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# Effect of serum and salivary levels of vitamins C and E on Oral Lichen Planus: A Systematic Review and Meta-Analysis

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## ABSTRACT

**Background:** Lichen planus is a chronic inflammatory disorder and various factors are involved in its development. One of the most important factors is the immune system. The first line of treatment for this disease is the use of corticosteroids, and the use of antioxidants (vitamin C and E) may help. These vitamins have the ability to prevent the multiplication and release of destructive free radicals in the cell membrane, and its deficiency may cause disruption of the immune system and the occurrence of disease. Many studies have been conducted in this field, which necessitates the need for a systematic review. Therefore, this study will be conducted with the aim of the effect of vitamins C and E on lichen planus.

**Method:** This study was conducted as a systematic review. Keywords were searched for the "Oral Lichen Planus" AND ((Ascorbic Acid OR Vitamin C OR Hybrin OR Magnorbin OR Ascorbate OR Magnesium Ascorbicum) OR (Vitamin E OR Tocopherols OR Tocotrienols)) in various scientific databases up to the end of [insert date]. Based on the types of studies included, random-effects models were employed to estimate the effect sizes in the meta-analysis, utilizing a heterogeneity assessment methodology. The results of the studies, along with the overall estimated effect size, were presented in a forest plot. Heterogeneity among the studies was evaluated using the $I^2$ statistic. To address statistical heterogeneity, we applied a stratified analysis approach. Additionally, to assess publication bias, we created a funnel plot and conducted the Begg and Egger tests. Meta-analysis and meta-regression were performed using STATA version 16 software.

**Results:** After removing duplicates, a total of 1,185 articles were identified, of which 8 studies were included in the meta-analysis. The findings indicated a strong, positive, and statistically significant relationship between Vitamin C and Oral Lichen Planus, with a standardized mean difference (SMD) of -1.71 (95% Confidence Interval [CI]: -2.34, -1.05; $p < 0.001$; $I^2 = 87.22\%$). Additionally, the meta-analysis examining the relationship between Vitamin E and Oral Lichen Planus also revealed a strong, positive, and statistically significant association, with an SMD of -0.96 (95% CI: -1.88, -0.04).

**Conclusion:** This study found a significant correlation between serum and salivary vitamin C levels and vitamin E levels in patients with oral lichen planus (OLP). However, serum vitamin E levels did not show a significant relationship with this condition. Additionally, a positive correlation between vitamin C and vitamin E was observed.

***Keywords:*** *Lichen planus, Oral, Ascorbic Acid, Vitamin E, and Systematic Review*

## 1. INTRODUCTION

Oral Lichen Planus (OLP) is a chronic, inflammatory mucosal condition characterized by the presence of white reticular striations, erosive lesions, and an associated burning sensation in the oral cavity. Affecting approximately 1-2% of the general population, OLP predominantly impacts middle-aged adults and is believed to have an autoimmune etiology, which

complicates its management(1).Patients with OLP often experience significant discomfort, affecting their ability to eat, speak, and maintain their oral hygiene, leading to a decline in overall quality of life(1).

Current treatment modalities for OLP primarily focus on symptomatic relief and may include topical corticosteroids, immunosuppressive agents, and other pharmacological therapies(2). However, these options often have varied efficacy and may be associated with significant side effects or long-term complications(2). As a result, there is a growing interest in exploring alternative therapies that may provide effective relief with a favorable safety profile(2).

Vitamins C and E have attracted attention in this context due to their well-documented antioxidant properties, which help to counteract oxidative stress and inflammation as the two key factors implicated in the pathogenesis of OLP(3). Vitamin C (ascorbic acid) plays a crucial role in collagen synthesis, immune function, and the modulation of inflammatory responses, while vitamin E (tocopherol) is known for its protective effects on cell membranes and its ability to suppress inflammato ry cytokines(4).

Despite the potential benefits of vitamins C and E in managing OLP, the existing literature presents mixed results regarding their efficacy. Some studies suggest positive outcomes, while others report negligible effects. Consequently, there is a need for a comprehensive assessment of the evidence to clarify the therapeutic role of these vitamins in OLP treatment.

The objective of this systematic review and meta-analysis is to evaluate the overall effect of vitamins C and E on clinical outcomes in patients with OLP, focusing on symptom relief and lesion improvement. By synthesizing the available data, this review aims to provide clearer guidance for clinicians in the management of OLP and contribute to the ongoing discussion regarding the use of nutritional supplements in inflammatory oral diseases.

