



Comparing the effects of lycopene and corticosteroids on oral lichen planus: a systematic review and meta-analysis

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ABSTRACT

Oral lichen planus (OLP) as an inflammatory disease is autoimmune in nature and there is no definitive treatment for it. Currently, topical and systemic corticosteroids have been adopted as the gold standard in the treatment of OLP, which have significant side effects. Nowadays, the tendency towards natural medicines with antioxidant properties as an alternative treatment has increased due to their low side effects. The main purpose of this systematic review and meta-analysis was to focus on comparing the effects of lycopene as an herbal intervention and corticosteroids on OLP in clinical trials. The search using keywords was done through provided databases from PubMed, Web of Science, Google Scholar, and Scopus until March 2023. After removing duplicate articles and screening them according to eligibility criteria, 5 articles remained and were considered for systematic review and meta-analysis. According to the meta-analysis, significant difference was not observed between the lycopene and corticosteroid groups in terms of reducing pain and improving clinical symptoms after treatment. Lycopene was tolerated well and no specific adverse effects were shown. The systematic review results showed the significant effect of lycopene in the treatment of OLP. The results of this meta-analysis can be useful because no significant side effects have been specified for lycopene. Hence, it might be used instead of steroids.

Implication for health policy/practice/research/medical education:

Based on the results of this meta-analysis, no significant difference was observed between the effects of lycopene and prednisolone in improving OLP symptoms. So far, no significant side effects have been reported for lycopene, which is why it can be used along with or instead of steroids that have many side effects.

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Introduction

Oral lichen planus (OLP) is an oral mucosal type of lichen planus with an unknown etiology (1-3). Its prevalence is 0.5-2.2% in the population and has a higher incidence rate in middle-aged women (4). OLP lesions can be white (keratotic lines) or red (bullous, atrophic and erosive forms). It is a chronic disease that a person suffers for years; it causes pain and irritation in the patient's mouth, and there is no definitive treatment for it (5,6). Also, the erosive and atrophic forms are clinically related to oral cancer development and need effective therapeutic interventions (2,7). The etiopathogenesis of OLP is unknown; however, several factors are responsible for the worsening of the disease, including infection, stress, genetics, psychological, and autoimmune (8).

Nowadays, the common treatment plan for OLP is using topical and systemic corticosteroids, which is actually a symptomatic treatment and does not completely remove the lesions, and the lesions recur after stopping the drug. Therefore, the patient has to use medicine for a long period of time (9). The use of steroids in various pharmaceutical forms, such as Orabase, has been the best method of treating OLP so far, which reduces inflammation, pain, burning sensation, and faster healing of lesions (8). The use of steroid-containing drugs is limited in frequent use due to their side effects (10,11).

One of the choices for treatment is herbal medicines that have been used for many chronic diseases and are also used in OLP. The administration of herbal medicines together with steroids in randomized controlled trials

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(RCTs) as a standard control provides an unbiased insight into the current guidelines for the spectrum of herbal therapies that can replace other treatments of OLP patients (12). Lycopene is a red color carotenoid and is soluble in fat, which gives a deep red color to crops and fruits like tomatoes (12,13). Because of its antioxidant activity, it has many benefits on human health, such as prevention of cancer cell multiplication, stimulation of growth factor, enforcement on the enzymes of phase II, adjustment of transcription and recovery of junctions' gap (12). By physical and chemical suppressing of free radicals, lycopene performs an antioxidant activity; it is also known as the most effective oxygen suppressing carotenoid (12,13).

The effectiveness of lycopene on the prevention and treatment of OLP and other oral diseases has been underestimated compared to studies that evaluated its role in public health (12-15). Lycopene has been reported to be effective in the management of OLP and has been shown to be involved in the prevention of oral cancer (16). Its precise role in the prevention of OLP has not been evaluated in previous studies; however, a significant decrease in lycopene levels has been recorded in patients with atrophic and erosive OLP (10).

In this study, our aim is to systematically review and perform a meta-analysis of gathered studies, which focused on the effect of lycopene and corticosteroids on the pain and severity of OLP lesions.

Materials and Methods

Searching sources and strategy

The current study has been carried out based on the Reference Items for Systematic Reviews (PRISMA) guidelines. The review protocol was registered on the PROSPERO database with registration ID: CRD42022353725. The keywords-based search was done through the provided databases from PubMed, Google Scholar, Web of Science and Scopus to March 2023. We added some papers by reviewing the references list of related articles as other sources. We used multiple combinations of keywords validated by Medical Subject Headings (MeSH) as a search strategy. Only English and Persian studies were included in the search. The search strategy keywords are presented in Table 1.

Eligibility criteria

All clinical trials in which the effects of lycopene and

corticosteroids on clinical symptoms and pain intensity of OLP had been compared were included in this systematic review.

