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Efficacy of Placental Extract in the Management of Oral Submucous Fibrosis -A Systematic Review

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KEYWORDS

Intralesional, Oral Mucosa, Precancerous Conditions, Treatment Outcome, Placental extract

ABSTRACT:

Introduction: Oral Submucous Fibrosis (OSMF) is a chronic, progressively debilitating disorder with no standardized treatment protocol. Although placental extract is commonly used for its therapeutic benefits in the management of OSMF, it is not included in recent treatment consensus guidelines due to limited supporting evidence. This systematic review aimed to overcome these lacunae by evaluating the clinical effectiveness of placental extract in OSMF management

Objectives: To comprehensively analyse and compare the clinical effectiveness of intralesional placental extract in the management of OSMF

Methods: All the clinical studies that evaluated the effectiveness of placental extract and compared it with intralesional corticosteroids in the treatment of oral submucous fibrosis were included using extensive database searches conducted in PubMed, Cochrane, ProQuest, and Google Scholar published from January 1st 2015, to November 30st 2025.

Results: Eleven clinical trials (two randomized and nine non-randomized trials) comprising 525 patients fulfilled the inclusion criteria. Patients were monitored for three to twelve months. These findings demonstrated a statistically significant reduction of symptoms of OSMF among individuals receiving intralesional placental extract and corticosteroids

Conclusions: Placental extract demonstrated superior symptomatic improvement in OSMF, particularly in reducing burning sensation, and is supported by a strong safety profile with no documented adverse effects.

1. Introduction

Oral Submucous Fibrosis (OSMF) is a chronic, progressive disorder of the oral mucosa. Due to its significant risk of developing into oral squamous cell carcinoma (OSCC), it is classified as an oral potentially malignant disorder (OPMD) [1]. OSMF typically presents with clinical symptoms like burning sensation, xerostomia, limited mouth opening, and difficulty in swallowing, all of which interfere with vital oral functions such as chewing and speaking, eventually impacting the patient's nutritional status and overall quality of life [2]. The World Health Organization (WHO) 2021 defined OSMF as “a chronic, insidious disease that affects the oral mucosa, initially resulting in loss of fibroelasticity of the lamina propria and as the disease advances, results in fibrosis of the lamina propria and the submucosa of the oral cavity along with epithelial atrophy” [3]. Globally, approximately five million individuals are affected by OSMF, with a disproportionately high prevalence reported in South and Southeast Asia, accounting for 10.54% of cases worldwide [4,5]. Malignant transformation in OSMF is about 4.5 to 7.6 %, emphasizing the need for timely diagnosis and early intervention [6]. Areca nut chewing, often as part of betel quid (BQ), remains the primary etiological factor, and the International Agency for Research on Cancer (IARC) has classified the areca nut as a Group 1 human carcinogen due to its proven carcinogenic potential. [7,8] Nutritional deficiencies primarily those related to iron, zinc, and vitamins, as well as irritants like capsaicin, which is present in spicy food, are the additional contributing factors. [9]

Management of oral submucous fibrosis (OSMF) remains a challenge, and no universally accepted

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treatment protocol currently exists. Current medical approaches largely aim to reduce burning sensation and improve mouth opening by minimizing fibrosis by hyaluronidase, antioxidants, micronutrients, corticosteroids, and placental extract [10]. Among these, placental extract is increasingly used in routine practice because of its anti-inflammatory, antioxidant, and tissue-regenerative properties, which may help reduce fibrosis and enhance mucosal healing [12]. However, despite its frequent clinical use, the recent OPMD consensus guidelines (2022) did not include intralesional placental extract as a recommended therapy, primarily due to a lack of consolidated high-quality evidence [13]. This lacuna in literature highlights the need to evaluate the existing available evidence of intralesional placental extract and determine its potential role as a standard treatment option in the management of OSMF.

2. Methods

Focused question and protocol registration

Implementing the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) criteria and the "Participants, Intervention, Control, and Outcome (PICO)" framework. The research question investigated was: How effective is intralesional placental extract in treating oral submucous fibrosis? The review protocol was registered in PROSPERO CRD420251242062 and following PRISMA guidelines.