## 2. METHODS

### Type of Research

This research was classified as a secondary study conducted through a systematic review and meta-analysis and the research protocol was approved by Ethical committee of Golestan University of Medical Sciences. (Registration number: IR.GOUMS.REC.1401.377)

### Sample Size and Study Population

The study population included all articles and documents available in international databases that were published in reputable scientific journals from the inception of these journals until 2024. As this study utilizes a systematic and methodical approach, it was categorized as a secondary study, which retrieved all relevant information related to the research area published in English up to 2024. Consequently, methods for sample selection and considerations regarding sample size were not applicable.

Initially, to investigate the relationship between vitamins C and E and their efficacy in improving Oral Lichen Planus, all articles pertaining to this condition were reviewed. Among these studies, only those that examined the status of vitamins C and E underwent detailed analysis, from which relevant indicators were extracted or computed based on the available data.

To maximize the retrieval of relevant and credible studies, a comprehensive search was conducted in the following databases: PubMed, Web of Science, Scopus, ProQuest, Wiley, Cochrane, and Embase. The search strategy employed was:

(Oral Lichen Planus) AND ((Ascorbic Acid OR Vitamin C OR Hybrin OR Magnorbin OR Ascorbate OR Magnesium Ascorbicum) OR (Vitamin E OR Tocopherols OR Tocotrienols))

The search criteria for each database were as follows:

- **PubMed:** The advanced search option was utilized, placing the terms from the search strategy in the Title/Abstract field. Additionally, a search using Mesh terms was conducted for comprehensive retrieval, focusing on major topics with the following command: [Mesh] "Lichen Planus" [Mesh] AND "Vitamin C" [Mesh] AND "Vitamin E".
- **Web of Science:** The search encompassed all sub-databases, querying the specified concepts in the Topic field (which includes title, abstract, author keywords, and Keywords Plus) to ensure maximal comprehensiveness.
- **Scopus:** Relevantarticles were searched using the specified terms in the Title/Keyword/Abstract fields; the Advanced Document Search was also employed in Author codes, Index Terms, and Keywords.
- **Cochrane:** The search was conducted in two phases, initially querying research concepts in the Title/Keyword/Abstract fields, followed by a re-search using Medical Terms (Mesh).
- **ProQuest:** Two searches were executed in this database: one using the search strategy in the Abstract field and another using the Subject Heading (MAIN SUBJECTS) field.
- **Embase:** Searches were performed in the Title/Abstract/Keywords fields and utilizing the Entree thesaurus.

- **Wiley:** The Advanced Search was carried out to ensure comprehensive retrieval of results across three stages: Title, Keyword, and Abstract fields.

Records identified from these databases were imported into EndNote version 20 (Thomson Reuters, California, USA) to create a comprehensive library of articles focused on Oral Lichen Planus and vitamins C and E. Any ambiguities in the retrieved records were addressed in collaborative sessions among the research team, and duplicate records were removed using the functionalities of EndNote.

**Selection Criteria for Studies**

A study selection team, composed of two members, was established to evaluate the search results. A selection guideline was developed, outlining the research objectives, questions to be addressed, and a standardized selection process. This included a checklist for recording reviewed studies and instructions for documenting the quantity and statistics of excluded studies. The decision to retain or exclude a study during screening was based on the title and abstract. Articles deemed irrelevant were excluded, and efforts were made to obtain the full texts of the remaining records for comprehensive evaluation.

**Criteria for Inclusion and Exclusion of Studies**

All cross-sectional, case-control, cohort, and ecological studies examining the relationship between Oral Lichen Planus and vitamins C and E were considered. The inclusion process adhered to the established protocol, encompassing both international and national search engines.

**Quality Assessment of Studies**

The quality of the articles was evaluated by two independent assessors using the Newcastle-Ottawa Scale (NOS), which consists of nine items. Articles scoring above seven were classified as high quality, those scoring between five and seven as moderate quality, and scores below five as low quality. Discrepancies between the evaluators were resolved through discussion with another team member.

