

REVIEW

Antioxidant treatments in patients with oral submucous fibrosis: A systematic review

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Abstract

Introduction: Oral submucous fibrosis (OSMF) is a well-known precancerous oral lesion, characterized by scarring, tissue fibrosis, and premalignant lesions. The goal of clinical treatment is to reduce inflammation and improve patients' quality of life by enhancing mouth opening among others. Antioxidant treatment has shown promising results in inducing regression of lesions and preventing OSMF in high-risk individuals. This study investigates the effectiveness of various antioxidant agents against OSMF.

Materials and Methods: The study followed PRISMA guidelines and searched three scientific databases: PubMed, Web of Science, and Scopus, using specific algorithms related to “antioxidant treatment,” “burning sensation,” and “mouth opening.” The quality assessment of controlled clinical studies adhered to Cochrane guidelines.

Results: The analysis included 19 clinical trials comparing different treatments, including various antioxidants. Aloe vera, curcumin, and lycopene, among others, showed positive outcomes in treating OSMF by improving burning sensation, mouth opening, tongue protrusion, and cheek flexibility.

Conclusion: Antioxidant therapies are found to be effective in treating OSMF, even when compared to conventional treatments such as corticosteroids. The study highlights the need for further research and standardization of clinical protocols.

KEYWORDS

antioxidant treatment, burning sensation, mouth opening, OSMF (oral submucous fibrosis), premalignant oral lesions

1 | INTRODUCTION

Oral precancerous lesions are clinical presentations of the oral mucosa that have the potential to transform into cancer and are known as “potentially malignant disorders”.¹ Oral submucous fibrosis (OSMF) is a common oral precancerous lesion, mostly in Asian countries, especially in areas with a culture of betel nut chewing. It is a chronic disease that causes scarring, tissue fibrosis, and precancerous lesions.² OSMF is possibly the most common oral mucosal disorder among regular chewers of betel nut in its various forms.³ Genetic predisposition to the effects of toxic substances plays an important role in the

development of OSMF.⁴ Recently, altered levels of several oxidative stress markers such as malondialdehyde and 8-hydroxy-2'-deoxyguanosine (8-OHdG) and antioxidant enzymes such as superoxide dismutase and ceruloplasmin have been found in patients with OSMF. This demonstrates the role of oxidative stress in the pathogenesis of OSMF.^{5,6} The objectives of clinical treatments are to relieve troublesome symptoms and improve mouth opening to enhance the quality of life for patients. Current methods of treating OSMF vary as there is no standardized treatment protocol.² Antioxidants are compounds used by aerobic organisms to protect themselves from oxidative stress induced by free radicals and reactive oxygen species. They

