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Antioxidants for the management of oral leukoplakia: A systematic review of randomized controlled trials

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ABSTRACT

Introduction: Oral leukoplakia (OL) is a potentially malignant disorder characterized by non-scrabble white lesions that may turn into invasive carcinoma if left untreated. Few antioxidant treatments have shown promising results in the regression of lesions and prevention of their progression to carcinoma. We aim to summarize the current evidence on the effectiveness of antioxidants in the management of OL.

Materials and methods: The present systematic review followed PRISMA guidelines and involved a thorough search of three scientific databases: PubMed, Scopus, and Cochrane. We used specific algorithms related to the keywords "antioxidant" and "Oral leukoplakia" to identify randomized controlled trials (RCTs) that have explored the utility of antioxidants in the management of OL. The risk of bias assessment was conducted using the Cochrane risk of bias tool (ROB 2.0), ensuring the reliability of our findings.

Results: Out of 2490 articles retrieved, only thirteen RCTs involving 1147 participants fulfilled the inclusion criteria. Lycopene was found to be the most consistently effective antioxidant, showing significant effectiveness in reducing lesion size, both in oral and topical forms. The trials incorporating other antioxidants, including vitamin A, vitamin C, β-carotene, and curcumin, demonstrated mixed results. Severe heterogeneity was detected in treatment forms, dosage, administration frequency, treatment duration, and follow-up time among all included trials.

Conclusion: Lycopene may play a significant role in the non-surgical management of OL. Future research with large-scale, well-designed, randomized controlled trials with standardized dosing, delivery methods, and outcome measures is mandatory to provide more robust evidence on the available antioxidant therapy for OL.

1. Introduction

Oral leukoplakia (OL) is a widely recognized oral potentially malignant disorder (OPMD) that affects people of all age groups, genders, and ethnic backgrounds on a global scale.[1] Epidemiological studies have shown a higher incidence in males, especially older adults, and individuals with a history of tobacco use, alcohol consumption, and betel quid chewing.[2,3] Smoking has been identified as the primary risk factor, with smokers being six times more likely to develop OL.[1] Alcohol is acknowledged as a distinct risk factor for OL.[4] The consumption of betel quid is a major cause in Southeast Asia, and it is accountable for the higher occurrence of OL in this area.[5,6]

OL is pathologically characterized by epithelial hyperplasia, keratinization, and dysplastic changes, which mean continuity of morphological alterations that might lead to invasive carcinoma if left untreated.[7] Genetic and epigenetic changes, such as mutations in tumor suppressor genes, activation of oncogenes, and disruption of cell cycle control mechanisms, have been identified through molecular studies.[8]

Presently, numerous therapeutic alternatives exist for OL, encompassing surgical intervention, laser ablation, photodynamic therapy, cryotherapy, and topical therapy, and none are considered entirely curative.[9,10] The overall recurrence rate after complete surgical excision of OL lesions was 25 % with an average follow-up time of 76.8 months in a meta-analysis (n = 204) of 5 observational studies on OL surgical therapy.[10] The recurrence rate after photodynamic therapy for OL was 25 %, according to a meta-analysis (n = 182) of 5 trials.[10] In a

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meta-analysis (n = 4292) of 27 observational studies on laser management for OL, 24 % of OL lesions recurred after complete remission.[11] The total recurrence rate after cryotherapy for OL was 16 %. Even though precision medicine that uses "omics" sciences (genomics, transcriptomics, epigenomics, proteomics, and metabolomics) to integrate data and create highly predictive models of the biological system has been explored for several diseases, for OL, it is still in its infancy. A recent non-randomized controlled trial last year reported the use of immune checkpoint therapy with Nivolumab (programmed cell death 1 protein inhibitor), which showed lesion reduction by size and severity of dysplasia after treatment.[12]