**Data Collection Method**

Data related to Oral Lichen Planus and vitamins C and E were extracted and stored in a standardized data sheet designed in Excel 2016. Prior to extraction, the data sheet underwent a pilot test on five articles. After the pilot test, modifications were made, and data from the remaining studies were extracted and documented. The recorded items included:

- Article title
- First author's name
- Year of publication
- Article code (PMID or DOI)
- Journal name
- Journal page numbers
- Sampling method
- Sample size
- Duration of sample collection
- Age group classifications
- Gender ratio
- Study type
- Assessment methods for Oral Lichen Planus and vitamins C and E
- Indices of association (OR, RR, RD) and reported standard error.

Effect size indices and 95% confidence intervals were calculated using prevalence data, standard deviation, and sample size via statistical software.

**Data Analysis Method**

Meta-analysis was performed on the results of the included studies for the systematic review, particularly focusing on those exhibiting minimal methodological heterogeneity. Depending on the types of studies, either fixed or random effect models were employed for estimating indices. Characteristics of the studies and overall estimated indices were displayed using stacked charts. Heterogeneity among groups was assessed using Cochran's Q test ($p < 0.1$) and the $I^2$ statistic. To address statistical heterogeneity, a stratified analysis method was utilized. Publication bias was assessed using funnel plots and

Egger's regression model. STATA version 16 software was used for conducting the meta-analysis and meta-regression.

## 3. RESULTS

This study was conducted by searching the databases Cochrane, Google Scholar, ProQuest, PubMed, Scopus, Wiley, and WOS. The initial search yielded a total of 1348 articles. After removing 37 duplicates, 1311 articles were excluded based on title and abstract screening. A total of 38 articles underwent full-text assessment, of which 30 were excluded, leaving 8 articles deemed fully relevant to the topic. The reasons for exclusion included insufficient information (19 articles), inappropriate study design (8 articles), and the lack of an English version (3 articles). Ultimately, 8 studies were included in the systematic review and meta-analysis (Figure 1).

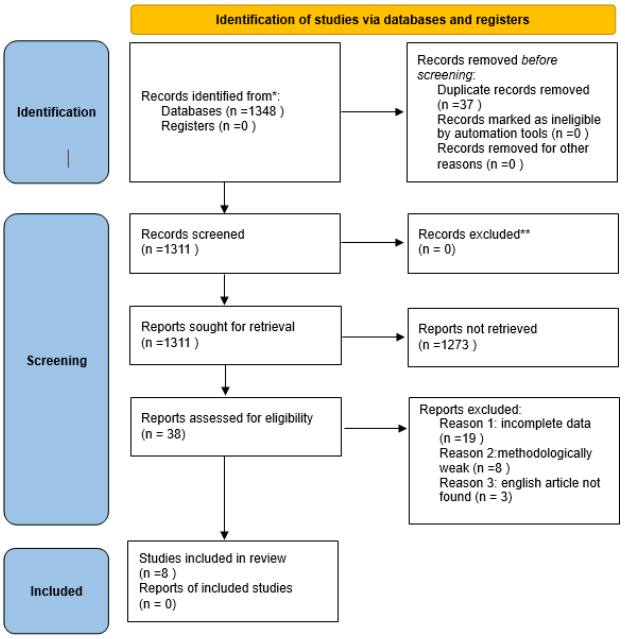


**Figure1: PRISMA 2020 flow diagram**

The final analysis comprised 8 articles: seven articles focused on Vitamin C and six ones Vitamin E. Most studies were conducted after 2011, with only 3 published before that year. The majority of the studies were originated from Iran (3 articles), followed by India (2 articles), Japan (2 articles), and Australia (1 article). All studies evaluated the effects of Vitamins E and C on oral lichen planus using a case-control design. Of the 8 articles, 6 assessed vitamin levels in serum, while 2 assessed these levels in saliva (Tables 1).

