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Lycopene And Vitamin E Combination for The Management Of Oral Potentially Malignant Disorders – A Systematic Review

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ABSTRACT

Background: Oral potentially malignant disorders (OPMDs) refer to all epithelial lesions and conditions with an increased risk for malignancy. Oral leukoplakia and Oral Submucous Fibrosis are the most common OPMD. Lycopene is a non-provitamin A carotenoid that gives some vegetables and fruits their red color. Vitamin E also called as α-Tocopherol is a non-enzymatic antioxidant. Lycopene and Vitamin E has been proved to be the most potent scavenger of free radicals in various in-vivo and in-vitro studies.

Aim: To assess the effectiveness of lycopene and vitamin E as a combination for the management of Oral Potentially Malignant Disorders.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA) was followed. The studies included in this systematic review were identified by a comprehensive search from electronic databases until June 2021 using keyword search and MeSH terms. Risk of bias was assessed using RevMan 5 tool.

Results: The search yielded a total of 306 articles out of which 3 articles were included based on the eligibility criteria. From the 3 included studies, a sample size of 182 patients have proven that lycopene and vitamin E combination can be used in the treatment of oral potentially malignant disorders. Among the three clinical trials, one had low risk of bias and other two had intermediate risk of bias. Based on the Oxford Centre for Evidence level, Grade B recommendation is given.

Conclusion: This systematic review highlights the effectiveness of lycopene and vitamin E combination for the management of oral potentially malignant disorders which can be implicated by the practitioners. The average improvement in mouth opening was 6.575 and 91% patients have shown significant improvement in burning sensation. Based on the current evidence, Lycopene and Vitamin E combination could be considered a safe and effective therapeutic modality in the management of Oral Potentially Malignant Disorders.

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Keywords: *Alpha Tocopherol, Oral precancerous lesion, Tomato extract, Leukoplakia, Lichen Planus, Oral submucous fibrosis*

INTRODUCTION

Oral potentially malignant disorders (OPMDs) refer to all epithelial lesions and conditions with an increased risk for malignancy.[1] OPMDs includes Oral Leukoplakia, Erythroplakia, Erythroleukoplakia, Oral Submucous Fibrosis (OSMF), Erosive Lichen Planus, Oral Lichenoid reaction, Palatal lesions in reverse smokers, Lupus erythematosus and Actinic cheilitis of lower lip.[2] In the early stages most of these disorders are asymptomatic and diagnosed by dental practitioners during routine clinical examination.

The overall prevalence of oral potentially malignant disorders worldwide was 4.47%.[3] The most prevalent OPMDs were oral submucous fibrosis (4.96%) and leukoplakia (4.11%). The frequency of OPMDs in India was 6.36%.[4] Rates of oral cancer in India are high, that is, 20 per 100,000 population and accounts for over 30% of all cancers in the country.[5] Majority of the oral cancers are preceded by visible clinical changes in the oral mucosa in the form of white or red patches which may or may not be associated with added signs and symptoms. Overall Malignant transformation (MT) rate across all OPMD groups was 7.9%. MT rates of the specific OPMD subgroups were as follows: Lichen Planus 1.4%, Leukoplakia 9.5, Oral Lichenoid Lesions 3.8%, Oral Submucous Fibrosis 5.2%, Erythroplakia 33.1%, and Proliferative Verrucous Leukoplakia 49.5%. Malignant transformation rate is higher in moderate/severe dysplasia cases when compared to mild dysplasia with an odds ratio of 2.4. [6]

OPMDs may exhibit epithelial dysplasia or less frequently, oral squamous cell carcinoma at baseline presentation. Those that are not malignant are at risk for malignant transformation, therefore, early detection and management of OPMDs are critical and may reduce the cancer-specific morbidity and mortality. There is biopsychosocial morbidity associated with OPMDs, which can influence a patient's quality of life.[7] Various treatment modalities practiced for the management of OPMD are observation, systemic and topical medications, herbal medications, surgical excision, laser surgery, cryosurgery, photodynamic therapy and many more.