There has been a continuous effort to develop novel treatment interventions that specifically target the fundamental molecular pathways responsible for the growth of OL and mitigate the likelihood of malignant transformation. In recent years, there has been a growing interest in investigating the use of antioxidants as adjunctive medicines for the treatment and prevention of OL. Oxidative stress is characterized by an uneven generation of reactive oxygen species (ROS) and the protective mechanisms of antioxidants.[13] It plays a significant role in the development and advancement of OL.[14] The oral cavity, which is regularly exposed to external cancer-causing agents and harmful microorganisms, experiences oxidative harm to its cellular components, including DNA, proteins, and lipids.[14,15] The DNA damage caused by reactive oxygen species (ROS) can lead to permanent damage.[14,15] Antioxidants, natural or synthetic substances, exert cytoprotective effects by scavenging free radicals, counteracting ROS, and regulating redox signaling pathways important in cellular growth, survival, and inflammation.[16,17] Multiple epidemiological studies have demonstrated evidence of a negative correlation between the consumption of antioxidants in one's diet and the chance of developing oral cancer. Individuals who are most vulnerable, namely smokers, are also the ones who have the lowest intake of fruits and vegetables.[18,19] Consequently, a hypothesis emerged suggesting that incorporating antioxidants could potentially contribute to both primary prevention and secondary prevention for persons at risk.[18] This also implied that diets rich in antioxidants and antioxidant therapy may protect against the development and progression of oral OL. In the early 90s, few studies started to explore the utility of antioxidants in OL.[20] Ever since several studies have explored the utility of different established antioxidants in the management of leukoplakia. Even though significant advancement has happened in the field of management of leukoplakia, evidence regarding therapeutic potential of antioxidants in the management of this potentially malignant disorder is still inconclusive. This systematic review aims to assess the existing information on the effectiveness of antioxidant supplementation in the management of OL. This knowledge can aid in creating precise therapy strategies that enhance efficacy and ensure patient safety.

2. Material and methods

A systematic review was conducted to evaluate the efficacy the available antioxidants in the management of OL. The study followed the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions, and the findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21] The protocol was documented and registered.

2.1. Search strategy

We searched three prominent academic databases, including PubMed, Scopus, and the Cochrane Database, to identify literature related to the use of antioxidants for oral leukoplakia. Boolean operators (AND, OR) also were used to make the search effective. A detailed search strategy is provided in Supplementary Tables 1–3.

We aimed to address the following research questions: Are antioxidants effective in the management of OL? Which of the available antioxidants is the most efficacious in the management of OL? Accordingly, the PICO was formulated as follows:

P- Patients with OL
I- Any antioxidants
C- Placebo or any other treatment
O- Complete cure/partial cure/recurrence

Records were identified by utilizing customized search terms for each search engine and downloaded into a citation manager (Zotero, version 6.0.15). Duplicates were then automatically removed. Two separate reviewers (DG and KF) conducted the screening process, which consisted of two distinct steps. The screening process involved initially reviewing titles and abstracts, followed by a thorough examination of full texts. Any record that satisfied the eligibility requirements was subsequently included in the study. Any difference of opinion between the reviewers was resolved by discussion with the third reviewer (SV). The third reviewer was responsible for scanning the grey literature database and conducting the citation search.

2.2. Inclusion and exclusion criteria

2.2.1. The inclusion criteria

Randomized control trials using antioxidants for the management of oral leukoplakia published between January 2000 and June 2024.

2.2.2. The exclusion criteria

Cross-sectional studies.
Single arm studies.
Animal experiments.
Invitro studies.
Literature reviews and systematic reviews.
Letter to Editor.
Conference abstracts.

2.3. Data extraction and synthesis

Two reviewers (DG and KF) separately extracted the data into a data collection form. The obtained data was inputted into the data gathering form in Excel. The form was designed per the Cochrane Handbook for the systematic review of intervention guidelines. The data obtained from randomized controlled trials (RCTs) were categorized into the following sections: demographic characteristics, intervention characteristics, outcome measures, primary results, and follow-up data.

2.4. Risk of bias

Two reviewers independently assessed the risk of bias using the Cochrane risk of bias tool (ROB 2.0).[22]

3. Results

Initial searches of the three databases yielded a total of 2490 articles (Pubmed = 1354, Scopus = 1021, and Cochrane n = 115). After eliminating 561 duplicate entries, a total of 1929 articles were obtained. After a thorough review of the titles and abstracts, 1624 articles were deemed irrelevant and eliminated. A full-text reading was conducted to analyze 26 articles selected from 305 retrieved articles, and finally, 12 RCTs met the inclusion criteria. An additional 28 articles were identified through citation searching and thoroughly reviewed, and one RCT was selected for inclusion. Ultimately, thirteen randomized controlled trials that aligned with our specific outcome criteria were incorporated in our review. The detailed selection of studies is shown in Fig. 1.

