as compared to group 2. The difference is significant statistically
6	Singh D et al.[16] *2014*	**No** – 44 **Age**:Mean ± D Gr1-29.41 ± 9.11 Gr-225.59 ± 6.98	**Group** - Lai DR classification G1-22 (lycopene) G2-22 (intralesional injections of betamethasone)	MO,BS	MO & BS – SSD in both groups
7	Patil S *et* al[17] *2014 india*	**No** - 68 **Age(mean)**-30.9 ± 12.8 years	**Group** G1-34 (spirulina) G2-34 (lycopene)	MO,BS, UL,P	MO – SSD in G2 BS – SNSD in both groups
8	Elizabeth N et al.[18] *2014 india*	**No** - 38 **Age** range of 33 and 67 years	**Group** – Gr1-(19)lycopene + Triamcinolone + Hyaluronidase Gr2-(19)intralesional injection of steroids and Hyaluronidase	MO	SSD
9	Omar A et al.[19] 2015 pakistan	**No** – 45 **Age range-** 36.49 ± 11.82 Years	**Group** – G1- Methylprednisolone acetate G2-Lycopene G3-Methylprednisolone acetate and lycopene	MO	Between groups1 and 2-SNSD between groups 1 and 3-SSD between group 2 and 3-SSD
10	Nayak A et al.[20] 2015 india	**No** – 72 **Age** – not mention	G1-24 –lycopene G2-24-Lycopene and vit E Gr 3-24- placebo	MO,BS,UL	SSD in G1 & G2
11	Patil *et* al[21] *2015* India	**No** - 120 **mean Age** - 31.6 ± 12.7 years	**Groups**-G1-60- Lycopene G2-60- aloe vera	MO,BS,TP,P, DS	MO – SSD BS Intragroup-SSD Intergroup-SNSD
12	Kopuri RK et al.[22] 2016 India	**No** - 30 **Age**-above age 15	**Group**-G1-15- lycopene G 2- 15-curcumine	MO,BS, BL, FB	MO - G1 showed a better results but did not differ enough to be statistically significant BS - Group 2 showed a better results but did not differ enough to be statistically significant
13	*Kaur et* al[23] *2016 india*	**No** - 30 patients **Age** range of 18–49 years	**Groups** – G1- 15 lycopene with intralesional steroids and hyaluronidase G2 – 15 intralesional steroids and hyaluronidase alone	MO,BS	MO & BS – Intragroup - SSD
14	P Prerna et al.[24] 2018 India	**No** - 90 **mean age** of 32 years	**Groups** -G 1-30-curcumin Gr2-30-lycopene G 3-30- placebo	MO,BS, TP, CF	MO & BS- Between group 1 and 3-SSD Between group 2 and 3-SSD Between group 1 and 2-SNSD
15	*Patil S et* al[25] *2018 India*	**No** - 120 **Age** −31.6 ± 12.7 years	**Groups**-G1-60 (oxitard) G2-60 (lycopene)	MO,BS, TP,P, DS	MO – SSD in G1 BS – SNSD in both groups
16	S Gragi et al.[26] 2018 india	**No** - 60 **Age**- <30 years	**Groups**- given by Khanna and Andrade 1995 G1-30-lycopene G2- 30-curcumin	MO, BS	MO, BS – Intragroup – SSD Intergroup – SNSD

MO – Mouth opening, BS – Burning Sensation, TP – Tounge protrusion, CF – Cheek flexibility, P –Pain, DS – Difficulty in swallowing, FB – Fibrous bands, SSD – Statistically significant difference, SNSD – Statistically non significant difference, G1 – Group 1, G2 – Group 2, G3 – Group 3.

Table 3
Showing details of population, study groups and outcome (PICO) of included non - randomized controlled trials.

S.no	Author, year and country	Population details		Variables evaluated	Outcomes
		No/Age	Study groups		
1	*S.Sunderraj et* al[27] *2012 India*	**No**- 20 **Age**- 15 years and above	**Group**-G – 10 (lycopene) G −10 (multivitamine)	MO,BS	MO & BS – G1 showed 80% complete response G2 showed 30% complete response
2	Gavirangaiah *et* al[28] *.2018 india*	**No** - 84 **Age** -18-62 years	**Group**-G1- 30 (lycopene) G2-30 (serratiopeptidase) G 3–24 (placebo)	MO, BS, TP, FB & UI	MO – SNSD BS – SSD between G1 & G3 and between G2 & G3.
3	Joseph *et* al.[29]2019 India	**No** - 45 patients **Age** – not mention	**Group** – according to More et al. G1-15 (lycored) G2-15 (lycored and intralesional hyaluronidase) G3-15 (placebo	MO, BS, FB	MO & BS – SSD between G1 & G3 and G2 & G3 SNSD between G1 & G2

Table 4
Showing details of comparator groups.

