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Platelet-rich fibrin in the management of oral mucosal lesions: a scoping review

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Abstract

Objectives Oral mucosal lesions are prevalent and often cause pain, thus impacting patients' quality of life. Platelet-rich fibrin (PRF) has emerged as a promising autologous biomaterial for wound healing, yet comprehensive evidence regarding its efficacy in treating oral mucosal lesions is limited. This study aims to update the current evidence on the effectiveness of PRF in treating various types of oral mucosal lesions.

Materials and methods We conducted a literature search in PubMed, Scopus, Embase, and Web of Science databases until April 2024. The search included studies that investigated the use of PRF in treating oral mucosal lesions. Twelve studies met the inclusion criteria, comprising three case reports, three randomized controlled trials, two animal studies, three split-mouth trials, and one retrospective study. We performed data extraction according to a predefined form.

Results PRF was applied in two forms—membranes and injectable gels—to treat a range of oral mucosal lesions, including ulcerative, red and white, pigmented, and potentially malignant or malignant lesions. Compared to control groups or conventional treatments, PRF generally demonstrated superior outcomes regarding faster healing, lesion size reduction, symptom relief, and lower recurrence rates. Histological and molecular analyses from some studies also indicated PRF's regenerative and anti-inflammatory effects.

Conclusion PRF shows promise as an effective and safe alternative to current treatments for oral mucosal lesions due to its autologous nature, ease of preparation, and wound-healing capabilities. However, further research is needed to standardize PRF preparation protocols and confirm its long-term efficacy across different lesion types.

Keywords Platelet-Rich Fibrin, Oral Ulcer, Mucositis, Mouth Neoplasms, Lichen Planus, Regeneration

Introduction

A wide range of oral mucosal lesions have a global prevalence ranging from 4.9% to 64.7%[1]. These lesions significantly impact quality of life by impairing functions and affecting psychological well-being [2]. Oral mucosal lesions have various causes, such as inflammation, infection, and neoplasm. [3]. These lesions are categorized into four groups: ulcerated, red and white, pigmented, and exophytic, based on their characteristics [4]. Not all lesions in these categories are malignant, but many can undergo malignant transformation. This underscores the importance of early detection and

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intervention. Local treatments are more effective than systemic treatments because they minimize side effects, reduce drug resistance risks, and target lesions while requiring smaller therapeutic doses directly [5, 6].

In 2001, Platelet-rich fibrin (PRF) was introduced as a second-generation platelet concentrate [7]. PRF stands out for its effectiveness in wound protection and creating a healing-friendly environment. It also excels at achieving hemostasis and outperforms commercial collagen membranes in terms of workability, strength, and clinical healing. Moreover, PRF is cost-effective, poses no allergy risks, and is readily accessible in clinical settings [8]. Despite the wide prevalence and significant impact of oral mucosal lesions, more comprehensive evidence regarding using PRF as a treatment strategy is needed. Our scoping review aims to address this gap by exploring the existing literature. We focused on evaluating its efficacy and practical application in clinical settings. PRF is an autologous biomaterial that accumulates platelets, leukocytes, and immunity promoters from the patient's blood and releases cytokines in a fibrin clot [9]. PRF contains a high concentration of leukocytes and releases growth factors slowly. It is produced using a standardized protocol that is cost-effective and simple. Since the fabrication of PRF does not require anticoagulants or activators like bovine thrombin, its application has low associated risks, as bovine thrombin has been linked to antibody formation and potential bleeding complications [10, 11].

Platelets, leukocytes, and the flexible fibrin matrix are the primary components contributing to the biological activities of PRF. Platelets contain various platelet-derived proteins stored in different granules, with alpha granules being the main reservoirs of growth factors. These growth factors, including TGF-β, PDGF, IGF1, VEGF, EGF, and immune cytokines like IL-1β, IL-6, IL-4, and TNF-α, play critical roles in wound healing processes like cell proliferation, angiogenesis, extracellular matrix synthesis, and remodeling. Leukocytes in PRF consist of neutrophils, lymphocytes, and macrophages that regulate various stages of inflammation and transition wounds from inflammatory to proliferative/remodeling phases [12, 13].

Thrombin present in the blood sample converts fibrinogen into insoluble fibrin. The speed of polymerization significantly influences the final fibrin matrix's characteristics. In Platelet-Rich Plasma (PRP) preparation, bovine thrombin, and calcium chloride lead to rapid fibrin polymerization, resulting in a rigid fibrin network that quickly releases growth factors [12, 14]. In contrast, PRF processing involves slow and natural fibrin polymerization due to physiologic thrombin concentrations. Thus, the fibrin matrix is flexible with slow-release properties [12].

Leukocytes and immune cytokines, enriched in PRF, are vital for tissue regeneration, as they facilitate cellular communication and the transition between inflammation and repair in the wound healing process.

Studies indicate that reducing the relative centrifugation force enhances the regeneration potential of PRF by increasing platelet and leukocyte numbers and growth factor levels [10, 12].

The production process is what distinguishes PRF from other platelet-rich products like PRP. To prepare PRF, blood is collected without anticoagulants and centrifuged. After centrifugation, there are three distinct layers: the upper acellular plasma, the lower red blood cell, and the middle fibrin clot [15]. Figure 1 illustrates the various fabrication methods of PRF [16]. PRF does not require anticoagulants and allows the natural wound-healing cascade to proceed without inhibition. Unlike PRP, there is no need for bovine thrombin, calcium chloride, or other activators [13].

The original PRF or leukocyte-PRF, or L-PRF, is created by collecting 10 mL of blood without anticoagulants and centrifuging it at 2700 rpm for 12 min at room temperature [17]. This produces a fibrin clot containing concentrated platelets and leukocytes.

Advanced PRF (A-PRF) uses lower centrifugal forces of 1500 rpm for 14 min, which results in higher concentrations of viable cells and increased growth factor release compared to L-PR [18]. An enhancement of A-PRF (A-PRF plus) has further reduced centrifugal speeds and time to 700 rpm for 3 min [19]. This lowers the g-force in A-PRF, resulting in more cells and factors.