3.1. General characteristics of the studies

The characteristics of the studies are presented in Table 1. Thirteen

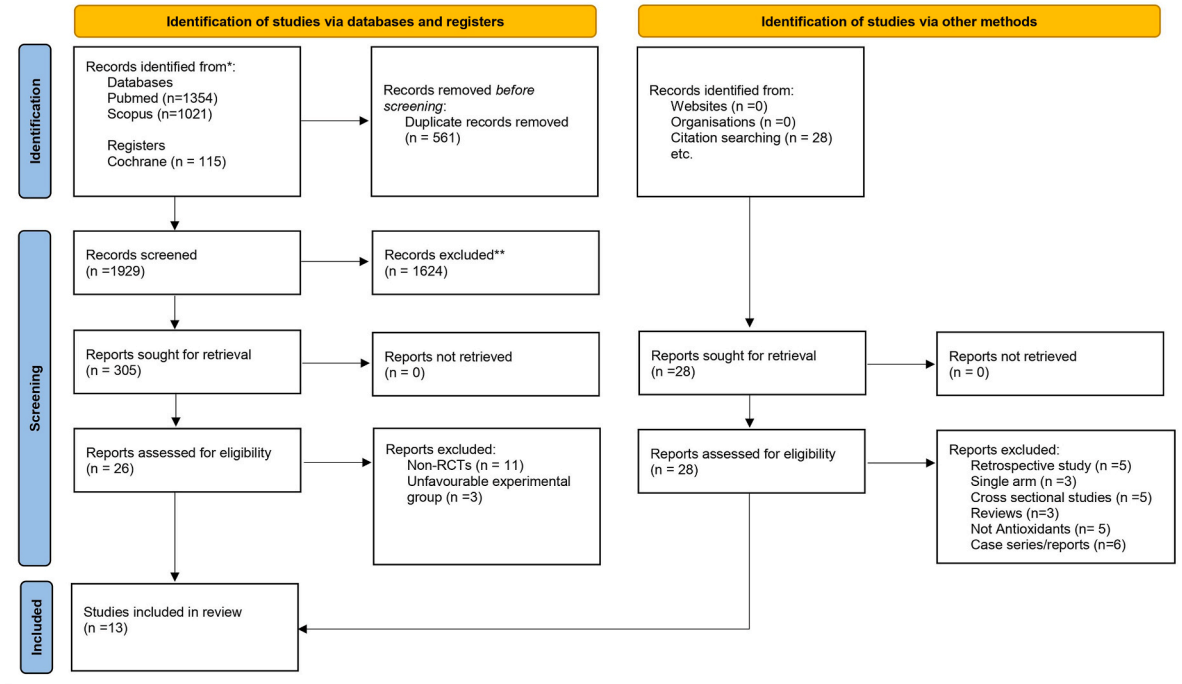

Fig. 1. Prisma flow chart of the review process.

included trials accounted for a total of 1147 participants. Out of the thirteen trials, one study each was from Italy,[23] USA,[23] and Japan,[24]; the rest was conducted in India. Eleven trials utilized a two-arm parallel design, and three trials utilized a three-arm parallel design. The duration of the trials varied. Three investigations employed an open follow-up approach,[24–26] One study had a duration of one year,[24] whereas the remaining studies had a duration of less than one year. Most of the studies compared two interventions or interventions with a placebo. Three trials evaluated the effect of the same interventions with varied dosages in different arms, either alone or in combination with others.[24,26,27] The primary outcome of all the trials was to evaluate the response toward treatment except for one study, which assessed the recurrence and appearance of new lesions or carcinoma after treatment.[23] Nevertheless, five studies additionally followed up on the patients and evaluated recurrence as well as progression of the lesion to higher grades of dysplasia or invasive cancer.[24–26,28,29]

3.2. Characteristics of the interventions

Lycopene was used in four trials, either alone[27,30–32] or in combination[31,32] among which two trials utilized capsule form,[27,31] whereas two used gel formulation[30,32] for topical application. Three trials explored the efficacy of curcumin.[29,31,33] Vitamin A was used as capsules[28,34] or in other forms like retinol cream,[35] retinyl palmitate, 13-*cis* retinoic acid (13cRA),[26] and synthetic retinoid fenretinide.[23] β carotene, vitamin C, vitamin E, and selenium were used in trials in combination with other antioxidants rather than sole intervention. Antioxidant-rich compounds, including raspberries,[25] Moringa leaves,[35] and Calendula officinalis,[30] were also used in individual trials. Three trials tested the efficacy of the same interventions in different forms and doses against each other[24,26,27]