Study	Control group
Kumar A et al.[11] 2007 & Singh D et al.[16] *2014*	Intralesional injections of betamethasone 2 1-mL ampoules
Chole RH et al.[12] 2011, India	Topical triamcinolone acetonide 0.1%.
Selvam et al.[14]2013 & *Kaur et* al[23] *2016 india*	intralesional injections of Dexamethasone 1.5 ml & Hyaluronidase 1500 IU mixed with lignocaine.
Patil S *et* al[17] *2014*	500 mg spirulina in 2 divided doses
Elizabeth N et al.[18] *2014 india*	Intralesional injections of Triamcinolone (Kenacort) 40 mg/ml, 1 ml & Hyaluronidase 1500 IU weekly
Omar A et al.[19] 2015 pakistan	Methylprednisolone acetate 20 mg/0.5 ml
Nayak A et al.[20] 2015 india	vitamin E (400 I·U.)
Patil *et* al[21] *2015* India	Aloe vera applied topically thrice daily
Kopuri RK et al.[22] 2016 India	Haridra 800 mg/day divided doses
P Prerna et al.[24] 2018 india	Curcumin 300 mg 1 tablet two times daily
Patil S et al[25] *2018 India*	2 oxitard capsules twice daily
S Gragi et al.[26] 2018 india	Curcumin 300 mg thrice daily
S.Sunderraj et al[27] *2012 India*	Multivitamins twice daily
Gavirangaiah *et* al[28] *.2018india*	Serratiopeptidase 30 mg daily in 3equally divided doses
Joseph *et* al.[29]2019 India	Hyaluronida intralesional injection 1500 IU twice weekly

3. Results

3.1. Literature search and study selection

Fig. 1 shows the study search process conducted according to the PRISMA guidelines. The initial online search yielded a total of 1461 studies. After removal of duplicate studies, the remaining 35 studies were screened for title and abstract. Out of 35 studies, 13 studies were found irrelevant (5 review and 8 irrelevant trial) and were excluded. Full-text articles of remaining 22 studies were obtained and thoroughly assessed for eligibility criteria by two authors. Of these, 3 studies were excluded due to non – inclusion of comparators in their studies. The remaining 19 studies met the eligibility criteria and were included in the systematic review.

3.2. General characteristics of the included studies

General characteristics of the included studies are listed in Table 2 for the sixteen randomized control trials[17–32] and Table 3 for three non-randomized control trials.[33–35] A total of 1181 subjects participated in the trials, with most of the trials conducted in India except one, which was conducted in Pakistan.[25] In most of the studies, diagnosis was based on both clinical and histopathological features whereas few studies[19,22,32,35] reported the grouping based on OSMF Classifications as shown in Tables 2 and 3

The age of participants ranged from 18 to 60 years with male dominance in most of the studies except one which showed female dominance.[25] The reported duration of intervention varies from 2 to 3 months in the included studies with a follow up period of 2–3 months.

3.3. Formulation

All studies used systemic lycopene in capsule form and the dose varied from 16 to 32 mg with duration of 6 weeks to 6 months. In sixteen studies lycopene was given alone, whereas in two studies[20,29] it was combined with intralesional steroids + hyaluronidase, and in one study[24] it was given with Triamcinolone + hyaluronidase. Comparison groups showed variability among the studies(Table 4).

3.4. Clinical parameters

The clinical parameters reported in the included studies (Tables 2 and 3) were mouth opening, burning sensation, reduction of ulceration, tongue protrusion, blanching and cheek flexibility. Out of nineteen studies, ten studies[19,20,22,23,25,29,32–35] used vernier caliper, three studies[17,21,30] used geometric scale/divider for measuring mouth opening and six studies[18,24,26–28,31] did not mention the scale of measurements for mouth opening. Similarly out of nineteen studies, eleven studies[20–23,26,27,29,30,32–34] used visual analog scale (VAS) for evaluating burning sensation, whereas the remaining studies did not report the scale of measurement for burning sensation.