Lycopene was discovered by Ernest et al. in 1959, is a fat soluble, non-provitamin A carotenoid that is responsible for red colors found mainly in tomatoes and others like carrots, watermelons and papayas. Lycopene is one of the most potent antioxidants among all the carotenoids with applications in oral diseases ranging from management of oral precancer to management of periodontal diseases. Lycopene has a high number of conjugated double bonds; therefore, it has a higher singlet oxygen quenching capacity. [8] Lycopene has been found to be three times more effective than beta carotene in arresting cell death by neutralizing of reactive nitrogen species.[9]

Lycopene appears to be a very promising antioxidant and protect cells against damage and play a protective role against progression of dysplasia by inhibiting tumor cell proliferation. In Vivo study on endothelial cells in liver of rats showed that lycopene inhibits hepatic fibrogenesis., and it may also exert a similar inhibition on the abnormal fibroblasts in OSMF.[10] Some in vitro experiments have shown that lycopene inhibits the growth process of human neoplastic cells by interfering in growth factor receptor signalling and reducing progression of cell cycle.[11] Lycopene has been reported to increase p53 protein levels which has tumour suppressor properties. Lycopene inhibits abnormal fibroblasts, regulates lymphocyte resistance to stress and suppresses the inflammatory responses.

Vitamin E also called as α-Tocopherol is a non-enzymatic antioxidant. It acts as a scavenger of free radicals, and it helps in maintaining membrane integrity. Vitamin E inhibits cell proliferation, platelet adhesion, monocyte adhesion and by inhibiting mutagenicity and nitrosamine formation it also inhibits cancer cell growth and differentiation. Vitamin-E neutralizes free oxygen radicals and inhibits

carcinogenic nitrosamine formation.[12] They may inhibit cancer development through several mechanisms like stimulation of wild-type p53, down regulation of mutant p53, activation of heat shock proteins, and an antiangiogenic effect mediated by blockage of transforming growth factor-alpha.[13] In several in vivo studies, vitamin E prevented the development of cancers in oral cavities.

The purpose of this systematic review was to assess the effectiveness of lycopene and vitamin E as a combination for the management of oral potentially malignant disorders.

MATERIALS AND METHODS

Study Design

Considering the availability of a vast variety of interventions for OPMD and the availability of numerous randomized controlled trials (RCTs), we decided to carry out a systematic review to determine the effectiveness of lycopene and vitamin E combination mainly with respect to improvement in mouth opening, burning sensation and clinical resolution of the lesion. For this study, we followed the guidelines given by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA). This systematic review was registered with PROSPERO (Reg ID: CRD42021252021).

Eligibility Criteria

Inclusion Criteria

Ø Studies using lycopene and vitamin E combination for the treatment of oral potentially malignant disorders especially leukoplakia, oral submucous fibrosis and erosive lichen planus

Ø Randomised clinical trials

Ø Studies that have compared the intervention either with placebo or with other drugs

Ø Publications in English language

Exclusion Criteria

Ø Studies using lycopene with other combinations

Ø Lycopene and vitamin E combination used for the treatment of other mucosal lesions

Ø Case reports, case series, literature reviews, letters to editor, retrospective studies and expert's opinion

Ø Publications in other languages

Information Sources

A systematic literature review was conducted for English language publications through the various search engines such as PubMed, Google Scholar, Science Direct, Scopus, Cochrane library, Web of Science, ClinicalTrial.gov and Latin American and Caribbean Health Sciences Literature (LILACS) up to June 2021. Hand searching of relevant articles was done until June 2021. Searched trial registration for unpublished work till June 2021. The references in the clinical trials were also screened for possible studies. Articles in English were only included in the systematic review.

Search Strategy

Population or patient- (Leukoplakias,Oral) OR (Oral Leukoplakia) OR (Oral Leukoplakias) OR (Leukokeratoses, Oral) OR (Oral submucous fibrosis) OR (Fibroses, Oral Submucous) OR (Fibrosis, Oral Submucous) OR (Oral Submucous Fibroses) OR (Submucous Fibroses, Oral) OR (Submucous Fibrosis, Oral) OR (Oral lichen planus) OR (Lichen Planus) OR (Unhealed Ulcer) OR (Actinic Cheilitis of Lower Lip) OR (Solar Cheilosis) OR (Oral Lichenoid Reactions) OR (Oral Lupus Erythematosus) OR (Palatal Lesions in Reverse Smokers) OR (Stomatitis Nicotina)

