# COMPARISON OF DIFFERENT DOSES OF LYCOPENE IN THE TREATMENT OF ORAL SUBMUCOUS FIBROSIS: A RANDMOIZED CONTROL TRIAL STUDY

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**By**

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**BATCH: 2021-2024**

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**Dr. Pooja Gupta**

# CONTENTS

# LIST OF TABLES/GRAPHS/ ABBREVIATION

## LIST OF TABLES

## LIST OF GRAPHS

## LIST OF ABREVIATION

| S. No. | Abreviation | Full form |
|---|---|---|
| **1** | OSMF | Oral submucous fibrosis |
| **2** | WHO | World Health Organization |
| **3** | BQ | Betel quid |
| **4** | ANOVA | Analysis of variance |
| **5** | SPSS | Statistical Package for the Social Sciences |
| **6** | P | Level of significance |
| **7** | OLP | oral lichen planus |

# ABSTRACT

**Introduction** An oral cavity condition that causes scarring over time is called oral submucous fibrosis (OSMF). Of all the dietary carotenoids, lycopene is a powerful antioxidant that is present in tomatoes. It is the most effective at quenching singlet oxygen and has a great ability to quench other free radicals in vitro. Hyaluronic acid is hydrolyzed by a protein called hyaluronidase, which is present in mammalian sperm and testes, changing the permeability of connective tissue.

**Objective** To compare and assess the efficacy of lycopene and lycopene hyaluronidase in the treatment of OSMF.

**Materials & Methods** The study included 30 OSMF patients who were split up into three groups. For three months, patients in Group A were given two equally split dosages of Lycostar 16 mg twice day. In Group B Lycostar and a 1500 IU intralesional hyaluronidase injection were administered twice a week for three months to the patients. Group C patients took medications that were a placebo. After three months, the patients had evaluated the mouth opening, visual examination, palpatory findings, and burning sensation.

**Results** A statistically significant difference was observed in mouth opening and burning sensation when lycopene and lycopene-hyaluronidase combination were given instead of a placebo.

**Conclusion** Regarding the treatment of oral submucous fibrosis, lycopene seems to be a very promising antioxidant in terms of both clinical and symptomatic improvement.

**Keywords** oral submucous fibrosis, blanching, fibrous bands, Lycopene, hyaluronidase.

# INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic oral disorder that leaves scars. A growing number of migrant groups are experiencing OSMF, which has led to its recognition as a global issue. Previously, it was thought to be a disorder unique to the Indian subcontinent, China, and other Asian regions. Over time, a number of therapeutic approaches have been developed, but no one treatment has been found as of yet.[1]

Chronic premalignant oral submucous fibrosis (OSMF) is characterised by fibroblastic alteration of the lamina propria and stiffness of the oral mucosa, which ultimately result in mucosal stiffness and functional morbidity of the oral cavity. Between 8 to 10% of OSMF have the potential to change malignantly.[2]

Oral Submucous Fibrosis (OSMF) is a potentially malignant disorder which was described by Schwartz in 1952 as "Atropica idiopathica mucosae oris" and later by Jens J. Pindborg in 1966 as "an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx. It is always linked to a juxtaepithelial inflammatory reaction, fibroelastic change of the lamina propria, and epithelial atrophy that causes the oral mucosa to stiffen, causing trismus and the inability to eat, even though it is sometimes preceded or associated with the formation of vesicles. In addition, the oral mucosa exhibits a leathery texture and blanching, the tongue moves less and becomes depapillated, the decreases mouth opening, and the uvula shrinks. Idiopathic scleroderma of the mouth, juxtaepithelial fibrosis, idiopathic palatal fibrosis, diffuse oral submucous fibrosis, and sclerosing stomatitis are other words used to characterise OSMF..[7]

Strong antioxidant lycopene is extracted from tomatoes using the Lyc-O-Mato technique, which preserves its original ratios to other ingredients in pharmaceutical products that are sold.[3]

Numerous investigations have demonstrated that lycopene is the most effective radical scavenger.[4]

In addition to being used in treating many medical ailments, its antioxidant qualities have also been assessed in the treatment of OSMF.[5]

Lycopene has demonstrated encouraging effects in mitigating signs and symptoms during the early stages of the disease when used in OSMF, at a daily dose of 16 mg. Although the ideal lycopene dosage has not yet been determined, research have shown that 4 to 8 mg of the vitamin daily is generally useful.[9]

It is commonly acknowledged that OSMF is a precursor to oral precancer..[10] This is a prevalent oral cavity issue among South Asians. It is believed to be complex, however a number of risk factors, including genetic vulnerability, collagen abnormalities, eating areca nuts, eating spicy food, and nutritional deficiencies, have been proposed..[6] strongly connect with the eating of betel quid and areca nut. those with a strong pan-chewing habit. Tobaccos from Pan, Masala, Gutka, Mawa, and Mainpuri have a high likelihood of possessing OSMF.[8]

**India has a variety of quid formulations:-**

**Pan (betel quid)-** Betel quid is made out of slaked lime, areca nut (Areca catechu), catechu (Acacia catechu), and betel leaf (Piper betle), which can be eaten with or without tobacco.

**Pan masala**- a prepared food that is manufactured commercially and comes with or without tobacco. It comprises areca nut, slaked lime, catechu, and seasonings.

**Manipuri tobacco** A concoction of lime slaked with tobacco, finely chopped areca nut, cloves, and camphor is used in villages.

**Mawa-** Vendors sell Mawa wrapped in little balls of cellophane. Five to six grammes of areca nut shreds are arranged on a piece of cellophane, on top of which is 0.03 grammes of tobacco and a few drops of watery slaked lime.

**Tobacco-lime-** Making tobacco-lime dishes Khaini is a mixture of slaked lime and tobacco that has been sun-dried. This combination is occasionally smeared on the palm, put in the mouth, and sucked.

**Snuff**- It is made from finely powdered tobacco leaves that have been fire- and air-cured. Dry or moist, it can be used plain or used with other ingredients, and it can be sprayed orally or through the nose. It comes in a metal container, into which a twig is dipped before being applied to the gingiva and teeth.[11]

The main components of the areca nut are: Alkaloids, which include arecoline, areca idine, guvacine, and guvacoline; Flavonoids, which include gallic acid and areca tan nin, as well as catechins; and Copper.While the tannins in areca nut inhibit collagena ses to prevent collagen degradation, the alkaloids in areca nut stimulate fibroblast pr oliferation and produce greater collagen synthesis. Fibrosis is primarily caused by the combined action of areca nut tannins and alkaloids. Histologic alterations in the oral mucosa are caused by all of these substances.[12] Arecoline serves as the main alkaloid accountable for the pathophysiology of OSMF.[13]

Arecoline induces the fibroblast cells to release cytokines and growth factors that promote the deposition of collagen and inhibit its breakdown. Arecoline, an alkaloids found in areca nuts, is another carcinogenic substance that appears to be the main causative factor.[14]

In the past 40 years, the prevalence of OSMF cases has risen from 0.03% to 6.42%, making it a serious public health issue in India.[15]

In individuals with oral premalignant lesions, the prevalence of chewing betel quid (BQ), smoking tobacco, and drinking alcohol is around 82.9%, 95%, and 22.7%, respectively.[16]

It is frequently found in the Indian subcontinent and Southeast Asia. In India, the prevalence of OSMF ranges from 0.2% to 0.5%. Although it can occur at any age, young adults between the ages of 25 and 35 are the most likely to experience it (2nd–4th decade). This disease has a sneaky beginning that often takes two to five years to manifest.[13] The ratio of men to women is about 11:1.[17]

The most important clinicopathological characteristics of OSMF are fibrosis and hyalinization of subepithelial tissue, which have a significant impact on the patients' quality of life.[18]

For a very long time, chewing betel quid has been a common habit across the Indian subcontinent.[19] while Taiwan and other Asian nations also have the illness. Due to the large Indian immigrant population in South Africa, there are also a lot of OSMF patients there. The World Health Organisation (WHO) reports that there are more than 5 million OSMF sufferers worldwide.[20]

# AIM AND OBJECTIVES

**Aim:-**

To Assess the comparison of different doses of lycopene in the treatment of Oral Sub-Mucous Fibrosis.

**Objectives:-**

- To evaluate the efficacy of lycopene in the treatment of Oral Sub-Mucous Fibrosis.
- To evaluate the efficacy of lycopene with hyaluronidase in the treatment of Oral Sub-Mucous Fibrosis.
- To comparison the efficacy of lycopene and lycopene with hyaluronidase in the treatment of Oral Sub-Mucous Fibrosis.

# REVIEW OF LITERATURE

1. **Khanna S. S. and Karjodkar F. R. (2006)[17]** conducted a study on CIRCULATING IMMUNE COMPLEXES AND TRACE ELEMENTS (COPPER, IRON AND SELENIUM) AS MARKERS IN ORAL PRECANCER AND CANCER: a randomised, controlled clinical trial, To evaluate the levels of circulating immune complexes, trace elements (copper, iron and selenium) in serum of patients with oral submucous fibrosis (OSMF), oral leukoplakia (L), and oral squamous cell carcinoma (SCC), analyze the alteration and identify the best predictors amongst these parameters for disease occurrence and progression. Circulating immune complexes (CIC) were estimated using 37.5% Polyethylene Glycol 6000(PEG) serum precipitation. Serum estimation of copper (Cu), Iron (Fe) and selenium (Se) was done using the Oxalyl Dihydrazide method, Colorimetric Dipyridyl method and the Differential Pulse Cathodic Stripping Voltametry respectively. The data analysis revealed increased circulating immune complex levels in the precancer and cancer patients. Serum copper levels showed gradual increase from precancer to cancer patients. However, serum iron levels were decreased significantly in the cancer group. Selenium levels showed marked decrease in the cancer group. Among CIC, serum, copper, iron and selenium the best predictors for the occurrence of lesions were age, serum iron, CIC, serum selenium in the decreasing order. The present study shows that these immunological and biological markers may be associated with the pathogenesis of oral premalignant and malignant lesions and their progressions. Concerted efforts would, therefore, help in early detection, management, and monitoring the efficacy of treatment.