3.5. Main outcomes

Mouth opening – Most of the included studies showed statistically significant increase in mouth opening in lycopene group compared to other intervention like spirulina, intralesional injection of steroids & hyaluronidase, aloe vera, methylprednisolone acetate and placebo.[19,23–25,27] Study conducted by Subramaniam AV et al.,[21] Patil S et al.[31] and Gavirangaiah et al.[34] showed statistically non-significant difference in mouth opening by lycopene group as compared to ultrasound therapy, oxitard, and serratiopeptidase respectively. In three studies, lycopene was compared with combination therapy of lycopene, intralesional steroids and hyaluronidase, in which the combination therapy showed better results.[17,18,35] Kopuri RK et al.[28] and S Gragi et al.,[32] compared lycopene with curcumin and found both drugs effective in improving mouth opening.

Burning sensation – Out of nineteen studies, seventeen studies reported on this outcome. The results were found statistically significant among most of the studies except Kopuri RK et al.[28] and Patil S et al.,[31] who reported statistically non significant results with lycopene group as compared to curcumin and oxitard respectively. Whereas it was equally effective with that of the comparator drug (aloe vera, curcumin and lycopene + intralesional hyaluronidase) in few studies.[27,30,32,35]

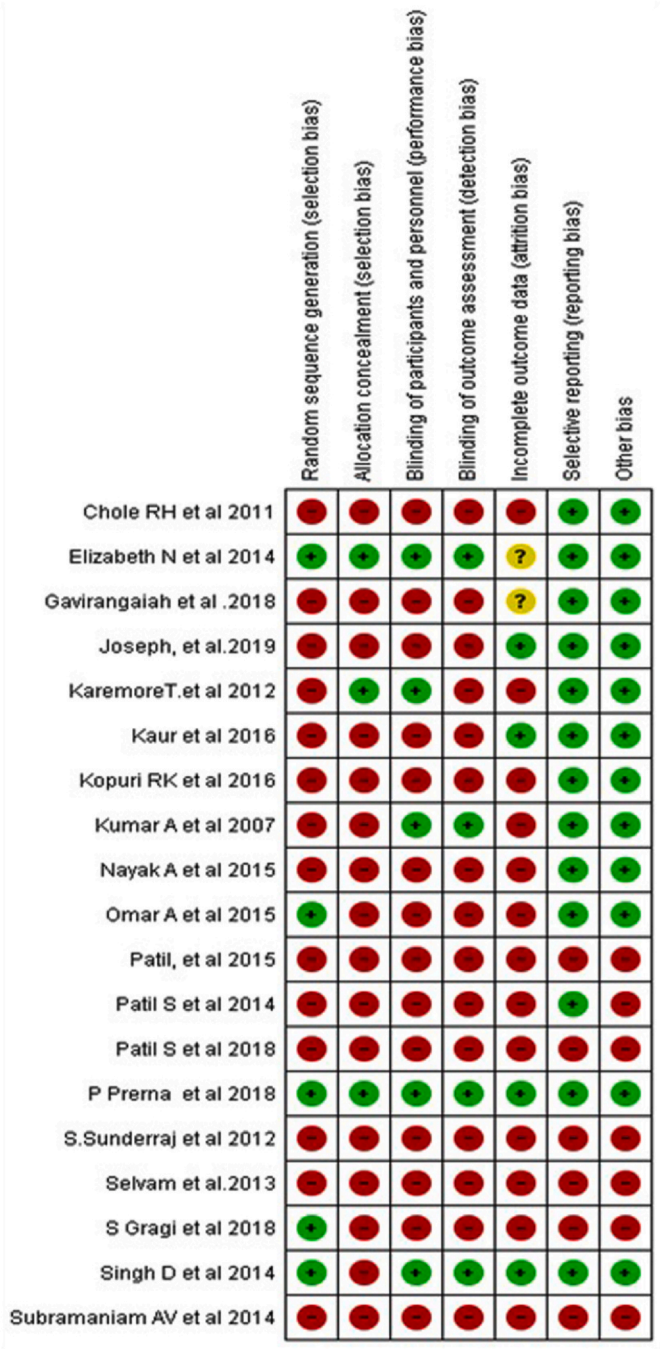

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

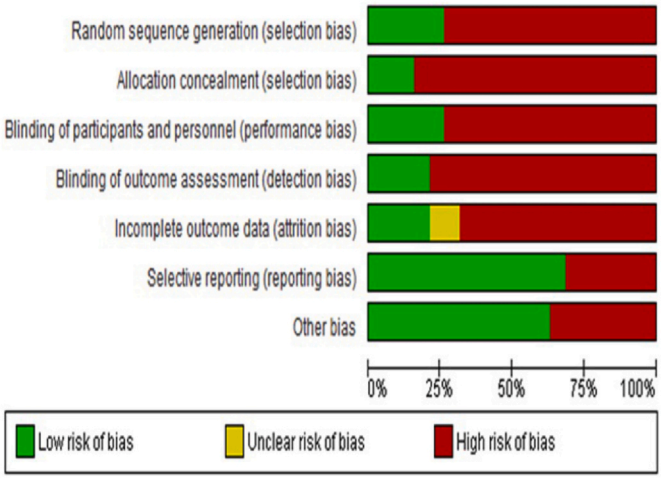

Fig. 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.6. Other outcomes

3.6.1. Tongue protrusion

Six studies reported on this outcome.[17,21,27,30,31,34]Three studies showed significant improvement in tongue protrusion in lycopene group.[17,21,27] Non-significant differences were obtained in two studies[30,34] whereas in one study,[31] significant improvement in tongue protrusion in favor of control group (oxitard) was reported.

3.6.2. Cheek flexibility

Only one study[30] reported on this outcome which showed non-significant difference between lycopene and curcumin group.

3.7. Side effects

Seven studies[17–20,23,31] showed no reported complications/side effects in lycopene group except one study[27] in which few patients reported nausea in the early visits, which was well tolerated.