**Table 1: Characteristics of included studies**

| First Author, citation | Country | Age Mean ±SD(Min-Max) | Men N (%) in case | Men N (%) in control | Study design | Population | Method of evaluation | Vitamin | Source of vitamin |
|---|---|---|---|---|---|---|---|---|---|
| Abdolsamadi H, et al. 2014 | Iran | Case:43.1±9.6, Control:40.1±6.1 | 14 (38.9 %) | 15 (41.7 %) | Case-control | Cases: referred to oral medicine department, Controls: healthy | Roe and Kuether for Vitamin C & ELISA for Vitamin E | Vitamin C & E | salivary |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tsunoda K, et al. 2021 | Japan | Case:67.6±10.6, Control:67.2±8.94 | 15 (All Female) | 10 (All Female) | Case-control | Cases: Magokoro Hospital, Controls: healthy volunteers from general population | Vit C= HPLC Vit & E= fluorescence method | Vitamin C & E | Serum |
| Barikbin B, et al. 2011 | Iran | Case: 41.63±13.03, Control:41.17±13.24 | 10 (33.3 %) | 10 (33.3 %) | Case-control | Case: dermatology clinic of Shohada-eTajrish Hospital, Control: healthy people | Vit C= Enzymatic colorimetry | Vitamin C | Serum |
| Rezazadeh F, et al. 2021 | Iran | Case: 48.03±11.57, Control:48.74±12.7 | 11 (32.4 %) | 18 (41.9 %) | Case-control | Cases: patients referred to the Oral Medicine Department of Shiraz Dental School, Controls: healthy patients | Vit C= Kiazistvitamin C kit &Vit E= HPLC | Vitamin C & E | Serum |
| Jolly M, et al. 1977 | Australia | Case: 49 (20-78), Control:47 (23-71) | 14 (24.1 %) | 7 (53.8 %) | Case-control | Cases: Sydney Dental Hospital, Controls: Healthy hospital staff | Plasma level kit & Plasma level kit | Vitamin C & E | Serum |
| Bhat S, et al. 2017 | India | Case: 41.23 ± 12.1, Control: 35.2±11.22 | 26 (86.7 %) | 14 (46.7 %) | Case-control | Cases: Department of Oral Medicine and Maxillofacial Radiology, Controls: Healthy people | 2,4 dinitrophenyl hydrazine (DNPH) Method | Vitamin C | Serum |
| Kaur J, et al. 2015 | India | Case: 49±5.8, Control:48.9±7 | 20 (50%) | 20 (50%) | Case-control | Cases: A patient population in Baba Nidhan Singh, | HPLC | Vitamin C & E | salivary |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Controls: Healthy people | | | |
| Nagao T, et al. 2001 | Japan | Case: 60.6±9.2, Control:60.7±9.1 | 15 (24.2 %) | 60 (24.2 %) | Case-control | Cases: general health and oral mucosal screening program, Control: Healthy people from the program | HPLC | Vitamin E | Serum |

**Table 2: NOS score and level of quality of the articles**

| | Dimensions of NOS | | | NOS score | Level of quality |
|---|---|---|---|---|---|
| **First Author, citation** | **Selection** | **Comparability** | **Exposure** | | |
| Abdolsamadi H, et al. 2014 | 3 | 1 | 3 | 7 | Good |
| Tsunoda K, et al. 2021 | 4 | 2 | 3 | 9 | Good |
| Barikbin B, et al. 2011 | 3 | 1 | 3 | 7 | Good |
| Rezazadeh F, et al. 2021 | 1 | 1 | 3 | 5 | Fair |
| Jolly M, et al. 1977 | 2 | 0 | 3 | 5 | Fair |
| Bhat S, et al. 2017 | 2 | 0 | 3 | 5 | Fair |
| Kaur J, et al. 2015 | 2 | 1 | 3 | 6 | Fair |
| Nagao T, et al. 2001 | 4 | 1 | 3 | 8 | Good |

The meta-analysis of the included articles investigating the relationship between Vitamin C and oral lichen planus revealed a strong, positive, and statistically significant association (Standardized Mean Difference [SMD] = -1.70, 95% Confidence Interval [CI]: -2.34 to -1.05) (Figure 2-4). A similar analysis of the relationship between Vitamin E and oral lichen planus also demonstrated a strong, positive, and statistically significant association (SMD = -0.96, 95% CI: -1.88 to