2. **SELVAM N.P. et. al. (2013)[14]** Conducted a study on LYCOPENE IN THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS, Oral Submucous Fibrosis is a potentially malignant disorder well known for its chronic and resistant nature. The conservative drug treatment that is currently available for this disorder is clearly inadequate. The aim of the study was to evaluate the efficacy of oral lycopene therapy when used in combination with conventional intralesional steroid therapy in the management of oral submucous fibrosis. 45 patients with oral submucous fibrosis (grade III and IV) were included under the study and were randomly divided into 3 groups consisting of 15 cases each: Group A (oral lycopene 16 mg/day with biweekly intralesional steroids and hyaluronidase), Group B (oral antioxidant capsules with biweekly intralesional steroids and hyaluronidase) and Group C (biweekly intralesional steroids and hyaluronidase alone). Mouth opening and burning sensation were recorded from baseline to 6 weeks. Cases were followed up to 3 and 6 months. There was significant increase in mouth opening among all the 3 groups. The results were statistically significant between Group A and C and Group B and C. Lycopene in combination with intralesional steroids and Hyaluronidase, is highly efficacious in improving the mouth opening and reducing other symptoms in patients with Oral Submucous Fibrosis. No side effects were reported with its usage.
3. **Nayak A. et. al., (2015)[6]** conducted a study on, EFFICACY OF LYCOPENE IN COMBINATION WITH VITAMIN E IN MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS - A CLINICAL PROSPECTIVE STUDY Background: Oral submucous fibrosis is a precancerous condition with 7-12% malignant potential rate. Present study was conducted with aim to elucidate the role of lycopene in treatment of oral submucous fibrosis. Material and methods:

4. The study group included 72 patients with OSMF. Out of 72, 24 patients were given lycopene, other 24 with lycopene + Vitamin E and remaining 24 were on placebo drug. Lycopene group patients received 8 mg Lycored TM per day in two divided doses of 4 mg each, second group with LYC-O-MATO soft gels while placebo group patients received placebo tablet twice a day. Patients were examined for changes in mouth opening and other clinical symptoms of OSMF during three months. Results: Lycopene in combination with vitamin E was found to be significantly efficacious in the improving signs and symptoms of OSMF. It was effective in reducing the objective signs of OSMF as demonstrated by the improved maximal mouth opening, and reduction in burning sensation, erosion/ ulceration. Conclusion: Lycopene in combination with vitamin E is a highly efficacious drug in the management of oral submucous fibrosis which is proven to be as safe and reliable treatment method.

5. **Holla V. A. et. al. (2016)**[19] conducted a study on RESEARCH ARTICLE A STUDY TO ANALYZE DIFFERENT PATTERNS OF QUID USAGE AMONG SUBJECTS WITH ORAL SUBMUCOUS FIBROSIS IN MANGALORE POPULATION Aim and Objectives. Oral submucous fibrosis (OSF) is a potentially malignant disorder associated with the usage of areca nut. Usage of processed forms of areca nut is popular among the youth and its carcinogenic effects are not well known. Due to large immigrant population, various patterns of areca nut usage are seen. The aim of this study is to assess the various quid chewing patterns and their association with severity of OSF. Materials and Methods. A cross-sectional study was carried out with 250 cases clinically and histologically diagnosed as having OSF lesion that were selected and subjected to a detailed habit history which was recorded through preformed questionnaire. The data obtained was statistically analyzed. Results. Among the 250 subjects, males were seen to be affected more than females within the age

group of 26–35 years and were having clinical stage I OSF. A combination of processed areca nut and processed tobacco was used by the majority of the subjects with duration of 1 to 5 years, at a frequency of 3 to 5 quids per day. Conclusion. The present study confirms the association between oral submucous fibrosis and the quid containing processed areca nut and processed tobacco and also highlights the increasing youth population using the processed forms of areca nut.

6. **Passi D. et.al. (2017)[18]** conducted a study on ORAL SUBMUCOUS FIBROSIS: NEWER PROPOSED CLASSIFICATION WITH CRITICAL UPDATES IN PATHOGENESIS AND MANAGEMENT STRATEGIES, ORAL SUBMUCOUS FIBROSIS (OSMF) is an oral precancerous condition characterized by inflammation and progressive fibrosis of the submucosal tissues resulting in marked rigidity and trismus. OSMF still remains a dilemma to the clinicians due to elusive pathogenesis and less well-defined classification systems. Over the years, many classification systems have been documented in medical literature based on clinical, histopathological, or functional aspects. However, none of these classifications have achieved universal acceptance. Each classification has its own merits and demerits. An attempt is made to provide and update the knowledge of classification system of OSMF so that it can assist the clinicians, beneficial in researches and academics in categorizing this potentially malignant disease for early detection, prompt management, and reducing the mortality. Along with this, pathogenesis and management have also been discussed.

7. **Tejasvi Avinash M. L. et. al. (2019)[11]** conducted a study on A CORRELATION BETWEEN ORAL MUCOSAL LESIONS AND VARIOUS QUID-CHEWING HABIT PATTERNS: A CROSS-SECTIONAL STUDY, Quid-chewing habit is a common and old tradition in India. It causes various potentially malignant

disorders. Therefore, a study was undertaken to analyze the association of various quid-chewing habit patterns and different oromucosal lesions. A cross-sectional study was conducted on 150 cases, where all the individuals selected were having quid-chewing habit and oromucosal lesions. Detailed habit history was taken through preformed questionnaire, clinical examination was done, and the lesion was subjected to incisional biopsy and confirmed histopathologically. The male to female ratio of various quid-chewing habit and oromucosal lesions was 9:1. The middle aged were more commonly involved. Of the various types of quids chewed, a combination of processed betel and processed tobacco which is commercially available was used by majority of the individuals. Oral submucous fibrosis (OSMF) was seen in majority of the cases. Interpretation and The present study confirms the association between betel, tobacco, and various lesions such as OSMF, leukoplakia, chewer's mucosa, lichenoid reaction, and chemical burn. It also confirms the strong association of betel to OSMF and tobacco to leukoplakia.

8. **Jain A. et. al. (2019)**[13] conducted a study on ORAL SUBMUCOUS FIBROSIS IN PEDIATRIC PATIENTS: A SYSTEMATIC REVIEW AND PROTOCOL FOR MANAGEMENT, To conduct a systematic review evaluating the cases of oral submucous fibrosis in paediatric patients. Systematic review was conducted using PRISMA guidelines. The article focused on oral submucous fibrosis in paediatric patients were included. A total of five manuscripts were included in our systematic review. The prevalence of OSMF in paediatric patients, gender distribution, causes, and clinical presentation were reviewed. On systematically reviewing, a total of 10 cases of OSMF in paediatric patients were found. The youngest patient reported to be diagnosed with OSMF was of 2.5 years of age. Female preponderance was noticed. All the patients had the habit of areca nut chewing which subsequently led to fibrosis. Conclusion. Such a rapid increase

in the rate of OSMF among paediatric population is a potential danger to the society. The habit of areca nut chewing is the major cause for this dreadful condition. Lack of health consciousness and low level of education are the major factors for initiation of this habit among children. Therefore it is imperative for the parents and school as well as government authorities to take serious actions.

9. **Johny J. et. al. (2019)[3]** Conducted a study on COMPARISON OF EFFICACY OF LYCOPENE AND LYCOPENE-HYALURONIDASE COMBINATION IN THE TREATMENT OF ORAL SUBMUCOUS FIBROSIS, Oral submucous fibrosis (OSMF) is a chronic progressively scarring disease of the oral cavity. Lycopene is a powerful antioxidant obtained from tomatoes and has the highest singlet oxygen quenching capacity and a high capacity of quenching other free radicals in vitro among dietary carotenoids. Hyaluronidase is a substance prepared from the testes and semen of mammals that modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid. To evaluate the efficacy of lycopene and lycopene− hyaluronidase combination, and to compare the efficacy of lycopene and lycopene−hyaluronidase combination in the treatment of OSMF. The study consisted of 45 patients with OSMF divided into three equal groups. Patients in Group A were given Lycored 16mg daily in two equally divided doses for 3 months. Patients in Group B were given LycoRed along with hyaluronidase intralesional injection of 1500 IU twice weekly for 3 months. Patients in Group C were given placebo capsules. Patients were evaluated after 3 months. The following parameters were recorded: mouth opening, visual inspection, palpatory findings, and burning sensation. There was statistically significant change in mouth opening and burning sensation for lycopene and lycopene–hyaluronidase combination than in the placebo group in the treatment of OSMF, but the lycopene–hyaluronidase combination did not show any statistically significant change when compared with lycopene alone.

Lycopene appears to be a very promising antioxidant in the management of oral submucous fibrosis, both in clinical and symptomatic improvement.

10. **Shih Y.H., et. al. (2019)[10]** conducted a study on ORAL SUBMUCOUS FIBROSIS: A REVIEW ON ETIOPATHOGENESIS, DIAGNOSIS, AND THERAPY, Oral submucous fibrosis (OSF) is characterized by abnormal collagen deposition. It is a precancerous disorder and transforms into a malignant tumor in 1.5–15% of all cases. Symptoms include submucous fibrosis, ulceration, xerostomia, a burning sensation, and restricted mouth opening. All of these greatly interfere with patient quality of life. The present review introduces OSF from a molecular perspective and summarizes what is known about its underlying mechanisms, diagnostic biomarkers, and therapeutic interventions. In addition to the aggressive treatment of OSF, its prevention is also important. Future research should, therefore, focus on improving the oral health literacy of the patients susceptible to OSF.

11. **More C. B., Rao N.R. (2019)[12]** Conducted a study on PROPOSED CLINICAL DEFINITION FOR ORAL SUBMUCOUS FIBROSIS JOURNAL OF ORAL BIOLOGY AND CRANIOFACIAL RESEARCH, Oral Submucous Fibrosis (OSMF) is an insidious, chronic, complex, crippling, debilitating, irreversible, progressive, scarring, potentially malignant and collagen metabolic disorder, induced by a known carcinogen areca nut; wherein the oral mucosa, and occasionally the pharynx and esophagus is subjected to various pathological changes with significant clinical manifestations at different stages of progression, leading to functional morbidity; and with a risk of malignant transformation in the overlying epithelium. Although the condition is mainly diagnosed based on classic clinical manifestations, the commonly used existing definition for oral submucous fibrosis is primarily based on histological features. The authors have conducted extensive clinical research studies on OSMF and intends to propose a new clinical definition as ‘a debilitating, progressive,

irreversible collagen metabolic disorder induced by chronic chewing of areca nut and its commercial preparations; affecting the oral mucosa and occasionally the pharynx and esophagus; leading to mucosal stiffness and functional morbidity; and has a potential risk of malignant transformation.' Thus, a new clinical definition is put forward so as to assist the academicians, researchers and clinicians in terming and grouping this disease according to its clinical and biological behaviour for its subsequent management.

12. **Gupta N. et. al. (2020)[5]** Conducted a study on EFFICACY OF LYCOPENE IN MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS– A SYSTEMATIC REVIEW AND META-ANALYSIS, To evaluate the efficacy of lycopene in the management of Oral Submucous Fibrosis (OSMF). 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 Nonrandomized) involving lycopene as one of the intervention. 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. 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.