Injectable PRF (I-PRF) is prepared with lower centrifugation speeds and formulated as an injectable liquid rather than gel, allowing earlier release of growth factors [20].

Additionally, there are other methods, like titanium-PRF (T-PRF), which involves collection in titanium tubes, and Concentrated Growth Factors (CGFs) with varying centrifugation times, that produce fibrin matrices with unique characteristics [21, 22].

These PRF protocol modifications present diverse options, but standardization and comparison of formulations need further optimization and research. Understanding the influence of preparation methods on composition and efficacy will be necessary. Various PRF modalities offer distinct advantages and applications. I-PRF provides a convenient liquid formulation that can be used alone or combined with biomaterials. However, it has a shorter duration of growth factor release and is less suitable for situations requiring a solid matrix. L-PRF provides a strong, solid fibrin matrix

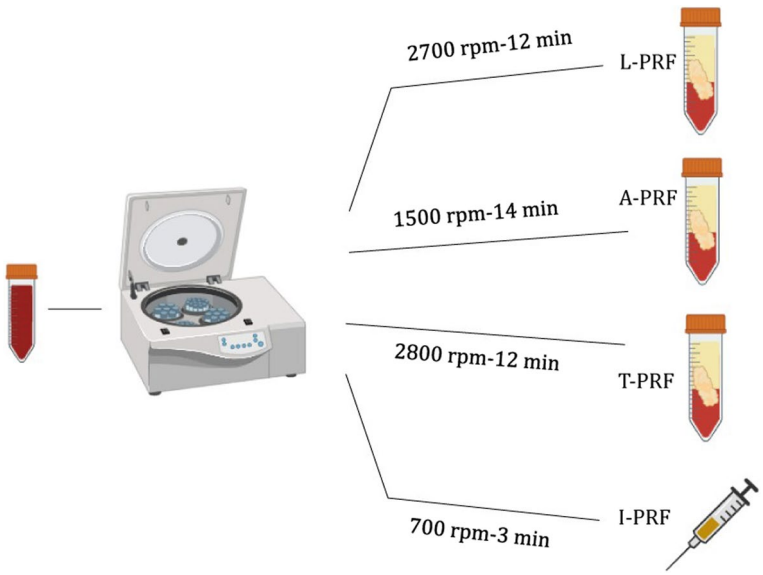

Fig. 1 Fabrication methods of PRF. (L-PRF: Leukocyte-Platelet Rich Fibrin, A-PRF: Advanced Platelet Rich Fibrin, T-PRF: Titanium Platelet Rich Fibrin, and I-PRF: Injectable Platelet Rich Fibrin) [16]

that can be easily handled in surgical applications, with a slow and sustained release of growth factors, though it is non-injectable. A-PRF enhances tissue regeneration by releasing higher concentrations of growth factors over time and improving immune response, though it requires more complex preparation. T-PRF leverages titanium tubes' improved hemocompatibility and fibrin network structure and offers a denser fibrin network and prolonged growth factor release. It is a costly alternative for periodontal and soft tissue regeneration and sinus lift treatments [23–25].

PRF offers a multifaceted mechanism of action that can be promising for wound healing applications, such as treating oral mucosal lesions, as illustrated in Fig. 2.

Cell recruitment

PRF contains chemotactic cytokines such as neutrophil-activating peptide (CXCL7), platelet factor 4 (PF4), and

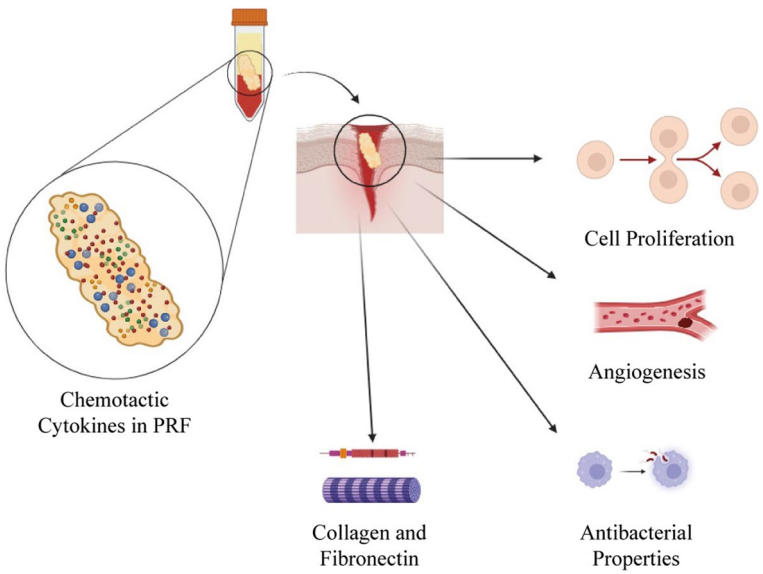

Fig. 2 Mechanism of action of PRF in wound healing. PRF induces cell proliferation, angiogenesis, and collagen and fibronectin formation. It also helps wound healing by showing antibacterial properties

SDF-1α (factor 1— derived from stromal cells), which encourage inflammatory cell infiltration to the wound site [26].

Cell proliferation and angiogenesis

PRF also provides growth factors, including platelet-derived growth factor (PDGF), transforming growth factor (TGF-β1), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and hepatocyte growth factor (HGF) that stimulate the proliferation of fibroblasts, epithelial cells, and vascular endothelium, promoting tissue regeneration and angiogenesis [26].

Extracellular matrix synthesis

The fibrin matrix within PRF facilitates cell migration and proliferation, synthesizing essential components like collagen type I and fibronectin to form a new tissue matrix [27].