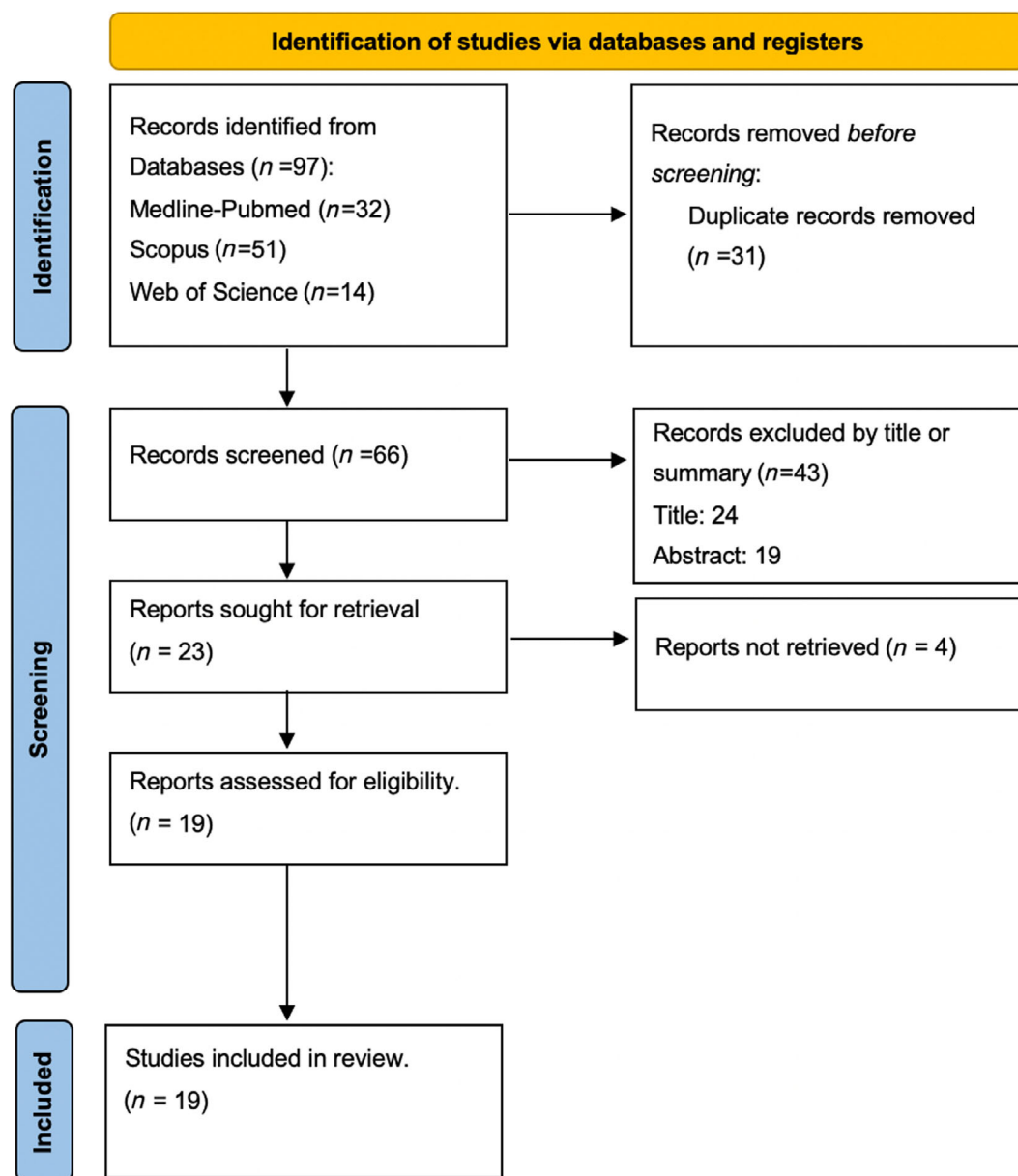


FIGURE 1 Flow chart following the PRISMA statement (2020), in which the study selection process and results of the bibliographic search for this systematic review are graphically represented, including reasons for excluding some of the studies.

are mainly used in the treatment of premalignant oral lesions and in preventing the recurrence of the initially treated lesion.⁷ Lycopene is a potent and important antioxidant that has twice the oxygen-neutralizing capacity of beta-carotene. It is a safe and reliable drug used as a first-line treatment in the initial management of OSMF, and other premalignant pathologies. In fact, there are recent works that support it.^{7,8} Aloe vera, due to its high concentration of antioxidants, helps neutralize free radicals and has been used to alleviate symptoms or prevent diseases related to oxidative stress.^{9,10} Curcumin is a plant phenol widely used as a spice (in curry) and food coloring agent. It has antioxidant activity that can significantly reduce oxidative stress levels.¹¹ In vivo and in vitro studies have shown that antioxidant treatments can prevent the initiation of DNA damage and are involved in

anti-promotion mechanisms such as apoptosis.¹⁰ They are primarily used for preventing lesions in high-risk individuals. This study aims to review the existing literature on the effectiveness of antioxidant compounds in OSMF treatment.