3.3. Characteristics of the outcome measures

Seven out of 13 investigations utilized lesion measurement of the lesion as the clinical metric for evaluating change.[25,28,30,32–35] Additionally, three research studies incorporated photography to measure the lesion's size accurately.[25,30,34] Five of the investigations evaluated the number of patients showing complete or partial response.[24,26,27,31,32]For two trials, complete response was defined as the complete disappearance of the lesion.[29,32] However, another two trials defined complete response when there was no evidence of a lesion for at least four weeks.[26,27] Histological features were evaluated as a part of treatment response in five studies.[24–28,33] Three investigations utilized distinct categories for clinical assessment. Mane et al. used the bi-dimensional assessment of lesions and color photography, along with the van der Waals (OLEP) staging system, to quantify the clinical and histological aspects of oral leukoplakia.[28] Mallery et al. used a responsiveness score that considered the magnitude of changes in lesional size, histologic grade, and loss of heterozygosity.[25] In the study by Nagarajan et al., the assessment of the treatment response included size and surface texture, salivary pH, and fractal analysis.[34]

3.4. Beneficial effects of specific antioxidant lycopene

Antioxidant lycopene has been shown to show consistent results in four trials. Regardless of the form, whether taken orally or applied as a topical agent, lycopene has demonstrated effectiveness in remission OL. Two studies reported 4 mg capsules on a daily dosage as effective.[27,31] Gel preparation containing 2 mg of lycopene was adequate for topical application when used daily.[30,32] Further, lycopene was found to be more effective than curcumin in a direct comparison trial.[31]

3.5. Mixed findings on vitamin A and curcumin

As for both of these antioxidants, the results were inconsistent as some studies showed their effectiveness demonstrating significant benefit, in contrast to other studies that did not show a difference between the groups that used and the control groups. Two studies where curcumin capsules were taken orally were shown to be effective in OL remission.[29,31] In contrast, topical application of curcumin did not show any reduction in the size of the lesion.[33] Curcumin, in combination with lycopene, was shown to be more effective than curcumin.[31] Mane et al. did not find any significant reduction with vitamin A capsules (50000 IU), whereas Nagarajan et al. demonstrated effectiveness with 200000 IU, indicating dosage might be a significant factor.[34] 13-cis retinoic acid

Table-1
Characteristics of the included trials in detail.