Intervention- (Systemic medications) OR (Systemic agents) OR (Drug Administration, Systemic) OR (Systemic Drug Administration) OR (Systemic Administration) OR (Administrations, Systemic) OR (Systemic Administrations) OR (Administration, Systemic Drug) OR (Administrations, Systemic Drug) OR (Drug Administrations, Systemic) OR (Systemic Drug Administrations) OR (Therapeutics) OR (Lycopene) OR (Carotenoids) OR (Vitamin E) OR (α-Tocopherol)

Selection Process

The titles and abstracts of all retrieved articles were screened by 2 independent reviewers, and irrelevant studies were excluded. If title and abstract screening didn't provide adequate clarity for the paper, the full text of the paper was assessed. Full texts of the potentially relevant studies were obtained and thoroughly assessed by the 2 reviewers for inclusion; disagreements were resolved through discussion. Additionally, we manually searched the reference lists of the collected studies and relevant reviews for additional studies.

Data Extraction

The data was extracted from the studies that were included based on the inclusion criteria by two independent authors after assessing the titles and abstracts of potential studies identifies by search strategy. Data extraction for characteristics of the included studies and the variables of outcome were tabulated.

For all the included clinical trials the following data were recorded

1. Author, year of publication and location of the study
2. Study design and level of evidence
3. Sample size and disease condition
4. Details of the drugs tested
5. Drug dosage, form and duration
6. Outcome measure
7. Follow up
8. Response rate
9. Adverse effects

Risk Of Bias Assessment

The risk of bias of RCTs was investigated independently by both the authors using the modified version of Cochrane's tool for assessing the risk of bias using RevMan 5 software.[14]

RESULTS

Study Selection

The initial search identified 306 articles selected from all databases, out of which 34 were duplicates. After the first screen, 256 records were excluded because they failed to meet the inclusion criteria. Following these exclusions, 16 full text articles were assessed for eligibility and 13 were excluded with reasons. 3 articles were excluded because they were not done in OPMD, 3 because they had no histologically proven OPMD, 3 because they used lycopene and vitamin E alone and 4 because they were literature reviews. A total of 3 randomized controlled trials met our inclusion criteria and were accepted for systematic review, it included 7 treatments, 3 pairwise comparisons, involving 182 patients. The number of records identified in the search to the number of studies included in the review, results of the search and selection process is described as a flow diagram in Figure 1.