2 | MATERIALS AND METHODS

The present systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.¹² The study was registered in PROSPERO with the registration number CRD42023428709. The databases used for the literature search were Medline-PubMed (United States National Library of

	Generate randomized sequence (selection bias)	Allocation concealment (selection bias)	Blinding evaluation of results (detection bias)	Follow-up and exclusions (attrition bias)	Selective description (reporting bias)	Other biases
Patil <i>et al.</i> 2018 (15)	?	?	+	+	+	-
Chandrashekar <i>et al.</i> 2021 (16)	+	?	+	-	+	-
Rai <i>et al.</i> 2019 (17)	+	+	+	-	+	+
Beenakumary <i>et al.</i> 2019 (19)	-	?	+	+	+	-
Kanjani <i>et al.</i> 2017 (22)	+	?	+	+	+	+
Amuradha <i>et al.</i> 2016 (23)	?	+	+	+	+	-
Singh <i>et al.</i> 2019 (24)	?	?	+	-	+	-
Yadav <i>et al.</i> 2014 (25)	+	?	+	+	+	+
Mahato <i>et al.</i> 2019 (21)	-	-	+	-	+	-
Patil <i>et al.</i> 2014 (26)	?	?	+	+	+	+
Verma <i>et al.</i> 2022 (27)	-	-	+	+	+	-
Bohra <i>et al.</i> 2021 (18)	-	-	+	+	+	-
Sudarshan <i>et al.</i> 2012 (28)	?	+	+	+	-	-
Johny <i>et al.</i> 2019 (20)	-	-	+	+	+	-
Rajbhoj <i>et al.</i> 2021 (29)	?	?	+	?	+	+
Patil <i>et al.</i> 2015a (30)	?	?	+	+	+	+
Piyush <i>et al.</i> 2019 (31)	?	?	+	+	+	-
Arakeri <i>et al.</i> 2020 (32)	?	?	+	+	+	+
Patil <i>et al.</i> 2015b (33)	?	?	+	+	+	+

FIGURE 2 Evaluation of risk of bias of randomized studies according to the Cochrane guidelines. Yellow icon: Unclear risk of bias; Red icon: High risk of bias; Green: Low risk of bias.

Medicine), Web of Science, and Scopus. The objective was to identify articles on antioxidant treatments in patients with OSMF in order to address the following PICO question¹³: “Can antioxidant treatments be effective in patients with Oral Submucous Fibrosis, reducing the burning sensation and improving mouth opening and which one shows better improvements?” P (population): Patients with OSMF. I (intervention): Treatment with antioxidant compounds. C (comparison): Compared to control group or non-antioxidant treatments or other antioxidants. O (outcomes): Treatment efficacy assessed through the parameters: O1. Burning sensation, O2. Mouth opening, O3. Tongue protrusion and cheek flexibility.

Scientific articles published in scientific databases were selected according to the following inclusion criteria:

-*Study design*: studies on humans, ≥ 5 patients, randomized clinical trials, prospective and retrospective cohort studies, and controlled randomized clinical trials; publications in English or Spanish between January 2010 and December 2022.

-*Patient*: patients with OSMF.

-*Intervention*: Treatment with antioxidant compounds, especially aloe vera, curcumin, and lycopene. Type of control: OSMF patients

who have been treated with other pharmacological OSMF therapies or other antioxidants or placebo.

-*Outcomes*: Studies providing data on the efficacy of antioxidant treatment in relation to the burning sensation in the mouth, improvement in mouth opening, and/or assessing treatment efficacy through visual and palpation examination of the oral cavity, among others.

Literature reviews, systematic reviews or meta-analyses, in vitro and animal studies, as well as expert reports, were excluded. Studies that lacked clarity in their data or required further clarification were also excluded.

An automated search was conducted in the three aforementioned databases to identify the PICO question (PubMed, Scopus, and Web of Science). The Boolean search algorithms applied in the three databases used the following keywords: oral submucous fibrosis, antioxidant treatment, burning sensation, and mouth opening. The literature search was conducted using the combinations of the following Medical Subject Heading (MeSH) and text key words: (“antioxidant s”[All Fields] OR “antioxidants”[Pharmacological Action] OR “antioxidants”[MeSH Terms] OR “antioxidants”[All Fields] OR “antioxidant”[All Fields] OR “antioxidating”[All Fields] OR “antioxidation”[All Fields] OR “antioxidative”[All

TABLE 1 Data extracted from the analysed studies were classified according to their respective variables: authors and year, study groups, treatment, age, gender, typology study.

