Systematic Review

Platelet-rich Fibrin: A Systematic Review of Its Action

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Abstract

Purpose: We aim to conduct a literature review on actions of platelet-rich fibrin (PRF), preclinical studies in PRF utility, and its potential uses in clinical settings. **Methods:** We conducted a literature review based on primary studies conducted on PubMed and Europe PMC between 2012 and 2022. We included 42 articles in this review from the results of our search. **Results:** Epithelial tissues act as a barrier from mechanical, chemical, and temperature damage. Naturally, hemostasis acts to reduce blood loss and creates initial fibrin matrices after traumatic events or injuries. PRF is a second-generation platelet concentrate, commonly made in the form of leukocyte and PRF due to leukocyte content. Fibrin matrices in PRF allow more sustained growth factors release when compared to PRP, the first-generation platelet concentrate. PRF comes from increased proliferation and differentiation mediated by reduced proliferation of inflammatory cells and sustained release of growth factors and cytokines. **Conclusions:** PRF action comes from increased proliferation and differentiation from growth factors and cytokines. PRF may reduce inflammation and fibrosis to improve soft-tissue and bone healing and allow for better graft integration.

Keywords: Biocompatible material, biological activity, platelet-rich fibrin, tissue healing

Introduction

Epithelial tissues play a significant role as the primary barrier from mechanical, chemical, and temperature exposure. After injury, hemostasis in the form of platelet plugs functions to reduce blood loss and creates initial fibrin matrices. Inflammation and proliferation help restore tissue integrity and function.[1] It is known that inflammatory signals are mediated by damage-associated molecular patterns (released by necrotic tissues) and pathogen-associated molecular patterns (from bacteria).[2,3] Release of inflammatory cytokines helped neutrophil and monocyte adhesion and was mediated by lipopolysaccharide, interferon-γ, interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), or platelet-derived growth factor (PDGF) and activated by nuclear factor-kappa B pathway.[1,4]

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate, commonly made in the form of leukocyte- and PRF (L-PRF) owing to the high leukocyte composition. Fibrin matrices in PRF allow more sustained and prolonged release of growth factors when compared to PRP, the first-generation platelet concentrate. The PRF contains biologically important cytokines in tissue repair, including transforming growth factor (TGF)-β, PDGF, insulin-like growth factor (IGF)-1, VEGF, EGF, IL-1β, IL-6, TNF-α, and IL-4.[5,6] The PRF itself is of significant clinical interest due to simple preparation and numerous growth factors. Therefore, we aim to elucidate its action in organisms.

Methods

This narrative review focused on PRF and its role in tissue healing. Keywords used were "((platelet rich) AND (fibrin)) AND (((scar) OR (fibrosis))". The data were collected between December 12 and 15, 2022. Studies obtained ranged from 2012 to 2022, written in English, and has been peer-reviewed. The studies obtained were original researches. All searches

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were manually conducted when all authors were present and immediately reviewed based on the above criteria. In case of any disagreements of inclusion, discussion was held for the inclusion or exclusion. Assessment of bias was conducted using the Cochrane Risk of Bias tool and jointly reviewed by all authors. All syntheses of data were written as narratives. All studies were summarized and are presented in Tables 1 and 2. This study was conducted in accordance with the PRISMA algorithm as shown in the Figure 1.

Results and Discussion

We obtained 1060 hits from Europe PMC and 50 hits from PubMed. After eliminating duplicate articles, we manually screened 1106 abstracts and eliminated 1040 abstracts based on the criteria used. We attempted to retrieve 66 articles; 5 of those were unable to be obtained. Eligibility screening, where we read each paper individually, resulted in the elimination of 16 studies. The final articles to be included amounted to 45 articles. To analyze the risk of bias, we utilized Cochrane Risk of Bias tools. The results were elaborated in narrative literature review format.