3.8. Quality of included studies

The results of the quality assessment were evaluated according to Cochrane and ROBINS Tools. Based on Cochran's quality assessment tool for randomized control trial, only three studies[22,24,30] showed good quality assessment (Fig. 2). Remaining 13 studies showed poor quality with majority having selection and detection bias (Fig. 3).For non randomized control trial moderate risk were found in bias due to confounding and serious risk bias in measurements of outcomes in all studies.

3.9. Meta-analysis results

Out of nineteen studies, eighteen studies[17–33,35] on mouth opening and fifteen studies[17–23,26,27,29–33,35] on burning sensation were selected for meta-analysis. Results of mouth opening and burning sensation were expressed into mean and proportion based on data retrieved from the studies.

The analysis (Forest and Funnel plot: Figs. 4, 5, 6 and 7) revealed non-significant difference in the effects of lycopene and control groups (other interventions), in reducing the burning sensation and improving mouth opening in management of OSMF (see Fig. 6).

4. Discussion

Lycopene is a fat-soluble carotenoid discovered by Ernest et al., in 1959.[36] Tomatoes and tomato-based products are the primary sources of lycopene in the human diet.[37] Lycopene exerts its antioxidant (AO) activity by physical and chemical quenching of free radicals and is the most efficient singlet oxygen quenching carotenoid.[38] This unique biochemical property of lycopene render it capable to protect cellular components against specific types of damage from highly reactive oxygen species (ROS) like superoxide and hydroxyl radicals.[39] It neutralizes ROS twice as effectively as β-carotene and ten times as effectively as α-tocopherol, and is 100 times efficient than that of Vitamin-E and 125 times that of glutathione.[40] Studies have shown that it is also capable of modulating a number of other factors, such as regulation of growth factor signaling, apoptosis induction, metastasis and angiogenesis, modulating the anti-inflammatory and phase II detoxification

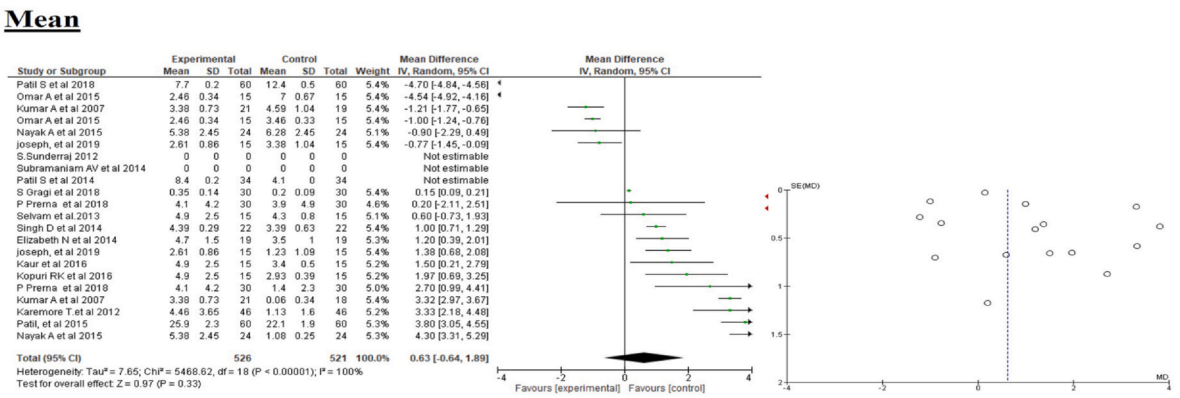

Fig. 4. Forest & Funnel plot of comparison: 1 Mouth opening, outcome: 1.1 mouth opening.