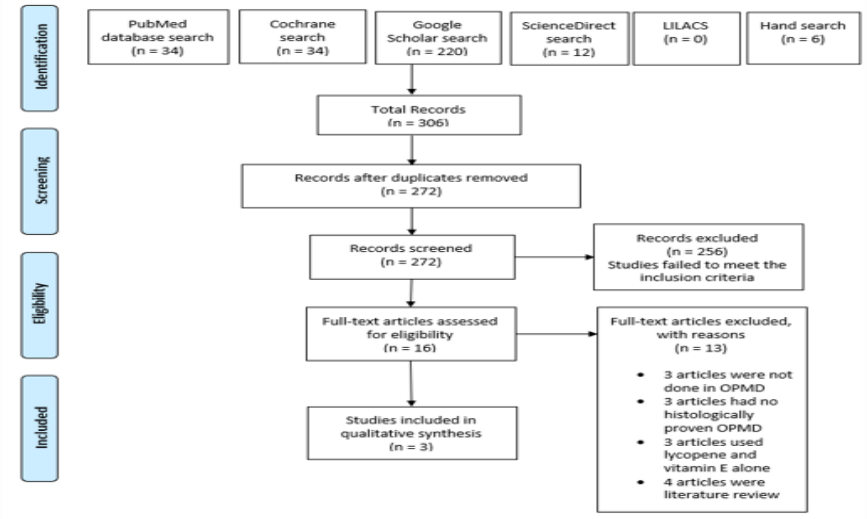


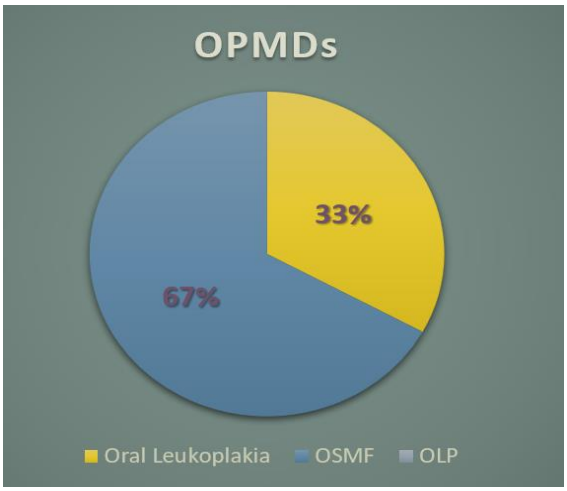
FIGURE 1: depicts the search strategy using PRISMA flowchart

Study Characteristics

The characteristics of all the included studies are summarized in Table 1. All the included clinical trials were published after 2011 and had patients of age group ranging from the second decade to the fifth decade, and male population were more commonly involved in the trial. All the clinical trials had used lycopene and vitamin E combination for the treatment of oral potentially malignant disorders. A total of 182 oral potentially malignant disorders patients were reported in all 3 clinical trials and its distribution is represented in Graph 1. In the majority of the studies, lycopene and vitamin E combination was used for the management of OSMF and leukoplakia. We could not find any other OPMDs being treated with this combination.

TABLE 1: Data Extraction And Characteristics Of The Included Studies

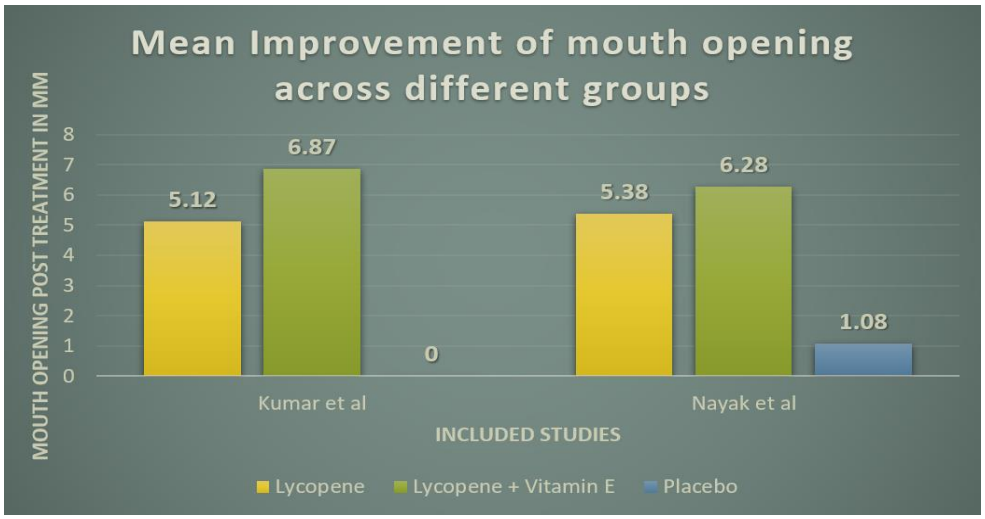
S.No	AUTHOR/ YEAR/ JOURNAL	STUDY DESIGN	SAMPLE	TREATMENT	DOSAGE, FREQUENCY AND DURATION	OUTCOME MEASURES	FOLLOW UP	RESPONSE	ADVERSE EFFECTS & DROP OUT
1	K Kumar V et al 2019 Journal of advanced medical and dental sciences research	RCT	50 clinically and histologically confirmed OSMF patients were randomly divided into 2 groups	Group A – Lycopene Group B – Lycopene + Vitamin E	Lycopene 8mg Lycopene 8mg + Vitamin E 400 IU For 3 months	Improvement in mouth opening and burning sensation	5 Months	Mean mouth opening in Group A was 5.12 ± 1.65 mm and in Group B was 6.87 ± 2.01 mm. Improvement in burning sensation was 88% in group A and 96% in group B	Not mentioned
2	Nayak A et al 2015 Journal of advanced medical and dental sciences research	RCT	72 clinically and histologically confirmed OSMF patients were randomly divided into 3 groups	Group A – Lycopene Group B – Lycopene + Vitamin E Group C - Placebo	Lycopene 8mg in 2 equally divided doses Lycopene 8mg + vitamin E 400 IU + selenium 200 mcg in 2 equally divided doses Placebo capsules once daily For 3 months	Improvement in mouth opening and burning sensation. Presence or absence of erythematous areas/ ulcerations/ erosions	5 Months	Improvement in mouth opening was 75% in group A, 83% in group B and 4% in group C Improvement in burning sensation was 83% in group A, 92% in group B and 67% in group C	No drop outs Adverse effects not mentioned
3	Patel et al 2014 Journal of Indian Academy of Oral Medicine & Radiology	RCT	60 clinically and histologically confirmed Oral Leukoplakia patients were randomly divided into 2 groups	Group A – Lycopene + Vitamin E Group B – Placebo capsules	Lycopene 6mg + vitamin E 400 IU + selenium 200 mcg in 2 equally divided doses Placebo capsules once daily For 3 months	Clinical resolution of the lesion Post treatment biopsy with degree of dysplasia	6 Months	Mean improvement of lesion in Group A was 85% and in Group B was 17%	Drop outs Group A – 9 Group B – 10 No adverse effects