Platelet-rich fibrin effect on wound healing

PRF has a positive impact on healing process after injury, evidenced with increased tissue regeneration and decreased apoptosis. In a rat tibial fracture model, PRF increased initial fracture healing (meanwhile, hyaluronic acid improved healing in all phases).[7] Comparison of inorganic bovine bone (anorganic bovine bone [ABB]), PRF, collagen membrane (CM), and its combination in tibial defect healing showed that ABB and PRF combination increased healing in a similar fashion with ABB and CM combination, but ABB and PRF combination is less costly to prepare and inherently autologous.[8] A sheep model of tibial defect showed that biphasic calcium phosphate used in conjunction with PRF resulted in increased tissue repair.[9] A rabbit tibial fracture model showed platelet-rich fibrin matrix-silver nanoparticle combination increased lamellar and Haversian canal formation in the 4th week.[10] Tibial fracture healing in a rat model was improved when PRF was used when compared with CM.[11]

In addition to tissue repair, PRF has been studied for its utility in chronic wounds. Singampalli *et al*. showed improved ulcer healing after administration of PRF due to increased and sustained release of growth factors and cytokines.[12] PRF may help prevent inflammation and scar formation in chronic ulcer when used in conjunction with negative pressure drainage.[13] Kartika *et al*. have studied advanced PRF (A-PRF) usefulness, either alone or in conjunction with HAp, in diabetic ulcer. The combination of A-PRF and HAp increased angiogenesis from VEGF and PDGF release, suppressed IL-6-associated inflammation, and increased granulation tissue formation.[14]

Platelet-rich fibrin effect on bone regeneration

In a rabbit model of dental extraction, PRF helped the regeneration of alveolar bone (although concentrated growth factor showed better result).[15] Administration of L-PRF in conjunction with low-level laser radiation in rabbit calvarial defect model increased bone regeneration.[16] In a rat model of lumbar laminectomy, increased new bone formation was observed in 5 weeks after administration of PRF. In addition, PRF prevented epidural fibrosis and reduced inflammatory cell density when compared to Adcon gel or HAp gel.[17]

Human studies showed that PRF improved alveolar bone healing after endodontic surgery. A combination of PRF and hydroxyapatite showed better results than PRF and alendronate or PRF alone.[18] Similarly, Revathy *et al*. showed increased bone regeneration after mandibular third molar extraction after PRF administration.[19] Eid *et al*.'s study showed similar effectiveness of PRF when compared to hydroxyapatite and calcium silicate-based cement for pulpotomy. Nevertheless, PRF-treated group showed a lower canal obliteration rate.[20] PRF also prevented adhesion, infection, bleeding, granulation, and osteal stenosis.[21]

Platelet-rich fibrin effect on soft-tissue healing

Another study showed that PRF improved tenocyte viability and differentiation after Achilles tendon injury in rats.[22] A study by Dietrich *et al*. also provided a similar result: PRF improved Achilles tendon healing in rats, even when compared with PRP. The improvement comes from the increased synthesis of type I collagen.[23] Chuang *et al*. compared PRF releasate (PRFr) and PRFr-stem cell combination in a rat sciatic nerve injury model and proved that showed that PRFr-stem cell combination improved nerve healing.[24]

PRF also improved dog periodontal tissue healing after debridement and mucoperiosteal flap to treat periodontitis.[25] Improvement of tympanic membrane healing after perforation in rats was observed after administration of PRF.[26] In addition to improving tissue healing, PRF prevented peritoneal adhesion after laparotomy in rats. The observed effect was thought to occur due to increased mesothelial cell proliferation and inhibition of fibroblasts and inflammatory cell proliferation and infiltrations.[27]

A study showed the benefits of PRF as a suitable alternative to CM for oral mucosal defect repair graft with lower pain level on the 15th day.[28] Dutta *et al*. also utilized PRP and PRF for third molar extraction graft, with lower pain and tissue edema, also improving soft-tissue repair. Nevertheless, bone regeneration was better in hyaluronic acid graft group.[29]