13. **Rao N.R. et. al. (2020)[7]** Conducted a study on ORAL SUBMUCOUS FIBROSIS: A CONTEMPORARY NARRATIVE REVIEW WITH A PROPOSED INTER-PROFESSIONAL APPROACH FOR AN EARLY DIAGNOSIS AND CLINICAL MANAGEMENT, Oral Submucous fibrosis

(OSMF) has traditionally been described as “a chronic, insidious, scarring disease of the oral cavity, often with involvement of the pharynx and the upper esophagus”. Millions of individuals are affected, especially in South and South East Asian countries. The main risk factor is areca nut chewing. Due to its high morbidity and high malignant transformation rate, constant efforts have been made to develop effective management. Despite this, there have been no significant improvements in prognosis for decades. This expert opinion paper updates the literature and provides a critique of diagnostic and therapeutic pitfalls common in developing countries and of deficiencies in management. An inter-professional model is proposed to avoid these pitfalls and to reduce these deficiencies.

14. **Thakur V. et. al. (2020)[8]** Conducted a study on A SHORT REVIEW ON OSMF: ORAL SUB MUCOUS FIBROSIS Oral submucous fibrosis (OSMF) is a premalignant condition caused by betel chewing. OSMF is a premalignant condition that can lead to oral cancer. A risk that is further increased by concomitant tobacco consumption. OSMF is a diagnosis based on clinical symptoms and confirmation by histopathology. Major constituents of betel quid are arecoline from betel nuts and copper, which are responsible for fibroblast dysfunction and fibrotic band formation. drug therapy include antifibrotic, anti-inflammatory, and antioxidants, homemade remedies including turmeric and tulsi. Prevention is most important in case of OSMF, because severe cases of OSMF are irreversible.

15. **Ahmad T. et. al. (2021)[15]** Conducted a study on AN OVERVIEW OF EFFECT OF LYCOPENE AND CURCUMIN IN ORAL LEUKOPLAKIA AND ORAL SUBMUCOUS FIBROSIS, The purpose of the current article was to evaluate

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

16. **Hui Xu et. Al., (2021)[20]** Conducted a study on RESEARCH ACHIEVEMENTS OF ORAL SUBMUCOUS FIBROSIS: PROGRESS AND PROSPECT, Oral submucous fibrosis (OSMF) is a kind of chronic, insidious disease, and it is categorized into potentially malignant disorders (PMD), which poses a global and regional problem to public health. It is considered to be a multifactorial disease, such as due to areca nut chewing, trace element disorders, and genetic susceptibility. However, there is still no unanimous conclusion on its pathogenesis, diagnosis, and treatment strategies. Hence, this article provides a comprehensive review and prospect of OSMF research,

providing scholars and clinicians with a better perspective and new ideas for the research and treatment of OSMF.

17. **Asdullah M. et. al. (2022)**[1] conducted a study on COMPARING THE EFFICACY OF LYCOPENE & LYCOPENE WITH HYALURONIDASE IN MANAGEMENT OF ORAL SUB MUCOUS FIBROSIS-A CLINICAL STUDY. Oral submucous fibrosis (OSMF) is a scarring disease of the oral cavity that develops over time. Lycopene is a potent antioxidant found in tomatoes that has the best singlet oxygen quenching capability and a strong capacity to quench other free radicals in vitro of all the dietary carotenoids. A protein called hyaluronidase, which is found in mammalian sperm and testes, hydrolyzes hyaluronic acid to alter the permeability of connective tissue. To determine the effectiveness of lycopene and lycopenehyaluronidase in treating OSMF, as well as a comparison of their effectiveness. 45 people with OSMF were enrolled in the study and divided into three groups. Patients in Group A received two evenly divided doses of Lycored 16 mg twice daily for three months. Patients in Group B received LycoRed and a 1500 IU intralesional injection of hyaluronidase twice a week for three months. Patients in Group C received placebo pills. The patients were evaluated at the end of three months. We observed the opening of the mouth, visual examination, palpatory findings, and burning sensation. For lycopene and lycopene–hyaluronidase combination, there was a statistically significant difference in mouth opening and burning sensation compared to placebo.

18. **Gopinath D. et. al. (2022)**[2] Conducted a study on COMPARATIVE EFFICACY OF INTERVENTIONS FOR THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS, Oral submucous fibrosis (OSMF) is a chronic premalignant condition and is characterized by fibroblastic change of lamina propria and

stiffness of oral mucosa. Though there are several treatment options available, the best agent is not yet identified. This study assessed the comparative efficacy and safety of medical interventions in the management of OSMF. A systematic review was performed to identify randomized controlled trials (RCTs) that compared the efficacy of interventions for OSMF with each other, or placebo. A network meta-analysis was performed, and the interventions were ranked according to their efficacy based on the surface under the cumulative ranking. (PROSPERO Registration no: CRD42021255094). Thirty two RCTs comprising 2063 patients were eligible for quantitative analysis. In terms of therapeutic efficacy in the improvement of mouth opening Oxitard, a herbal formulation was ranked as the most efficacious agent, [MD, 10.29 (95%CI 6.34–14.25)] followed by combination therapy of Lycopene with corticosteroids and hyaluronidase [MD, 7.07 (95%CI 1.82–12.31)]. For improvement of burning sensation aloe vera was ranked first [MD, 6.14 (95%CI 4.58–7.70)] followed by corticosteroids with antioxidants [MD, 6.13 (95%CI 4.12–8.14)] and corticosteroids in combination with hyaluronidase with antioxidants [MD, 5.95 (95%CI 3.79–8.11)]. In terms of safety, most of the drugs were reported to cause mild adverse effects only. Significant inconsistencies could be identified in the analysis for both the outcomes assessed and were further explored. Our study highlighted the potential efficacy of several agents over placebo in the improvement of mouth opening and burning sensation in OSMF patients. However, the RCTs lacked methodological soundness. Well-designed studies with a larger number of participants with a rigorous randomization process and stringent methodology are recommended to strengthen the results obtained, which may help to construct a clinical guideline for OSMF management.

19. **Patil S. et. al., (2023)**[4] conducted a study on COMPARATIVE STUDY OF THE EFFICACY OF LYCOPENE AND ALOE VERA IN THE TREATMENT OF ORAL SUBMUCOUS FIBROSIS. Background and Aim: Oral submucous

fibrosis (OSMF) is a high-risk premalignant condition largely seen in the Indian subcontinent. A number of studies have proven the use of antioxidants in the management of OSMF. Therefore, the aim of the present study was to compare the efficacy of two antioxidants, lycopene and aloe vera in the management of OSMF. Material and Methods: One hundred and twenty clinicopathologically diagnosed OSMF patients, were included in the study. They were divided equally into, Group A (lycopene group) and Group B (aloe vera group). Group A was administered 8mg lycopene in two divided doses of 4mg daily and Group B was given5mg aloe vera gel to be applied topically thrice daily for 3 months. Different clinical parameters were evaluated at regular intervals and data was analyzed using the Student's paired *t*-test and Chi-square test. $P < 0.001$ was considered to be statistically significant. Results: Clinical improvements in mouth opening and tongue protrusion were significant in Group A ($P < 0.001$). Subjective symptoms of burning sensation ($P = 0.007$), pain associated with the lesion ($P = 0.005$), and difficulty in swallowing and speech ($P = 0.003$) improved in both the groups, but were insignificant. There was a mild to moderate decrease in the size of the lesion. Conclusion**:** The present study concludes that though, there is no definitive treatment for the condition; however, lycopene can bring about significant clinical improvements in the symptoms like mouth opening and tongue protrusion when compared to aloe vera. Both the drugs appear to be promising in the treatment of OSMF.

20. **Karemore TV, Motwani M.(2023)[9]** Conducted a study on EVALUATION OF THE EFFECT OF NEWER ANTIOXIDANT LYCOPENE IN THE TREATMENT OF ORAL SUBMUCOUS FIBROSIS., Background and objective**:** Oral submucous fibrosis (OSMF) is a well-known premalignant condition encountered in Indian population. Although the disease is advancing rapidly, its reliable treatment modality for its various stages has not yet evolved. The aim of the present study is to compare the effect of newer antioxidant

lycopene with a placebo in conjunction with the cessation of causative habit in the treatment of OSMF. Materials and methods**:** The study group included 92 patients with OSMF. The OSMF diagnosis was established through a composite of accepted clinical and histopathological characteristics. Out of 92, 46 patients were given lycopene and remaining 46 were on placebo drug. Lycopene group patients received 8 mg Lycored TM per day in two divided doses of 4 mg each, while placebo group patients received placebo tablet twice a day. Patients were examined for changes in mouth opening and other clinical symptoms of OSMF during three months and were followed up for next two months. Results: Lycopene was found to be significantly efficacious in the amelioration of signs and symptoms of OSMF. It was effective in reducing the objective signs of OSMF as demonstrated by the improved maximal mouth opening, percentage of which was 69.56%($P<0.05$). Interpretation and conclusion**:** Reactive oxygen compounds or free radicals have been implicated as one of the major harmful factors for premalignant and malignant conditions. Present study concludes that lycopene, a newer antioxidant, appears to be a very promising drug in the management of OSMF.

21. **Xiaofeng Qin et. al. (2023)**[21] conducted a study on ORAL SUBMUCOUS FIBROSIS: ETIOLOGICAL MECHANISM, MALIGNANT TRANSFORMATION, THERAPEUTIC APPROACHES AND TARGETS Oral submucosal fibrosis (OSF) is a chronic, progressive and potentially malignant oral disorder with a high regional incidence and malignant rate. With the development of the disease, the normal oral function and social life of patients are seriously affected. This review mainly introduces the various pathogenic factors and mechanisms of OSF, the mechanism of malignant transformation into oral squamous cell carcinoma (OSCC), and the existing treatment methods and new therapeutic targets and drugs. This paper summarizes the key molecules in the pathogenic and malignant mechanism of

OSF, the miRNAs and lncRNAs with abnormal changes, and the natural compounds with therapeutic effects, which provides new molecular targets and further research directions for the prevention and treatment of OSF. The present study was done to compare the efficacy of Lycopene & Lycopene with Hyaluronidase in management of Oral Sub Mucous Fibrosis.

# MATERIAL AND METHODS

**Study Area:-**

The study was performed in the Department of Public Health Dentistry, Babu Banarasi Das College of Dental Sciences, Lucknow, Uttar Pradesh.

The state capital of Uttar Pradesh, India, is Lucknow.

The city is situated at an elevation of 123meters (404ft) above sea level. Lucknow district Covers an area of 2,528 square kilometers (976 sqm).

It is surrounded on Eastern side by district Barabanki, on the western side by district Unnao, on southern side by Raebareli and on the northern side by Sitapur and Hardoi.