Sustained growth factor release

PRF modulates the gradual and prolonged release of growth factors from its fibrin network. This controlled release maintains the healing cascade by continuously signaling cells, promoting hemostasis, stimulating angiogenesis, and providing stimuli for proliferation and remodeling [28].

In summary, these mechanisms of modulating inflammation, stimulating cell proliferation, vascularization, matrix synthesis, and exerting antimicrobial effects [29] sustainably can promote wound healing, suggesting PRF's potential efficacy for treating oral mucosal lesions.

Platelet concentrates, including PRF, have shown potential for application in various medical and dental fields, as illustrated in Figs. 3 and 4. They have been utilized in wound healing, chronic diabetic wounds, scar treatment, androgenetic alopecia, skin rejuvenation, and chronic pain conditions like knee arthrosis, degenerative disc disease, facet pathologies, and sacroiliitis [30–33].

In dentistry, PRF has exhibited positive effects in healing after vital amputation and regeneration of immature permanent teeth [34]. For instance, Alagl et al. conducted a study evaluating the efficacy of platelet-rich plasma (PRP) as a scaffold in teeth with complete pulp degeneration. After 12 months, all teeth in the PRP group resolved symptoms such as pain, swelling, fistulas, and sensitivity to percussion and palpation. Besides, 93% of cases showed increased root length or apical closure [11]. In periodontal treatments, PRF enhances periodontal repair by reducing pocket depths, improving attachment levels, and demonstrating significant clinical improvements in furcation defect regeneration [35–38]. For example, in a randomized clinical trial, Sharma et al. used PRF combined with open flap debridement for mandibular degree II furcation defects compared to debridement alone. The results showed that the PRF group had significantly greater reductions in probing depth, improved clinical attachment levels, and enhanced bone defect fill [12].

It is also considered an alternative to invasive procedures for covering gingival recessions. It also plays a role in guided bone regeneration, extraction socket management, and sinus elevation procedures [39–42]. In a case series by Mazor et al., 25 sinus floor augmentations with simultaneous implant placement were performed on 20

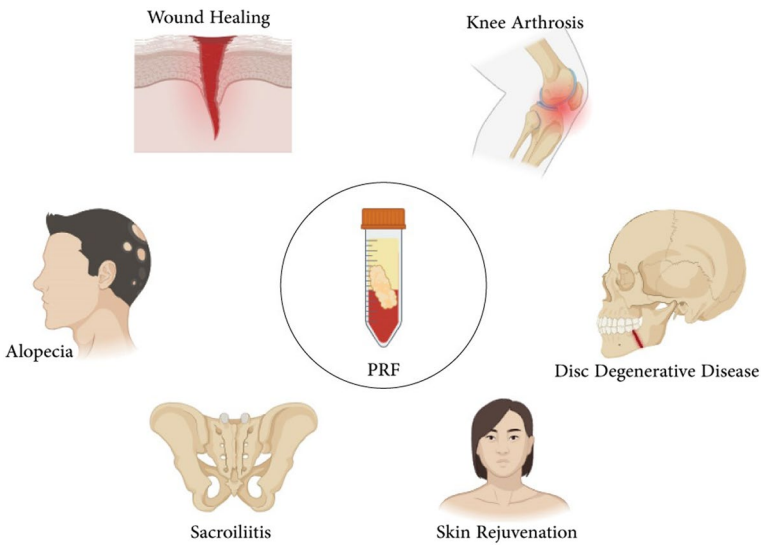

Fig. 3 Medical applications of PRF. PRF is being used in various medical fields, from accelerating wound healing and treatment of dermal diseases to cartilage regeneration

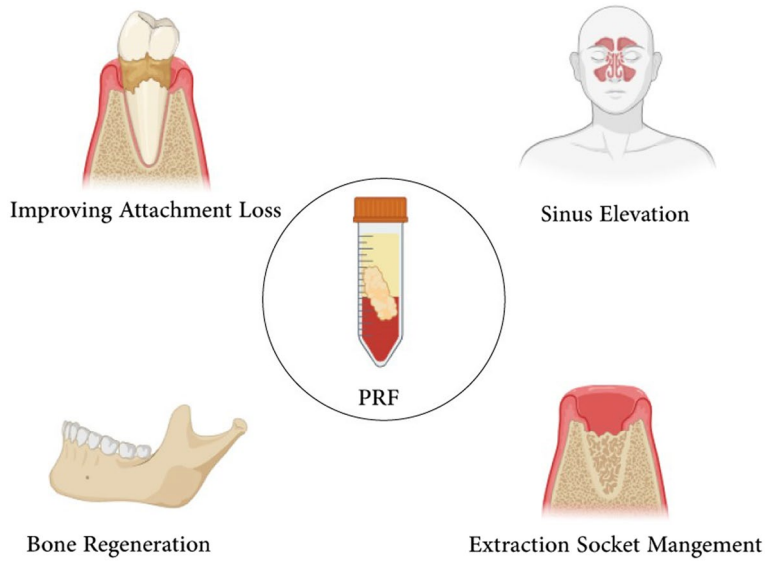

Fig. 4 Dental applications of PRF. PRF has various oral applications, specifically in bone regeneration to improve attachment loss, manage extraction sockets, and elevate sinus

patients using PRF as grafting material. After six months, the results showed significant bone gain around implants (mean 10.1 mm), and histologic analysis confirmed well-organized and vital bone formation [13].

Materials and methods

PubMed/Medline, Scopus, Embase, and Web of Science electronic databases were searched up until April 2024 using a combination of Medical Subject Heading (MeSH) terms and free-text words with Boolean operators as follows:

("Platelet-rich fibrin" OR "PRF") AND ("Oral mucosal lesion" OR "Oral mucosal ulcer" OR "Oral candidiasis" OR "Thrush" OR "aphthous stomatitis" OR "Lichen planus" OR "Oral mucositis" OR "Squamous cell carcinoma" OR "Recurrent herpes labialis" OR "Leukoplakia" OR "Ulcerated lesion" OR "Red lesion" OR "white lesion" OR "Pigmented lesion" OR "Exophytic lesion" OR "bullous lesion" OR "Hyperkeratosis" OR "Oral premalignant lesion").

