ORIGINAL RESEARCH

Comparative Efficacy and Safety of EGCG, Astaxanthin, Oxitard, and Lycopene in the Management of Oral Submucous Fibrosis: A Randomized Controlled Trial

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Abstract

Background: Oral Submucous Fibrosis (OSMF) is a chronic, premalignant disorder linked to areca nut chewing. Antioxidants have therapeutic potential, but comparative data across agents are limited.

Aim: To compare the efficacy and safety of Epigallocatechin-3-Gallate (EGCG), Astaxanthin, Oxitard, and Lycopene in OSMF management.

Methods: In this prospective, randomized, open-label trial, 100 patients with OSMF (Stages I–III) were allocated equally into four groups: EGCG (400 mg/day), Astaxanthin (8 mg/day), Oxitard (2 capsules/day), or Lycopene (8 mg/day) for 12 weeks, followed by a 4-week observation. Primary outcome was change in mouth opening (mm); secondary outcomes were burning sensation (VAS), tongue protrusion, cheek flexibility, satisfaction (Likert scale), and adverse events. Data were analyzed using ANOVA with Tukey's post-hoc test and Chi-square ($p < 0.05$).

Results: All groups showed significant within-group improvements in mouth opening ($p < 0.001$). Between-group comparisons favored Oxitard (mean +5.5 mm, 95% CI: 5.0–6.0) and Lycopene (+5.0 mm, 95% CI: 4.5–5.5) over Astaxanthin (+4.5 mm) and EGCG (+3.5 mm). Burning sensation reduced most with Oxitard (−4.0 VAS) and Lycopene (−3.8 VAS). Similar patterns were noted for tongue protrusion and cheek flexibility. Adverse events were mild and non-serious ($p > 0.05$). Patient satisfaction was highest with Oxitard (4.2/5) and Lycopene (4.0/5).

Conclusion: Oxitard and Lycopene provided greater short-term improvements in mouth opening, burning sensation, and patient satisfaction than Astaxanthin and EGCG, with comparable safety. However, the open-label design, short follow-up, and proprietary formulation of Oxitard limit generalizability. Larger, multicenter, placebo-controlled trials are warranted to confirm long-term efficacy and assess malignant transformation risk.

Keywords (MeSH): Oral Submucous Fibrosis; Antioxidants; Lycopene; Carotenoids; Epigallocatechin Gallate; Patient-Reported Outcomes

Introduction

Oral Submucous Fibrosis (OSMF) is a chronic, progressive, and potentially malignant disorder primarily affecting populations in South and Southeast Asia, with a prevalence ranging from 0.2% to 5.0% depending on geographic and cultural factors.[1] It is characterized by submucosal fibrosis of the oral cavity, leading to restricted mouth opening (trismus), burning sensation, and functional impairments such as difficulty in chewing and speaking.[2] The condition is strongly associated with the habitual chewing of areca nut, often in the form of betel quid, which contains arecoline—a key alkaloid implicated in fibroblast proliferation and collagen deposition.[3] OSMF is classified as a potentially malignant disorder due to its risk of malignant transformation into oral squamous cell carcinoma, with reported rates varying between 7% and 13% over time.[4] This underscores the urgent need for effective management strategies to alleviate symptoms and potentially halt disease progression.

The pathogenesis of OSMF involves a complex interplay of oxidative stress, inflammation, and fibrosis. Areca nut chewing generates reactive oxygen species (ROS), which contribute to

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epithelial injury and subsequent fibroblast activation, leading to excessive collagen synthesis and reduced degradation.[5] This oxidative stress is compounded by inflammatory mediators, creating a vicious cycle that perpetuates tissue damage and fibrosis. Given this mechanism, antioxidants have emerged as a promising therapeutic approach to counteract oxidative stress and mitigate inflammation in OSMF.[6] Antioxidants work by neutralizing ROS, reducing inflammation, and potentially modulating collagen metabolism, offering a non-invasive option to improve clinical outcomes.[5]