	Author, year	Age (years)	Sex (M/F)	Groups (number of people)	Treatment and pharmaceutical form	Frequency of administration (a day)	Duration of treatment (months)	Follow-up (weeks)	Main conclusions
1	Patil et al. 2018 ¹⁵	31.6 ± 12.7	64 M 56 F	120 A: 60 B: 60	A: oxitard (Cap) B: lycopene (Cap) 4 mg (LycoredTM, Jagsonpal Pharmaceuticals, New Delhi, India)	2	3	4, 8, 12	Clinically significant improvements in mouth opening and tongue protrusion were observed in group A
2	Chandrashekar et al. 2021 ¹⁶	30.17 ± 7.71	40 M	40 (49) ^a A: 20 (24) ^a B: 20 (25) ^a	A: curcumin (Cap) 5 mg B: curcumin (P)	2	2	2, 4, 6, 8	Total reduction in burning sensation in all 40 patients after 4 weeks, and mouth opening improved in both groups
3	Rai et al. 2019 ¹⁷	33.43 ± 8.55	103 M 16 F	119 (147) ^a A: 39 (49) ^a B: 40 (49) ^a C: 40 (49) ^a	A: antioxidant SM Fibro (Cap) (WARREN NXGEN DIVISION, Indoco Remedies Ltd, Mumbai, Maharashtra, India) B: curcumin + piperine (Turmix) (T) C: curcumin + piperine (Turmix) (T + M)	2 3 3 + 2	3	2, 4, 6, 8, 10, 12	Significant improvements in mouth opening, burning sensation, and tongue protrusion were observed in all groups
4	Bohra et al. 2021 ¹⁸	29.2 ± 5.3	29 M 13 F	42 A: 21 B: 21	A: Kali Haldi (P) + aloe vera (G) B: hydrocortisone 25 mg/mL and hyaluronidase 1500 IU (I) + antioxidants (Cap) SM Fibro	3 1 (a week)	3	2, 4, 6, 8, 10, 12	Statistically significant improvements were observed in both groups after 3 months, but symptomatic improvement was more evident in group A in mouth opening, burning sensation and cheek flexibility
5	Beenakumary et al. 2019 ¹⁹	M: 28.32 ± 6.69 F: 40.12 ± 5.16	40 M 20 F	60 A: 20 B: 20 C: 20	A: lycopene (Cap) 2 mg B: lycopene (Cap) + dexamethasone (I) + local anesthesia (I) C: dexamethasone (I) + hyaluronidase (I) + local anesthesia (I)	2 2 2 (a week)	12	4, 8, 12	The results showed that the maximum reduction in pain was observed in group C. In terms of mouth opening improvement, group C showed the highest improvement, followed by group B and group A, respectively
6	Johny et al. 2019 ²⁰	No data available	No data available	39 (45) ^a A: 13 (15) ^a B: 13 (15) ^a C: 13 (15) ^a	A: lycopene (Cap) 16 mg B: lycopene (Cap) 16 mg + hyaluronidase (I) 1500 IU C: placebo (Cap)	2 2 + 2 (a week) 2	3	12, 24	Significant improvements in mouth opening and burning sensation were observed in lycopene and lycopene + hyaluronidase groups. Lycopene appears to be a very promising antioxidant in the management of OSMF. Lycopene + hyaluronidase did not give a statistically significant result compared to lycopene alone

TABLE 1 (Continued)