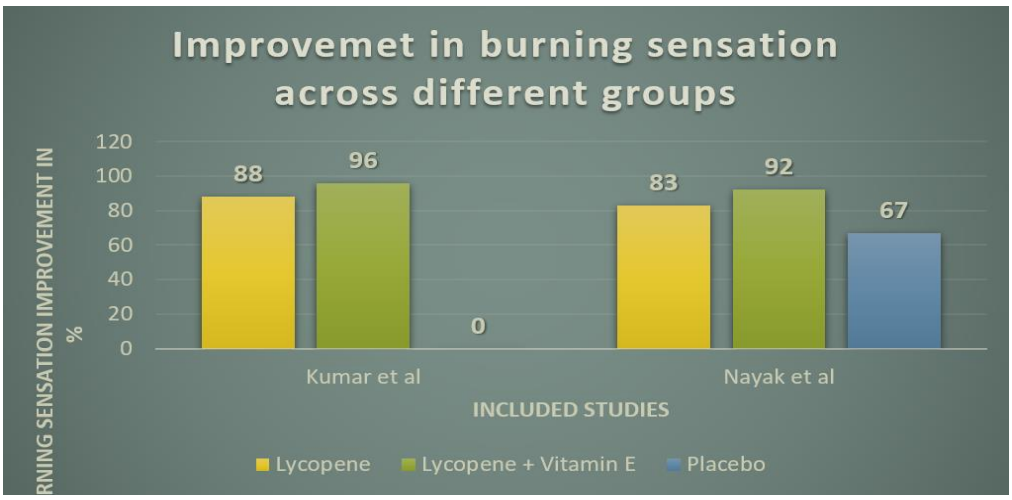
GRAPH 1: represents number of oral potentially malignant disorders in the included studies

For The Management Of Osmf

2 studies used lycopene and vitamin E combination for the management of OSMF and compared their efficacy with lycopene used alone or placebo capsules. [15,16] On comparing the mean improvement of mouth opening post-treatment across different group, lycopene and vitamin E group showed significant improvement in mouth opening following treatment and is represented in Graph 2. Average improvement in mouth opening in lycopene and vitamin E was 6.575 mm. Comparison of improvement in burning sensation post treatment for Lycopene group, Lycopene and vitamin E combination group and placebo capsules group is given in Graph 3. Lycopene and vitamin E group showed significant improvement in burning sensation. Average improvement in burning sensation in lycopene and vitamin E group was 94%.