Titles and abstracts were screened, followed by a full-text review of potentially relevant studies. Two reviewers independently assessed eligibility, and disagreements were resolved by consensus.

All types of studies in English that investigated the use of PRF in treating oral mucosal lesions were included. Reviews, editorials, opinions, and letters to the editor were excluded, as well as studies that were not published in English. Studies not directly investigating the use of PRF in treating oral mucosal lesions were excluded after a full-text review.

Results

The application of PRF for treating various oral mucosal lesions was explored. Figure 5 illustrates the PRISMA Extension for Scoping Reviews (PRISMA-Scr). Eight studies utilized PRF in membrane form [8, 43–49], while five employed injectable or gel formulations [28, 35, 50–52].

In terms of study designs, the included studies included five randomized controlled trials [35, 45, 46, 50, 51], two prospective studies [43, 44], three case reports/series [8, 52, 53], two animal studies [48, 49], and one retrospective study [28].

The centrifugation speed for PRF preparation varied. Five studies used 3000 rpm for 10–12 min [8, 43–46], one study used 1500 rpm [vokur48], three studies at 700 rpm for 3 min [35, 50, 51], and four studies did not specify the speed [28, 49, 52, 53].

Regarding outcomes, nine studies reported improved or complete healing [8, 28, 43–46, 49, 52, 53]. One animal study reported no significant differences in healing compared to control groups [48].

Six studies demonstrated decreased pain levels [35, 44–46, 50–52].

Four studies observed no recurrence of lesions [8, 43, 44, 53], while two reported recurrence [28, 45]. Additionally, four studies noted a reduction in lesion size [35, 44, 50, 51].

The varying outcomes across studies highlight the importance of PRF preparation methods, lesion type, and individual patient characteristics. The differences in centrifugation speed and duration may influence

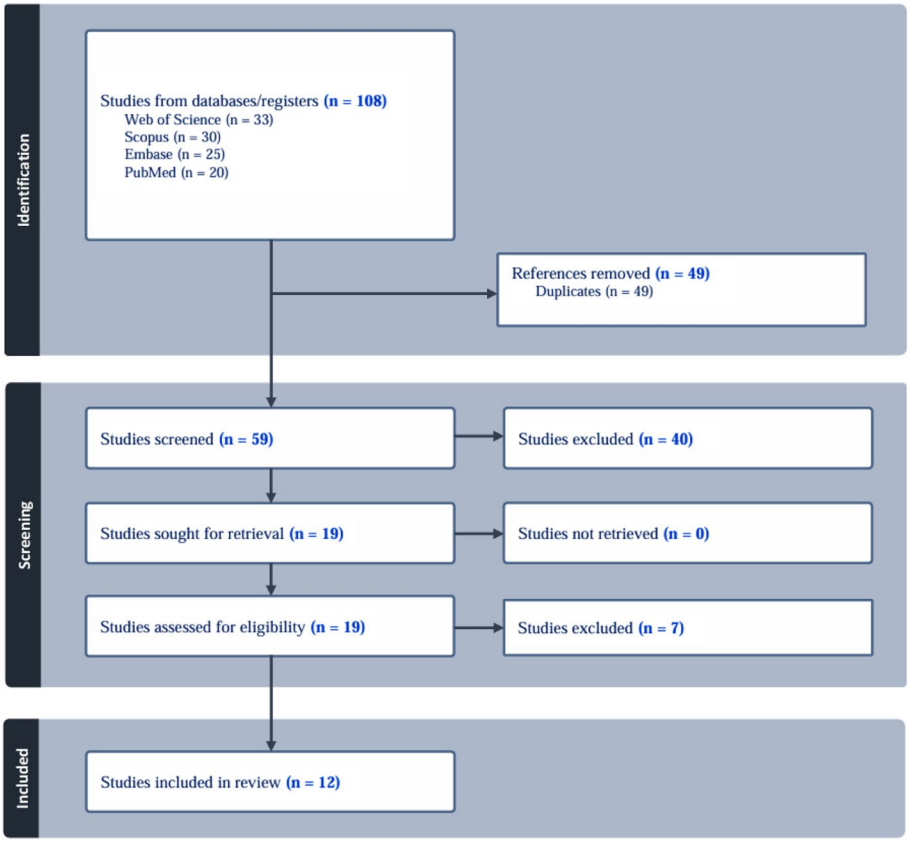

Fig. 5 PRISMA Extension for Scoping Reviews

the concentration of growth factors and the mechanical properties of PRF, thus affecting its clinical efficacy. Moreover, the form of PRF (membrane vs. injectable) seems to play a role in the outcomes. Table 1 summarizes the data from the included studies.

The application of PRF for red and white oral mucosal lesions

The gold standard treatment for white lesions such as leukoplakia is surgical excision, often using CO2 laser, and careful long-term follow-up to monitor malignant transformation. For oral lichen planus, the gold standard treatment involves topical corticosteroids for mild to moderate cases and systemic corticosteroids for severe or resistant cases [4].

Mohanty et al. utilized PRF membranes in a case report study to treat hyperkeratotic lesions in the oral mucosa. The patient, a 65-year-old male smoker, had a non-tender white lesion in the lower anterior vestibule and attached gingiva. The blood sample was centrifuged (3000 rpm for 12 min). These PRF clots were pressed between two flat surfaces while glass slabs were covered with sterile wet gauze to form the PRF membrane. After excising the lesion with a partial thickness excision technique, the PRF membrane was used to cover the wound and sutured to the mucosal margins. Wound healing was clinically evaluated after seven days. [8]. The membrane showed good elasticity but required careful handling. After 24 h of placing a pressure dressing on the area, it was observed that the PRF membrane had integrated well into the site. After seven days, the area showed mild erythema and pain at the suture removal points but no signs of necrosis. Subsequent evaluations at 15, 30, and 60 days revealed complete clinical wound healing with mild fibrosis. After one year of follow-up, the patient remained asymptomatic with no signs of lesion recurrence [8]. This suggests that PRF membranes may provide a stable and conducive environment for wound healing, possibly due to their ability to release growth factors that promote tissue regeneration.