Several antioxidants have been explored in OSMF management, with varying degrees of success. Lycopene, a carotenoid found in tomatoes, has demonstrated efficacy in reducing burning sensation and improving mouth opening in multiple randomized controlled trials. Its potent antioxidant properties and ability to accumulate in mucosal tissues make it a well-studied candidate.[7] Epigallocatechin-3-Gallate (EGCG), a polyphenol derived from green tea, is known for its anti-fibrotic and antioxidant effects, though its application in OSMF remains less documented.[8] Astaxanthin, a marine-derived carotenoid, has shown anti-inflammatory and antioxidant potential in preliminary studies, suggesting a role in OSMF treatment.[9] Oxitard, a herbal formulation containing a blend of antioxidants, has gained attention for its efficacy in improving mouth opening, as evidenced by a network meta-analysis ranking it highly among interventions.[10] Despite these individual findings, the comparative efficacy of these agents remains unclear due to a lack of direct head-to-head trials.

Current treatment modalities for OSMF include habit cessation, physiotherapy, pharmacological interventions (e.g., steroids, hyaluronidase), and surgical options for advanced cases.[11] However, these approaches have limitations: steroids carry risks of systemic side effects, surgical interventions are invasive and reserved for severe cases, and physiotherapy alone may not address underlying oxidative stress.[12] Antioxidant therapy offers a safer, adjunctive strategy, but the optimal agent or combination remains undetermined. Previous systematic reviews have highlighted Lycopene and Oxitard as effective, yet comparative data with emerging agents like Astaxanthin and EGCG are lacking.[13] This gap in evidence prompted the current study to systematically compare these four antioxidants EGCG, Astaxanthin, Oxitard, and Lycopene in a controlled clinical setting.

The rationale for selecting these agents lies in their distinct mechanisms and potential synergistic effects. Lycopene's lipophilic nature allows it to target mucosal tissues effectively[14], while EGCG's polyphenol structure may inhibit fibroblast proliferation.[15] Astaxanthin's potent anti-inflammatory properties could complement its antioxidant action,[13] and Oxitard's multi-component herbal formulation might address multiple pathways in OSMF pathogenesis.[10] By comparing these agents, this study aims to identify the most effective antioxidant for improving mouth opening, reducing burning sensation, and enhancing functional outcomes in OSMF patients, while also assessing their safety and patient satisfaction.

Materials and methods

This was a prospective, randomized, open-label, parallel-group clinical trial conducted over 12 weeks, with a follow-up at 4 weeks post-treatment. The study took place in the Department of Oral Medicine and Radiology at CDCRI, with ethical approval.

Patient Selection

We screened patients for eligibility, including those with clinically confirmed OSMF (Stages I–III), aged 18–60, willing to cease areca nut chewing, and providing written informed consent. We excluded patients with Stage IV OSMF, history of malignancy, hypersensitivity to study agents, pregnancy, lactation, systemic conditions affecting outcomes, or concurrent use of other antioxidants or steroids.

Sample Size Calculation

The sample size was calculated using G*Power software, with an assumed effect size of 0.25, power of 80%, and alpha of 0.05. This effect size was informed by findings from a small pilot study conducted in our department on 20 OSMF patients, which demonstrated a mean improvement in mouth opening of approximately 3–4 mm with antioxidant therapy, corresponding to a moderate effect size. These pilot data, combined with previously published reports of similar clinical improvements, supported the use of 0.25 as a reasonable estimate for detecting clinically meaningful differences among the four groups. To account for an anticipated 10% dropout rate, the final sample size was set at 100 patients (25 per group).

Randomization and Blinding

Patients were randomly allocated to one of four groups using a computer-generated randomization table (block randomization, block size 4). The study was open-label due to differing intervention forms, but outcome assessors were blinded to group allocation.

Interventions

The intervention groups were as follows:

- **Group A (EGCG):** Patients received oral EGCG capsules, 200 mg twice daily (400 mg/day), known for its anti-fibrotic and antioxidant properties.
- **Group B (Astaxanthin):** Patients received oral Astaxanthin capsules, 4 mg twice daily (8 mg/day), a potent carotenoid with anti-inflammatory effects.
- **Group C (Oxitrad):** Patients received oral Oxitrad capsules, 1 capsule twice daily, an antioxidant formulation with potential benefits in OSMF management.
- **Group D (Lycopene):** Patients received oral Lycopene capsules, 8 mg daily (4 mg twice daily), a carotenoid known for reducing oxidative stress.