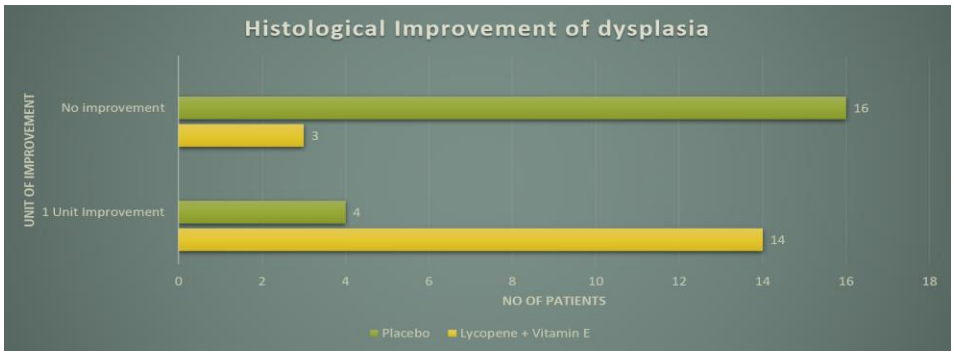
GRAPH 2: represents mean improvement in mouth opening post treatment in the included studies



GRAPH 3: represents improvement in burning sensation post treatment in the included studies

For The Management Of Leukoplakia

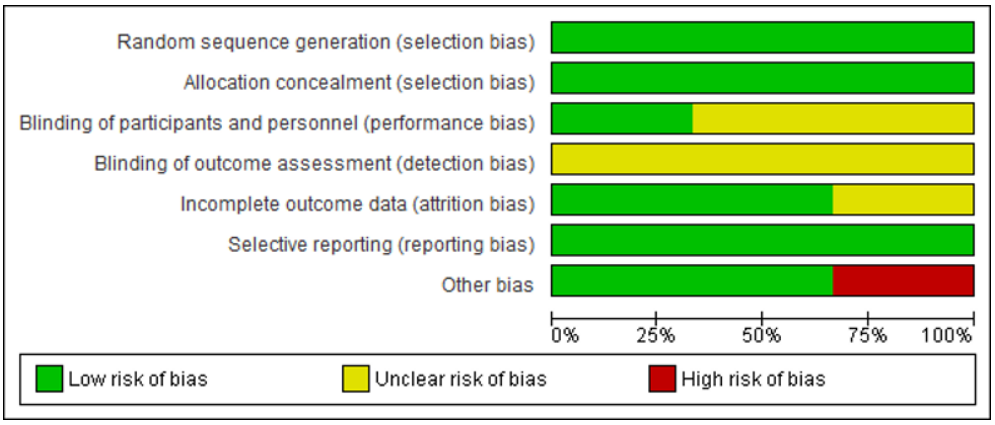
1 study used lycopene and vitamin E combination for the management of leukoplakia and compared their efficacy with placebo capsules.[17] Comparison of histological improvement of dysplasia post treatment for Lycopene and vitamin E combination group and placebo capsules group is given in Graph 4. Patients receiving lycopene in combination with vitamin E had statistically significant improvements both clinically and histologically as compared to those receiving placebo and with no side effects.



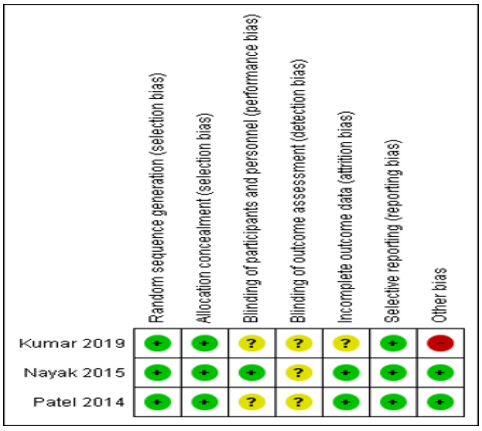
GRAPH 4: histological improvement of dysplasia post treatment in the included studies

Risk Of Bias In Individual Studies

Author's judgements about each risk of bias item presented as percentages across all included studies given in graph 5. The main methodological limitations detected were referred to blinding and recruitment bias. Author's judgements about each risk of bias item for each included study given in graph 6. Of the 3 clinical trials, one study presented with moderate risk of bias and two studies with low risk of bias.



GRAPH 5: represents Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



GRAPH 6: represents Risk of bias summary: review authors' judgements about each risk of bias item for each included study

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Level Of Evidence

Evidence level of each included studies summarised in Table 2. Based on the Oxford Centre for Evidence level, Grade B recommendation is given. All the studies confirmed that Lycopene and Vitamin E combination showed significant improvement in Oral Potentially Malignant Disorders.