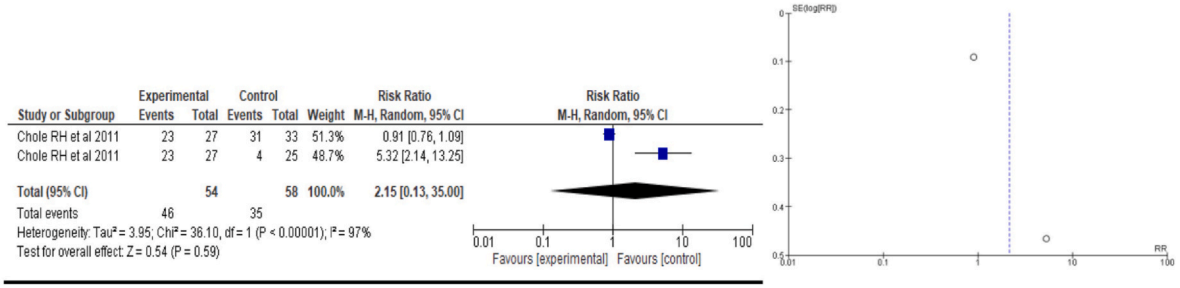

Fig. 5. Forest & Funnel plot of comparison: 2 Mouth opening, outcome: 2.1 mouth opening.

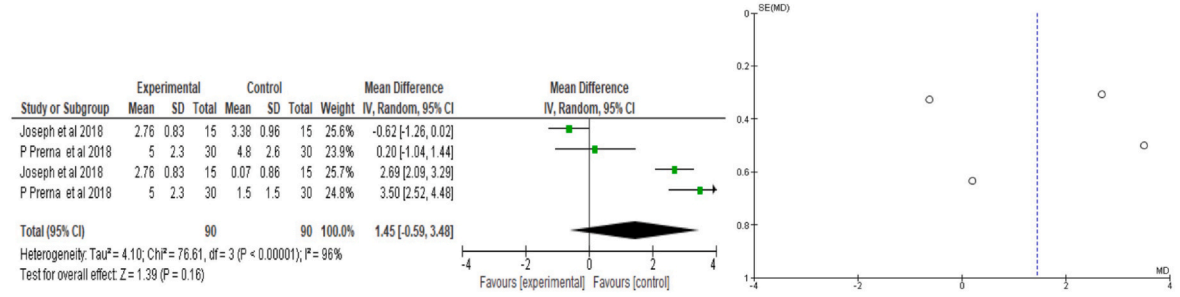

Fig. 6. Forest & Funnel plot of comparison: 1 Burning sensation, outcome: 1.1 burning sensation.

enzymes activities.[40] This could be the reason for lycopene being indicated for various potentially malignant diseases and malignancies apart from cardiovascular diseases, osteoporosis and neurodegenerative disease.

Oral Submucous Fibrosis (OSMF) is one such potentially malignant disease which apart from being chronic and insidious, has also a high rate of malignant transformation. Various interventions (medicinal and non-medicinal) have been tried in OSMF and use of lycopene in this condition is also not new. But the lack of systematic analysis evaluating its effectiveness to that of other interventions in OSMF encouraged the present systematic review with the research question "Is lycopene effective in management of Oral Submucous Fibrosis ?".

After extensive search nineteen clinical trials were included in this review. All included studies reported that lycopene was effective in clinical improvement of mouth opening and reducing burning pain. Most of the studies used vernier caliper for mouth opening measurements and visual analog scale for burning sensation, both of which are well known and standard methods of measurements.

In various studies lycopene was compared with single interventions like betamethasone,[22] spirulina,[23] curcumin,[28,30,32] aloe vera,[27] multivitamin,[33] placebo[17–19,26,30,34,35] and ultrasonography.[21] When compared with spirulina and aloe vera, lycopene was more effective in improving mouth opening, whereas all three were equally effective for reducing burning sensation. When compared to betamethasone (intralesional injections),[22] placebo and multivitamin,[33] lycopene was more effective in improving both mouth opening and reducing burning sensation, whereas lycopene was equally effective to that of Curcumin in improving mouth opening and reducing burning sensation.[28,30,32] On the contrary ultrasonogarhy was more effective than lycopene in improving mouth opening.[21] Similar to this Oxitard, a drug made from combination of various herbs was also more effective in improving mouth opening and reducing burning sensation as compared to