According to provisional Year report of India, Lucknow City had a population of 2,815601, of which 1,470,133 were men and 1,345,468 women. This was an increase of 25.36% compared to the 2001 census report of India.

The city has a total literacy level in 2011-2022 of 82.50% compared to 69.7% for Uttar Pradesh as a whole.

**Study Design:-**

The study is a double blinded parallel multiple arm randomized control trial to compare the efficacy of lycopene & lycopene with hyaluronidase in management of Oral Sub-Mucous Fibrosis.

**Study Population:-**

A randomized control trial was conducted on patients aged 18 to 65 years of age with OSMF.

**Inclusion criteria:-**

- Both male and female genders.
- Participant age 18 to 65.
- Participants without known systemic illness.
- History of the habit of chewing areca nut or any of its commercial products.
- Burning sensation on eating spicy food.
- Participants with Grade 2 OSMF.

**Exclusion Criteria:-**

- Participants with known systemic illness.
- Patients who are on medication.
- Patients who do not give consent.

**Pilot Study**

Pilot study was conducted in Babu Banarasi Das College of Dental Sciences, Lucknow. A total of 9 participants, 3 each group were recruited to check the feasibility of the study and subjects included in the pilot study were excluded in the main study.

**Sampling Technique :-**

• A simple random sampling was used.

**Sample Size Estimation:-**

The sample size determination was carried out using the previous literature[1]. A sample size was calculated by 95% confidence interval and 5% margin of error. A total of 200 patients were screened out of which 110 fulfilled the eligibility criteria. From the 110 eligible study participants, final required sample size of 30 subjects were randomly selected. Then the participants were divided into three groups and 10 subjects were included in each group.

**Schedule Of The Survey:-**

The collection of the patients was done from May 23 till June 23.
In the 1st and 2nd week of July 23, groups were assigned to the patients.
From 3rd week of July interventions was given to the patients. Then patients were examined every week from first week of August till October 23.

**Ethical Consideration:-**

The Ethical Clearance was obtained from the Institutional Ethical committee (IEC) of Babu Banarasi Das College Of Dental Sciences, Lucknow, Uttar Pradesh.

The required official permission to select and collect the relevant data from selected subjects was solicited and obtained from the Principal of the Babu Banarasi Das College Of Dental Sciences, Lucknow.

**Consent:-**

After describing the goal of the study to the subjects, informed written agreement was obtained.

**Calibration and Training:-**

The researcher received training and calibration in the Department of Public Health Dentistry at Babu Banarasi Das College of Dental Sciences in Lucknow prior to the study. The investigator received training on the outpatients under the supervision of a qualified individual. To evaluate the consistency of intra-examiner reproducibility and intra-examiner reliability, about eight subjects were investigated. 90% agreement was anticipated for the majority of the assessments.

**Clinical Examination :**

The research was carried out at the Babu Banarasi Das College of Dental Sciences, BBDU, Lucknow, in the Department of Public Health Dentistry. All study participants underwent a clinical examination by the investigator, a single examiner, using standardized equipment in artificial lighting. We adhered to the ADA specification type III examination. Subjects examined were seated on dental chair with the examiner standing by the side of the chair.

A study specific proforma was used to record and evaluate demographic details, medical and dental history of each participant.

**Recording clerk:-**

Recording clerk was assigned to record the data of study participants. The Recording clerk was well versed pertaining to terms and codes of the survey prior to survey to avoid any error while recording data of study participants.

**Survey forms:-**

Appropriate number of Study specific specially designed proforma was used during the study.

**Trial design:-**

Allocation Ratio: 1:1:1

**Allocation Sequence:-**

Participants were allocated to groups on the basis of envelope method.

For this reason, a box holding hidden envelopes was used.. Each envelope carried either code "A". "B" or code "C". Participants who were selected to participate in the study were each asked to pick a concealed envelope from the box. Participants were allocated to the respective group.

**Type of randomization:-**

Simple Randomization was the type of randomization used for the study.

**Unit of randomization:-**

OSMF Grade 2 was used as unit of randomization.

**Blinding:-**

The study was a double blinded parallel multiple arm randomized control trial. The study subjects remained blind to the lycopene and hyaluronidase injection and the placebo that they were given to the population. The investigator remained blinded to the lycopene and hyaluronidase injection which were given to the study participants. To ensure this the interventions were kept in brown colored opaque containers. They were each labeled as either code "A", "B" or "C". The codes weren't cracked until the clinical experiment was over.

**Implementation:-**

Participants were assigned to the group and generation of sequence was done by the organizing clerk.

**Ethical Issues:-**

The nature and purpose of the study was explained to the Institutional Review Board and ethical clearance was obtained and permission to conduct the main study in the colleges was obtained by the Institutional Ethical Committee of Babu Banarasi Das College of Dental Sciences.

**Intervention:-**

Total 30 patients with signs and symptoms of grade 2 OSMF were recruited for the study. They were explained about the disease condition and its premalignant potential and then counselled to stop the habit of using areca nut in all its forms. Complete oral prophylaxis was done to improve the oral hygiene as well as to motivate the patients to stop the habit.

Patients were divided into 3 groups consisting of 10 each (group A, group B and group C)

**Group A -** Patients received two evenly divided doses of Lycopene (Lycostar capsule) 16 mg twice daily for 3 months.

**Group B** - Patients received Lycopene (Lycostar capsule, Mankind Pharmaceuticals, India) and a 1500 IU intralesional injection of hyaluronidase (Hynidase; Rallis India Ltd, Mumbai, India) twice a week for 3 months.

**Group C** - Patients received placebo pills.

Patients were evaluated every week during the treatment period of 3 months. The following parameters were recorded every week during the study period.

**Burning sensation:-**

It was recorded at baseline before the start of the treatment and at the end of every week for a period of 3 months during treatment using visual analog scale for pain. It will be scored from Non-verbal pain Scale 0-10 purely based on patient's response (score 0-no pain; score 10-severe pain)

**Mouth opening:-**

Using vernier callipers, the mesio-incisal edge of the maxillary right central incisor and the mesio-incisal edge of the mandibular right central incisor were measured in order to determine the mouth opening. The counterpart on the left side was utilised for measurement if one or both of the teeth were missing. Mouth opening was measured at baseline, prior to the commencement of the treatment, and then at the

conclusion of each week for the three months that the medication was administered. It was also noted during the three-month follow-up period following therapy.

**Habits:-** The habit of tobacco eating of the patients were recorded.

**Visual and Palpatory changes:-**

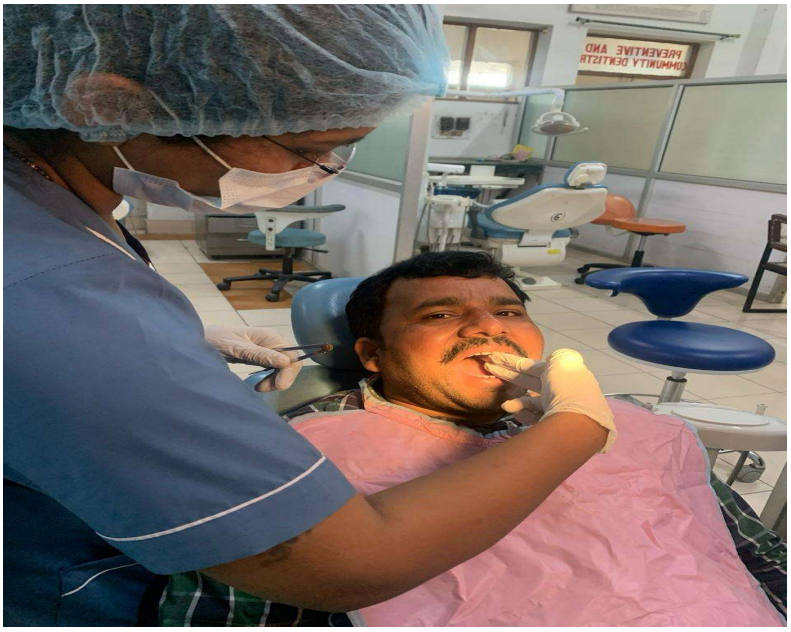
Grade 2 OSMF[6] was observed at baseline before start of treatment among patients in group A, B and C and post treatment at 3 month follow up period.

**Materials and Instruments:-**

- Examination gloves
- Mouth mask
- Head cap
- Patient Drape
- Plain Mouth mirrors
- Vernier caliper (Calibrated)
- Sterilized cotton and gauze pieces
- Cotton holder
- Disposable glasses
- Visual analog scale
- Kidney tray
- Diagnostic tools (mouth mirror, tweezer, probe) sterilized
- Lycopene (Lycostar capsule, Mankind Pharmaceuticals, India**)** 16mg
- 1500 IU intralesional injection of hyaluronidase (Hynidase; Rallis India Ltd, Mumbai, India)

**Data Analysis:-**

Data so collected were tabulated and statistically analyzed using the SPSS version 22.0. To assess the efficiency of the treatment, an unpaired ANOVA test was used. $P < 0.005$ was designated as the significance level.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# RESULTS

In the present study 30 patients with signs and symptoms of OSMF were recruited and were divided into 3 groups. The descriptive statistics included mean, standard deviation, frequency and percentage. The level of the significance for the present study was fixed at 5%. The intergroup comparison was done using the One way ANOVA test followed by post Hoc Analysis depending upon the normality of the data.

**Variation (mean) of burning sensation between the three groups**

The mean change in the pre and post treatment values in the Lycopene-Hyaluronidase was 3.87±1.19, in the Lycopene was 2.75±0.91 and in the control group was 0.84±0.76. The intergroup comparison between three groups was statistically significant when analyzed using One Way ANOVA with p value less than 0.001. The post hoc analysis revealed a statistically significant difference between two group - Lycopene vs Control and Control vs Lycopene- Hyaluronidase. Non-significant difference was observed for Lycopene-Hyaluronidase vs Lycopene.