Author, year	Age (years)	Sex (M/F)	Groups (number of people)	Treatment and pharmaceutical form	Frequency of administration (a day)	Duration of treatment (months)	Follow-up (weeks)	Main conclusions
7 Mahato et al. 2019 ²¹	34.75 ± 11.53	35 M 5 F	40 A:10; i.d.: >35 mm B:10; i.d.: 30.1–35 mm C: 10; i.d.: 20–30 mm D:10; i.d.: <20 mm	In the 4 groups, BIOCUMIN (T) (curcumin (500 mg), piperine (5 mg) and lycopene (25 mg))	2	3	12	Significant improvement was observed in mouth opening, burning sensation, mucosal flexibility and tongue protrusion
8 Kanjani et al. 2019 ²²	Between 19 and 70	41 M 4 F	45 A: 15 B: 15 C: 15	A: spirulina (500 mg) + isometric exercises with the mouth for (20 min) B: spirulina (500 mg) + exercises with a threaded conical screw (10 times) C: spirulina (500 mg) + exercises with a mouth stretching device (10 times)	2	3	2, 4, 6, 8, 10, 12	All the groups have shown statistically significant improvement in burning sensation, mouth opening, tongue protrusion, and cheek flexibility. Group C patients have shown better results followed by Group B and Group A patients
9 Amuradha et al. 2017 ²³	32.7 ± 10.3	63 M 11 F	74 A: 37 B: 37	A: aloe vera 30 mL (juice) + aloe vera 5 mg (G) B: hydrocortisone acetate 25 mg/mL and hyaluronidase 1500 IU (I) + Cap SM Fibro (antioxidant supplement)	2 + 3 1 (a week) + 2 (a day)	3 1.5 + 3	4, 8, 12	Both Group A and Group B subjects showed statistically significant improvements in burning sensation, mouth opening, cheek flexibility and tongue protrusion
10 Singh et al. 2016 ²⁴	Between 30 and 35	35 M 2 F	40 A: 20 B: 20	A: aloe vera (G) + physiotherapy B: antoxid™ Dr. Reddy's Product (Cap) + physiotherapy	Aloe vera 2 physiotherapy 4 (a week) Antioxid 2 physiotherapy 4 (a week)	3	2, 4, 6, 8, 10, 12	Aloe vera with the physiotherapy exercises provide better results in reducing burning sensation and improving mouth opening, tongue protrusion and cheek flexibility in comparison to antioxidants
11 Yadav et al. 2014 ²⁵	39.35 ± 12.3	31 M 9 F	40 A: 20 B: 20	A: dexamethasone (4 mg) and hyaluronidase (1500 IU) (I) B: Turmix (curcumin) 300 mg (T)	1 (a week) 2	3	4, 8, 12	Burning sensation improved in both the groups. Complete resolution of burning sensation was noted with turmix. The interincisal distance improved in both the groups, being bigger in group A. Tongue protrusion showed greater recovery at the end of first month in group A when compared with group B.

(Continues)

TABLE 1 (Continued)

	Author, year	Age (years)	Sex (M/F)	Groups (number of people)	Treatment and pharmaceutical form	Frequency of administration (a day)	Duration of treatment (months)	Follow-up (weeks)	Main conclusions
12	Patil et al. 2014 ²⁶	31.6 ± 12.7	64 M 56 F	120 A: 60 B: 60	A: oxiard (Cap) B: aloe vera 5 mg (G)	2 3	3	3, 5	Oxiard shows significant clinical improvements over aloe vera, in mouth opening, tongue protrusion, difficulty swallowing and speaking, and pain associated with injury in patients with OSMF
13	Verma et al. 2022 ²⁷	Between 21 and 30	140 M 64 F	240 A: 68 B: 68 C: 68	A: 2 mL a mix of hyaluronidase and dexamethasone 40 mg/mL (I) + lycopene 10 000 µg + topical triamcinolone B: pentoxifylline 400 mg TDS (T) + lycopene 10 000 µg + topical triamcinolone C: myosone eprisonone hydrochloride 50 mg BD (T) + lycopene 10 000 µg + topical triamcinolone	Biweekly 1 1	1.5	1, 2, 3, 4, 5, 6	The patients which received intralesional dexamethasone and hyaluronidase along with oral Lycopene showed better clinical and symptomatic improvement
14	Sudarshan et al. 2012 ²⁸	Between 17 and 40	No data available	20 A: 10 B: 10	A: aloe vera 5 mg (G) B: antioxidant (Cap) (Lekar Pharma Ltd, Daman, Gujarat, India)	3 2	3	2, 4, 6, 8, 10, 12	Aloe vera group showed a better response against OSMF symptoms. It showed a statistically significant reduction in burning sensation, improvement in mouth opening, and cheek flexibility on comparing with the antioxidant group
15	Rajbhoj et al. 2021 ²⁹	Between 15 and 55	55 M 5 F	60 A: 30 B: 30	A: curcumin gel 5 mg (Curenex oral gel [®]) (G) + physiotherapy B: aloe vera (Aloe Vera 100% relief) (G) + physiotherapy	3–4 + 5	1.5	2, 4, 6	There was an improvement in burning sensation and mouth opening, but the Aloe Vera gel showed a statistically better improvement than curcumin gel in burning sensation after 6 weeks of treatment (Aloe vera gel shower better improvement in mouth opening compared to curcumin gel but the results were not statistically significant)
16	Patil et al. 2015a ³⁰	31.2 ± 12.4	24 M 18 F	42 A: 21 B: 21	A: spirulina 500 mg B: aloe vera (G) (SheetalLab, Surat) 5 mg	3	3	4, 8, 12	Both the drugs showed improvement in the condition. Spirulina can bring about significant clinical improvements in clinical symptoms and mouth opening than aloe vera