Screening and selection

Duplicate articles were removed at the beginning of the screening. According to the relevance of the title and abstract of retrieved studies, primary selection was performed. Then, the full text of the articles was assessed to confirm their eligibility of them. Endnote X9 was used to enter studies.

Data extraction

A checklist for data extraction was designed by the researchers who did the screening and study selection. The authors' names, year of publication, number of patients, gender, mean age, involved area, and the type of lesion were extracted from studies. The information was extracted and entered into the table by two independent researchers.

Quality valuation

In this study, we used the Joanna Briggs Institute (JBI) checklist (17) to evaluate the nominated articles and the risk of bias in studies. It includes 13 criteria for RCT studies. Each item was answered with "yes", "no" or "unclear".

Statistical analysis

To indicate heterogeneity between studies, we used I^2 statistic and Cochran's test in this analysis. For I^2 coefficient less than 50% and the P greater than 0.1, there was no significant heterogeneity between studies. Then, the comprehensive meta-analysis software version 2.0 was applied for meta-analysis, and $P < 0.05$ criterion was considered to report the statistical significance of the data.

Results

Search and selection results

After a wide search in the aforementioned databases and other sources, the data were collected. In the PRISMA flowchart (Figure 1), details of a number of studies obtained from each database, screening, and study selection procedure are presented. After the removal of duplicate articles and screening abstract, 10 articles remained. After reading the full text of the articles based on the eligibility criteria, 5 studies were excluded due

Table 1. Search strategy keywords

| Concepts | Search strategy |
|--------------|--|
| Population | Oral precancerous lesion(s) OR oral lichen planus OR oral premalignant lesion(s) OR lichen planus |
| Intervention | Lycopene OR Lycomato OR All trans Lycopene OR Prolycopene OR (13-cis)-isomer OR Pro-lycopene |
| Comparison | Corticosteroid OR prednisolone OR predonine OR betamethasone OR steroid |
| Outcome | Treatment OR healing OR regeneration OR improvement OR effect OR pain OR symptom OR clinical sign OR management OR VAS |

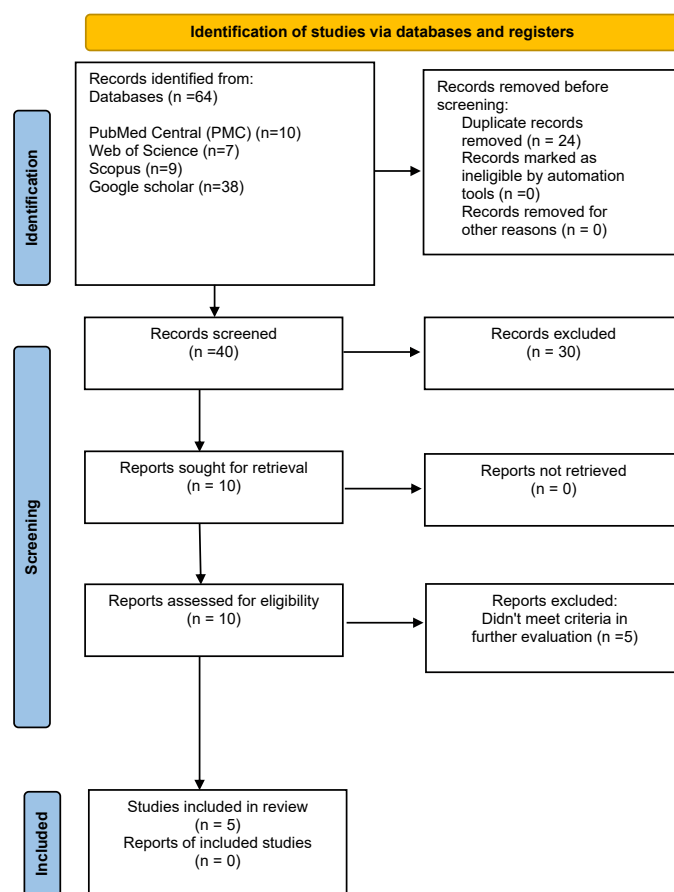


Figure 1. The flowchart of the study selection using PRISMA 2020.

to not meeting the criteria in the subsequent evaluation (5,8,18-20). Therefore, 5 studies were considered for systematic review (6,15,21-23).