Pathak et al. also evaluated the effect of the PRF membrane on the healing of several oral mucosal lesions, leukoplakia, lichen planus, and oral submucous fibrosis after excision in a prospective study. Blood was centrifuged (at 3000 rpm for 10 min). After the excision of lesions, the PRF membrane was sutured in place. [43]. All surgical

Table 1 A summary of the included studies

Study/ Year	Experimental setup	Mucosal lesion	Conventional treatment	Form of PRF application	Comparison group	Application site	Time of evaluation	Main parameter evaluation	Overall outcome
Mohanty et al (2014)	Case report	White lesion	surgical excision	Membrane	NA	lower anterior vestibule and attached gingiva	After 1, 7, 15, 30, and 60 days, and one year	Healing	**Healing**: Asymptomatic with no signs of recurrence
Pathak et al. (2015)	RCT	Leukoplakia, OLP, oral submucous fibrosis	Leukoplakia: surgical excision OLP: topical corticosteroids for mild to moderate cases	Membrane	NA	Buccal mucosa, tongue, lower labial mucosa, vestibule, gingiva, alveolar mucosa, palate	Before the intervention, after 7, 15, 30, and 60 days	MMO, Pain, Healing, Recurrence	**MMO:** Increased in oral submucous fibrosis, Reduced in other lesions of posterior buccal mucosa **Healing:** Low scores (maximum 2) except for 1 case/ complete healing by day 60 **Pain:** Decreased over time except for 1 case **Recurrence:** None observed
Saglam et. al. (2021)	Split-mouth trial	Erosive OLP on buccal mucosa	topical corticosteroids for mild to moderate cases	Injectable	0.2 ml methylprednisolone acetate intralesional injection	Injected at four different endpoints at the periphery of the erosive OLP lesion on buccal	Before the intervention, after the last injection, 1, 2, and 6 months	Pain, satisfaction, OHIP-14, lesion size	**Pain reduction, satisfaction, quality of life improvement, and lesion size:** corticosteroid = i-PRF
Bennardo et al (2021)	Split-mouth trial	Symptomatic OLP on the buccal mucosa	topical corticosteroids for mild to moderate cases	Injectable	0.5 ml TA intralesional injection	Injected directly into the subepithelial connective tissue at the center of the lesion	Before the intervention, after 4 weekly injections, 3 and 9 months	Lesion size, VAS pain score	**lesion size and pain:** TA = i-PRF

Table 1 (continued)

Study/ Year	Experimental setup	Mucosal lesion	Conventional treatment	Form of PRF application	Comparison group	Application site	Time of evaluation	Main parameter evaluation	Overall outcome
Tewari et al (2020)	RCT	Pigmented, OLP, Papilloma, Ulcers, Erythroleukoplakia	Pigmented: No treatment, only observation OLP: topical corticosteroids for mild to moderate cases Papilloma: surgical excision	Membrane	Individualized treatment for each case	Tongue Buccal Mucosa Lower lip Mucosa Vestibule Retromolar Trigone Soft Palate	After 7, 15, and 30 days	color of the tissue, granulation tissue, bleeding, suppuration, pain, contour irregularity, and cosmetic appearance, healing	**Irregularity and cosmetic appearance**: Patients on a longer follow-up have shown complete epithelialization without any known case of recurrence of disease **Healing**: significant improvement
Al-Hallak et al (2021)	Split-mouth trial	Symptomatic OLP on the buccal mucosa	topical corticosteroids for mild to moderate cases	Injectable	0.5 ml TA intralesional injection	Connective tissue just under a clinical extension of recognized OLP lesion on the buccal mucosa	Before the intervention, after 2 and 4 weeks	Pain, severity, lesion size	**Reducing Symptoms:** Both Effective **Pain reduction:** TA > i-PRF
Horii et al (2014)	Animal trial	Mucositis induced by chemotherapy	supportive care, including pain management, oral hygiene, and nutritional support	Membrane	Fibrin group., Control group	left cheek	After 3, 6, 10, and 14 days	weight, Macroscopic analysis of the ulcer area, Histopathology, MPO activity	**Histopathologic, MPO activity**: The PRF group exhibited significant improvements in the size and histologic features of the ulcer and in the myeloperoxidase activity compared with the control group **weight**: The body weight showed a tendency to decrease within the first 3 days

Table 1 (continued)

Study/ Year	Experimental setup	Mucosal lesion	Conventional treatment	Form of PRF application	Comparison group	Application site	Time of evaluation	Main parameter evaluation	Overall outcome
Vokurka et al (2020)	Animal trial	Surgical creation of artificial round defects	-	Clot	PRP + CM, PRF + CM, EMD + CM, CM alone, or left untreated as a negative control	maxillary region	After 1, 7, and 28 days	Histopathological, Molecular, Healing	**Healing:** This experimental study did not confirm any significant improvement in soft tissue healing when applying a combination of CM with PRP, PRF, or EMD compared with CM alone or untreated controls **Histopathological, Molecular**: At day 7, proliferating granulation tissue filling the empty space after phagocytosis of necrotic tissue was detected around the defect
Miranda et al (2023)	Retrospective study	Oral mucositis	supportive care, including pain management, oral hygiene, and nutritional support	Gel	NA	Buccal mucosa, tongue, labial commissure, lower lip	NS	Pain, Lesion dimensions, Presence of granulation tissue, Recurrence	Complete healing after an average of three applications (range: 2–8) **Recurrence**: Only 1 case after 5 months
Gasparro et al (2019)	Case report	plasma cell mucositis	topical and systemic corticosteroids	Injectable	NA	left side of the buccal mucosa	once a month during the first 6 months after the treatment	Pain Healing	**Pain:** from score 7(before the treatment), gradually reduced to 0 at the fourth infiltration **Healing:** not complete healing was observed but the perilesional inflammatory infiltrate reduction was observed after 6 months