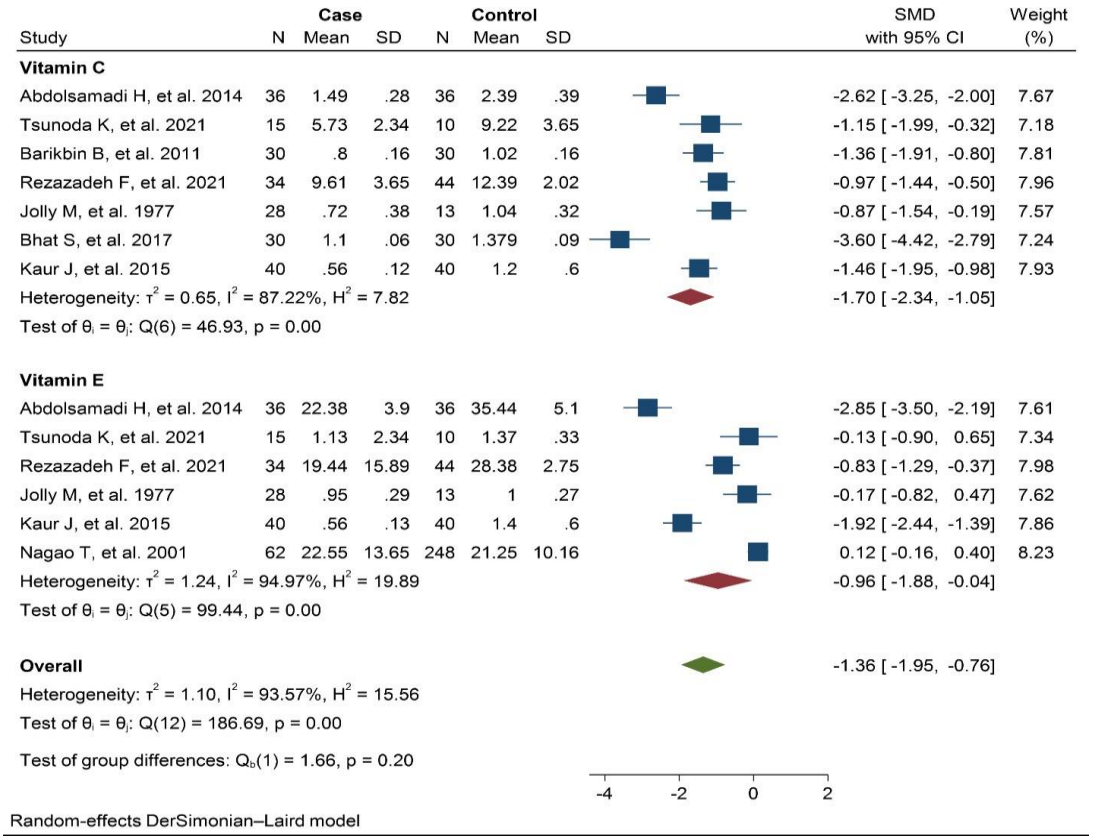


**Figure2: Forest Plot of the Association between Vitamin E and C with Oral Lichen Planus**

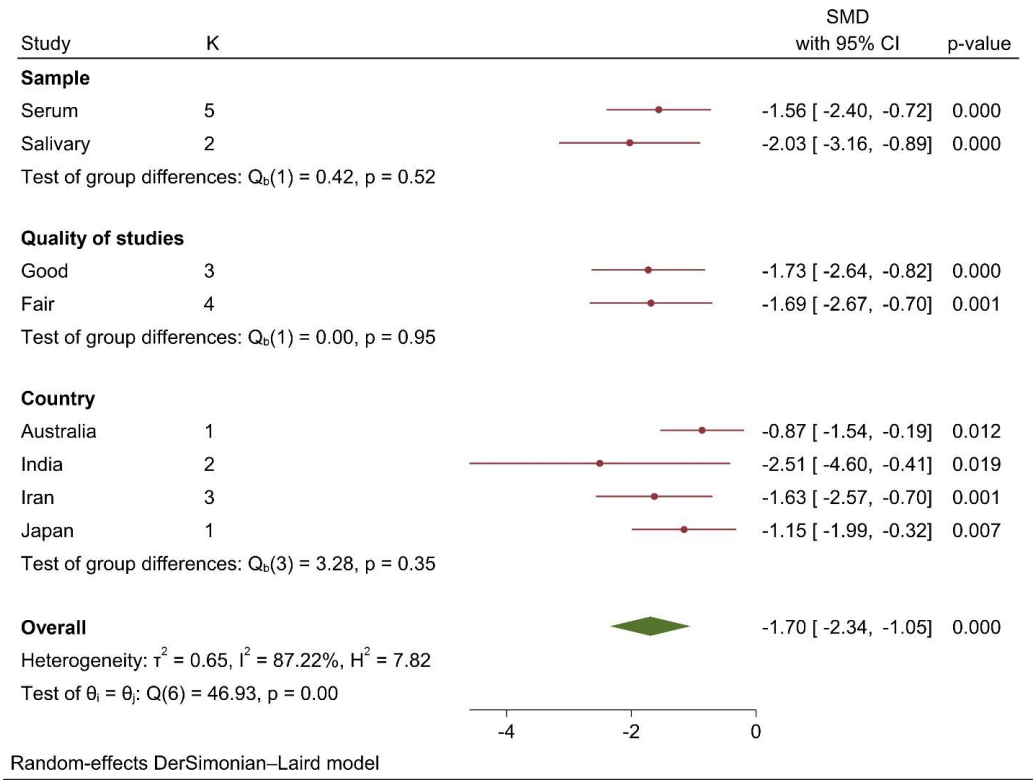


**Figure 3: Forest Plot of the Association between Vitamin C and Oral Lichen Planus Based on Subgroup Analysis by Sample Type, Study Quality, and Country**

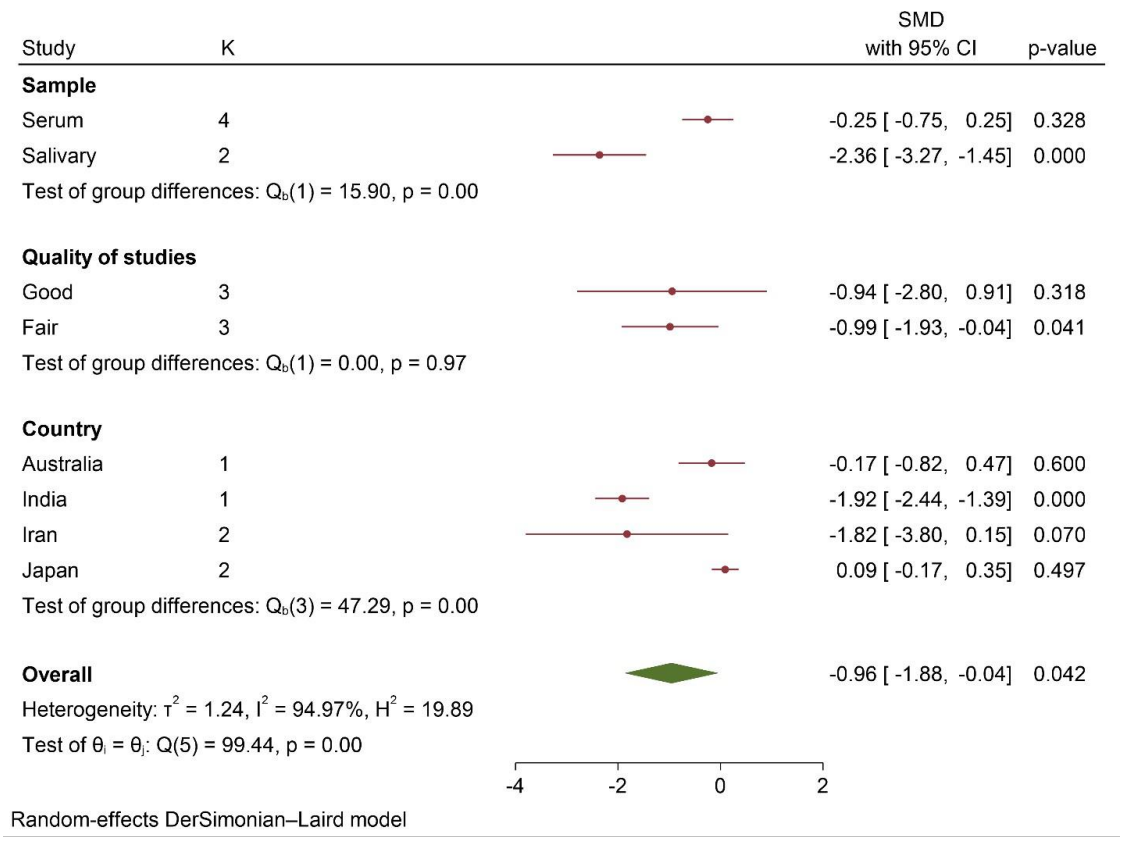


**Figure 4: Forest Plot of the Association between Vitamin E and Oral Lichen Planus Based on Subgroup Analysis by Sample Type, Study Quality, and Country**

## Subgroup Analysis

### Vitamin C Subgroup Analysis

The analysis of the relationship between Vitamin C and oral lichen planus within subgroups indicated that 5 serum samples exhibited a strong association (SMD = -1.56, 95% CI: -2.40 to -0.72). Additionally, 2 saliva samples showed that the mean level of Vitamin C in patients saliva was significantly lower than the control group (SMD = -2.03, 95% CI: -3.16 to -0.89) (Figure 3).