Characteristics of included studies

All studies were RCTs and included cases of OLP diagnosed by histopathology. A total of 148 (female = 95 and male = 53) participants with symptomatic OLP participated in the RCTs. The female gender was predominance and the age range of participants was 14-75 years. Buccal mucosa was more involved compared to other mucosa, followed by the gingiva, tongue, lips, and hard palate. The common types of lesions, which were detected in the participants were mixed, followed by atrophic, erosive, and reticular types (Table 2). The patients in the lycopene group took lycopene soft gel capsules (10 mg/d) and the patients in the control group took prednisolone tablets (40 mg/d) for 8 weeks. Reduction of pain and improvement of clinical symptoms were two factors considered to highlight the effects of lycopene and corticosteroids. Pain reduction was evaluated by visual analog scale (VAS) and the improvement of clinical symptoms was evaluated by Thongprasom scale (24). The side effect of lycopene was observed in only one study, which was mainly flatulence

followed by nausea (23). In two studies the adverse effects in steroids groups were reported, including facial puffiness, gastrointestinal disturbances, mild headache, dizziness, epigastric distress, and general weakness (21,23).

Risk of bias assessment

Table 3 shows the quality of the selected studies, where all of them were ranked high and included in this review.

Meta-analysis results

Figures 2 and 3 show the forest plot comparing the main effect of lycopene and corticosteroid (prednisolone) on the pain and clinical symptoms of patients with OLP. Based on the results of our meta-analysis, no statistically significant difference was observed between the lycopene and prednisolone groups in post-treatment pain reduction and clinical sign improvement ($P > 0.05$).

Discussion

The effectiveness of a new drug for a disease could be assessed only in comparison with the standard therapy under standard treatment status. Currently, the dominant and standard treatment of OLP is corticosteroids, and its effect on the relief of signs and symptoms of OLP has been

Table 2. The characteristic of study participants and type of lesions

| Author/ Year | Total number Female/male (n) | Mean age and range | Involved area (n) | Type of lesion (n) |
|---------------------------|---------------------------------|--------------------|--|--|
| Eita et al, 2022 (6) | 20, Female (14), male (6) | 51.50 ± 8.00 | Buccal mucosa (15) Gingiva (4) Lip (1) Tongue (3) Hard palate (1) | Erosive (20) |
| Budakoti et al, 2022 (15) | 40, Female (25), male (15) | 30-60 | Buccal mucosa (40) | Erosive (40) |
| Hazza, 2021 (22) | 40, Female (24), male (16) | 52.1±4.2 | Buccal mucosa (40) | Erosive or atrophic (40) |
| Eita et al, 2021 (21) | 20, Female (14), male (6) | 45.90 ± 9.63 | Buccal mucosa (17) Gingiva (3) Lip (1) Tongue (4) Hard palate (1) | Erosive (20) |
| Kushwaha et al, 2017 (23) | 28, Female (18), male (10) | 20-65 | Buccal mucosa (28) Gingiva (11) Lip (9) Tongue (8) Hard palate (2) | Reticular/plaque (7) Atrophic (12) Erosive (9) |

Table 3. Quality of the selected studies

| Studies (author and year) | Score based on the Joanna Briggs Institute (JBI) checklist | | | | | | | | | | | | |
|---------------------------|--|---|---|---|---|---|---|---|---|----|----|----|----|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| Eita et al, 2022 (6) | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | U |
| Budakoti et al, 2022 (15) | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | U | Y | Y |
| Hazza, 2021 (22) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y |
| Eita et al, 2021 (21) | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Kushwaha et al, 2017 (23) | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | N | Y |

Y: yes; N: no; U: unclear.

proven in earlier studies (25-30). However, due to their complications and adverse effects, the continuous use of corticosteroids is limited (31,32). Herbal and natural therapies are safe and abundant, and have lower costs compared to other drugs. In the treatment of OLP, some herbal therapies have been administered (33-36).

OLP, due to its chronic autoimmune nature, has a negative impact on the psychological well-being of the involved individuals. The use of medicine for a long time and the recurrence of lesions can adversely affect the quality of life of patients with OLP. The clinical trials' evidence could provide an effective and safe therapy for long-term treatment. Considering this view, a systematic review of lycopene therapy in OLP and a comparison of lycopene treatment with corticosteroids was done.

Previous systematic reviews assessed the impact of all herbal medicines in treating OLP compared with other active treatments or placebos. Two of them represented that none of the herbal medicines has a significant effect in treatment compared to other interventions (37,38). In one systematic review, the effects of curcumin and aloe vera showed reasonable evidence for the treatment of

OLP (39).