Table 1 (continued)

Study/ Year	Experimental setup	Mucosal lesion	Conventional treatment	Form of PRF application	Comparison group	Application site	Time of evaluation	Main parameter evaluation	Overall outcome
Mahajan et al (2018)	RCT	NS	-	Membrane	Bovine collagen membrane	NS	After 7, 15, 30, and 60 days	Healing, Pain, Recurrence, Fibrosis, Scar hypertrophy, Vestibular depth reduction	**Healing and pain:** PRF = Collagen **Fibrosis, Scar hypertrophy, and vestibular depth reduction:** PRF < Collagen **Recurrence:** only 1 case in PRF
Debnath et al. (2018)	Case report	Pyogenic granuloma	surgical excision	Membrane	NA	Exposed bone surface, right mandibular front tooth region	After two weeks, and 12 months	Histopathological evaluation, Healing	**Healing**: a complete epithelialization over the denuded bone surface was seen **Histopathological evaluation**: The epithelium appeared to be hyperplastic and edematous and was infiltrated with inflammatory cells
Poddar et al. (2023)	RCT	NS	-	Membrane	Bovine collagen membrane	NS	After 3, 7, and 30 days	Pain, Clinical Healing, Granulation Tissue, Wound Contracture, Complications	**Pain:** PRF < Collagen (on days 3 and 7) **Clinical healing:** PRF > Collagen (on days 7 and 30) **Improved granulation tissue:** PRF > Collagen (on day 7) **Epithelialization, wound contracture, and complications:** No notable differences by day 30

NA Not Applicable/, *RCT* Randomized Clinical Trial/, *MMO* Maximum Mouth Opening/, *OLP* Oral Lichen Planus/, *i-PRF* Injectable Platelet-Rich Fibrin/, *OHIP-14* Oral Health Impact Profile-14/, *VAS* Visual Analogue Scale/, *TA* Triamcinolone/, *NS* Not Specified/, *MPO* Myeloperoxidase/, *EMD* Enamel Matrix Derivative/, *CM* Collagen Matrix

sites showed progressive healing over 60 days, with complete healing observed in all cases. Patients with oral submucous fibrosis experienced increased mouth opening after treatment, while those with lesions in the posterior buccal mucosa had reduced mouth opening due to surgical fibrosis. Pain gradually decreased in most cases, except for one patient with a lesion on the ventral surface of the tongue, likely due to constant movement causing trauma. Healing scores remained low, except for one patient who developed a successfully treated infection. No recurrence of the lesion or symptoms was observed in any patient [43].

Saglam et al. evaluated the efficacy of injectable PRF for treating erosive oral lichen planus in a randomized clinical trial [50]. The blood was centrifuged with low centrifugal force (700 rpm for 3 min) [35]. The participants received injections of PRF or methylprednisolone acetate (as a control group) over four sessions with a 15-day interval between sessions [50].

PRF and methylprednisolone acetate showed a significant reduction in pain, lesion dimensions, and 14-item oral health impact profile (OHIP-14) and a significant increase in satisfaction compared to baseline. Pain levels after the last injection were lower in the PRF group, and satisfaction levels were high. However, there was no significant difference in pain, satisfaction, and OHIP-14 values between them. The pain and satisfaction values of the PRF group after 6-month follow-up significantly differed from those associated with the last injection in that group [50]. Compared to the corticosteroid, I-PRF provided longer-lasting pain relief, higher patient satisfaction in the 6th month, and a favorable safety profile and minimal risk of systemic side effects. Their findings indicate that PRF could be a viable alternative to conventional treatments since it offers a potentially safer profile without compromising efficacy.

Bennardo et al. compared the effectiveness of injectable PRF for treating symptomatic oral lichen planus in a randomized clinical trial. PRF was prepared at room temperature with low centrifugal force (700 rpm for 3 min). The intralesional injections of PRF or triamcinolone acetonide (as a control group) were carried out once a week for four weeks [51]. Both treatments effectively reduced the lesions' extension and improved symptoms. The average reduction in the size of the affected area and pain was greater in the PRF group. However, there was no statistically significant difference in the changes in lesion extension between the two treatment protocols. No side effects were observed in any of the cases. During the follow-up period, one-third of the patients experienced a reappearance of symptoms after 4 or 5 months [51]. The lack of significant differences between treatment groups suggests that PRF could be a valuable alternative in cases where corticosteroids are contraindicated or cause adverse effects.

In a prospective study, Tewari et al. assessed the effectiveness of PRF membrane grafts in treating various red and white oral mucosal lesions, lichen planus, leukoplakia, and erythroplakia. Blood samples were centrifuged (3000 rpm for 10 min). Surgical excision was performed using CO2 laser excision and PRF membrane grafting. Lesions were monitored at 1-, 3-, 7-, 15, and 30-day follow-ups [44].

The redness disappeared in all patients after 30 days. Granulation tissue was observed in 85.3% of patients after seven days, 20.6% after 15 days, and none after 30 days. Bleeding was observed in 5.9% of patients on the day of surgery, and it was conservatively managed. Suppuration was detected in 2.9% of patients after seven days and 2.9% at the 30-day follow-up. None of the patients complained of pain after completing the course of postoperative analgesics. Contour irregularity was noted in 11.8% of patients after 15 days and 2.9% of patients at 30-day follow-up [44].

Al-Hallak et al. evaluated the efficacy of injectable PRF for treating oral lichen planus in a randomized clinical trial [35]. PRF was prepared at room temperature with low centrifugal force (700 rpm for 3 min). The therapeutic procedure involved 1 ml intralesional injections of PRF or 0.5 ml intralesional injection of triamcinolone acetonide (as a control group) once a week for four weeks [35].