TABLE 1 (Continued)

Author, year	Age (years)	Sex (M/F)	Groups (number of people)	Treatment and pharmaceutical form	Frequency of administration (a day)	Duration of treatment (months)	Follow-up (weeks)	Main conclusions
17 Piyush et al. 2019 ³¹	Between 17 and 70	70 M 20 F	90	A: curcumin + piperine 300 mg (T) (Turmix; Sanat Pharmaceuticals; Bulandshahr, Uttar Pradesh, India)	2	1.5	4, 8, 12, 16, 20, 24, 28, 32, 36	Statistically significant improvement in clinical findings was observed in both Curcumin and Lycopene treatment groups in comparison with placebo. The therapeutic efficacy of Curcumin and lycopene was found to be almost equal in OSMF patients
18 Arakeri et al. 2020 ³²	A: 29.9 ± 8.5 B: 28.8 ± 6.7	400 M	400	A: lycopene 8 mg (Cap) (LycoredTM, Jagsonpal Pharmaceuticals, New Delhi)	2	3	1, 2, 3, 6, 12, 18, 24, 30, 36	Treatment with lycopene led to improvement in the symptoms of OSMF. The results highlight the importance of retreatment of lycopene for its long-term effect on alleviation the symptoms of OSMF
19 Patil et al. 2015 ³³	31.6 ± 12.7	64 M 56 F	120	A: oxitard (Cap)	2	3	4, 8, 12	Oxitard capsules can bring about significant clinical improvements in OSMF in the symptoms like mouth-opening, tongue protrusion, burning sensation, difficulty in swallowing and speech and pain associated with the lesion, thereby improving the quality of life of the affected individuals

Abbreviations: Cap, capsule; F, female; G, gel; I, injection; i.d., interincisal distance; IU, interational units; M, male; M, mouthwash; OSMF, oral submucous fibrosis; P, mucoadhesive patch; P, powder; T, tablet.
*Number of patients who started the study.

Fields] OR “antioxidatively”[All Fields] OR “antioxidatives”[All Fields] OR “antioxidizing”[All Fields]) AND (“therapeutics”[MeSH Terms] OR “therapeutics”[All Fields] OR “treatments”[All Fields] OR “therapy”[-MeSH Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “treatment s”[All Fields]) AND (“oral submucous fibrosis”[All Fields] OR “OSMF”[All Fields])) AND (2012:2022[pdat]). The keywords were combined using the operators AND, OR, NOT to obtain the best search results. For the article selection, the initial screening was done based on the title and study type. After this first selection, screening was conducted by reading the abstracts, and once included, each full article was analyzed based on the type of antioxidant used for OSMF treatment and the number of patients with OSMF treated.