The PICO criteria applied were:

- Population (P): Individuals diagnosed with OSMF without any prior treatment.
- Intervention (I): Administration of intralesional placental extract (IPE)
- Comparison (C): Placebo or Any other medicinal treatment or any other treatment modality
- Outcome (O):

1. Primary outcome: Increased mouth opening (MO) and decreased burning sensation (BS)
2. Additional outcomes: Enhancement in cheek flexibility and tongue protrusion.

Eligibility Criteria

Inclusion criteria:

1. Primary research publications, such as clinical trials, both randomized and non-randomized
2. Studies evaluating intralesional placental extract for the treatment of OSMF, either monotherapy or in comparison with other therapies.
3. Articles published within the last five years (January 2015 to November 2025) to include the most recent developments in OSMF management.
4. Histopathological and/or clinical validation of the diagnosis of OSMF
5. Studies reporting clinical outcome measures, such as MO, BS, tongue protrusion, and cheek flexibility.
6. All articles published only in English

Exclusion criteria:

1. Studies not published in English, case reports, case series, review articles, monographs, retrospective studies, short communications, letters to the editor, commentaries, and animal studies were excluded
2. Studies involving patients with systemic illnesses, pregnant or breastfeeding women, individuals with restricted mouth opening due to other conditions (such as pericoronitis, space infections, abscesses, fractures), presence of other potentially malignant disorders (like oral leukoplakia or oral lichen planus), or history of hypersensitivity to placental extract were excluded

Search strategy

A comprehensive search was conducted in PubMed, Cochrane, ProQuest, and Google Scholar for studies published in English. The search strategy incorporated a combination of keywords, including (OSMF) OR (antifibrotic) AND (mouth opening) OR (cheek flexibility) OR (tongue protrusion) OR (trismus) AND (intralesional dexamethasone) OR (intralesional hydrocortisone) OR (intralesional placental extract) OR (intralesional hyaluronidase) OR (intralesional triamcinolone acetonide) AND (intralesional injection) OR (intraoral submucous injections). After removing

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irrelevant studies based on titles and abstracts, two independent reviewers assessed the full texts of potentially eligible articles. Studies meeting the inclusion criteria were re-evaluated in a second stage and re-labelled accordingly. Any disagreements were arbitrated by a third reviewer

Data collection process

The data were compiled using a structured data extraction form, which documented the following information: study time frame, author name, research title design, population, randomization method, types of interventions and comparators, participant characteristics (age and gender), inclusion and exclusion criteria, timing of measurements, primary and secondary outcomes and conclusion. A narrative synthesis was planned, primarily concentrating on intervention details, participant characteristics, and outcome assessments to synthesize the outcomes of the studies reviewed.

Quality assessment

Risk of bias was evaluated using design-specific assessment tools. Randomized controlled trials (RCTs) were appraised with the Revised Cochrane Risk-of-Bias tool (RoB 2), while non-randomized controlled trials (NRCTs) were examined using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) [14].

Two reviewers independently conducted all assessments, applying ROBINS-I for non-randomized studies and RoB 2 for randomized trials. Any disagreements were arbitrated by a third reviewer

GRADE assessment

The quality of evidence was appraised using the GRADE approach, considering factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each domain was appraised for methodological quality, relevance, and reliability of effect estimates. Based on this evaluation, the overall certainty for each outcome was determined. Outcomes were then graded as high, moderate, low, and very low [15]

3. Results

Literature search and study selection

A total of 362 articles were retrieved through an initial manual search. Twenty-five articles remained after irrelevant and duplicate papers were eliminated. Three studies, including two systematic reviews and one retrospective study, were excluded after the titles and abstracts were screened. Following the assessment of the full texts of the remaining twenty-two articles for eligibility, three studies cannot be retrieved and eight studies were excluded. In total, eleven articles met all inclusion criteria and were considered for this systematic review(Figure1).