By the end of the treatment, PRF and triamcinolone acetonide groups experienced a reduction in pain and burning sensation, with a 68.5% reduction in the PRF group and a 90% reduction in the triamcinolone acetonide group. Regarding the reticular erythematous ulcerative (REU) scores, the PRF group showed a 74% reduction in REU scores, and the triamcinolone acetonide group showed a 91% reduction. The two groups had no significant difference in pain and REU scores. During the follow-up, only two patients (16.7%) reported mild symptoms of recurrence on both sides of the buccal mucosa [35]. Although reduction of pain and REU had a nonsignificant trend favoring triamcinolone acetonide in this study, they showed that PRF could be a potentially safer alternative for corticosteroids.

The application of PRF for pigmented oral mucosal lesions

For pigmented melanotic macules, the gold standard treatment usually involves no intervention unless there are cosmetic concerns or suspicion of malignancy. In cases where treatment is desired, surgical excision or laser ablation is typically employed [4].

In the study by Tewari et al., two cases of pigmented melanotic macules were treated with CO2 laser excision

followed by PRF membrane grafting. PRF membranes were centrifuged at 3000 rpm for 10 min. The melanotic macule lesions showed complete re-epithelialization within seven days post-operatively. Patients reported mild post-operative pain up to day 3, which resolved after analgesic medication. At the 30-day follow-up, both cases showed excellent healing with no recurrence, no redness, and good integration of the PRF membrane with minimal inflammation. The grafted PRF membrane appeared to stimulate regeneration of the pigmented lesions after surgical excision. Based on these outcomes, the study concluded that PRF membrane grafts can be an effective therapy for pigmented melanotic macules of the oral mucosa [44].

While the standard approach for melanotic macules often involves observation or conventional surgical methods, this study's use of PRF membrane grafts suggests a potential alternative that may enhance wound healing and reduce recurrence.

The application of PRF for ulcerative oral mucosal lesions

The gold standard treatment for chemotherapy-induced mucositis primarily involves supportive care, including pain management, oral hygiene, and nutritional support. For plasma cell mucositis, the standard treatment includes topical and systemic corticosteroids, with immunosuppressants used in resistant cases [4].

Tewari et al. also assessed seven cases of ulcerative lesions in their study, and PRF membrane showed the capability to effectively reduce redness, pain, granulation tissue, suppuration, bleeding, and contour of the mucosa [44].

In a study led by Horri et al., the efficacy of PRF in treating chemotherapy-induced mucositis was explored. Oral mucositis was chemically induced in hamsters. On day 4, hamsters were randomly divided into three treatment groups: PRF membrane applied to lesions, fibrin sealant applied to lesions, and no treatment control. The PRF membranes were prepared from healthy human donors according to an established protocol [49].

The PRF treatment group showed better weight gain from days 4–14 compared to fibrin and control groups, although not statistically significant. Macroscopically, the PRF group had a significantly smaller ulcer area compared to fibrin and control groups starting on day 5 through day 14, with minimal scarring by day 14. Histologic analysis on day 14 showed that the PRF group had significantly reduced inflammation and faster healing than the control group. Myeloperoxidase (MPO) activity, a marker of inflammation, was significantly lower in the PRF group compared to the control on day 6 [49]. This suggests that PRF could play a role in mitigating the adverse effects of chemotherapy by promoting faster tissue repair and reducing inflammation.

Vokurka et al. conducted an animal study to investigate the efficacy of PRP, PRF, and EMD (Enamel Matrix Derivative) in treating surgical defects. This study was conducted with five treatment groups: CM (Collagen Matrix) alone, CM with PRP, CM with PRF, CM with EMD, or untreated control. PRF was prepared from 8 mL peripheral blood spun without anticoagulant in a centrifuge for 14 min at 1500 rpm. PRP was prepared by double centrifuging peripheral blood with heparin [48].

On Day 1, defects displayed edema, necrosis, hemorrhages, fibrin, and acute inflammation without re-epithelialization. By Day 7, there was granulation tissue, acute inflammation, and initial re-epithelialization at wound edges. By Day 28, there was complete re-epithelialization with some immature epithelium and chronic inflammation. Despite these changes, no significant differences between treatments were observed, except in the EMD group on Day 28, which showed increased angiogenesis and inflammation [48]. This lack of difference might indicate that the benefits of PRF are context-dependent and potentially influenced by factors such as lesion type, location, and the specific preparation and application method of PRF.

Miranda et al. explored platelet-rich fibrin gel for Oral mucositis treatment. Autologous platelet gel was prepared to obtain a platelet concentrate with 2×10^6 platelets/μL. Platelet gel was applied to the oral mucositis lesions every 14 days [28].

Patients with oral mucositis showed complete response after a median of 3 platelet gel applications (range 2–8). No adverse effects were observed, except mild burning in 2 patients initially. During follow-up, no recurrence of lesions was seen in treated areas, except in one case at five months [28].

In a case study, Gasparro et al. used injectable platelet-rich fibrin (i-PRF) to treat Plasma cell mucositis (PCM) in the oral mucosa. A 78-year-old woman was diagnosed with PCM based on a biopsy. Four months after the last treatment, i-PRF was prepared from 20 mL of the patient's blood. Blood was centrifuged at 700 rpm for three min. I-PRF was injected weekly for two months at four sites around the lesion. No side effects were reported. Initially rated at 7, pain dropped to 0 by the fourth session. Although the lesion didn't fully heal, inflammation was reduced by the 6-month follow-up, with no further treatments administered [52].

The application of PRF for Oral potentially malignant disorders

The gold standard treatment for oral potentially malignant disorders generally involves surgical excision and close follow-up [4].

Mahajan et al. assessed the efficacy of PRF membranes in treating potentially malignant oral mucosal lesions in a randomized controlled trial [45]. Patients were divided into two groups: one group received PRF membrane grafts and the other received collagen. PRF membrane was centrifuged at 3000 rpm for 10 min [45].