**Table 1: Mean+SD of burning sensation between the three groups**

| | **Mean** | **Std Deviation** | **P value** | **Significance** |
|---|---|---|---|---|
| Lycopene-Hyaluronidase | 3.87 | 1.19 | 0.001 | Significant |
| Lycopene | 2.75 | 0.91 | | |
| Controls | 0.84 | 0.76 | | |

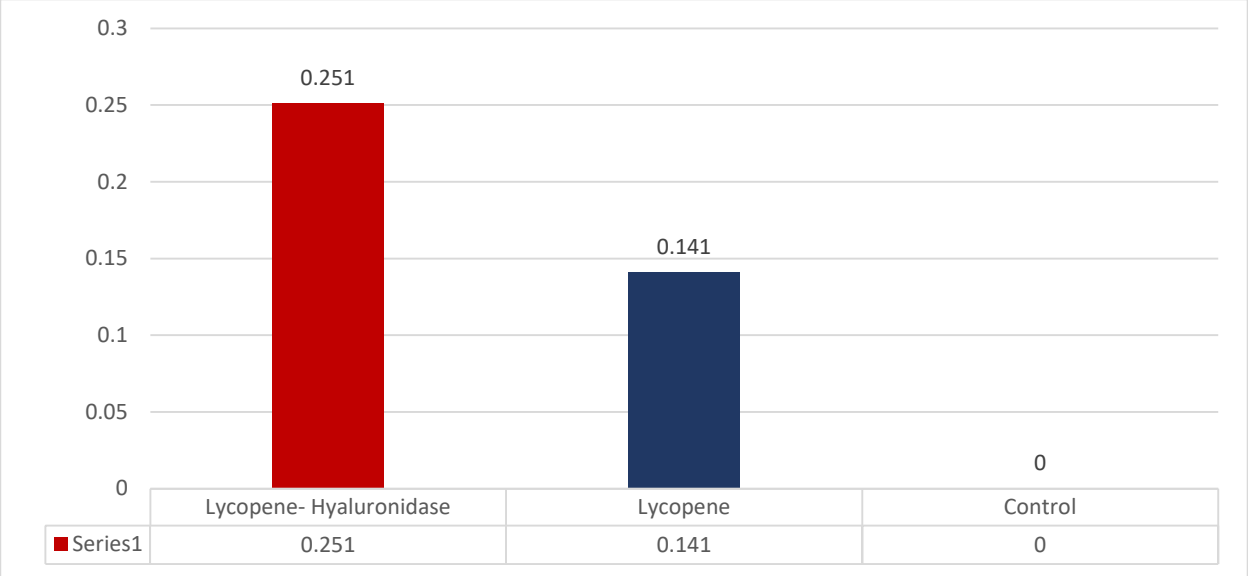
*ANOVA applied; $p<0.05$*

**Table 1.1: Post Hoc Analysis for burning sensation of three groups**

| | Mean | Std Deviation | P value | Significant |
|---|---|---|---|---|
| Lycopene- Hyaluronidase vs Lycopene | 1.12 | 0.85 | 0.781 | Non-Significant |
| Lycopene vs Control | 1.91 | 0.82 | 0.001 | Significant |
| Control vs Lycopene-Hyaluronidase | 2.03 | 0.86 | 0.001 | Significant |

*Post Hoc Tukeys applied; p<0.05*

**Graph 1: Post Hoc Analysis for burning sensation of three groups**



**Variation (mean) of Mouth Opening between the three groups**

The mean change in the pre and post treatment values in the Lycopene-Hyaluronidase was 3.45±1.04, in the Lycopene was 2.49±0.89 and in the control group was 1.02±0.72. The intergroup comparison between three groups was statistically significant when analyzed using One Way ANOVA with p value less than 0.001. The post hoc analysis revealed statistically significant difference between two group - Lycopene vs Control and Control vs Lycopene- Hyaluronidase. There was non-significant difference for Lycopene-Hyaluronidase vs Lycopene.

**Table 2: Mean+SD of Mouth Opening between the three groups**

| | **Mean** | **Std Deviation** | **P value** | **Significance** |
|---|---|---|---|---|
| Lycopene-Hyaluronidase | 3.45 | 1.04 | 0.001 | Significant |
| Lycopene | 2.49 | 0.89 | | |
| Control | 1.02 | 0.72 | | |

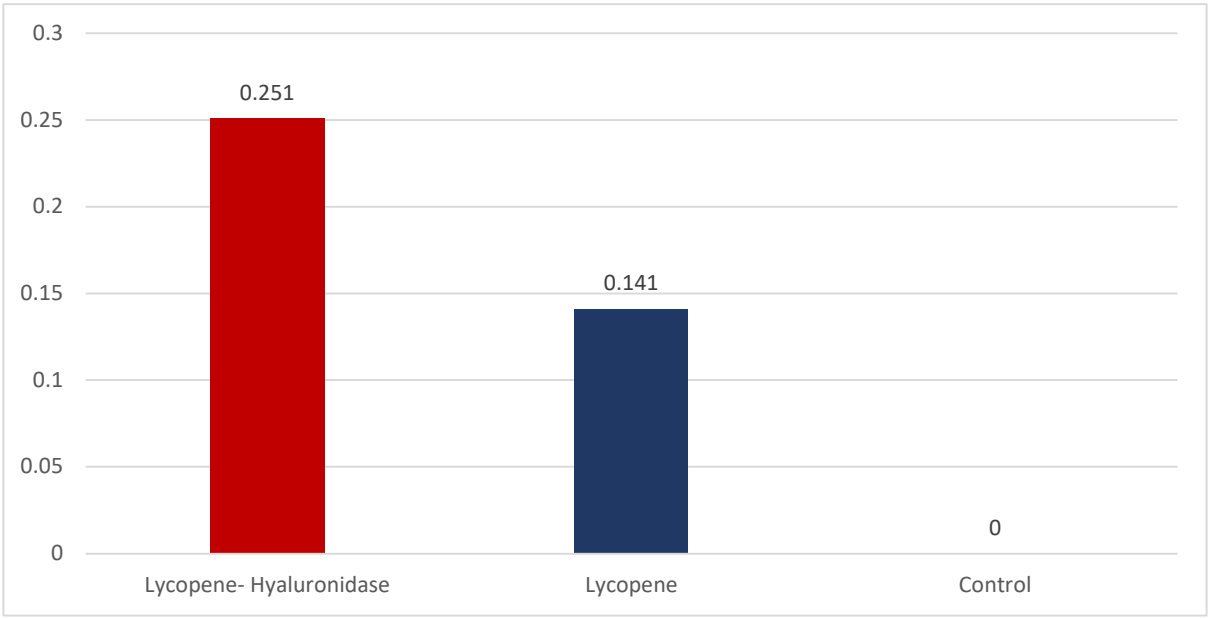
*ANOVA applied; $p<0.05$*

**Table 2.1: Post Hoc Analysis_Mouth Opening between the three groups**

| | Mean | Std Deviation | P value | Significant |
|---|---|---|---|---|
| Lycopene- Hyaluronidase vs Lycopene | 0.94 | 0.72 | 0.391 | Non-Significant |
| Lycopene vs Control | 1.47 | 0.91 | 0.001 | Significant |
| Control vs Lycopene-Hyaluronidase | 2.43 | 0.93 | 0.001 | Significant |

*Post Hoc Tukeys applied; p<0.05*

**Graph 2: Mean of Mouth Opening between the three groups**



**Variation (mean) of Visual and Palpatory findings between the three groups**

The mean change in the pre and post treatment values in the Lycopene-Hyaluronidase was 0.251±0.171, in the Lycopene was 0.141±0.102 and in the control group was 0.000±0.000. The intergroup comparison between three groups was statistically significant when analyzed using One Way ANOVA with p value less than 0.001. The post hoc analysis revealed statistically significant difference between two group - Lycopene vs Control and Control vs Lycopene-Hyaluronidase. Non-Significant difference was observed for Lycopene- Hyaluronidase vs Lycopene.

**Table 3: Mean + SD of Visual and Palpatory findings between the 3 groups**

| | **Mean** | **Std Deviation** | **P value** | **Significance** |
|---|---|---|---|---|
| Lycopene-Hyaluronidase | 0.251 | 0.171 | 0.001 | Significant |
| Lycopene | 0.141 | 0.102 | | |
| Control | 0.000 | 0.001 | | |

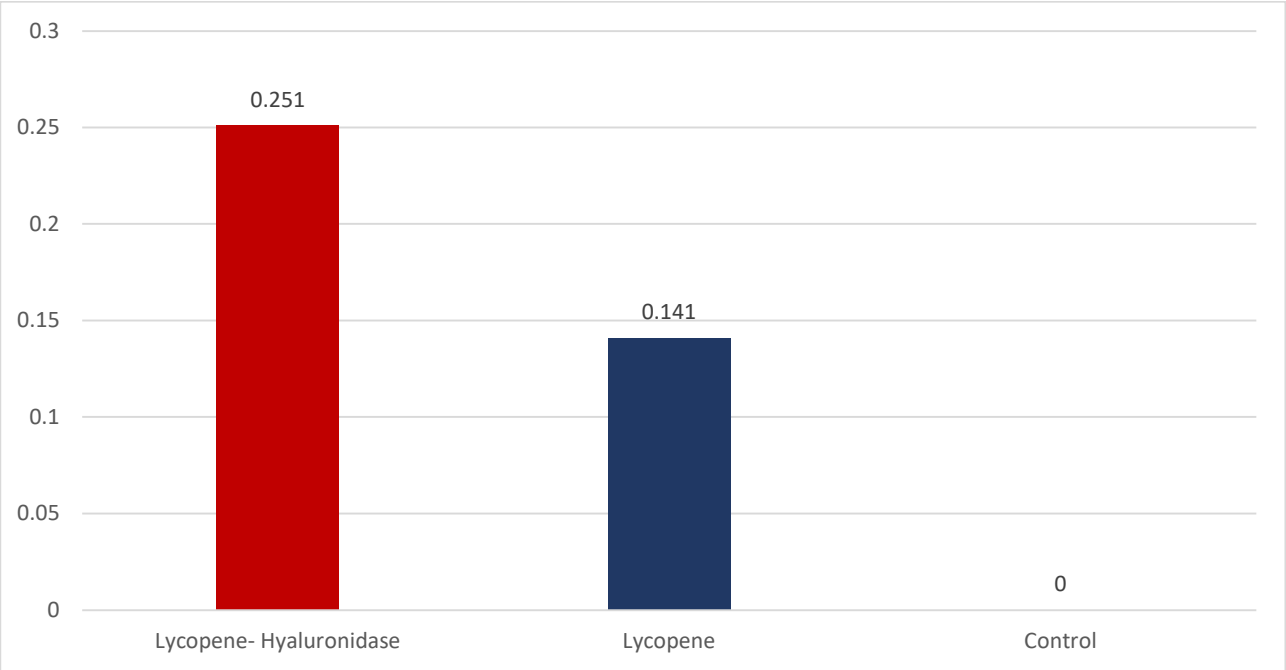
*ANOVA applied; $p<0.05$*

**Table 3.1: Post Hoc Analysis Visual and Palpatory findings between the 3 groups**

| | Mean | Std Deviation | P value | Significant |
|---|---|---|---|---|
| Lycopene- Hyaluronidase vs Lycopene | 0.110 | 0.76 | 0.252 | Non-Significant |
| Lycopene vs Control | 0.141 | 0.79 | 0.001 | Significant |
| Control vs Lycopene-Hyaluronidase | 0.321 | 1.02 | 0.001 | Significant |