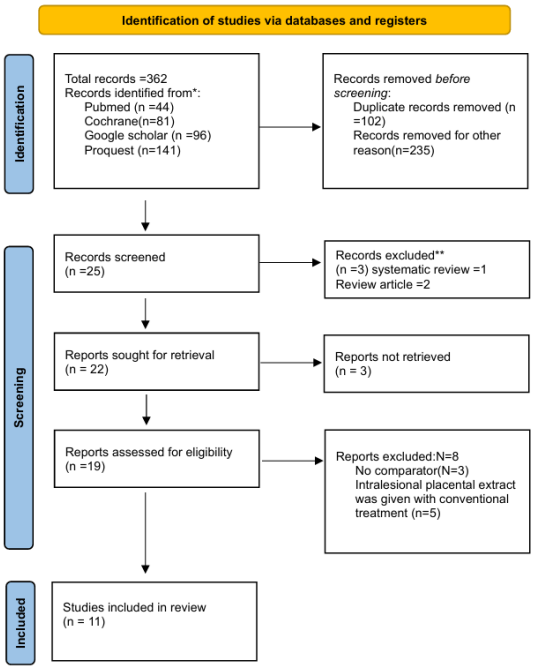

Figure 1: The Prisma flowchart

General characteristics of the studies

The included studies are summarized (Table 1). A total of 525 participants were included in these trials. All eleven included studies were conducted in India, with diagnosis based on clinical evaluation and in some studies, the patients were evaluated histopathologically. Participant's age ranged between 18 to 60 years, with a predominant male population. The follow-up period varied between 8 to 16 weeks.

Formulation -intervention and control group

Across the included studies, intralesional placental extract (IPE) was generally administered in doses ranging from 1–4 ml once weekly, with a few studies adopting biweekly protocols. A group of studies by

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Table 1: Characteristics of the studies included

Author and year	Study design	Formulation and duration of Intralesional Placental extract [IPE]	Control group	Sample size Placental extract /control	**Sex**/Age	Outcome measures and follow-up time	Main outcome Results [MO and BS]	Secondary Outcome results
Jay goyal et al 2024 [15]	RCT	2ml of IPE once weekly	Intralesional 1ml of Hyaluronidase with 1ml of dexamethasone	40/40	M-45 F-35	Follow up of 12 weeks	Statically Significant difference P<0.001 in both groups	-
Zuali et al 2023[16]	RCT	1 ml of IPE, once a week for five consecutive weeks	Transverse division of fibrotic bands in the submucosal plane under general anaesthesia.	29/29	M-18 F-40	Follow up of 5 weeks	Statically Significant difference in mouth opening in Fibrotomy group Statically Significant difference in IPE group in burning sensation	-
Joshna EK et al 2023[17]	Non RCT	2ml of IPE once weekly	Intralesional Dexamethasone 4 mg + hyaluronidase 1500 IU	18/17	M-25 F-5	Follow up of 6 weeks	Statistically significant intergroup difference (P < 0.001), shows control has better results in MO and BS	-
Almasri et al 2021[18]	Non RCT	4ml of IPE once weekly	Intralesional 10 ml of triamcinolone and 1500 IU of hyaluronidase	60/60	M-75 F-45 Mean age - 25.4	Follow up for 12 weeks	Statically Significant difference between two groups in MO and BS	-
Doyal roy et al 2021[19]	Non RCT	2ml of IPE once weekly	Intralesional 1ml of 40mg triamcinolone acetonide at weekly interval of 10 weeks	16/16	Mean age - 32	Follow up- 10 weeks	Statistically significant greater reduction in BS was observed in control group compared to placental group (P ≤ 0.001) statistically significant greater increase in MO was observed in placental extract compared to control group (P ≤ 0.001)	No significant difference
Meena et al 2020[20]	Non RCT	2ml of IPE once weekly	Intralesional 40 mg of triamcinolone acetonide with 1500 IU of hyaluronidase	30/30	M-43 F-17 Mean age - 31.6	Follow up of 3 months	Statically Significant difference between two groups in MO and BS	-