Platelet-rich fibrin effect on graft integration

Improvement of wound healing, graft integration, and reduced necroses was observed after PRF administration in a rat model of full-thickness skin graft.[30] PRF also increased stem cell differentiation on mouse periodontal ligament stem cell cultures as a model for periodontal defect graft in mice. An increase of differentiation was observed through the increased expression of *COL1A, Pn,* and *RUNX2*. Additionally, a combination of PRF and cell culture improved bone regeneration.[31]

Table 1: Summary of studies

Author(s)	Subjects	Methods	Results	Conclusions
Akyildiz *et al*. (2018)[7]	Adult SD rats as tibial bone defect model	Rats were divided into 3 groups: PRF, HAp, control. Tibial fracture was fixated with titanium plate and PRF or HAp injection was given at the site of bone defect	Total ossification area was highest in PRF, lower in HAp, and lowest in control groups in 2nd week (26.1±6.6% vs. 54.7±9.7% vs. 75.3±19.2%; $P<0.001$) and HAp was highest in the 6th week (76.3±21.7% vs. 88.8±13.3% vs. 50.7± 28.2%; $P=0.008$) Fibrosis area was lowest in PRF, higher in HAp, and highest in control in the 2nd week (73.90±6.58% vs. 45.28±9.72% vs. 24.67±19.16%; $P<0.001$) and HAp was lowest in 6th week (23.66±21.71% vs. 11.21±13.36% vs. 49.28±28.16%; $P=0.008$)	HAp improves bone healing in all phases while PRF is most effective in early phase
Li *et al*. (2022)[15]	Rabbit	PRF, PPP, or CGF was created from rabbit blood. Rabbit was randomized into PPP, CGF, PRF, or control. Bilateral tooth extraction was conducted, and ABW and ABH were evaluated through CT	There was an increase in alveolar bone resorption in each group, but the treatment group had lower resorption. The trabeculae in the CGF group returned well, while those in the PPP and PRF groups were operational. There was an increase in BMP-2 and ALP expression in the treatment group	Administration of PRF, CGF, and PPP is effective in regenerating bone, but CGF is more effective at inducing bone and tissue repair
Yuvasri and Rai (2020)[35]	Chronic venous ulcer patients	RCT comparing Unna's paste versus PRF on chronic venous ulcer	PRF reduced ulcer size (86.03±19.510% vs. 71.97±29.358%) although the difference is not significant ($P=0.223$)	PRF improved wound healing when compared to Unna's paste
Singh *et al*. (2022)[18]	Endodontic patients	RCT between PRF + HAp, and PRF + alendronate on bone healing 12 months after endodontic surgery	Improvement was observed in PRF and HAp groups, but no significant difference was observed between PRF and PRF + alendronate	PRF in in combination with HAp is an acceptable alternative for alveolar bone healing