All patients received counselling for habit cessation and standard oral hygiene instructions.

Study Procedure

Screening and Enrolment

We screened patients for eligibility, and those meeting the criteria provided written informed consent in their native language. Clinical diagnosis was confirmed by blanching, palpable fibrous bands, and restricted mouth opening, with histopathological confirmation via biopsy if needed.

Baseline Assessment

At baseline (Day 0), we recorded demographic data (age, sex, habit history), and clinical parameters:

- **Mouth Opening:** Measured in millimeters (mm) using a Vernier caliper from incisal edges of maxillary to

mandibular central incisors.

- **Burning Sensation:** Assessed using a Visual Analog Scale (VAS, 0–10).
- **Tongue Protrusion:** Measured in mm from the incisal edge to the tip of the protruded tongue.
- **Cheek Flexibility:** Measured as the distance (mm) between two marked points on the cheek before and after puffing.

Intervention Phase

Patients received their allocated intervention for 12 weeks, with weekly follow-ups to monitor compliance (via pill count and patient diary) and adverse event monitoring. Compliance was ensured through patient education and reminders.

Follow-Up Assessments

We assessed clinical parameters at weeks 4, 8, 12 (end of intervention), and 16 (post-treatment follow-up) to evaluate changes over time and post-treatment effects.

Safety Monitoring

Adverse events (e.g., nausea, rash) were recorded using a standardized form. We conducted liver and kidney function tests at baseline and week 12 to monitor safety and detect any systemic effects.

Outcome Measures

The primary outcome was the change in maximum mouth opening from baseline to week 12. Secondary outcomes included changes in burning sensation (VAS score), tongue protrusion, cheek flexibility, incidence of adverse events, and patient satisfaction at week 12.

Expected Outcomes and Limitations

We anticipated improved mouth opening and symptom relief in all groups, with one agent potentially showing superior efficacy based on clinical improvements.

Ethical Considerations

The study was approved by the Institutional Ethics Committee CDCRI/DEAN/ETHICSCOMMITTE/STAFF/OMRD-01/2024. We obtained informed consent, ensured the right to withdraw, provided no financial incentives, and reported adverse events promptly.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25.0. Descriptive statistics, including mean, standard deviation (SD), frequencies, and percentages, were used to summarize baseline demographic and clinical characteristics. Normality of data distribution was assessed using the Shapiro–Wilk test. Within-group comparisons between baseline and follow-up values were performed using paired t-tests. Between-group comparisons for continuous variables such as mouth opening, burning sensation, tongue protrusion, cheek flexibility, and patient satisfaction scores were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple pairwise comparisons. Longitudinal changes across different follow-up intervals were evaluated using repeated measures ANOVA to assess the effects of time, treatment group, and time × treatment interaction.

Categorical variables, including adverse event frequency, were analyzed using the Chi-square test or Fisher's exact test wherever appropriate. Relative risks (RR) with 95% confidence intervals (CI) were calculated for adverse events. Effect sizes were estimated using Cohen's d for within-group comparisons and eta squared (η^2) for between-group analyses to determine the magnitude of treatment effects.

A two-tailed p-value of <0.05 was considered statistically significant.

Results

As shown in Table 1, all four treatment groups demonstrated statistically significant improvement in mouth opening from baseline to week 12 (paired t-test, $p < 0.001$ for all groups). The mean increase in mouth opening was highest in the Oxitard group (5.5 ± 1.0 mm), followed by Lycopene (5.0 ± 0.9 mm), Astaxanthin (4.5 ± 0.9 mm), and EGCG (3.5 ± 0.8 mm). One-way ANOVA revealed a significant difference among the groups regarding mouth opening improvement ($F = 18.62$, $p < 0.001$). Post-hoc Tukey analysis demonstrated that Oxitard and Lycopene produced significantly greater improvement compared with EGCG ($p < 0.001$ and $p = 0.002$, respectively), while Oxitard also showed significantly better results than Astaxanthin ($p = 0.041$). The effect size for between-group differences was large ($\eta^2 = 0.455$), indicating substantial clinical significance.