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Ankur et al 2020[21]	Non RCT	1ml of IPE once weekly	Intralesional 40 mg of triamcinolone acetonide	15/15	M-27 F-3 Mean age	Follow up for 8 weeks	Statically Significant difference between two groups in MO and BS	-
Shinde CV et al 2020[22]	Non RCT	2 ml of IPE once weekly	Intralesional 40 mg of triamcinolone acetonide weekly once	20/20	M-32 F-8 Mean age - 38	Follow up of 10 weeks	Statically Significant difference between two groups in MO and BS	Statistically significant difference in tongue protrusion and cheek flexibility in control group
Kisave p et al 2020[23]	Non RCT	2 ml of IPE once in week of 3 months	Biweekly intralesional injections of Dexamethasone (4mg/ml) plus Hyaluronidase 1500 IU in buccal mucosa for a period of 12 weeks.	20/20	M-35 F-25 Mean age- 29.5	Follow up 12 weeks	Statistically significant difference in mouth opening in control group P<0.001 and Statistically significant difference in burning sensation P < 0.001 in placental group	No Statistically significant difference in check flexibility
Niranjan reddy 2020[24]	Non RCT	2 ml of IPE biweekly	Intralesional 40 mg of triamcinolone acetonide biweekly with 1500 IU of Hyaluronidase	15/15	M-24 F-6 Mean age - 26	Follow up of 4 months	Statically Significant difference between two groups in MO and BS	-
Priyanka singh et al 2016[25]	Non RCT	2 ml of IPE biweekly	1.5 ml of Dexamethasone with 2% lignocaine weekly once	10/10M: F-2.75:1 Mean age -37.5	10M: F-2.75:1 Mean age - 37.5	MO and BS Follow up of 8 weeks	Statistically significant difference in mouth opening and burning sensation in placental group p value of 0.0005 Statistically significant difference in mouth opening and burning sensation of 0.000 in control group	-

Meena et al., Shinde et al., Doyal Roy et al., and Niranjan Reddy et al. administered 2 ml of IPE, while their control groups consistently received 40 mg triamcinolone acetonide, either alone or combined with 1500 IU hyaluronidase at similar intervals.

Similar studies cited below used IPE in different formulations. Jay Goyal et al. used 2 ml IPE weekly, with a control regimen of 1 ml hyaluronidase plus 1 ml dexamethasone. Zuali et al. administered 1 ml IPE weekly for five weeks, while the control group underwent fibrotomy under general anaesthesia. Joshna et al. provided 2 ml IPE weekly, and controls received 4 mg dexamethasone combined with 1500 IU hyaluronidase. Almasri et al. administered 4 ml IPE weekly, with controls treated using 10 ml intralesional triamcinolone plus 1500 IU hyaluronidase. Kisave et al. administered 2 ml IPE weekly for three months, whereas the control group received biweekly dexamethasone (4 mg/ml) and 1500 IU hyaluronidase. Ankur et al. administered 1 ml IPE weekly, with the control group receiving 40 mg triamcinolone acetonide.

Clinical parameters

All eleven studies primarily evaluated MO and BS as outcomes. Cheek flexibility and tongue protrusion were considered as secondary outcomes.

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Mouth opening: Out of the eleven studies, five studies (Zuali et al., Alamari et al., Niranjan Reddy et al., Ankur et al., Priyanka Singh et al.) utilized a vernier calliper for measurement, three Studies (Jay Goyal et al., Joshna E.K. et al., Meena et al.,) employed a scale, and remaining three studies did not specify the measurement tool used.

Burning sensation: Five used the Visual Analog Scale (Zuali et al., Joshna E.K. et al., Doyal Roy et al., Shinde et al., Priyanka Singh et al.) to assess burning sensation, one studies (Jay Goyal et al) applied the Likert numerical scale, while the remaining studies did not mention the assessment method

Main outcomes

Mouth opening

All included studies reported improvement in MO and reduction in BS following IPE. Jay Goyal et al., demonstrated significant improvement in MO with IPE, while Meena et al., Doyal Roy et al., Joshna E.K. et al., Kisave et al., Ankur et al., and Priyanka Singh et al. who used intralesional corticosteroid as control groups has significant improvement in MO compared to IPE. Zuali et al. showed that MO improved in the fibrotomy group, Almasri et al., Shinde et al., and Niranjan Reddy et al. reported significant MO improvement with both IPE and corticosteroids groups, with no clear difference between groups.

Burning sensation

Burning sensation is one of the major symptoms of oral submucous fibrosis and significantly impairs patients' quality of life. Four studies Zuali et al., Ankur et al., Parag Kisave et al., and Priyanka Singh et al. reported a statistically significant reduction in BS with IPE. In contrast, studies conducted by Jay Goyal et al., Meena et al., Doyal Roy et al., and Joshna E.K. et al. demonstrated a significant improvement in BS with intralesional corticosteroids. Similarly, and Alamari et al. and Shinde et al. reported reduced BS in both groups. However, the difference between the two groups was not statistically significant.