Kornsuthisopon *et al*. (2020)[25]	Dogs with periodontitis	Alveolar bone crest was debrided, continued with mucoperiosteum flap, and PRF was given in treatment group	PRF improved periodontal parameter but not alveolar bone healing. PRF also reduced inflammation and fibrosis through suppression of TNFA and IL1B while increased expression of TIMP1, COL1A1, COL3A1, PDGFB, TGFB1, and VEGFA on the 7th and 14th days	PRF application on open flap debridement improved wound healing and suppressed inflammation
Ondur *et al*. (2020)[8]	Lambs with hard tissue defects	Randomized, crossover trial on tibial defect crossed over between anorganic bovine bone, PRF, and collagen membrane	ABB + CM and ABB + PRF showed best regeneration ($P=0.006$; $P=0.011$; $P=0.005$ on the 10th, 20th, and 40th days). No significant difference between PRF + ABB or CM + ABB ($P=0.057$; $P=0.200$; $P=0.686$ on 10th, 20th, and 40th days)	The use of ABB + PRF provides equivalent results to ABB + CM, but PRF is autologous, cheaper than CM, and easier to use
Demirel *et al*. (2018)[17]	SD rats undergoing laminectomy L3–L4	After laminectomy, Adcon gel, HAp gel, ad PRF, or PRF was administered locally. After 5 weeks, fibrosis, inflammation, hemorrhage, angiogenesis, and bone regeneration were examined	Acute inflammatory cell density, angiogenesis, bone regrowth, and hemorrhage were equal in all groups, but higher bone formation was slightly higher in PRF group. Epidural fibrosis and inflammatory cell density are significantly lower in PRF group ($P=0.048$ and $P=0.044$)	PRF improves hemostasis and prevents epidural fibrosis
Ensari *et al*. (2017)[50]	SD as model of tympanic membrane perforation	After perforation, PRF was applied and histopathological analysis was conducted	Healing time of tympanic membrane in PRF is reduced (10.3±2.18 days vs. 17±2.40 days; $P<0.001$)	PRF membrane allows for faster healing and becomes potential graft material
Revathy *et al*. (2018)[19]	25 patients (aged 18–35 years) who underwent bilateral mandibular third molar extraction	Autologous PRF was applied on one side, while the contralateral side was left as a control. Radiological examinations were carried out at the 1st, 3rd, and 6th months after surgery to see bone regeneration	The side that received PRF showed better bone healing and repair at 1, 3, and 6 months ($P=0.06$; $P<0.001$; and $P<0.001$). There was a difference in the side that received PRF after multivariate analysis ($P=0.001$)	Autologous PRF enhances and accelerates bone repair after molar extraction