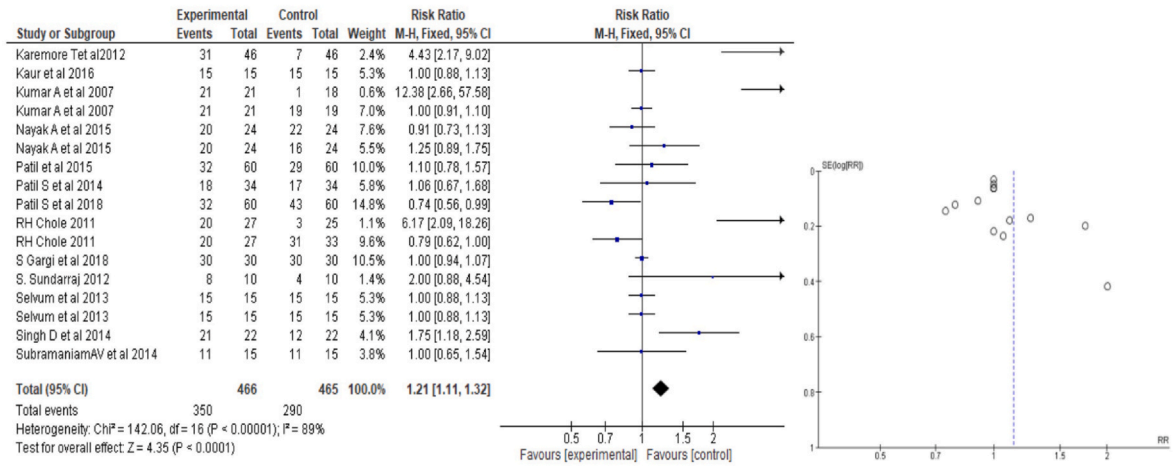

Fig. 7. Forest & Funnel plot of comparison: 2 Mouth opening, outcome: 2.1 mouth opening.

lycopene.[31]

Lycopene when compared with interventions in combination with lycopene like steroid therapy in combination with lycopene and steroid + hyluronidase therapy in combination with lycopene, the combination therapies showed statistically significant improvement in mouth opening and reducing burning sensation.[17,18,25,35] Thus combination of antioxidant, antiinflammtory and fibrinolytic therapy proves to give better results.

Lycopene makes up the largest proportion of carotenoids which have potential health benefits. The daily dietary allowance of lycopene is 0.5–27 g per person per day.[41] Bioavailability of lycopene can be affected by a number of factors with only 10–30% of the total ingested lycopene being absorbed by the human body.[42] Singh D et al. (2012)[43] repored no adverse effects at the highest intake level (3 g/kg/day) of lycopene. In present review the dose range of lycopene varied from 16 to 32 mg per day, which was well tolerated.

The results of meta – analysis showed non-significant difference between lycopene and other interventions regarding mouth opening and burning sensation, indicating that lycopene is equally effective to that of other interventions used in OSMF treatment. But it would be recommended that the evidence obtained from above studies should be interpreted cautiously. The main limitations being the relative paucity of databases mainly due to their inaccessibility and the considerable heterogeneity and high risk of bias observed in the short listed studies. Only three studies[22,24,30] showed better methodology to be followed with less risk of bias overall as compared to others. Also the post treatment follow-up of patients has not been mentioned in most of the studies which is an important determinant for considering the drug efficacy in a chronic pre-malignant condition like OSMF.

Therefore it could be recommended that to exactly define the efficacy of lycopene as compared to other interventions, more standard and uniform clinical trials on larger population should be carried out. Also considerations should be given to the factors affecting the variations in the outcomes of the trials. These factors could be; additional dietary intake of lycopene through fruits and vegetables, fat intake, probiotics, genetic differences in metabolism and similar other individual or population based factors.

Despite of the above mentioned limitations, the present review has tried to summarize the available evidence on the effectiveness of lycopene in the management of OSMF.

5. Conclusion

Lycopene could be considered a safe and effective therapeutic modality for patients with chronic condition like OSMF. But well-designed standard and uniform clinical trials are still required to accurately provide the evidence of effectiveness of lycopene as compared to other interventions in the management of OSMF.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

We would like to thank Dr. Dheeraj Kalra for his work on meta-analysis. This is a non-funded study.