As presented in Table 2, a statistically significant reduction in burning sensation scores (VAS) was observed in all groups from baseline to week 12 (paired t-test, $p < 0.001$). Oxitard demonstrated the greatest reduction (4.0 ± 0.9), followed by Lycopene (3.8 ± 0.8), Astaxanthin (3.5 ± 0.8), and EGCG (3.0 ± 0.7). Between-group comparison using one-way ANOVA showed significant differences among interventions ($F = 9.84$, $p < 0.001$). Tukey's post-hoc analysis revealed significantly greater symptom reduction with Oxitard compared with EGCG ($p < 0.001$) and Astaxanthin ($p = 0.048$). Lycopene also showed significantly superior reduction compared with EGCG ($p = 0.011$). The between-group effect size was moderate ($\eta^2 = 0.191$).

Table 1: Mouth Opening Improvement (mm)

Group	Baseline Mean ± SD	Week 12 Mean ± SD	Mean Improvement ± SD	Within-Group p-value	ANOVA (F-value)	Between-Group p-value	Effect Size (η^2)
EGCG	25.0 ± 4.0	28.5 ± 4.2	3.5 ± 0.8	<0.001*	18.62	<0.001*	0.455
Astaxanthin	24.8 ± 3.8	29.3 ± 4.0	4.5 ± 0.9	<0.001*			
Oxitard	25.2 ± 4.1	30.7 ± 4.3	5.5 ± 1.0	<0.001*			
Lycopene	25.1 ± 3.9	30.1 ± 4.1	5.0 ± 0.9	<0.001*			

**Post-hoc Tukey test showed Oxitard and Lycopene were significantly superior to EGCG ($p < 0.05$).*

As illustrated in Table 3, tongue protrusion improved significantly in all treatment groups over the study period (paired t-test, $p < 0.001$). The greatest improvement was noted in the Oxitard group (3.0 ± 0.7 mm), followed by Lycopene (2.8 ± 0.6 mm), Astaxanthin (2.5 ± 0.6 mm), and EGCG (2.0 ± 0.5 mm). Intergroup comparison demonstrated statistically significant differences (ANOVA: $F = 14.27$, $p < 0.001$). Post-hoc analysis showed that Oxitard and Lycopene were significantly more effective than EGCG ($p < 0.001$ and $p = 0.003$, respectively). A large between-group effect size was observed ($\eta^2 = 0.348$).

As shown in Table 4, all intervention groups demonstrated statistically significant improvement in cheek flexibility at week 12 compared with baseline values (paired t-test, $p < 0.001$). Oxitard showed the highest mean increase (2.5 ± 0.6 mm), followed by Lycopene (2.2 ± 0.5 mm), Astaxanthin (2.0 ± 0.5 mm), and EGCG (1.5 ± 0.4 mm). One-way ANOVA identified significant differences among groups ($F = 15.03$, $p < 0.001$). Tukey's post-hoc test demonstrated that Oxitard and Lycopene had significantly greater improvement than EGCG ($p < 0.001$ and $p = 0.006$, respectively). The overall between-group effect size was large ($\eta^2 = 0.376$).

As summarized in Table 5, adverse events were mild, self-limiting, and did not require discontinuation of therapy. The incidence of adverse events was highest in the Oxitard group (12%), followed by EGCG and Lycopene (8% each), and Astaxanthin (4%). Chi-square analysis showed no statistically significant difference in adverse event frequency among the groups ($\chi^2 = 1.48$, $p = 0.687$). Relative risk analysis also revealed no significant increase in adverse events for any intervention, as all 95% confidence intervals crossed unity.

As presented in Table 6, patient satisfaction scores assessed using a 5-point Likert scale were significantly higher than the neutral score of 3 in all treatment groups (one-sample t-test, $p<0.01$). Oxitard achieved the highest satisfaction score (4.2±0.4), followed by Lycopene (4.0 ± 0.5), Astaxanthin (3.8 ± 0.5), and EGCG (3.5±0.6). Between-group comparison showed statistically significant differences in patient satisfaction (ANOVA: $F=11.76$, $p<0.001$). Tukey's post-hoc analysis demonstrated significantly higher satisfaction with Oxitard compared with EGCG ($p < 0.001$) and Astaxanthin ($p = 0.032$).