Risk of Bias assessment

For evaluating the quality of the included studies, RoB2 tool was applied for randomized controlled trials (Figure 2,3) and ROBINS-I tool for non-randomized trials (Figure 4,5). In randomized controlled trial conducted by Jay Goyal et al. it was observed there was low risk for randomization, intervention deviations, and missing data, but high risk in outcome measurement and reported results (Figure 2,3). Among the nine non-randomized studies, three studies (Shinde et al., Joshana et al., Priyanka et al. showed low risk of bias. Four studies (Meena et al., Kisave et al., Ankur et al., Doyal Roy et al.) had a moderate risk of bias. Two studies (Alamari et al., Niranjan Reddy et al.) exhibited high risk of bias, in confounding and selection of reported results (Figure 4,5).

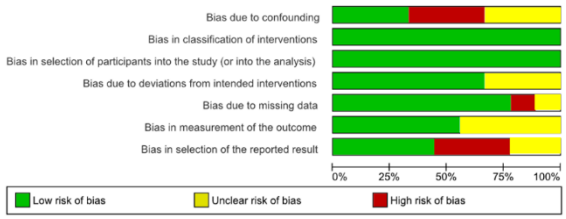

Figure 2: Risk of bias graph of non-randomized control trial

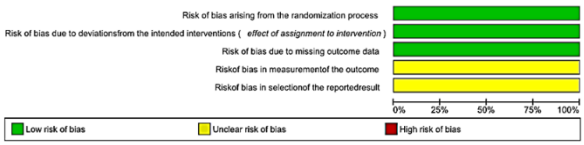

Figure 3: Risk of bias graph - Randomized control trial

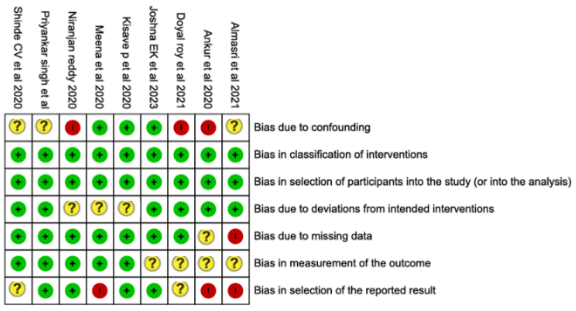

Figure 4: Risk of bias summary of non-randomized control trial

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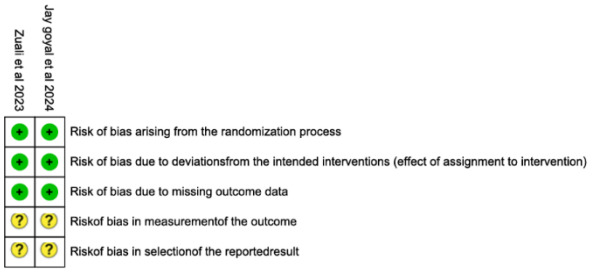

Figure 5: Risk of bias summary of Randomized control trial

GRADE assessment

GRADE evaluation of the eleven included studies, only two studies (Jay Goyal et al. and Zuali et al) retained a 'moderate certainty' rating, while the other nine were classified as 'low certainty'. The majority were reduced in quality due to key methodological shortcomings, including lack of randomization, small participant numbers, and inadequate reporting of blinding methods. (Table 2)

4. Discussion

Oral submucous fibrosis is a persistent, progressive disorder classified as an oral potentially malignant disorder and remains a major public health challenge in several regions of the world [27]. The primary objective in OSMF management is to alleviate inflammation and enhance mouth opening, ultimately improving the patient's oral function and overall quality of life [29].

Placental extract has gained interest as a therapeutic option due to its anti-inflammatory, antioxidant, and tissue-regenerative properties. Its hydroxyproline-rich peptides support antioxidant activity, while bioactive compounds such as cyclo-trans-4-L-hydroxyprolyl-L-serine contribute to tissue repair [32]. The presence of Fibroblast Growth Factors (FGFs) further promotes healing and may help reduce fibrotic changes [33]. This systematic review examined and compared the therapeutic effectiveness of intralesional corticosteroids and placental extract in the treatment of OSMF.