References

1. Rao NR, Villa A, More CB, Jayasinghe RD, Kerr AR, Johnson NW. Oral submucous fibrosis: a contemporary narrative review with a proposed inter-professional approach for an early diagnosis and clinical management. *J of Otolaryngol - Head & Neck Surg.* 2020;49(3):1–11.
2. Das M, Manjunath C, Srivastava A, Malavika J, Ameena MVM. Epidemiology of oral submucous fibrosis: a review. *Int J Oral Health Med Res.* 2017;3(6):126–129.
3. Murti PR, Bhonsle Rb Gupta PC, Daftary DK, Pidborg JJ, Mehta FS. Etiology of oral submucous fibrosis with special reference to the role of arecanut chewing. *J Oral Pathol Med.* 1995;24:145–152.
4. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol.* 1966;22(6):764–779.
5. More CB, Rao NR. Proposed clinical definition for oral submucous fibrosis. *Journal of Oral Biology and Craniofacial Research.* 2019;9(4):311–314.
6. Prabhu RV, Prabhu V, Chatra L, Shenai P, Suvarna N, Dandekeri S. Areca nut and its role in oral submucous fibrosis. *J Clin Exp Dent.* 2014;6(5):e569–e575.
7. More CB, Rao NR, More S, Johnson NW. Reasons for initiation of areca nut and related products in patients with oral submucous fibrosis within an endemic area in Gujarat, India. *Subst Use Misuse.* 2020;55(9):1413–1421.
8. Rao NR, More CB, Brahmbhatt RM, Chen Y, Ming Wk. Causal inference and directed acyclic graph: an epidemiological concept much needed for oral submucous fibrosis. *Journal of Oral Biology and Craniofacial Research.* 2020;10(4):356–360.
9. Aggrawal N, Bhateja S. OSMF-A review. *Res & Rev Health Care Open Acc J.* 2018;2(1):107–113.
10. Chourasia NR, Borle RM, Vastani A. Concomitant association of oral submucous fibrosis and oral squamous cell carcinoma and incidence of malignant transformation of oral submucous fibrosis in a population of Central India: a retrospective study. *J Maxillofac Oral Surg.* 2015 Dec;14(4):902–906.
11. More CB, Gavli N, Chen Y, Rao NR. A novel clinical protocol for therapeutic intervention in oral submucous fibrosis: an evidence based approach. *J Oral Maxillofac Pathol.* 2018;22(3):382–391.