No.	Author, year	Age(years)	Sex(M/F)	Total number of participants)		Treatment and pharmaceutical form	Frequency of administration (a day)	Duration of treatment	Follow-up(weeks)	Outcome measurement	Results	Long term follow up and recurrence
1	Ansari et al., 2023	No data available	No data available	65 (72)	A: 33 (36)	A: Moringa oleifera leaves extract mucoadhesive gel (2 %)	3	3	Monthly during treatment period	Reduction in size	Both treatments reduced the size of lesion. Moringa demonstrated more significant reduction compared to Retinol ($p < 0.05$)	Long term follow up missing. No data on recurrence
					B:32 (36)	B: Retino-A 0.1 % cream	3					
2	Ahmad et al., 2023	No data available	No data available	283 (300)	A:94 (100)	A: curcumin capsules 500 mg	1	3	Every 30 days during treatment period; monthly during follow up period for 3 months	Number of patients with complete cure/partial cure	Participants cured with oral curcumin - 51 %.	Long term follow up missing. No data on recurrence
					B:95 (100)	B: oral lycopene tablet 4 mg	1				Participants cured with oral lycopene-63 %	
					C:94 (100)	C: 4 mg of lycopene tablet + 500 mg curcumin capsule	1				Participants cured with combination curcumin and lycopene- 72 %	
3	Fathima et al., 2022	45.15 ± 11.37	17 M 3 F	20 (23)	A: 10	A: 1 % (w/v) Bleomycin solution + oral antioxidant	1 for bleomycin solution, 2 for antioxidant capsule	3	3 months	Reduction in lesion size and histopathologcal dysplastic features	Significant reduction in lesion size with belomycin antioxidant treatment. ($p < 0.05$)	Long term follow up missing. No data on recurrence
					B:10	B: curcumin oral gel + oral antioxidant	6 for curcumin oral gel, 2 for antioxidant capsules				Reduction in gradess of dysplasia after treatment with curcumin oral gel, but no difference in size	
4	Mane et al., 2021	A: 43 ± 4.9	No data available	30	A: 15	A: topical 5 % Imiquimod + benzocaine jelly	3(per week)	1.5 months	Every week for 6 weeks; monthly during follow up period for 6 months	The clinical response measured by reduction in size and Van der Waals (OLEP) staging of oral leukoplakia	Significant reduction in lesion after treatment in Imiquimod,but not with Aquasol ($p < 0.05$)	No recurrence after 6 momths
		B: 42 ± 5.2			B: 15	B: tablet Aquasol (Vitamin A) (50,000 IU)	2					
5	Nagarajan et al., 2020	43.1	10 M	10	A: 5	A: capsule omeprazole of 20 mg	2	1 month	Every week for 4 weeks	Reduction in size and roughness of the lesion	Significant reduction is size and roughness with Omeprazole and Vitamin A, no difference between the groups ($p < 0.05$)	Long term follow up missing. No data on recurrence
					B: 5	B: capsule vitamin A 200000 I.U.	1(per week)					
6	Singh et al., 2017	No data available	A: 28M 2F	60	A: 30	A: Calendula officinalis gel containing antioxidants 2 mg by weight, per gram of gel	3	1 month	Every month during follow up period for 3 months	Reduction in size of the lesion	Significant reduction is size with Calendula and Lycopene gel, no difference between the groups ($p < 0.05$)	Long term follow up missing. No data on recurrence
			B: 22M 8F		B: 30	B: lycopene gel containing lycopene antioxidant 2 mg by weight, per gram of gel.	3					
7	Kuriakose et al., 2016	No data available	A: 79M 32F	223	A: 105 (111)	A:600 mg capsules of curcumin, reconstituted with turmeric oil and dispensed in capsules (3.6 g/day)	2	6 months	Monthly for 12 months	Number of patients with complete response/ partial response based on clinical and histological criteria	Significantly better response with curcumin clinically and histologically ($p < 0.05$)	Treatment longer than 6 months did not show additional benefit.
			B: 82M 30F		B: 108 (112)	B: placebo capsules containing cellulose	2					
8	Mallery et al., 2015	44 to 77 (mean 62.2 ± 1.8)	A: 15M 7F			A:bioadhesive gels that contained either 10 % w/w freeze dried black raspberries (BRB)		12 weeks	Every 10–14 days during treatment period	Reduction in size of the lesion, histology grade and Loss of heterozygosity events	Significant reduction in lesional sizes, histologic grades with BRB ($p < 0.05$)	2 lesions progressed to higher dysplasia in 4–31 months follow up.

(*continued on next page*)

Table-1 (*continued*)

No.	Author, year	Age(years)	Sex(M/F)	Total number of participants)		Treatment and pharmaceutical form	Frequency of administration (a day)	Duration of treatment	Follow-up(weeks)	Outcome measurement	Results	Long term follow up and recurrence
		32 to 78 (mean 57.7 ± 2.9)	B: 9M 9M			B: Placebo	4					
9	Nagao et al., 2015	A: 64.8 ± 10.0	A: 13M 10 F	33 (46)	A: 16 (23)	A: 10 mg day^{-1} of beta-carotene and 500 mg day^{-1} of vitamin C	1	1 year	Monthly during follow up period for 6 months	Number of patients with complete cure/partial cure	Beta-carotene and vitamin C were neither effective for clinical remission, nor for protection against the development of cancer	2 patients each from both groups developed oral cancer within 60 months follow up
		B: 65.9 ± 8.7	B: 12M 11F		B:17 (23)	B: 50 mg day^{-1} of vitamin C	1					
10	Patel et al., 2014	47	A: 19M 2F	41	A: 21	A: 6 mg of lycopene + vitamin E (400 I.U.) + selenium (200 mcg)	2	3 months	Every 15 days during treatment period; every month during follow up period for 3 months	Reduction in size and number of patients with complete cure/partial cure	Significant reduction in size after combination treatment. Significant number of patients with complete and partial response ($p < 0.05$)	Long term follow up missing. No data on recurrence
			B: 19M 1F		B: 20	B: placebo capsules	1					
11	Papadimitrakopoulou et al., 2009	A: 56.9 ± 14.0	A: 45M 36F	154 (162)	A: 77 (81)	A:13-cis retinoic acid 13cRA (0.5 mg/kg/d orally for 1 year followed by 0.25 mg/kg/d orally for 2 years)	1	3 years	3 months and 2 years of follow-up whenever possible	Number of patients with complete cure/partial cure	Response to 13cRA was significantly better than BC + RP and RP alone. Response to BC + RP was significantly better than RP alone ($p < 0.05$)	4 patients from 13cRA group, 5 pateints from BC + RP group and 2 from RP alone group developed oral cancer within 60 months follow up
		B:55.0 ± 12.2	B: 24M 21F		B: 42 (45)	B: beta-carotene (BC) (50 mg/d orally) + Retinyl palmitate RP (25,000 U/d orally)	1					
		C: 55.4 ± 14.4	C: 16M 20F		C: 35 (36)	C: Retinyl palmitate (RP) (25,000 U/d orally)	1					
12	Chiesa et al., 2005	No data available	A: 60M 24F	170	A: 84	A: 4-HPR orally at a dose of 200 mg day^{-1} (2 capsules of 100 mg)	2	1 year	Every 2 months for 1st year; every 3 months for 2 nd year; every 4months for 3rd year; every 6 months thereafter	Number of patients with recurrences	Fenretinide protected against relapses and new lesions up to 19 months after randomization.	Study was underpowered and provided no indication to whether 4-HPR protects against oral cancers in this high-risk population
			B: 61M 25F		B: 86	B: Placebo was not given						
13	Singh et al., 2004	No data available	A: 15M 5F	58	A: 20	A: 8 mg lycopene daily	2	3 mon-ths	Every 7–10 days during the treatment period and then every 15 days during the follow up period for 2 months	Number of patients with complete cure/partial cure	Patients receiving 8 mg as well as 4 mg of lycopene in showed highly significant difference in response as compared to placebo ($p < 0.05$)	Long term follow up missing. No data on recurrence
			B: 14M 6F		B:20	B: 4 mg lycopene daily	2					
			C: 15M 3F		C:18	C: Placebo capsules were given.	2					