Mouth opening

All included studies reported an improvement in MO following IPE administration. However, when compared with intralesional corticosteroids, several studies (Meena et al., Doyal Roy et al., Joshna E.K. et al., Kisave et al., Ankur et al., and Priyanka Singh et al.) demonstrated significantly greater improvement in MO in the corticosteroid groups compared to IPE. In contrast, studies by Almasri et al., Shinde et al., and Niranjan Reddy et al. reported significant improvement in MO in both groups, with no statistically significant intergroup difference. Zuali et al. observed superior improvement in MO in the fibrotomy group compared to IPE. Overall, these findings suggest that while IPE contributes to improvement in MO, Intralesional corticosteroids demonstrated more consistent improvement

Burning sensation

IPE demonstrated a favourable effect on symptomatic relief. Four studies (Zuali et al., Ankur et al., Kisave et al., and Priyanka Singh et al.) reported a statistically significant reduction in BS with IPE. Conversely, studies by Jay Goyal et al., Meena et al., Doyal Roy et al., and Joshna E.K. et al. found greater improvement with intralesional corticosteroids. Alamari et al. and Shinde et al. reported reductions in burning sensation in both treatment arms, without a statistically significant difference between groups. These findings indicate that both IPE and corticosteroids are effective in reducing BS, with neither modality demonstrating consistent superiority across studies.

None of the included studies reported adverse effects associated with intralesional placental extract across all included studies. This favourable safety profile contrasts with the known potential adverse effects of repeated intralesional corticosteroid injections, such as mucosal atrophy and secondary infections, suggesting that IPE may serve as a safe therapeutic alternative or adjunct in selected patients.

Table 2:Grade assessment

Study (Author, Year)	Study Design	Initial Quality	GRADE quality assessment	Justification

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Jay goyal et al 2024 [15]	RCT	High	Moderate	Downgraded for imprecision due to modest sample size (n=80) and lack of significant superiority of either intervention.
Zuali et al 2023[16]	RCT	High	Moderate	Downgraded for imprecision due to a relatively modest sample size (n=58) and performance bias as post-operative jaw-opening exercises were unsupervised and conducted at home, leading to potential inconsistencies in patient compliance
Joshna EK et al 2023[17]	Non-RCT	Low	Low	Serious risk of bias (non-randomization), small sample, and inconsistency (control performing better).
Almasri et al 2021[18]	Non-RCT	Low	Low	High risk of bias, unclear allocation, and absence of statistically significant differences across outcomes.
Doyal roy et al 2021[19]	Non-RCT	Low	Low	Serious methodological limitations, heterogeneity in outcomes (placental extract better for MO, control better for BS).
Meena et al 2020[20]	Non-RCT	Low	Low	Lack of randomization, unclear blinding, and non-significant findings leading to imprecision.
Ankur et al 2020[21]	Non-RCT	Low	Low	Small sample (n=30), non-random allocation, and lack of significant improvement in primary outcomes.
Shinde CV et al 2020[22]	Non-RCT	Low	Low	Serious bias, small sample, inconsistent secondary outcomes (control superior in flexibility).
Kisave p et al 2020[23]	Non-RCT	Low	Low	High risk of bias, small sample size, inconsistent directional effects across outcomes.
Niranjan reddy 2020[24]	Non-RCT	Low	Low	Methodological limitations, variability in injection frequency, and non-significant results.
Priyanka singh et al 2016[25]	Non-RCT	Low	Low	Small sample (n=20), serious bias, and inconsistent statistical superiority in both groups.

Limitations and Future Scope

Despite promising observations, this review has limitations, including relatively small sample sizes, heterogeneous treatment durations, and variability in outcome assessment. A significant limitation is the overall low quality of evidence, as the review includes only two randomized and nine non-randomized studies, limiting strong clinical recommendations. Long-term follow-up data were lacking, and dosing protocols were inconsistent. Future studies must emphasize robust, multicentre randomized controlled trials conducted under standardized research frameworks and extended follow-up to establish definitive clinical guidelines. With more robust evidence, placental extract could be confidently integrated into the standard therapeutic framework for the management of oral submucous fibrosis.

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