According to their results, by the 30th day, most patients reported no pain, and by the 60th day, all exhibited excellent healing. PRF Group showed higher instances of complications like scar hypertrophy and fibrosis. This suggests that while PRF effectively promotes healing, the risk of certain complications needs to be managed carefully, perhaps by optimizing PRF preparation protocols. Only a minor percentage in the collagen group experienced lesion recurrence [45].

In a similar randomized controlled trial study, Poddar et al. compared collagen and PRF membranes for post-operative healing after oral mucosal lesion surgery [46].

Based on their results, PRF showed a better reduction in pain, improved clinical healing, and good granulation presence than the collagen group. There were no significant differences between the two groups for the post-operative parameters checked on the 30th day (Epithelialization, Wound Contracture, and Complications) [46].

The application of PRF for exophytic lesions of oral mucosa

The gold standard treatment for pyogenic granuloma is surgical excision with removal of local irritants [4].

Debnath et al. used a PRF membrane to treat recurrent pyogenic granuloma in a case study of a 28-year-old female. The membrane was placed on the exposed bone and sutured [53].

The findings showed complete epithelialization at a 2-week follow-up; no recurrence was noted at a 12-month follow-up [53].

Discussion

PRF seems to be a valuable biomaterial in treating oral mucosal lesions. It offers significant advantages over conventional treatment options. PRF is distinguished by its three-dimensional fibrin matrix, which forms a dense, elastic, and flexible scaffold. This matrix is formed through the polymerization of fibrinogen, which is activated during centrifugation [44]. Its autologous nature eliminates the risk of allergic reactions and minimizes the need for donor-site morbidity [43]. The result is a biocompatible, biodegradable scaffold supporting cell adhesion and proliferation. The scaffold provided by PRF aids in managing intraoral wounds where primary closure is not feasible. It reduces complications such as granulation tissue formation, bleeding, and trismus [43].

The structural integrity of PRF, combined with its ability to slowly release growth factors, provides a stable environment conducive to wound healing. The PRF matrix's elasticity, flexibility, and strength make it well-suited for handling and suturing. PRF membranes are thin yet robust enough to resist tearing, which is crucial for effective application in the dynamic environment of the oral cavity [45]. Its superior workability and tear strength improve clinical outcomes, including enhanced epithelialization and reduced post-operative complications [43].

The therapeutic benefits of PRF are primarily attributed to its rich content of growth factors and cytokines, including PDGF, VEGF, and TGF-β, which are released upon platelet activation. These growth factors are crucial in cellular growth, proliferation, and differentiation, significantly contributing to accelerated wound healing [26].

PRF's slow and sustained release of these bioactive molecules ensures prolonged stimulation of the healing process, which is advantageous for treating chronic and complex oral mucosal lesions. This contrasts with Platelet Rich Plasma (PRP) and other autologous platelet concentrates, which, despite their efficacy, often require the addition of anticoagulants or thrombin and involve more complex preparation processes. The absence of such additives in PRF preparation reduces the risk of adverse reactions and simplifies its application in clinical settings [35].

However, PRF has limitations. For instance, the preparation process needs to be fast, or the fibrin polymerizes. The size is also limited, so it can only be applied to smaller defects [43].

Conclusions and future prospects

The studies on using PRF in managing various oral mucosal lesions show several limitations that must be acknowledged. Many of the studies were conducted on small sample sizes or as individual case reports, which limits the generalizability of the results. Additionally, the follow-up periods in most studies could have been more extended, raising concerns about the long-term efficacy and potential recurrence of the lesions treated with PRF. A key limitation of some studies was focusing on using PRF membranes for post-excision wound healing rather than direct lesion treatment. Future research should evaluate the efficacy of PRF in direct application for treating lesions. The preparation and handling of PRF membranes pose challenges due to their fragility and limited bulk, restricting their application to smaller or more superficial defects. Variability in PRF preparation protocols across studies also complicates the ability to compare results and standardize treatment outcomes. Moreover, while studies have used

PRF in combination with other biomaterials like collagen matrices, some studies failed to demonstrate significant improvements in healing, highlighting the need for more robust comparative research.

Despite the limitations, PRF has shown considerable promise as a therapeutic option for oral mucosal lesions. The studies reviewed demonstrate the efficacy of PRF in promoting healing and reducing symptoms and minimal recurrence rates in most red and white oral mucosal lesions, pigmented lesions, ulcerative lesions, and even in the context of potentially malignant lesions.

PRF is biocompatible, biodegradable, and has a low risk of allergic reactions. These make PRF an emerging alternative to conventional treatments such as corticosteroids, especially for patients unresponsive to or unable to tolerate them. PRF, in comparison to corticosteroids, offers a viable and safer option, particularly for long-term use. Integrating PRF with surgical procedures has shown benefits in promoting wound healing and reducing recurrence rates. However, larger-scale, multicenter trials with standardized protocols and longer follow-up periods are essential to establish PRF as a standard treatment. These studies will help clarify the role of PRF in oral mucosal lesion management and potentially expand its applications in clinical practice.

Abbreviations

PRF	Platelet-rich fibrin
PRP	Platelet-rich plasma
A-PRF	Advanced PRF
T-PRF	Titanium-PRF
I-PRF	Injectable PRF
CGFs	Concentrated Growth Factors
CXCL7	Neutrophil-activating peptide
PF4	Platelet factor 4
SDF-1α	Factor 1— derived from stromal cells
PDGF	Platelet-derived growth factor
TGF-β1	Transforming growth factor
VEGFl	Vascular endothelial growth factor
EGF	Epidermal growth factor
HGF	Hepatocyte growth factor
OHIP-14	14-item oral health impact profile
REU	Reticular erythematous ulcerative
MPO	Myeloperoxidase
EMD	Enamel Matrix Derivative
PCM	Plasma cell mucositis

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Authors' contributions
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