(13cRA) was more effective than retinyl palmitate in terms of clinical remission. However, there was no impact on oral cancer-free survival. Fenretinide, a synthetic retinoid, exhibited excellent tolerability and showed efficacy in reducing relapses and the formation of new leukoplakia both during and after treatment.[23] The trial was stopped prematurely due to a significantly low number of participants and lacked sufficient statistical power to demonstrate any preventive benefit against oral cancer.

3.6. Effect of combination treatments

There were four trials[24,26,31,32] conducted using more than one antioxidant at the same time by combining two or more in the same arm. Lycopene and curcumin combination was shown to be more effective than individual treatments.[31] The combination of β carotene and vitamin C was neither effective for clinical remission nor protection against progression into invasive cancer.[24] A formulation comprising 6 mg of lycopene + vitamin E (400 I.U.) + selenium (200 mcg) was effective in clinical and histological remission.[32] A combination of β carotene and retinyl palmitate showed a better response than treatment with retinyl palmitate alone.[26]

3.7. Safety and tolerability of the interventions

Only three studies reported on the safety and tolerability of the interventions used in the trials.[25,26,28] In the three-arm trial using 13cRA, it was reported that cheilitis, conjunctivitis, and skin reaction were significantly more common in the patients on 13cRA compared to others on β carotene and retinyl palmitate combination or retinyl palmitate alone.[26] Other than those, arthralgia, myalgia, headache, and gastrointestinal symptoms were also reported by several patients using 13cRA. Six patients discontinued the 13cRa treatment because of the toxicities. The other two studies reported that the interventions did not cause any reactions in patients and was tolerable.

3.8. Risk of bias

Out of the thirteen trials, one study exhibited an overall low risk of bias according to the standards employed in the critical evaluation of studies.[24] Nine studies were determined to have an unclear risk of bias.[23,25–30,32,35] The remaining studies were deemed to have a high risk of bias.[31,33,34] The results are shown in Fig. 2.

4. Discussion

This systematic review assessed the effectiveness of various antioxidants in the management of oral leukoplakia (OL). Lycopene emerged as the most consistently effective antioxidant, showing significant effectiveness in reducing lesion size both in oral and topical forms. Four trials demonstrated its success, where two trials[27,31] studied lycopene in capsule form, and another two,[30,32] studied its topical form. Both 8 mg and 4 mg lycopene capsules elicited a histological response devoid of any adverse effects, albeit with a limited follow-up period of only 2 months. Additionally, lycopene was more effective when combined with curcumin in one study. However, the findings for other antioxidants, such as vitamin A and curcumin, were mixed. Vitamin A showed variable results based on variable dosages ranging from no significant effect at 50,000 IU in one study[28] to a substantial impact at 200,000 IU in another study.[34] Similarly, curcumin in oral form showed benefits in two trials,[29,31] but its topical application failed to show a reduction in lesion size. In some cases, combination treatments, such as lycopene with vitamin E and selenium, also demonstrated clinical remission. Despite these positive findings, the review identified inconsistencies, particularly in studies involving β-carotene and vitamin C, which did not show clinical remission or prevention of malignant transformation. Notably, three trials highlighted recurrence and progression to dysplasia or invasive cancer even after antioxidant treatment.[24,26]