12. Khan S, Sinha A, Kumar S, Iqbal H. Oral Submucous Fibrosis: current concepts on aetiology and management – a review. *J Indian Acad Oral Med Radiol.* 2018;30(4):407–411.
13. More CB, Rao NR, Hegde R, Brahmbhatt RM, Shrestha A, Kumar G. Oral submucous fibrosis in children and adolescents: analysis of 36 cases. *J Indian Soc Pedod Prev Dent.* 2020;38:190–199.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA group. preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097https://doi.org/10.1371/journal.pmed1000097.
15. Page J. *Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) edited by julian PT higgins, jelena savovic, mathew. Jonathan AC Sterne on Behalf of the Development Group for RoB 2*. 0 20th October 2016; 0 20th October 2016.
16. Risk of bias in non-randomized studies of interventions (ROBINS-I): detailed guidance edited by jonathan AC sterne, julian PT higgins, Roy G Elbers and Barney C Reeves on Behalf of the Development Group for ROBINS-I Updated 20 October 2016.
17. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103:207–213.
18. Chole RH, Balsaraf VS, Dangi BS, et al. A randomized controlled trail of lycopene in oral submucous fibrosis.Journal of the Indian association of public health dentistry2011;3(18):1156-1159.
19. Karemore TV, Motwani M. Evaluation of the effect of newer antioxidant lycopene in the treatment of oral submucous fibrosis. *Indian J Dent Res.* 2012;23:524–528.
20. Selvam NP, Dyanand AA. Lycopene in the management of oral submucous fibrosis. *Asian J Pharmaceut Clin Res.* 2013;6(3):58–61.
21. Subramaniam AV, Subramaniam T, Agrawal N. Assessment of the effectiveness of antioxidant therapy(lycopene) and therapeutic ultrasound in the treatment of oral submucous fibrosis. *Int J Pharm Therapeut.* 2014;5(5):344–350.
22. Singh D, Shashikanth MC, Misra N, Agrawal S. Lycopene and intralesional beta-methasone injections in the management of oral submucous fibrosis. *J Indian Acad Oral Med Radiol.* 2014;26:264–268.
23. Patil S, Khandelwal S, Maheshwari S. Comparative efficacy of newer antioxidants spirulina and lycopene for the treatment of oral submucous fibrosis. 2014;3(6):482–486.
24. Elizabeth N, Gurumani S, Bala AG, Tukalan G. A comparative study between management of oral submucous fibrosis". *J Evol Med Dent Sci.* 2014;3(47):11344–11348.
25. Arshad O, Siddiqi KM, Rana ZA. Oral submucous fibrosis: comparision of different treatment modalities. *Pakistan Oral & Dental Journal.* 2015;35(3):364–369.
26. Nayak A, Anitha B, Bhattacharya A, Podder S. Efficacy of lycopene in combination with vitamin E in management of oral submucous fibrosis – a clinical prospective study. *J Adv Med Dent Sci Res.* 2015;3(3):21–25.
27. Patil S, Sghaireen MG, Maheshwari S, Kunsi SR, Sahu R. Comparative study of the efficacy of lycopene and aloe vera in the treatment of oral submucous fibrosis. *International Journal of Health & Allied Sciences.* 2015;4(1):13–17.
28. Kopuri RK, Chakravarthy C, Sunder S, Patil RS, Shivraj W, Arakeri G. A comparative study of the clinical efficacy of lycopene and curcumin in the treatment of oral submucous fibrosis using ultrasonography. *J Int Oral Health.* 2016;8(6):687–691.
29. Kaur H, Singh A, Goyal S. Use of lycopene in the management of oral submucous fibrosis: a clinical study. *Int Med and Dent Sci.* 2016;5(2):1229–1235.
30. Piyush P, Mahajan A, Singh K, Ghosh S, Gupta S. Comparison of therapeutic response of lycopene and curcumin in oral submucous fibrosis: a randomized controlled trial. *John Wiley Oral Diseases.* 2019;25(1):73–79.
31. Patil S, Yadav N, Zoubi IAA, et al. Comparative study of the efficacy of newer antioxitands lycopene and oxitard in the treatment of oral submucous fibrosis. *Pesq Bras Odontoped Clin Integr.* 2018;18(1):e4059.
32. Saran G, Umapathy D, Misra N, et al. A comparative study to evaluate the efficacy of lycopene and curcumin in oral submucous fibrosis patients: a randomized clinical trial. *Indian J Dent Res.* 2018;29:303–312.
33. Sunderraj S, Sharma R, Agarwal V, Narang P, Reddy YG, Sharma AK. An in vivo study to determine the efficacy of lycopene as compared to multivitamin preparation in the treatment of oral submucous fibrosis. *J Indian Acad Oral Med Radiol.* 2012;24(3):190–193.
34. Gavirangaiah RH, Sowmya GV, Manjunathan BS, Astekar M. Efficacy of lycopene and serratiopeptidase in the management of oral submucous fibrosis: a placebo-controlled follow up study. *World J Pharmaceut Res.* 2018;7(16):707–718.
35. Johny J, Bhagvandas SC, Mohan SP, Punathil S, Moyin S, Bhaskaran MK. Comparison of efficacy of lycopene and lycopene–hyaluronidase combination in the treatment of oral submucous fibrosis. *J Pharm Bioall Sci.* 2019;11:S260–S264.
36. Saawarn N, Shashikanth MC, Saawarn S, Jirge V, Chaitanya NC, Pinakapani R. Lycopene in the management of oral lichen planus: a placebo-controlled study. *Indian J Dent Res.* 2011;22:639–643.
37. Nguyen ML, Schwartz SJ. Lycopene: chemical and biological properties. *Food Technol.* 1999;53:38–45.
38. Stahl W, Sies H. Lycopene : a biologically important carotenoid for humans. *Arch Biochem Biophys.* 1996;336:1–9.
39. Giovannucci E. Response: Tomatoes, tomato-based products, lycopene, and prostate cancer: review of the epidemiologic literature. *J Natl Cancer Inst.* 1999;91(15):1331a–1331.
40. Przybylska S. Lycopene – a bioactive carotenoid offering multiple health benefits: a review. *Int J Food Sci Technol.* 2020;55(1):11–32.
41. Jian WC, Chiou MH, Chen YT, et al. Twenty-eight-day oral toxicity study of lycopene from recombinant Escherichia coli in rats. *Regul Toxicol Pharmacol.* 2008;52(2):163–168.
42. Rao AV, Ray MR, Rao LG. *Lycopene. Adv Food Nutr Res.* 2006;51:99–164.
43. Singh D, Aggarwal S. Lycopene in oral diseases. *Guident.* 2012;5(3):73–74.