*Post Hoc Tukeys applied; p<0.05*

**Graph 3: Post Hoc Analysis Visual and Palpatory findings between the three groups**



## INTRA GROUP COMPARISON OF BURNING SENSATION IN 3 GROUPS

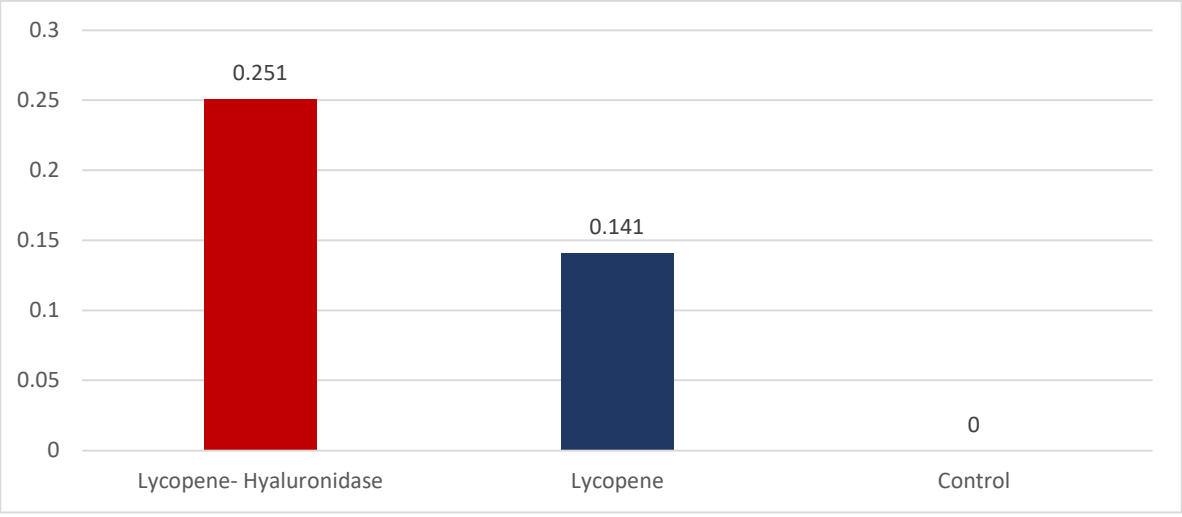
The mean change in the Pre and Post-treatment values in the Lycopene-Hyaluronidase was 3.87±1.19, in the Lycopene was 2.75±0.91 and in the control group was 0.84±0.76. The intragroup comparison between pre and post treatment values in three groups was statistically significant when analyzed using paired T test with p value less than 0.001.

**Table 4: Intra group comparison of burning sensation in 3 groups**

| | Mean | Std Dev | P value | Significance |
|---|---|---|---|---|
| Lycopene-Hyaluronidase | 3.87 | 1.19 | 0.001 | Significant |
| Lycopene | 2.75 | 0.91 | 0.001 | Significant |
| Control | 0.84 | 0.76 | 0.001 | Significant |

T test; $p<0.05$

**Graph 4: Intra group comparison of burning sensation in 3 groups**



## INTRA GROUP COMPARISON OF MOUTH OPENING IN THREE GROUPS

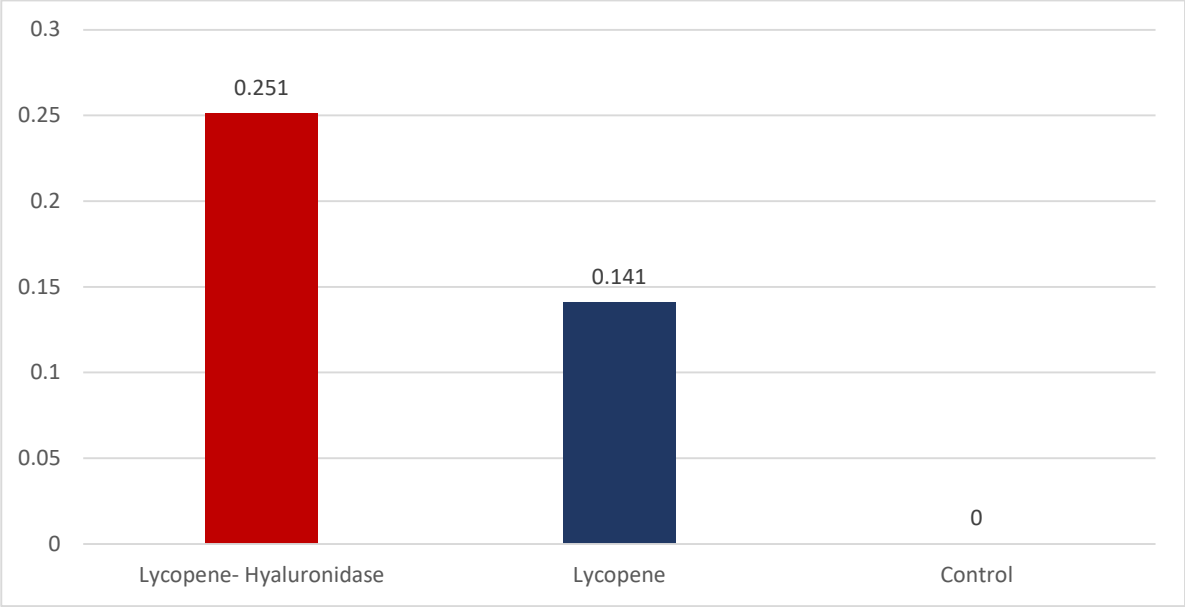
The mean change in the pre and post treatment values in the Lycopene-Hyaluronidase was 3.45±1.04, in the Lycopene was 2.49±0.89 and in the control group was 1.02±0.72. The intragroup comparison between pre and post treatment values in three groups was statistically significant when analyzed using paired T test with p value less than 0.001.

**Table 5: intra group comparison of mouth opening in three groups**

T test; $p<0.05$

| | **Mean Diff between pre and post treatment** | **Std Deviation** | **P value** | **Significant** |
|---|---|---|---|---|
| Lycopene-Hyaluronidase | 3.45 | 1.04 | 0.001 | Significant |
| Lycopene | 2.49 | 0.89 | 0.001 | Significant |
| Control | 1.02 | 0.72 | 0.001 | Significant |

**Graph 5: intra group comparison of mouth opening in three groups**



## INTRA GROUP COMPARISON OF VISUAL AND PALPATORY FINDINGS IN THREE GROUPS

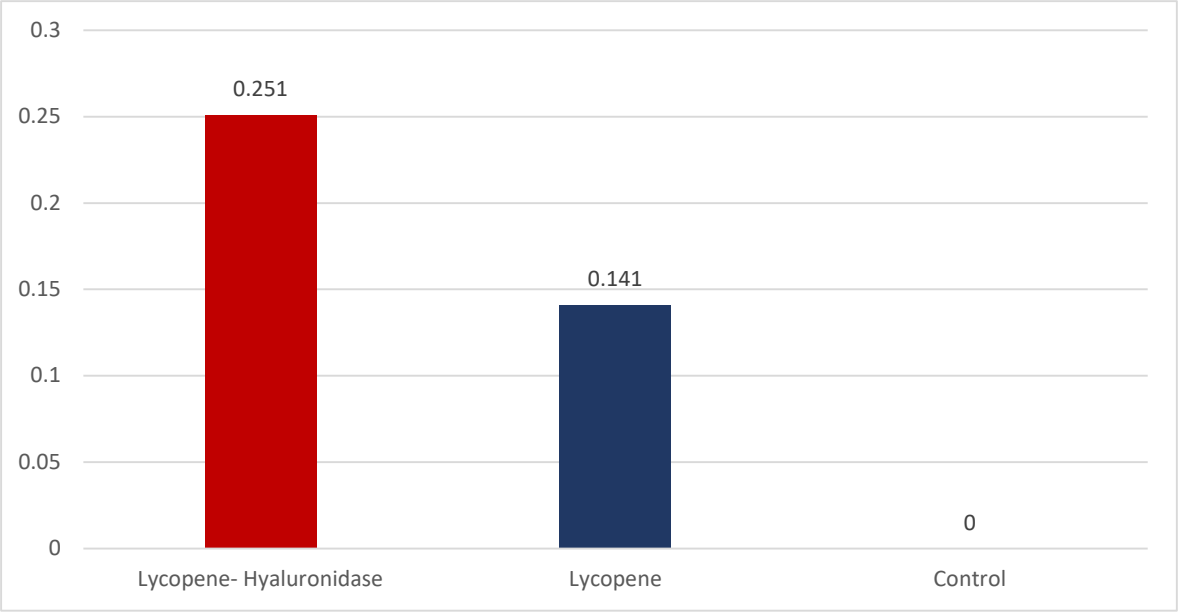
The mean change in the pre and post treatment values in the Lycopene-Hyaluronidase was 0.251±0.171, in the Lycopene was 0.141±0.102 and in the control group was 0.000±0.000. The intragroup comparison between pre and post treatment values in Lycopene- Hyaluronidase and Lycopene was statistically significant when analyzed using paired T test with p value less than 0.001.