TABLE 2: Evidence Level Of Included Studies Oxford Centre for Evidence – Based Medicine (OCEBM) 2011 Levels of Evidence

S. No.	Author And Year	Study Design	Level Of Evidence
1.	Kumar et al 2019	RCT	2b
2.	Nayak et al 2015	RCT	1b
3.	Patel et al 2014	RCT	1b

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

DISCUSSION

OPMDs are at increased risk for malignant transformation, therefore early diagnosis and management are critical to prevent it.[18] All the included studies were from India this is because southeast Asia has the highest prevalence of oral potentially malignant disorder.[19] 2 clinical trials were conducted on 122 oral submucous fibrosis cases and 1 clinical trial on 60 oral leukoplakia cases. We could not find clinical trials on any other OPMDs.

Quality assessment was done with Cochrane risk of bias tool using Revman review manager. Two studies had low risk of bias; this study was done on OSMF and leukoplakia and one study had intermediate risk of bias. Based on the Oxford Centre for Evidence level, level 1b was given for 2 clinical trials and 2b for 1 clinical trial. The Grade of recommendation was B.

The average improvement in mouth opening was 6.575 and 91% patients have shown significant improvement in burning sensation. All the included studies compared lycopene and vitamin E groups to either placebo capsules or lycopene used alone. And our findings confirmed that Lycopene and Vitamin E combination showed significant improvement in Oral Potentially Malignant Disorders when compared to other interventions. A meta-analysis conducted by Roopashri Rajesh Kashyap generated treatment ranking of various herbal derivatives in the management of mouth opening. It also confirmed that lycopene administered along with vitamin E was the most effective treatment and the second effective drug was aloe vera gel.[20]

A total of 9 drop outs from 182 patients. The main reason was because of the low patient compliance. During the period of active treatment, no patients reported undesirable side effects proving the safety of drugs in the management of oral potentially malignant disorders. Lycopene lacks the beta-ionone ring structure and is therefore devoid of pro-vitamin A activity and related side effects.[21]

The limitations of this study must be taken into account, with careful interpretation of the results obtained. One of the difficulties was that we could not find any studies using lycopene and vitamin E combination for the management of OPMDs other than OSMF and Leukoplakia. Follow-up of oral potentially malignant disorders are importance to check for prognosis of the treatment, risk of malignant transformation, recurrence rate and long-term effectiveness of systemic medications in treatment of oral potentially malignant disorders.[22] This systematic review highlights that the follow-up time was only 6 - 12 months ideally a 5 years follow-up is required and the long-term effectiveness of the drugs has not yet been established. The important heterogeneity observed was due to the variability of the study samples, the follow-up period, the study design, comparison group and outcome measures. In

turn, the different molecular or histological grades of the lesions, which can influence the lesion responding to therapy, were not taken into account. So, we could not perform meta-analysis for our study. The proper choice of systemic drug formulation and regime requires further trial.

A daily dosage of 8mg of lycopene with 400 IU vitamin E for a period of 12 weeks showed better performance when compared to other different dosages.

CONCLUSION

All the studies confirmed that Lycopene and Vitamin E combination showed significant improvement in Oral Potentially Malignant Disorders. A proper study design evaluated the outcome measures like size of the lesion, level of dysplasia and follow-up of 6 months post treatment and with minimal side effects was a study done with lycopene and vitamin E combination for the management of leukoplakia. The lycopene and vitamin E drug combination in treatment of oral submucous fibrosis demonstrated average improvement in mouth opening of 6.575 and 91% patients have shown significant improvement in burning sensation with no adverse effects. The literature search revealed no randomized clinical trial using lycopene and vitamin E combination for the treatment of oral lichen planus; hence this systematic review does not have any conclusive evidence for the management of oral lichen planus and other OPMDs. The follow up period was less than 1 year in all the trials, ideally a 5 years follow-up is required and the long-term effectiveness of the drugs has not yet been established. All the clinical trials used lycopene and vitamin E in systemic formulations, future studies should focus more on targeted topical drug delivery systems. This systematic review of 3 clinical trials and a sample of 182 OPMDs highlights the effectiveness of lycopene and vitamin E combination for the management of oral potentially malignant disorders which can be implicated by the practitioners.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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