Risk of bias assessment was conducted to analyze the methodological quality of the included articles, considering rigor, credibility, and study relevance. The quality assessment of controlled clinical studies was conducted following the Cochrane Handbook 5.1.0 guidelines (<http://handbook.cochrane.org>). Publications were considered “low risk of bias” when they met all the criteria, “high risk of bias” when one or more criteria were not met, indicating a potential bias that weakens the reliability of the results, and “unclear bias” (either due to lack of information or uncertainty regarding the potential for bias).¹⁴

3 | RESULTS

A total of 97 articles were obtained from the initial search process: Medline-PubMed ($n = 32$), Scopus ($n = 51$), and the Web of Science ($n = 14$). Out of the publications analyzed, 23 were identified as potentially eligible articles through screening by titles and abstracts. The full-text versions of the identified articles were acquired and subjected to a comprehensive evaluation. Consequently, a total of 19 articles fulfilled the predetermined inclusion criteria and were ultimately incorporated into this systematic review according to the flowchart of Figure 1. The articles were classified based on their risk of bias according to the criteria of Figure 2.

All the studies measured the progression of the OSMF in terms of mouth opening,^{15–33} 17 articles reported on burning sensation,^{16–33} 16 articles discussed tongue protrusion^{15–18,21,26,28,31,33} and 8 articles examined cheek flexibility.^{16,18,21–24,28,31} Regarding the type of the study, 17 articles were prospective clinical trials,^{15,16,18–25,27–33} 1 was a parallel-group randomized monocentric trial,¹⁷ and 1 was a prospective, randomized, single-blind study.²⁶ A total of 1721 patients were treated. Table 1 shows a classification of the data extracted from the studies included in this systematic review, which contains the treatments for OSMF used in each case and the main characteristics of the intervention, as well as the main conclusions obtained in each of the studies.

4 | DISCUSSION

In this systematic review, the results obtained from the use of antioxidant compounds for treating OSMF were studied. The main objective was to evaluate the efficacy of these treatments on the variations of

burning sensation and mouth-opening parameters in OSMF. Second, the effectiveness of these compounds in improving tongue protrusion and cheek flexibility was also evaluated and, finally, the efficacy between the different types of antioxidant treatments was compared.

All the antioxidant treatments examined in this systematic review demonstrate potential for enhancing the various selected parameters. Nevertheless, owing to the extensive diversity of treatments, pharmaceutical formulations, combinations, durations, and other factors, the determination of the most effective antioxidant treatment presents challenges.

All patients treated with aloe vera showed an improvement in the parameters mouth opening,^{18,23,24,28–30} burning sensation,^{18,23,24,28,29} tongue protrusion^{23,24,28} and cheek flexibility.^{18,23,24,28} In addition, aloe vera showed better results when compared to curcumin²⁹ or other antioxidant compounds.^{18,24,28} However, if we compare the effects of spirulina with aloe vera, we can conclude that spirulina shows major clinical improvements.³⁰ Aloe vera contains many antioxidants, including α -tocopherol (vitamin E), carotenoids, ascorbic acid (vitamin C), flavonoids, and tannins.³⁴ For decades, a multitude of studies have demonstrated that aloe vera has important therapeutic uses in the management of different disorders such as diabetes, skin injuries, digestive tract disorders,^{35–37} and also oral lesion such as oral lichen planus³⁸ or recurrent aphthous ulcers.³⁹

Curcumin showed a significant improvement in the different variables studied, alone^{16,25,29,31} or together with other compounds such as piperine and/or lycopene.^{17,21} However, in comparison to other compounds such as cortisone²⁵ or aloe vera,²⁹ curcumin exhibits relatively lesser improvements. Curcumin exhibits a strong antioxidant effect through freeradical-scavenging and enzyme inhibition activities⁴⁰ and has been used as therapeutic agent in wound healing, diabetes, Alzheimer disease, Parkinson disease, cardiovascular disease, pulmonary disease, and arthritis.⁴¹ Although its use in oral pathologies is not so well known, several studies have demonstrated its benefits in this area.⁴²