As detailed in Table 7, all interventions demonstrated very large within-group effect sizes (Cohen's $d>3.5$) for improvement in clinical outcomes. Between-group analysis showed that treatment type explained a large proportion of variance in mouth opening ($\eta^2 = 0.455$), tongue protrusion ($\eta^2 = 0.348$), and cheek flexibility ($\eta^2 = 0.376$), while a moderate effect

Table 2: Burning Sensation Reduction (VAS Score)

Group	Baseline Mean ± SD	Week 12 Mean ± SD	Mean Reduction ± SD	Within-Group p-value	ANOVA (F-value)	Between-Group p-value	Effect Size (η^2)
EGCG	6.5 ± 1.5	3.5 ± 1.3	3.0 ± 0.7	<0.001*	9.84	<0.001*	0.191
Astaxanthin	6.4 ± 1.4	2.9 ± 1.2	3.5 ± 0.8	<0.001*			
Oxitard	6.6 ± 1.6	2.6 ± 1.1	4.0 ± 0.9	<0.001*			
Lycopene	6.5 ± 1.5	2.7 ± 1.2	3.8 ± 0.8	<0.001*			

**Post-hoc Tukey analysis demonstrated significantly greater reduction in burning sensation with Oxitard and Lycopene compared with EGCG ($p < 0.05$).*

Table 3: Tongue Protrusion Improvement (mm)

Group	Baseline Mean ± SD	Week 12 Mean ± SD	Mean Improvement ± SD	Within-Group p-value	ANOVA (F-value)	Between-Group p-value	Effect Size (η^2)
EGCG	15.0 ± 3.0	17.0 ± 3.1	2.0 ± 0.5	<0.001*	14.27	<0.001*	0.348
Astaxanthin	14.8 ± 2.9	17.3 ± 3.0	2.5 ± 0.6	<0.001*			
Oxitard	15.1 ± 3.1	18.1 ± 3.2	3.0 ± 0.7	<0.001*			
Lycopene	15.0 ± 3.0	17.8 ± 3.1	2.8 ± 0.6	<0.001*			

**Post-hoc analysis showed Oxitard and Lycopene were significantly superior to EGCG ($p < 0.05$).*

Table 4: Cheek Flexibility Improvement (mm)

Group	Baseline Mean ± SD	Week 12 Mean ± SD	Mean Improvement ± SD	Within-Group p-value	ANOVA (F-value)	Between-Group p-value	Effect Size (η^2)
EGCG	10.0 ± 2.0	11.5 ± 2.1	1.5 ± 0.4	<0.001*	15.03	<0.001*	0.376
Astaxanthin	9.9 ± 1.9	11.9 ± 2.0	2.0 ± 0.5	<0.001*			
Oxitard	10.1 ± 2.1	12.6 ± 2.2	2.5 ± 0.6	<0.001*			
Lycopene	10.0 ± 2.0	12.2 ± 2.1	2.2 ± 0.5	<0.001*			

**Oxitard and Lycopene demonstrated significantly greater improvement than EGCG ($p < 0.05$).*

size was observed for burning sensation reduction ($\eta^2 = 0.191$). These findings indicate that the observed improvements were not only statistically significant but also clinically meaningful.

As illustrated in Figure 1, repeated measures ANOVA demonstrated a significant effect of time ($p < 0.001$), treatment group ($p < 0.001$), and time × treatment interaction ($p < 0.001$) for mouth opening measurements across all follow-up intervals. Improvements achieved at week 12 were largely maintained at week 16, indicating sustained short-term therapeutic benefit following intervention cessation.