**Table 6: Intra group comparison of visual and palpatory findings in three groups**

| | **Mean Diff between pre and post treatment** | **Std Deviation** | **P value** | **Significant** |
|---|---|---|---|---|
| Lycopene-Hyaluronidase | 0.251 | 0.171 | 0.001 | Significant |
| Lycopene | 0.141 | 0.102 | 0.001 | Significant |
| Control | 0.000 | 0.000 | 0.001 | Significant |

T test; $p<0.05$

**Graph 6: Intra group comparison of visual and palpatory findings in three groups**



# DISCUSSION

Oral submucous fibrosis (OSMF) is a chronic premalignant condition and is characterized by fibroblastic change of lamina propria and stiffness of oral mucosa eventually leading to mucosal stiffness and functional morbidity of the oral cavity. The malignant transformation potential of OSMF ranges between 8 and 10% as it was also similarly found in a study conducted by Xiaofeng et al in 2023.[21]

The present study was done to compare the efficacy of Lycopene & Lycopene with Hyaluronidase in the management of Oral Sub Mucous Fibrosis. The required sample size of 30 subjects was randomly selected. Then the participants were divided into three groups and 10 subjects were included in each group which was in conjunction with a study conducted by T R Yoithapprabhunath et al in 2013 and a study conducted by A Kumar et al in 2007.[22,23]

T Karemore et al conducted a study in 2011 that estimated a possible improvement in the management of OSMF, resulting in reduced burning sensation and increased mouth opening, post administration of lycopene and with its combination with hyaluronidase which was also similarly observed in the results of the present study that indicated a significant improvement in the management of oral submucous fibrosis (OSMF) with the use of both lycopene and lycopene with hyaluronidase. The parameters evaluated, including burning sensation, mouth opening, and visual and palpatory findings, demonstrated notable variations between the groups.[24]

The burning sensation, a common symptom in OSMF, showed a substantial reduction in both lycopene and lycopene with hyaluronidase groups compared to the control group. The mean change in burning sensation was significantly higher in the lycopene with hyaluronidase group (3.87) compared to the lycopene group (2.75) and the control group (0.84). The post hoc analysis further supported these findings, revealing a statistically significant difference between the lycopene and control groups, as well as between the control and lycopene with hyaluronidase groups. However, no

significant difference was observed between lycopene and lycopene with hyaluronidase, suggesting that both interventions were equally effective in alleviating burning sensation, this was comparable with a study conducted by S Sunderraj et al in 2012, which was also an in-vivo study that positively supported the results of the present study, these similar findings were also supported by a systematic review conducted by Singh M et al in the year 2004.[25,26]

Mouth opening, another crucial aspect in OSMF management, demonstrated a significant improvement in both lycopene and lycopene with hyaluronidase groups compared to the control group. The mean change in mouth opening was again higher in the lycopene with hyaluronidase group (3.45) compared to the lycopene group (2.49) and the control group (1.02). Post hoc analysis revealed significant differences between lycopene and control groups, as well as between control and lycopene with hyaluronidase groups, with no significant difference between lycopene and lycopene with hyaluronidase. This implies that the combination of lycopene with hyaluronidase has an added advantage in improving mouth opening compared to lycopene alone.

The method and the experimental setting of the current study which included Visual and palpatory findings also exhibited significant improvements in both lycopene and lycopene with hyaluronidase groups compared to the control group, which were similar to a study conducted by Ali A. et al in 2020 where the methods of estimation of the variables and the experimental techniques used for their study were certainly comparable.[27]

The mean change in visual and palpatory findings was again higher in the lycopene with hyaluronidase group (0.251) compared to the lycopene group (0.141) and the control group (0.000). The post hoc analysis indicated significant differences between lycopene and control groups and between control and lycopene with hyaluronidase groups, with no significant difference between lycopene and lycopene with hyaluronidase. This suggests that both interventions were effective in improving visual and palpatory findings, with the combination providing no added advantage.

In the intra-group comparison, both lycopene and lycopene with hyaluronidase groups demonstrated significant improvements in burning sensation, mouth opening, and visual and palpatory findings when comparing pre and post-treatment values. The paired t-test results indicated statistically significant differences within each group, further supporting the efficacy of both interventions.[28]

OSMF is a precancerous disorder of the mouth that has a high risk of developing into malignancy. The two primary etiologic variables associated with OSMF are chewing tobacco and gutkha. Antioxidants have been demonstrated to be effective in a number of therapy and medications used in the management of OSMF. In order to manage the participants with OSMF, the current study compared and evaluated the effectiveness of lycopene antioxidant alone versus its combination with intralesional injection of hyaluronidase. The chronic and potentially cancerous oral condition known as oral submucous fibrosis (OSMF) is characterised by a malfunction in the metabolism of collagen and the buildup of collagen fibres in the oral tissues.[1] Burning pain in the oral mucosa, ulcers, blisters, decreased taste perception, dry mouth, and numbness in the lips and tongue are some of the symptoms that patients

OSMF is considered an oral potentially malignant disorder (OPMD) and is closely related to the occurrence of oral squamous cell carcinoma (OSCC) The disease affects normal oral function and social life, leading to dysfunctions in eating, chewing, pronunciation, and other functions, which affect patients' nutrition intake and social communication. The development of OSF involves factors such as miRNAs, lncRNAs, collagen gel contraction, fibroblast migration, and HIF-1a activation [21,28]

Lycopene is a carotenoid present in human blood and various tissues, with varying levels in different organs. It exhibits biological activities such as antioxidant activity, induction of cell-cell communication, and growth control, but does not have provitamin A activity. Epidemiological studies suggest that lycopene may have protective effects against certain types of cancer, particularly prostate cancer, and in vitro and in vivo studies support this conclusion. The major sources of lycopene in

the human diet are tomatoes and tomato products, with varying bioavailability from different food items. Lycopene oxidation products have been identified in human serum, and further investigation is needed to understand the suggested health effects of lycopene. Lycopene functions by reducing reactive oxygen species, diminishing the inflammatory response associated with OSMF, and modifying the expression of specific genes crucial for both collagen synthesis and breakdown. Moreover, it enhances lymphocyte stress resistance and decreases inflammation. The enzyme hyaluronidase plays a key role in altering tissue permeability. In our study, combining hyaluronidase with lycopene yielded improved results compared to lycopene alone, although this difference lacked statistical significance. [22,26,1]

Lycopene has shown promising effects in alleviating signs and symptoms of oral potentially malignant disorders (OPMDs) such as oral submucosa fibrosis (OSF), oral lichen planus (OLP), and leukoplakia. It is efficacious in reducing pain and promoting clinical resolution of OLP, comparable to prednisolone. Additionally, lycopene has shown comparable efficacy to conventional controls in improving mouth opening and tongue protrusion in patients with OSMF. In treating OSMF, lycopene alone or in combination with intralesional hyaluronidase has shown significant improvement in mouth opening and burning sensation compared to placebo. Lycopene gel has also shown equal improvement in clinical and biochemical parameters of periodontitis compared to minocycline hydrochloride microspheres. Numerous studies have examined the impact of lycopene on mouth opening in OSMF. A study conducted by Al-Maveri et al in the year 2022 and a subsequent investigation by Arakeri G et al in 2020 found that maximal mouth opening improved in 69.56% of individuals, indicating the efficacy of lycopene in reducing objective indicators of OSMF.[29,30]

A systematic review and meta-analysis conducted by Gupta N et al in the year 2019 evaluated the efficacy of lycopene in the management of Oral Submucous Fibrosis (OSMF). The review included 16 randomized control trials and 3 non-randomized control trials, comprising a total of 1181 subjects. The results showed non-significant

differences between lycopene and other interventions used in the treatment of OSMF. It was concluded that lycopene is a safe and equally effective therapeutic modality as compared to other interventions for patients with OSMF.[5]

A randomised clinical trial was conducted by Ali A et al in the year 2020 which compared the efficacy of lycopene gel with minocycline hydrochloride microspheres as an adjunct to nonsurgical periodontal treatment. The study found that both lycopene gel and minocycline hydrochloride microspheres showed significant improvements in clinical parameters and biochemical markers of periodontitis. The effect size estimation indicated that lycopene gel exhibited considerably greater efficacy than the control gel.[7] Another study done by Kumari KS et al in the year 2019 compared the efficacy of lycopene alone to a combination of lycopene and hyaluronidase for treating oral submucous fibrosis (OSMF). The study found that both lycopene alone and the combination treatment showed improvements in inter-incisal mouth opening in patients with OSMF. However, the difference between the two groups was statistically non-significant.[28]

In the present study both lycopene and lycopene-hyaluronidase combination showed significant improvements in mouth opening and burning sensation as compared to placebo which is similar to the clinical study conducted by Asdullah M et al in the year 2019 in which he compared the efficacy of lycopene alone and lycopene with hyaluronidase in the management of oral submucous fibrosis (OSMF). However, there was no significant difference between the two treatment groups.[1]

A systematic review and meta-analysis by Al-Maveri et al in the year 2022 investigated the efficacy of lycopene in the management of oral potentially malignant disorders (OPMDs). The review included 27 clinical trials on oral submucosa fibrosis (OSF), oral lichen planus (OLP), and leucoplakia. The results showed promising effects of lycopene in alleviating signs and symptoms of OSMF, and leucoplakia. However, further well-designed studies with long-term therapy and follow-up are recommended.[30]

Another systematic review and meta-analysis conducted by Gupta N et al in the year 2019 evaluated the efficacy of lycopene in the management of Oral Submucous Fibrosis (OSMF). The review included 16 randomized control trials and 3 non-randomized control trials, comprising a total of 1181 subjects. The results of the meta-analysis showed non-significant differences between lycopene and other interventions used in the treatment of OSMF. The review concludes that lycopene is a safe and equally effective therapeutic modality compared to other interventions for patients with OSMF. However, the review also highlights the need for further well-designed clinical trials to accurately assess the effectiveness of lycopene compared to other medicinal treatments in the management of OSMF.[5]

Our research also revealed a statistically significant difference between the lycopene and lycopene-hyaluronidase combinations and the control group. However, when compared to lycopene alone, the lycopene-hyaluronidase combination did not show a statistically significant change in mouth opening. Epithelial atrophy is the primary cause of the burning sensation in OSMF, resulting from juxtaepithelial inflammation, increased fibrosis, and weakened vasculature. Lycopene is crucial in reducing fibrosis and inflammation, promoting epithelial regeneration, and alleviating burning pain. While the combination of lycopene and hyaluronidase showed a greater reduction in the burning sensation on average compared to lycopene alone, this difference was not statistically significant. Importantly, neither lycopene nor the lycopene-hyaluronidase combo affected visual and palpatory findings, with most of these changes appearing irreversible.

In conclusion, both lycopene and lycopene with hyaluronidase showed efficacy in the management of OSMF, with significant improvements in burning sensation, mouth opening, and visual and palpatory findings. The combination of lycopene with hyaluronidase demonstrated superior outcomes in terms of burning sensation and mouth opening. These findings contribute valuable insights to the existing knowledge

on OSMF management and suggest potential avenues for further research and clinical applications.

# LIMITATIONS

Short-Term Focus: The study primarily focused on short-term effects, and the long-term impact of hyaluronidase, as demonstrated in prior studies, could not be thoroughly assessed. This limitation warrants further investigation into the sustained effects over an extended period.

Visual and Palpatory Findings: While the study revealed significant changes in mouth opening and burning sensation, it did not demonstrate substantial alterations in visual and palpatory findings. This raises questions about the comprehensive evaluation of OSMF-related manifestations.

Sample: The study was done on a limited number of individuals making the sample size small; so more number of individuals should be examined to get a more appropriate result.

Statistical Significance: Although certain trends suggested improved outcomes with the lycopene-hyaluronidase combination, the lack of statistical significance in some comparisons emphasizes the need for larger sample sizes to validate these trends.

Generalizability: Since the study was done only in the Department of Public Health Dentistry, Babu Banarasi Das College of Dental Sciences, Lucknow, Uttar Pradesh its external validity is questionable.