The findings of this review align with previous studies that suggest lycopene's role as a potent antioxidant in the management of another OPMD, oral submucous fibrosis (OSF)[36,37] Earlier studies have also highlighted lycopene's ability to modulate cell growth and play a role in immune and inflammatory diseases, including mucocutaneous diseases, neurological diseases, cardiovascular diseases, and cancer.[38] Conversely, although the results are mixed for vitamin A, its role was never assessed in any other OPMD. The inconsistency in the effectiveness of curcumin, β-carotene, and vitamin C align with previous findings on oral submucous fibrosis (OSMF).[36] This could be attributed to study design, dosage, or antioxidant formulation variations. Our review adds value by providing evidence on combination therapies, particularly the effectiveness of lycopene and curcumin when used together. While combination therapy has been underexplored in previous studies, the current review highlights its potential advantages in improving treatment outcomes for OL. Concordantly, the combination therapy has also proven beneficial in OSF.[36] The reports on low serum and salivary total antioxidant capacity (TAC) in lichen planus[39] and a significant reduction in lipid peroxidation in OL,[40] as well as the alteration in levels of superoxide dismutase in OL[41] are some of the evidence favoring altered level of antioxidants in OPMD. Therefore, we may say that the antioxidants may have the potential to manage OPMD because of their ability to counteract oxidative stress by scavenging ROS. This is especially relevant in OL, where oxidative damage to DNA, proteins, and lipids contributes to carcinogenesis.[14] Lycopene, in particular, has strong antioxidant properties and can regulate redox signaling pathways involved in cellular proliferation and survival, which may explain its effectiveness in lesion remission.[42] Lycopene mitigates the effects of ROS via radical addition, adduct formation or electron transfer to the radical.[43] Lycopene has been shown to improve the levels of enzymatic antioxidants (catalase, superoxide dismutase, and peroxidase) and nonenzymatic antioxidants, including vitamins C and E, by augmenting the cellular antioxidant defense system.[43] Curcumin, another antioxidant explored in this review, is known for its anti-inflammatory and antioxidant properties. Curcumin inhibits lipid peroxidation by oxidizing linoleate, a polyunsaturated fatty acid that forms a radical.[44] In vitro and in vivo testing on rat peritoneal macrophages showed that it scavenges superoxide anions, hydrogen peroxide, and nitrite radical. Inducible nitric oxide synthase (iNOS) in macrophages creates significant levels of NO for the 'oxidative burst'.[45] Curcumin decreases macrophage iNOS activity, lowering ROS production in response to oxidative stress.[45]

However, its inconsistent results owing to different formulations highlights the need for further investigation into its bioavailability and mechanism of action in OL. Similarly, the variation in vitamin A outcomes could be due to its role in cellular differentiation and epithelial repair. Vitamin A can interact with peroxyl radicals, functioning as a chain-breaking antioxidant prior to the radicals' engagement with lipids and the formation of hydroperoxides, thereby averting cellular harm.[46] Furthermore, it may enhance antioxidant activity indirectly by upregulating superoxide dismutase (SOD) and catalase.[46] Still, the dosage appears to play a critical role in determining its effectiveness.

It is significant to highlight that, despite surgery being the preferred option for many clinicians in the management of leukoplakia, there is a lack of randomized controlled trials comparing the outcomes of surgical excision with no treatment or placebo.[47,48] The sole data accessible is derived from observational studies that compare cancer incidence rates in individuals who received surgical therapy for oral leukoplakias in comparison to those who did not.[47,48] These studies exhibit diagnostic and inclusion criteria variations, follow-up intervals, participant demographics, and surgical procedures utilized.[49,50] The studies also exhibit considerable variability in outcomes and are even contradictory in their conclusions.