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Author(s)	Subjects	Methods	Results	Conclusions
Shanei *et al*. (2022)[16]	10 rabbits with calvarial defects	A total of 10 rabbits were divided into control, L-PRF, LLLT, and L-PRF + LLLT groups. A total of 40 calvarial defects measuring 8 mm were made in each mouse, and sacrifice was carried out at the 4th and 8th weeks	New bone formation was significantly higher in the L-PRF + LLLT group (P<0.001). 1 month after the procedure, the highest fibroblasts were in the control group and the lowest were in the L-PRF + LLLT group (118.6±6.9 vs. 24.0±3.2). In the PRF group, the percentage of bone formation was significantly higher than in controls but not significant in the PRF + LLLT group (13.2±2.8 vs. 2.0±1.2 vs. 19.0±3.8)	The combination of L-PRF + LLLT proved to be the best for accelerating regeneration and reducing fibrosis
Wong *et al*. (2020)[22]	18 adult male rabbits with Achilles tendon defects	A total of 18 adult rabbit models of Achilles tendon injury were created as control, PRF (0.5 cc), and denatured PRF (0.5 cc). At the 6th week, a sacrifice was carried out for ultrasonographic and histopathological analysis	There was an increase in the number of activated platelets at the injury site in the PRF group (P<0.05). In *in vitro* studies, PRF increased cell viability and gene expression for collagen I, collagen III, tenomodulin, and tenascin compared to culture methods (P<0.05). In addition, tendon improvements were seen in the group that received PRF. Histologically, the PRF group had more organized collagen, less vascularization, and minimal cartilage formation	PRF increases tenocyte viability and tenocyte differentiation into tendons. Giving PRF to tendon defects accelerates tissue healing
Singampalli *et al*. (2022)[12]	50 patients with chronic nonhealing ulcers aged 18–60 years	Subjects were divided into a control group and a group that received PRF for 6 weeks and the percentage reduction in ulcer size was calculated	There was a significant reduction in ulcer size in the PRF group (P<0.001) and diabetes or hypertension did not affect wound healing (P=0.75; P=0.87)	Significant reduction of ulcer size caused by release of growth factors and cytokines by PRF
Salih *et al*. (2018)[10]	20 rabbits aged 6–8 months for the tibia fracture model	Rabbits were divided into control, PRFM, AgNP, and PRFM + AgNP treatment. Sacrifice was carried out at the 2nd and 4th weeks on some subjects for histology examination	The AgNP + PRFM group showed the fastest tissue repair. Additionally, the group showed lamella and Haversian canal formation at week 4	The combination of AgNPs and PRFM provides faster bone repair
Nica *et al*. (2019)[30]	40 adult Wistar rats underwent full-thickness skin graft	Mice underwent skin grafting of 3 cm × 2 cm and were divided into control and PRF. On the 21st day, the remaining wound area was calculated	Epidermal necrosis was found in all groups, but there was a difference in the percentage of necrosis which was lower in the PRF group (14.9±5.1% vs. 28.5±9.2%; P<0.01)	PDF improves wound healing and full-thickness skin graft integration in mouse models
Sari *et al*. (2021)[21]	50 subjects aged 25–59 years who underwent endoscopic procedures for sinus polyposis	A prospective randomized controlled trial with control and PRF sides. PRF is placed on one side of the cavity resulting from middle meatus ethmoidectomy and Nasopore is placed to prevent PRF leakage. Follow-up was carried out until the 12th week	At week 1, there was no significant difference. At 2 weeks, granulation was moderate and crusting was lower on the PRF side (P=0.036; P=0.038). At week 3, adhesions, crusting, and granulation were lower on the PRF side (P=0.035; P=0.031; P=0.032). At week 4, there was no significant difference except for mild granulation (P=0.045). At week 8, there was no significant difference. At week 12, the PRF side had less stenosis (P=0.041)	PRF prevents adhesions, infection, bleeding, granulation, and ostium stenosis after the procedure
Tayşi *et al*. (2016)[11]	60 adult SD rats as tibial fracture model	Division into 5 groups: Sacrifice, control, monolayer collagen membrane, bilayer collagen membrane, and PRF	Development of new bone is higher (at the 7th and 28th days) in PRF group (P<0.01). PRF group showed lower fibrosis on 7th and 28th days (P<0.01)	PRF increases bone healing versus collagen membrane
Eid *et al*. (2022)[20]	63 patients with immature permanent molars	A randomized controlled trial of PRF, CSBC, and hydroxyapatite for pulpotomy. The subjects were then observed for up to 12 months	There was no significant difference in canal obliteration at 6 months (P=0.111), but it was significantly lower in PRF (P=0.014). Apical closure was not significant at 6 and 12 months (P=0.726; P=0.817)	The three materials have equivalent effectiveness, but the PRF group has a lower level of canal obliteration so that it makes it easier when retreatment is needed