Regarding the compound lycopene, numerous studies have shown statistically significant improvements in the parameters of mouth opening, tongue protrusion, and cheek flexibility.^{20,27,31,32} A significant improvement in the reduction of burning sensation was only demonstrated in the studies of Johny et al. 2019 and Arakeri et al. 2020.^{20,32} Lycopene has been also demonstrated to exert synergistic effects with other antioxidants,⁴³ as seen in the above-mentioned study where lycopene together with piperine and curcumin show a significant improvement in all the parameters studied.¹⁹ Lycopene has demonstrated potential therapeutic applications in various pathological conditions, offering protection against oxidative damage to lipids, proteins, and DNA. Additionally, it exhibits the ability to modulate cell growth and plays a role in immune and inflammatory processes. The investigation of lycopene's uses has been undertaken in several disorders, including cardiovascular diseases, neuronal diseases, different skin disorders, and various cancer types.⁴⁴ Lycopene also shows promising potential as an antioxidant treatment modality for oral leukoplakia, gingivitis, and periodontitis.⁴³

Although most of the studies included in this systematic review analyze treatments with aloe vera, curcumin, or lycopene, there are

also some studies that examine other antioxidant treatments such as spirulina and oxiard. Spirulina strongly induces antioxidant enzyme activity, helps to prevent lipid peroxidation and DNA damage, and scavenges free radicals this antioxidant activity makes it a potential treatment for different diseases as chronic obstructive pulmonary disease, muscle damage, and cardiovascular diseases among others.⁴⁵ Different studies included in this review demonstrate that spirulina together with mouth exercises improves significantly all the parameters analyzed in this review²² and it has even been shown, as mentioned above, that spirulina alone shows better results in mouth opening than aloe vera.³⁰ Although less common, this compound has also been shown to be effective in other oral pathologies such as oral lichen planus and periodontitis.^{46,47}

Oxiard is an herbal antioxidant formulation containing the extracts of *Mangifera indica*, *Withania somnifera*, *Daucus carota*, *Glycyrrhiza glabra*, *Vitis vinifera*, powders of *Emblica officinalis* and *Yashada bhasma*; and oils of *Triticum sativum*.²⁶ The number of studies on the efficacy of oxiard is very limited and most of them are those included in this review. Oxiard has been demonstrated to significantly improve mouth opening,^{15,26,33} tongue protrusion^{15,26,33} and burning sensation,^{26,33} even with better results than aloe vera.²⁴

The wide variety of studies, but without a specific clinical protocol, as well as the numerous differences in the pharmaceutical forms used, make it challenging to select an antioxidant of choice for treating OSMF. Several compounds, including aloe vera, curcumin, lycopene, and oxiard have shown improvements in the studied parameters related to the symptomatic expression of this disease. These studies suggest that antioxidants could be an alternative to conventional treatments such as those based on corticosteroids, but further assays to establish more precise conclusions are needed.

This systematic review presented some limitations. First of all, the topic under investigation requires a greater number of studies that delve deeper into treatments with antioxidant compounds for OSMF, involving a larger population sample. Besides, the variability in the follow-up period may have influenced the results in favor of one treatment over another. It is evident how antioxidant treatment is undervalued compared to other conventional treatment types. The results may also be limited due to a lack of an official and standardized protocol established by the scientific community, which should clearly define the ideal antioxidant or combination thereof for OSMF treatment.

5 | CONCLUSION

Within its limitations, this systematic review suggests that antioxidant compounds such as aloe vera, curcumin, and lycopene, among others, are effective in improving the parameters of burning sensation, mouth opening, tongue protrusion and cheek flexibility in OSMF. Likewise, antioxidant treatments have been shown to obtain beneficial results comparable to conventional treatments. This could highlight that they could be an alternative to the use of corticosteroids. However, it stands out the need for more clinical studies in humans that deeper into these treatments, adapting to clinical needs, as well as the

standardization of methodologies that allow for the establishment of an official and standardized protocol for healthcare professionals.

AUTHOR CONTRIBUTIONS

Martín Pérez-Leal: Conceptualization. Methodology. Project administration. Writing – original draft (equal). Investigation (lead); **Federico Lanciano:** Data curation. Formal Analysis (supporting). Investigation (supporting); **Nicla Flacco:** Formal Analysis (lead). Supervision. Writing – original draft (equal); **Cristina Estornut:** Validation (equal). Writing – original draft (equal); **María Carmen Carceller:** Validation (equal). Writing – review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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