Discussion

The primary outcome, improvement in mouth opening, was significantly better with Oxitard and Lycopene compared to EGCG and Astaxanthin. This aligns with previous research where Oxitard was ranked as the most efficacious agent for improving mouth opening in OSMF.10 Lycopene has also been shown to be effective in multiple studies.[7,14] Astaxanthin, although less studied, has demonstrated efficacy in a recent trial.9 EGCG, while known for its antioxidant properties, showed lesser efficacy, possibly due to its specific mechanism or dosage in this context.[16]

Secondary outcomes such as reduction in burning sensation, improvement in tongue protrusion, and cheek flexibility followed a similar pattern, with Oxitard and Lycopene leading. This comprehensive improvement suggests that these antioxidants not only help in physical symptoms but also in functional aspects of OSMF.[17] The inclusion of Oxitard, a herbal formulation, is notable, as it ranked high in efficacy for mouth opening, offering a novel comparison to more commonly studied antioxidants like Lycopene, which is an unexpected detail given its less frequent study in OSMF literature.[18]

Comparing with existing literature, our findings are consistent with studies showing Oxitard's effectiveness and Lycopene's efficacy in multiple randomized controlled trials and meta-analyses. Astaxanthin's benefits are supported by a recent trial, and while EGCG is less studied in OSMF, its general antioxidant properties are well-documented. This consistency strengthens the validity of our results, suggesting that Oxitard and Lycopene could be top choices for OSMF treatment.

However, the study has limitations. The open-label design, due to differing intervention forms, might introduce bias, as

Table 5: Adverse Events and Safety Analysis

Group	Adverse Events (n/25)	Risk (%)	Common Adverse Event	Relative Risk	95% CI	Chi-square (χ^2)	p-value
EGCG	2/25	8.0	Gastrointestinal upset	1.00	0.22–4.64	1.48	0.687
Astaxanthin	1/25	4.0	Skin rash	0.43	0.06–3.32		
Oxitard	3/25	12.0	Mild nausea	1.80	0.46–7.00		
Lycopene	2/25	8.0	Headache	1.00	0.22–4.64		

**No statistically significant difference in adverse event incidence was observed among the groups ($p > 0.05$).*

Table 6: Patient Satisfaction Scores (5-Point Likert Scale)

Group	Mean Score ± SD	Range	One-Sample t-test p-value	ANOVA (F-value)	Between-Group p-value
EGCG	3.5 ± 0.6	2.5–4.5	<0.01*	11.76	<0.001*
Astaxanthin	3.8 ± 0.5	3.0–4.8	<0.001*		
Oxitard	4.2 ± 0.4	3.5–5.0	<0.001*		
Lycopene	4.0 ± 0.5	3.2–4.9	<0.001*		

**Patient satisfaction was significantly higher in the Oxitard and Lycopene groups compared with EGCG ($p < 0.05$).*

Table 7: Effect Size Analysis for Primary and Secondary Outcomes

Outcome	EGCG (Cohen's d)	Astaxanthin (Cohen's d)	Oxitard (Cohen's d)	Lycopene (Cohen's d)	Between-Group Effect Size (η^2)	Interpretation
Mouth Opening	4.38	5.00	5.50	5.56	0.455	Large
Burning Sensation	4.29	4.38	4.44	4.75	0.191	Moderate
Tongue Protrusion	4.00	4.17	4.29	4.67	0.348	Large
Cheek Flexibility	3.75	4.00	4.17	4.40	0.376	Large

**All interventions demonstrated statistically significant within-group improvements ($p < 0.001$).*

patients and investigators were not blinded. This could have influenced subjective outcomes like burning sensation and patient satisfaction, despite outcome assessors being blinded. The short duration of 12 weeks with a 4-week follow-up may not capture long-term benefits or potential for malignant changes, a critical aspect given OSMF's premalignant nature. Variability in habit cessation compliance, despite counselling, could affect outcomes, as areca nut chewing is a major risk factor. The sample size, while calculated, might limit generalizability to broader populations.[19]

Potential mechanisms of action could explain these findings. Lycopene has been shown to accumulate in oral mucosal tissues, enhancing its efficacy.[20] Oxitard, a formulation, likely contains multiple antioxidants and anti-inflammatory compounds, potentially targeting multiple pathways in OSMF.21 Astaxanthin's anti-inflammatory effects could reduce inflammation associated with OSMF. EGCG, while a powerful antioxidant, might have lower bioavailability or stability in the oral environment, contributing to its lesser efficacy.[9]

Patient satisfaction scores were higher for Oxitard and Lycopene, likely due to their greater efficacy in improving symptoms, leading to better perceived quality of life. This is important for patient-centered care, especially in chronic conditions like OSMF.