Among the articles examining the direct relationship between Vitamin C and oral lichen planus, 3 were classified as good quality and 4 as fair quality. The good-quality articles demonstrated a strong, positive, and significant association between Vitamin C and oral lichen planus, indicating that the concentration of Vitamin C in the patient group was lower than the control group (SMD = -1.73, 95% CI: -2.64 to -0.82). The fair-quality articles also indicated a positive, strong, and statistically significant relationship (SMD = -1.69, 95% CI: -2.67 to -0.70) (Figure 3).

Regarding the country of origin, the articles investigating Vitamin C included 1 from Australia, 2 from India, 3 from Iran, and 1 from Japan. Given the limited number of studies from Australia and Japan, reports primarily relied on studies from India and Iran, which indicated that the Vitamin C concentrations in individuals from the patient group were significantly lower than the control group (India: SMD = -2.51, 95% CI: -4.60 to -0.40; Iran: SMD = -1.63, 95% CI: -2.57 to -0.70) (Figure 3).

### Vitamin E Subgroup Analysis

The analysis of the relationship between Vitamin E and oral lichen planus based on subgroups indicated that four articles serum samples showed no significant association (SMD = -0.25, 95% CI: -0.75 to 0.25). In contrast, two saliva samples revealed that the mean level of Vitamin E in saliva was significantly lower than the control group, indicating a strong, positive, and statistically significant effect (SMD = -2.36, 95% CI: -3.27 to -1.45).

Among the articles investigating the direct relationship between Vitamin E and oral lichen planus, three articles were classified as good quality and 3 as fair quality. The good-quality articles indicated a strong, positive, and significant association between Vitamin E and oral lichen planus, showing that the concentration of Vitamin E in the patient group was

lower than in the control group (SMD = -0.94, 95% CI: -2.80 to -0.91). The fair-quality articles also displayed a positive, strong, and statistically significant relationship (SMD = -0.99, 95% CI: -1.93 to -0.04) (Figure 4).

Regarding the country of origin, the studies investigating Vitamin E included 1 from Australia, 1 from India, 2 from Iran, and 2 from Japan. Due to the limited number of studies from Australia and India, reports primarily relied on studies from Iran and Japan. In Iran, the concentration of Vitamin E in the patient group was significantly lower than in the control group (SMD = -1.82, 95% CI: -3.80 to -0.15); however, no significant relationship was observed in Japan (SMD = 0.09, 95% CI: -0.17 to 0.35) (Figure 4).

The funnel plot distribution indicated no significant publication bias. Additionally, publication bias was assessed using the Egger and Begg tests, both showing no substantial bias (Egger test p-value = 0.10; Begg' test p-value = 0.20) (Figure 5).

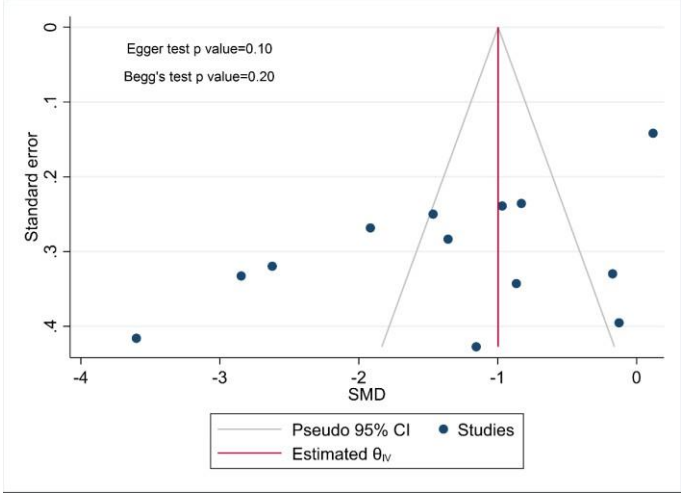


**Figure 5: Funnel Plot Assessing Publication Bias**

## 4. DISCUSSION

The present study aimed to evaluate the impact of vitamins C and E on oral lichen planus (OLP), a chronic autoimmune condition marked by inflammation of the oral mucosa(5). The etiology of OLP is multifactorial, involving immune dysregulation, increased oxidative stress, and potential nutritional deficiencies(6). Vitamins C and E, both recognized for their antioxidant properties, play crucial roles in modulating oxidative stress and immune responses, which may influence the pathogenesis of OLP(7).