The positive results of lycopene are due to its useful and extensive properties (40). Lycopene is a potent carotenoid antioxidant that effectively targets singlet oxygen and protects cells from oxidative damage. In addition, lycopene reduces the synthesis and release of many pro-inflammatory cytokines, such as interleukin 4, 6, 8 and tumor necrosis factor α , which in addition to reducing inflammation, inhibits the production and release of reactive oxygen species (41). It also plays a role in the regulation of hormonal and immune modulation, anti-proliferative and differentiation activities (42). The results of the control group can be attributed to the strong anti-inflammatory and immunosuppressive properties of corticosteroid drugs. They inhibit cellular immunity by inhibiting phagocytosis and releasing lysozyme and suppressing T cell function (43). The relative improvement of clinical symptoms and signs experienced in some patients of both study groups may be due to the fact that OLP is a dynamic disease with clinical manifestations that are constantly fluctuating. The lack of complete clarification of the cause of this disease makes various

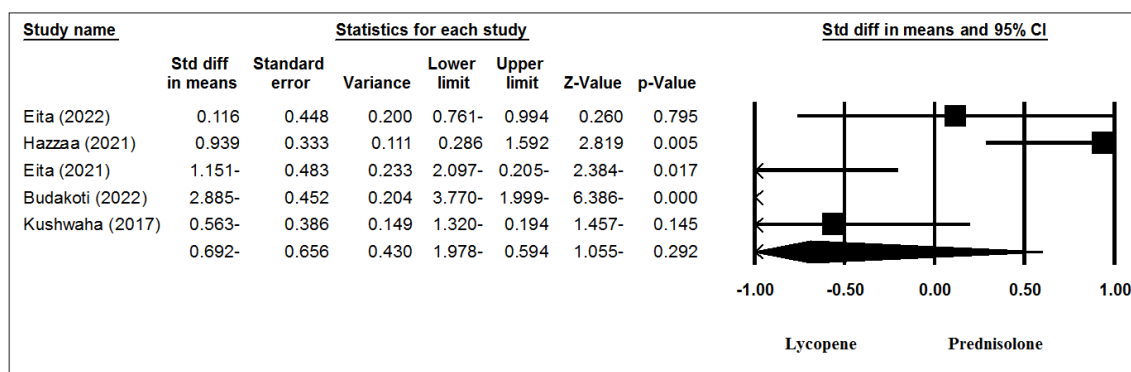


Figure 2. Forest plot comparing the effect of lycopene and prednisolone on clinical symptoms improvement in patients with oral lichen planus.

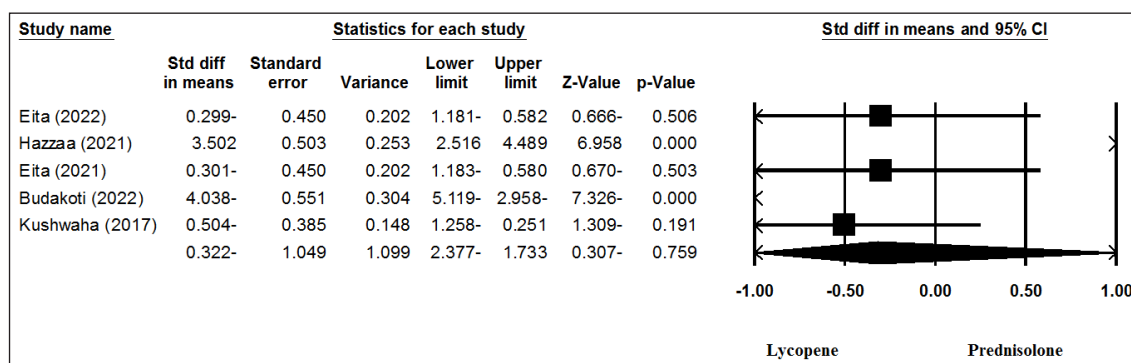


Figure 3. Forest plot comparing the effect of lycopene and prednisolone on pain reduction in patients with oral lichen planus.

treatment methods as palliatives of symptoms instead of real treatments (44).

The number of RCTs in this field was relatively less and there was a significant difference in study design, the dosage of medicine, different scoring patterns, and control groups. In order to be able to effectively investigate the effect of lycopene or other herbal medicines, studies with different doses and similar designs should be done so that the effective dose can be found. Also, to organize further meta-analysis, it is necessary to do uniform studies to reduce the amount of bias in the RCTs. Also, longer follow-up periods are needed along with the assessment of changes in quality of life.

Conclusion

The current paper showed proof to support the significant effect of lycopene in the treatment of OLP. The obtained results of the meta-analysis revealed that the effects of lycopene on the pain and clinical symptoms of OLP were not significantly different from corticosteroids, and no specific side effects were reported for it. Therefore, lycopene might be used alone or together with corticosteroid drugs to treat OLP. Of course, to prove this point, more clinical trials with low risks of bias in standard conditions are recommended.

Authors' contribution

Designing the study, searching for articles, analyzing data and preparing the final version of the article was done by PM. The draft of the article was prepared by RD. All authors were involved in reviewing of articles and data collection.

Conflict of interests

The authors have no conflict of interest to declare.

Ethical considerations

This systematic review study has been approved by the ethics committee of Tabriz University of Medical Sciences with the mentioned code of ethics (IR.TBZMED.REC.1401.227). Also, the authors of the article have reviewed the text plagiarism and data falsification.

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