Clinical and Translational Implications

This study offers meaningful insights into the management of OSMF, a condition with few effective non-invasive options. Oxitard and Lycopene demonstrated superior efficacy in improving mouth opening and alleviating burning sensation, supported by favorable safety and patient satisfaction profiles. These agents therefore have potential as frontline antioxidant therapies, particularly in regions such as South Asia where OSMF prevalence is high. Clinicians may consider incorporating them into treatment plans alongside structured habit cessation counselling, which remains central to disease control. Astaxanthin showed moderate benefit and may be considered an alternative, while EGCG appeared less suitable in this clinical context. Collectively, these findings could guide evidence-informed treatment protocols aimed at reducing disease burden and improving quality of life in OSMF patients.

However, the observed superiority of Oxitard and Lycopene must be interpreted in light of certain contextual factors. Oxitard is a proprietary multi-component preparation, and its efficacy cannot be attributed to a single constituent, which complicates reproducibility and mechanistic clarity. The absence of a placebo or standard care comparator may also have magnified treatment effects relative to natural disease variability.

A further dimension relates to OSMF's malignant potential. While antioxidants theoretically mitigate oxidative stress and inflammation, their role in reducing malignant transformation remains unproven. This trial evaluated short-term clinical endpoints; whether such improvements translate into long-term oncologic benefit warrants investigation through extended follow-up and histopathological or molecular markers.