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Xue *et al*. (2022) [13]	68 subjects were patients with chronic ulcers	Patients were divided into negative pressure drainage (control) and PRF + negative pressure drainage (treatment) and observed for wound healing for 3 months	Wound healing time was lower in the treatment group (P<0.001). WBC, CRP, and IL-6 levels were lower on day 14 (P<0.001). Bacterial cultures that gave positive results were lower in the treatment group (P<0.05). The total defect rate was lower in the treatment group (5.88% vs. 29.41%, P<0.001). Scarring levels were lower in the treatment group at 1 and 3 months (P<0.001)	PRF can prevent inflammation in wounds and prevent scar formation in chronic ulcer patients
Blatt *et al*. (2022) [32]	52 patients with osteonecrosis of the mandible	Prospective noninterventional study undergoing resection and debridement with PRF or without PRF (control) and observed for up to 42 days	There was no significant difference in wound healing (P=0.302), lesion downstaging (P=0.9), reduction in pain (P=0.169), or quality-of-life (P=0.9).	PRF as an adjuvant therapy does not bring meaningful results for the healing of mandibular osteonecrosis wounds
Waldner *et al*. (2022)[33]	20 patients with burns underwent debridement	Retrospective study between 2017 and 2018 who underwent enzymatic debridement combined with PRF or fibrin glue (BroKerF)	There was no significant difference between the epithelialization of patients who received PRF or fibrin glue (17.8±8.4 days vs. 23.1±7.9 days, P=0.12)	There was no significant difference between PRF or fibrin glue for wound healing in patients who received enzymatic debridement
Wang *et al*. (2020)[27]	84 male BALB/c mice aged 4–6 weeks underwent postlaparotomy adhesion model	After undergoing adhesion creation via laparotomy, mice were treated with PRF, sodium hyaluronic acid, or control and monitored for 28 days before undergoing sacrifice for histological examination	Fibrosis and the number of fibroblasts in the group receiving PRF were significantly lower than the other groups (P<0.05) and the number of mesothelial cells was higher (P=0.001). The severity of fibrosis and the number of inflammatory cells were lower in this group (P<0.05)	PRF applied during laparotomy can prevent adhesions by increasing mesothelial cell proliferation and inhibiting the proliferation and infiltration of fibroblasts and inflammatory cells
Dietrich *et al*. (2015)[23]	Achilles tendon injury model in mice	Rat Achilles tendon injury models were administered PRP, PRF, or as a control. Quantification of type I and type III collagen was carried out after 14 and 28 days	There were no significant differences between groups. A significant difference was found in the amount of collagen in the PRP group compared to controls (P=0.01). The amount of type I collagen was found in PRF and controls (P<0.05)	PRF brings accelerated wound healing when compared with PRP in the Achilles tendon injury model
Duan *et al*. (2018)[31]	25 periodontal defect model mice divided into control, collagen, collagen + cell culture, and collagen + cell culture + PRF groups	Implanted mouse periodontal ligament stem cell culture and sacrifice were carried out on the 12th and 24th days	PRF increases stem cell differentiation which is characterized by increased expression of COL1A, Pn, and RUNX2. The combination of PRF + cell culture increases bone regeneration in periodontal defects	PRF increases periodontal ligament stem cell proliferation and differentiation *in vitro* and *in vivo*
Kartika *et al*. (2021)[14]	30 subjects with diabetic ulcers in the A-PRF+HAp, A-PRF, and control groups	Subjects received treatment according to group and wounds were observed on day 0 (baseline), day 3, day 7, and day 14. Next, the levels of VEGF, PDGF, and IL-6 were assessed	VEGF levels were significantly higher in the treatment group after day 7 (P<0.001). PDGF levels were significantly higher after day 7 (P=0.049). IL-6 levels were significantly lower after day 7 (P=0.041). Changes in granulation index were significantly different on days 3, −7, and−14 (P<0.001; P=0.004; P=0.049)	It is proven that A-PRF + HAp is better in diabetic ulcers through increasing angiogenesis and reducing inflammation. In addition, A-PRF + HAp increased granulation compared with A-PRF alone
Reksodiputro *et al*. (2021)[34]	22 patients with vocal cord paralysis who underwent injection laryngoplasty	Patients were divided into groups that received microlobular fat and microlobular fat + PRF using a randomized clinical trial. Patients were observed at week 1, week 4–6, and week 8–10	There were no significant differences in MDVP parameters (P>0.1) and maximum phonation time	There were no significant differences in MDVP and maximum phonation time parameters between the control and PRF groups