# CONCLUSION

A double blinded parallel multiple arm randomised controlled clinical trial of concurrent parallel design was done to evaluate the efficacy of lycopene in the treatment of Oral Sub-Mucous Fibrosis and the parameters assessed were burning sensation, mouth opening and Visual and Palpatory findings. The present study contributes to the understanding of the potential benefits of lycopene and hyaluronidase in managing OSMF.

Using lycopene as an antioxidant to treat OSMF seems highly promising. With notable gains in burning sensation, mouth opening, and visual and palpatory findings, lycopene and lycopene combined with hyaluronidase shown success in the treatment of OSMF.

The combination of lycopene with hyaluronidase demonstrated superior outcomes in terms of burning sensation and mouth opening. While the combination showed some promising trends in reducing burning sensations and improving mouth opening, the lack of statistical significance in certain outcomes highlights the need for further research.

# RECOMMENDATIONS

Long-Term Follow-Up Studies: Future research should incorporate long-term follow-up assessments to better understand the sustained effects of treatments, particularly regarding the use of hyaluronidase in OSMF management.

Expanded Sample Size: Increasing the sample size in subsequent studies can enhance statistical power and improve the reliability of the observed trends, allowing for more definitive conclusions regarding the efficacy of lycopene and hyaluronidase combinations.

Comprehensive Evaluation: Given the limited impact on visual and palpatory findings, future investigations should consider a more comprehensive evaluation of OSMF manifestations, potentially involving additional clinical parameters.

Comparison with Other Therapies: Comparative studies with other existing therapies for OSMF could provide valuable insights into the relative effectiveness of lycopene and lycopene-hyaluronidase combinations.

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# ANNEXURE

# BABU BANARASI DAS UNIVERSITY

## BBD COLLEGE OF DENTAL SCIENCES, LUCKNOW

## INSTITUTIONAL RESEARCH COMMITTEE APPROVAL

The project titled **"Comparison Of Different Doses Of Lycopene In The Treatment Of Oral Submucous Fibrosis A Randomized Control Trial Study"** submitted by **Dr Pooja Gupta** Postgraduate student in the **Department of Public Health Dentistry** for the Thesis Dissertation as part of MDS Curriculum for the academic year 2021-2024 with the accompanying proforma was reviewed by the Institutional Research Committee in its meeting held on **14th September, 2022** at BBDCODS.

The Committee has granted approval on the scientific content of the project. The proposal may now be reviewed by the Institutional Ethics Committee for granting ethical approval.

**Prof. Dr. Puneet Ahuja**
Chairperson

**Dr. Mona Sharma**
Co-Chairperson

# BABU BANARASI DAS UNIVERSITY
## BBD COLLEGE OF DENTAL SCIENCES, LUCKNOW

**BBDCODS/IEC/09/2022** **Dated: 16th September, 2022**

**Communication of the Decision of the Xth Institutional Ethics Sub-Committee Meeting**

**IEC Code: 22**

**Title of the Project:** Comparison Of Different Doses Of Lycopene In The Treatment Of Oral Submucous Fibrosis A Randomized Control Trial Study.

**Principal Investigator:** Dr Pooja Gupta **Department:** Public Health Dentistry

**Name and Address of the Institution:** BBD College of Dental Sciences Lucknow.

**Type of Submission:** New, MDS Project Protocol

Dear Dr Pooja Gupta,

The Institutional Ethics Sub-Committee meeting comprising following members was held on 15th September, 2022.

| | | |
|---|---|---|
| 1. | Dr. Lakshmi Bala<br>Member Secretary | Prof. and Head, Department of Biochemistry |
| 2. | Dr. Praveen Singh Samant<br>Member | Prof. & Head, Department of Conservative Dentistry & Endodontics |
| 3. | Dr. Jiji George<br>Member | Prof. & Head, Department of Oral Pathology & Microbilogy |
| 4. | Dr. Amrit Tandan<br>Member | Professor, Department of Prosthodontics and Crown & Bridge |
| 5. | Dr. Rana Pratap Maurya<br>Member | Reader, Department of Orthodontics & Dentofacial Orthopaedics |

The committee reviewed and discussed your submitted documents of the current MDS Project Protocol in the meeting.
The comments were communicated to PI, thereafter it was revised.

**Decisions: The committee approved the above protocol from ethics point of view.**

Forwarded by:

**Prof. Dr. Puneet Ahuja**
Principal
BBD College of Dental Sciences
BBD University, Lucknow

PRINCIPAL
Babu Banarasi Das College of Dental Sciences
(Babu Banarasi Das University)
BBD City, Faizabad Road, Lucknow-226028

Lakshmi Bala 16/09/22

**Dr. Lakshmi Bala**
Member-Secretary
Institutional Ethics Sub-Committee (IEC)
BBD College of Dental Sciences
BBD University, Lucknow

Member-Secretary
Institutional Ethic Committee
BBD College of Dental Sciences
BBD University
Faizabad Road, Lucknow-226028

**Babu Banarasi Das College of Dental Sciences**
**(Babu Banarasi Das University)**
**BBD City, Faizabad Road, Lucknow – 227105 (INDIA)**

सहमति पत्र

अध्ययन शीर्षक.....
अध्ययन संख्या.....
प्रतिभागी के पूर्ण नाम.....
जन्म तिथि / आयु.....
प्रतिभागी का पता .....
फोन नं. और ई-मेल पता .....
योग्यता .....
व्यवसाय: छात्र / स्व कार्यरत / सेवा / ग्रहिणी .....
अन्य (उचित रुप मे टिक करें) .....
प्रतिभागी की वार्षिक आय .....
प्रत्याशीयो के नाम और प्रतिभागी से संबंध...(परीक्षण से संबंधित मौत के मामले मे मुआवजे के प्रयोजन के लिए)

1. मेरी पुष्टि है कि मैने अध्ययन हेतु सुचना पत्र दिनांक ..... को पढ व समझ लिया तथा मुझे प्रश्न पुछने या मुझे अध्ययन अन्वेषक ने सभी तथ्यों को समझा दिया है तथा मुझे प्रश्न पुछने के समान अवसर प्रदान किए गये।

2. मैंने यहॉ समझ लिया कि अध्ययन में मेरी भागीदारी पूर्णतः स्वैच्छिक है और किसी भी दबाव के बिना स्वतंत्र इच्छा के साथ दिया है किसी भी समय किसी भी कारण के बिना , मेरे इलाज या कानूनी अधिकारो को प्रभावित किए बिना , अध्ययन में भाग न लेने के लिए स्वतंत्र हुँ ।

3. मैंने यह समझ लिया है कि अध्ययन के प्रायोजक , प्रायोजक की तरफ से काम करने वाले लोग, आचार समिति और नियामक अधिकारियों को मेरे स्वास्थ्य रिकार्ड को वर्तमान अध्ययन या आगे के अध्ययन के सन्दर्भ देखने के लिए मेरी अनुमति की जरूरत नही है, चाहे मैने इस अध्ययन से नाम वापस ले लिया है। हॉलाकि मै यह समझता हुँ कि मेरी पहचान को किसी भी तीसरे पक्ष या प्रकाशित माध्यम में नही दी जायेगी।

4. मै इससे सहमत हूँ कि कोई भी डेटा या परिणाम जो इस अध्ययन से प्राप्त होता है उसका वैज्ञानिक उद्देश्य (ओं) के उपयोग के लिए मेरी तरफ से कोई प्रतिबंध नही है।
5. भविष्य के अनुसंधान के लिए भंडारित नमूना (ऊतक/रक्त) पर अध्ययन के लिए अपनी सहमति देता हुँ।

हॉ [ ] नही [ ] अनउपयुक्त [ ]

6. मै परीक्षण की अनुमति देता हुँ। मुझे इसके द्वारा यदि कोई परेशानी होती है, इसके बारे में जानकारी दे दी गई है। मैने रोगी जानकारी सूचना पत्र को पढ तथा समझ लिया है।

प्रतिभागी / कानूनी तौर पर स्वीकार्य प्रतिनिधि का हस्ताक्षर ( या अंगूठे का निशान.....

हस्ताक्षरकर्ता का नाम..... दिनांक .....अन्वेषक के हस्ताक्षर ..... दिनांक .....

अध्ययन अन्वेषक का नाम .....

गवाह के हस्ताक्षर ..... दिनांक .....गवाह के नाम .....

मैनें पीआईडी और विधिवत भरे सहमति फार्म का एक हस्ताक्षर की नकल प्राप्त की.

प्रतिभागी कानूनी तौर पर प्रतिनिधि का हस्ताक्षर/ अंगूठे का निशान ..... दिनांक.....

# Babu Banarasi Das College of Dental Sciences

**(Babu Banarasi Das University)**
**BBD City, Faizabad Road, Lucknow – 227105 (INDIA)**

**Consent Form (English)**

Title of the Study …….

Study Number……..
Subject's Full Name…….
Date of Birth/Age ……
Address of the Subject…….
Phone no. and e-mail address……
Qualification ……
Occupation: Student / Self Employed / Service / Housewife/
Other (Please tick as appropriate)
Annual income of the Subject……
Name and of the nominees(s) and his relation to the subject…… (For the purpose of compensation in case of trial related death).

1. I confirm that I have read and understood the Participant Information Document dated ……..for the above study and have had the opportunity to ask questions. **OR** I have been explained the nature of the study by the Investigator and had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and given with free will without any duress and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.
3. I understand that the sponsor of the project, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my Identity will not be revealed in any information released to third parties or published.
4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
5. I permit the use of stored sample (tooth/tissue/blood) for future research. **Yes [ ] No [ ] Not Applicable [ ]**
6. I agree to participate in the above study. I have been explained about the complications and side effects, if any, and have fully understood them. I have also read and understood the participant/volunteer's Information document given to me.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:……..
Signatory's Name……. Date …….
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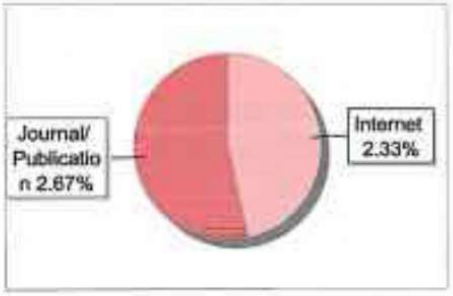


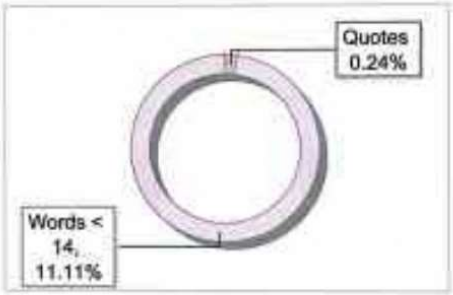


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