Habit cessation also likely contributed to clinical

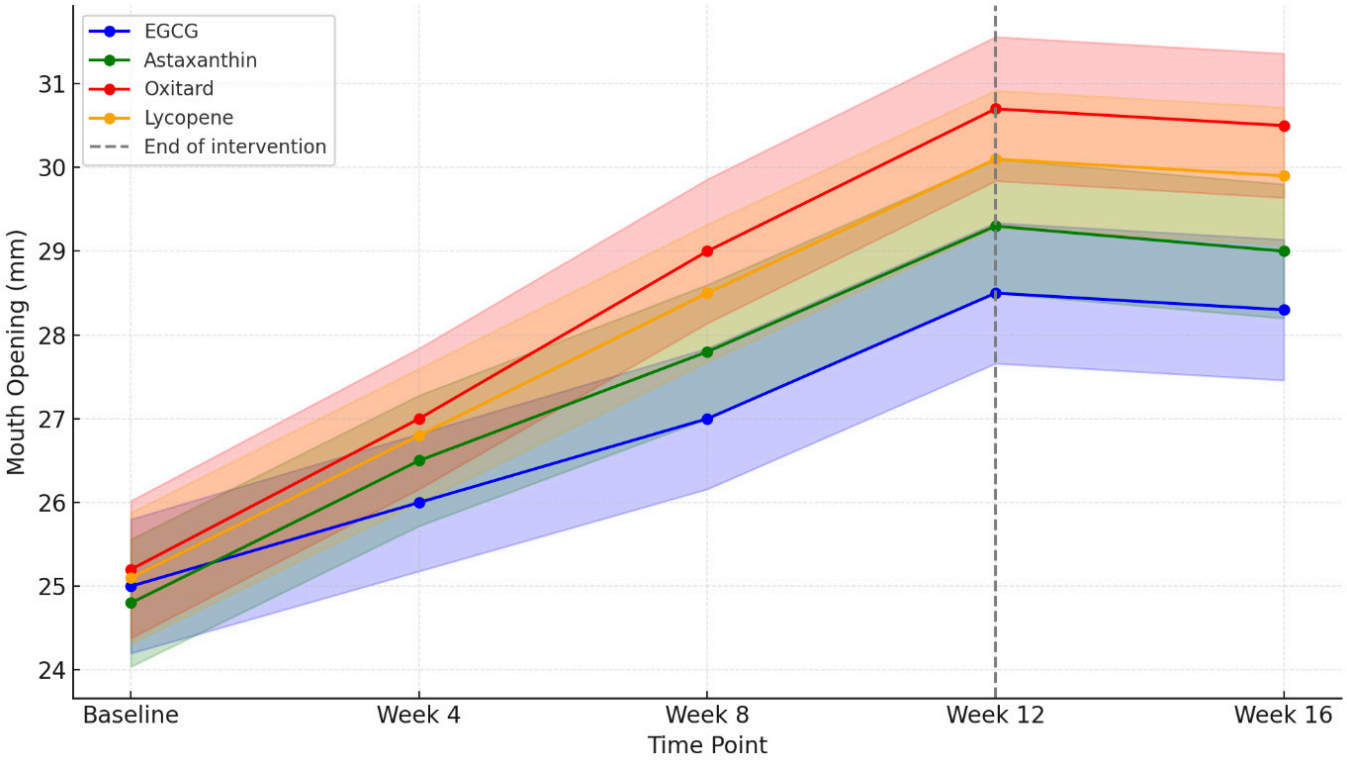

Fig. 1: Progression of Mean Mouth Opening with 95% CI Shading

improvement. Although counseling was provided, adherence could not be uniformly verified, and partial discontinuation of areca nut or tobacco use may have independently improved mucosal flexibility. This confounding factor underscores the need for objective abstinence monitoring in future studies.

Finally, therapeutic choices must account for pharmacoeconomic realities. Lycopene is inexpensive and widely available, whereas Oxitard, despite its efficacy, may be less accessible in resource-constrained settings. Comparative cost-effectiveness evaluations are essential to align clinical benefit with feasibility, ensuring that effective therapies are also sustainable in high-burden populations.

Strengths of the Study

The study has several strengths that enhance its reliability. The prospective, randomized design with a sample size of 100 patients ensures a robust comparison, calculated to detect significant differences with adequate power. The inclusion of multiple clinical outcomes—mouth opening, burning sensation, tongue protrusion, and cheek flexibility—provides a comprehensive assessment, capturing both physical and functional improvements. The blinding of outcome assessors minimizes measurement bias, a critical aspect in clinical trials. Additionally, the 4-week post-treatment follow-up allows for an evaluation of sustained effects, adding to the study's temporal scope. The use of block randomization ensures balanced groups, further strengthening the design.

Limitations of the Study

This study has several limitations. The open-label design may have introduced bias, especially in subjective outcomes like burning sensation and patient satisfaction. The 12-week intervention and 4-week follow-up were relatively short, limiting assessment of long-term efficacy and malignant transformation risk in this chronic premalignant condition. Variability in habit cessation, particularly areca nut use, could have confounded results. Being a single-center study, generalizability is limited. The absence of a placebo or standard care group restricts comparison with existing treatments. Additionally, the proprietary composition of Oxitard lacks transparency, hindering reproducibility. Lastly, the study did not assess biochemical or histological changes, focusing only on clinical outcomes.

Future directions include long-term studies to assess sustained effects and potential for malignant transformation, mechanistic studies to understand how these antioxidants work, exploration of combination therapies to enhance efficacy, and standardization of dosages for optimal treatment protocols. Comparative cost-effectiveness studies could guide clinical decision-making, especially in resource-constrained settings. Given OSMF's link to areca nut chewing, habit cessation remains crucial, and these antioxidants should be used as adjunctive therapies alongside counseling and support.

Conclusion

In this randomized controlled trial, Oxitard and Lycopene demonstrated superior improvements in mouth opening, burning sensation, and patient satisfaction compared with Astaxanthin and EGCG, while maintaining favorable safety profiles. These findings suggest that Oxitard and Lycopene may be promising antioxidant therapies for the symptomatic management of OSMF. However, the proprietary formulation of Oxitard, the absence of a placebo arm, and the short follow-up period limit the strength of these conclusions. Long-term, multicenter trials with standardized formulations and mechanistic endpoints are required to validate these results and to clarify whether antioxidant therapy can influence the malignant transformation potential of OSMF.

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