Another critical factor to consider is the lack of standardized protocols for evaluating outcomes in this field. Although much research has

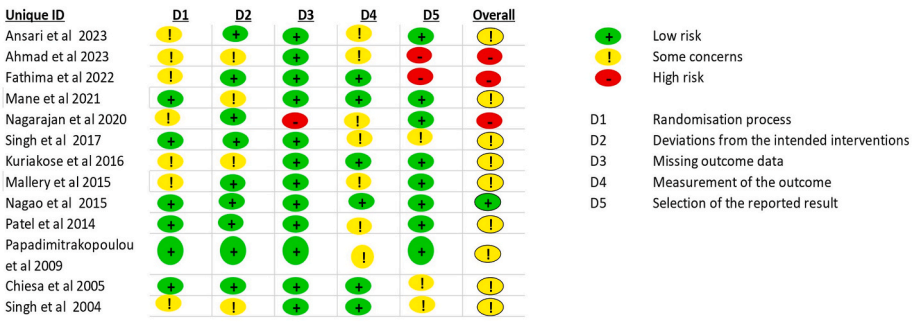

Fig. 2. Risk of Bias of the included trials.

evaluated the resolution of clinical and histological aspects, it is essential to acknowledge that these analyses may not substantially influence the malignant transformation of OL. Further, despite its clinical presentation, OL comprises a dysplastic component, and a substantial fraction harbors carcinomatous foci.[51] During histological investigation, the severity of epithelial dysplasia is often evaluated. Nevertheless, this evaluation is prone to considerable intra- and inter-observer subjectivity, which is a significant concern among pathologists.[52]

We observed significant heterogeneity in the study designs, intervention types, and outcome measures across the included trials. Ten of the thirteen studies used a two-arm parallel design, while the remaining three used a three-arm design, which impacted comparability. Dosages and formulations of antioxidants also varied, with some trials using oral capsules and others using topical gels or creams. The duration of follow-up was another source of variation, ranging from short-term studies (less than one year) to one study with a one-year follow-up. Short follow-up periods limit the ability to assess long-term outcomes such as recurrence and malignant transformation. The lack of standardization in outcome measures, with some studies focusing solely on lesion size and others evaluating histological changes, further contributed to heterogeneity. This variation makes it challenging to draw definitive conclusions. Further, the small sample sizes in many trials reduce the statistical power of the findings, particularly for vitamin A and curcumin. The reporting of safety and tolerability was limited, with only three studies providing details on adverse events, which hampers the comprehensive evaluation of antioxidant treatments. There was substantial heterogeneity in forms, dosage, administration frequency, treatment duration, and follow-up time among all included studies.

Despite the limitations, the findings of this review provide critical clinical insights. In both oral and topical forms, Lycopene appears to be a promising adjunctive treatment for OL and could be recommended in clinical settings. Its consistent efficacy across multiple studies suggests it may play a significant role in the non-surgical management of OL. The mixed results for vitamin A and curcumin indicate the need for further research to determine optimal dosing and formulations. Clinicians should exercise caution when recommending these treatments, particularly in light of the inconsistent evidence. Combination treatments, incorporating lycopene with curcumin or vitamin E and Selenium, show potential for enhanced efficacy and may offer a promising therapeutic approach. However, clinicians should remain mindful of the limited data on safety and long-term outcomes, particularly for high-dose vitamin A.

Future research should focus on large-scale, well-designed, randomized controlled trials with standardized dosing, delivery methods, and outcome measures to provide more robust evidence. Studies should incorporate long-term follow-up to assess recurrence and progression to dysplasia or invasive cancer. Further investigation is needed to explore the safety and tolerability of high-dose antioxidants, particularly vitamin A, and combination therapies. Bioavailability and formulation differences, especially for curcumin, should be a key focus of future research. As the next-generation sequencing technique becomes more accessible, it may help elucidate this antioxidant treatment's impacts at the molecular level. Linking antioxidant-tailored treatment with patient data, integrating omics-based features, and using artificial intelligence and machine learning may enable the clinical application of individualized OL treatment regimens by rapidly and cost-effectively analyzing patients' genetic and molecular profiles.

5. Conclusion

Based on the evaluation of treatment response, follow-up duration, and the intensity of side effects in the trials analyzed in this review, it can be inferred that lycopene shows potential as an effective antioxidant. Nevertheless, it is crucial to acknowledge that the effectiveness of the other antioxidants has only been assessed in a restricted number of studies. Therefore, further research, including bigger sample sizes and longer follow-up periods, is necessary before making relevant conclusions.

Parent consent

Not applicable.

Data availability statement

Not applicable.

Ethical clearance

Not applicable (Systematic review).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jobcr.2025.03.001.

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