Review of eight articles revealed a significant correlation between low levels of salivary or serum vitamin C and the incidence of OLP. Studies by Tsunoda(8) and Kaur(9) indicate that diminished vitamin C levels are associated with the development of lichen planus lesions. Vitamin C is essential for neutralizing reactive oxygen species (ROS), thereby protecting cellular structures from oxidative damage(10). Low levels of vitamin C may increase oxidative stress, exacerbating inflammation and tissue damage in OLP(8). Additionally, vitamin C is vital for the regeneration of vitamin E, another key antioxidant that protects cell membranes from lipid peroxidation. This interplay suggests that insufficient vitamin C may compromise the antioxidant defense system, leading to heightened inflammatory responses characteristic of autoimmune disorders(11).

Conversely, some studies challenge the definitive role of vitamins in OLP's pathogenesis. For instance, Rezazadeh et al.(12) found that the associations reported in earlier studies might stem from confounding factors such as dietary intake, socioeconomic status, or underlying health conditions influencing nutrient levels and immune function. Similarly, Jolly et al.(13) concluded that deficiencies in various vitamins, including C and E, do not appear to be primary contributors to the disease, suggesting a complex interplay between nutritional status and immune dysregulation(13).

Study findings also revealed that while salivary vitamin E levels were significantly lower in the patient group, serum levels showed no significant correlation with OLP. This discrepancy may reflect the difference between local and systemic factors, as vitamin E's protective effects may be more relevant in oral tissues where it directly mitigates localized oxidative stress and inflammation. Studies by Abdolsamadi and Kaur(7,9) noted a positive correlation between serum levels of vitamins C and E, suggesting that adequate vitamin C may enhance the regeneration of vitamin E, promoting a synergistic effect in antioxidant defense.

Moreover, findings from Nagao et al.(14) indicate that low levels of retinol and carotenoids are not risk factors for lichen planus. While these vitamins have potential immunomodulatory effects, their deficiencies may not consistently exacerbate the condition. This observation aligns with the understanding that various environmental and biological factors including

genetics, stress, and nutrition contribute to the onset and progression of OLP.

In conclusion, while our findings support the protective roles of vitamins C and E in mitigating oxidative stress and their potential associations with oral lichen planus, contrasting evidence suggests that these vitamins may not be universally critical across all populations. The complex interplay of vitamin deficiencies, oxidative stress, immune dysregulation, and underlying health factors underscores the need for comprehensive research. Future studies should more thoroughly examine these interactions to delineate the mechanisms by which vitamins C and E affect OLP and assess their potential as therapeutic targets.

## 5. CONCLUSION

This study demonstrated a significant relationship between serum and salivary levels of vitamin C and salivary vitamin E with Oral Lichen Planus (OLP). However, the serum level of vitamin E did not exhibit a significant association with Lichen Planus. Additionally, a positive correlation was observed between vitamin C and vitamin E. The precise etiology of OLP remains unknown, and the specific roles of these vitamins in the development of the disease are still unclear. This study has several limitations, underscoring the necessity for further research to elucidate the relationship between vitamins C and E and OLP.

## 6. ETHICAL DECLARATION

1. Protocol Development: The protocol for this study was developed in accordance with international ethical standards and principles. The protocol has been registered in Ethical committee of Golestan University of Medical Sciences (registration number: IR.GOUMS.REC.1401.377)

2. Conflict of Interest: The authors declare that they have no financial or non-financial conflicts of interest that could influence the study's conclusions or analyses.

3. Permissions and Approvals: All data and studies used in this meta-analysis were obtained from publicly available sources, and no illegal or unauthorized data from companies or organizations were utilized.

4. Respect for Human Rights: This article is based on data and results derived from previous studies. No human or animal testing was conducted in this research.

5. Transparency and Data Accessibility: All data and meta-data related to this study will be made available transparently for future review and subsequent research.

6. Accountability of Authors: The authors accept responsibility for all information and results presented in this study, confirming that this research was conducted based on scientific and ethical principles.

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