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Author(s)	Subjects	Methods	Results	Conclusions
Chuang *et al*. (2020)[24]	24 female SD rats aged 8–10 weeks with nerve injury model. Ischiadicus	Injury model nerve. Ischiadicus is made in mice and PRFr, PRFr + stem cells, stem cells, or controls are given to the lesions that have been made. Movement function was observed for 3 months and a sacrifice was carried out to see axon regeneration	The PRFr + stem cell group gave better results than the other groups. Neurological function was found significant in movement function (P<0.05)	PRFr + stem cell combination injection provides the best results for nerve repair
Bölükbaşı *et al*. (2013)[9]	6 lambs with tibial defect	Tibial defect left as control or given biphasic calcium phosphate, PRF, or both. Sacrifice occurred at 10th, 20th, and 40th days	Infiltrates were observed on the 10th day, while PRF + BCP group showed inflammatory cell infiltration on the 20th day (P=0.01). At the 40th day, PRF + BCP group has the highest new bone ratio (P<0.05)	PRF + BCP combination improved bone healing on tibial defect model
Dandekar *et al*. (2019)[36]	The patients were 20 subjects aged 20–59 years who underwent gingival recession reconstruction surgery	A randomized clinical study in patients undergoing reconstruction of Miller I and II gingival recession. Randomization of treatment (PRF membrane or chorionic membrane) was carried out for each subject	Chorionic membrane gave better results for attachment level (MD: 1.067; 95% CI: 0.42–1.70; P=0.002), recession height (MD: 1.20; 95% CI: 0.55–1.84; P=0.001), recession width (MD: −0.20; 95% CI: −0.67–0.27; P=0.39), width of keratinized gingiva (MD: 0.93; 95% CI: 0.43–1.43; P=0.001), and gingival thickness (MD: 0.09; 95% CI: 0.01–0.17; P=0.026)	Chorionic membranes have proven to be better than PRF membranes for treating gingival recession
Mahajan *et al*. (2018)[28]	30 patients from April 2015–September 2016 who will undergo lesion excision and grafting of the defect	Randomized clinical trial in patients undergoing resection of oral mucosal lesions to compare the effectiveness of PRF membranes against collagen membranes	In the PRF membrane group, pain on day 15 was significantly lower (P=0.014) without significant complications	PRF membranes are a good alternative to collagen membranes for grafts in oral mucosal defects
Kargarpour *et al*. (2020)[37]	Gingival fibroblast culture	Fibroblast cultures were exposed to PPP, C-PRF, and red blood clot for RT-qPCR and immunoassay examination	Exposure of fibroblasts to PRF and PPP resulted in increased expression of IL-11 and NADPH-oxidase 4. PPP and PRF lysates induced translocation of Smad2/3 to the nucleus and phosphorylation of Smad3. PPP and PRF are rich in active TGF-β	C-PRF and PPP have high TGF-β activity but are highly temperature sensitive
Yi *et al*. (2022)[38]	Gingival fibroblast culture in PRF matrix	A three-dimensional matrix made from i-PRF + alginate + gelatin was made. After that, fibroblast culture was carried out on the matrix created to see proliferation	The matrix degraded significantly in week 1 but persisted until week 6. It was found that PDGF-AA, -AB, -BB, VEGF, EGF, FGF, and TGF-β1 elongated from the matrix. The matrix is able to maintain fibroblast proliferation well	Matrix made from i-PRF is able to work as a biomaterial for the proliferation of gingival fibroblasts so that it can potentially function for repair of tissue defects
Dutta *et al*. (2016)[29]	40 patients who underwent third molar extraction	Patients were grouped into controls or receiving PRP, PRF, and HAp for defect repair. Patients were observed on days 3, 7, and 14. At the 1st, 2nd, and 6th months, radiological examinations were carried out	Pain, swelling scores, and soft-tissue repair index were better on days 3, 7, 14 in the groups receiving PRP and PRF compared to controls (P<0.05). Lamina dura repair, bone density, and trabeculae were lower at 1, 2, and 6 months in the groups receiving PRP and PRF (P<0.05)	PRP and PRF are better as graft raw materials compared to HAp in terms of pain relief, swelling, and soft-tissue repair. Bone regeneration was better in the group that received HAp
Espitia-Quiroz *et al*. (2022)[39]	Periodontal ligament fibroblast culture	Fibroblast culture was carried out on a HAp scaffold with PLGA and PRF to see cell proliferation and viability	The HAp group had low cell adhesion and viability, while the HAp + PLGA + collagen, HAp + PLGA + PRF, and HAp + PLGA + PRF + collagen groups had better viability although not significantly different in all treatment groups (P=0.474)	The effect of collagen on HAp + PLGA scaffolds combined with PRF increases fibroblast adhesion and proliferation and can be clinically beneficial

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Author(s)	Subjects	Methods	Results	Conclusions
Bucur *et al*. (2019)[40]	Standard human fibroblast culture (L929)	ABC and PRF were taken from human subjects. Fibroblast culture was carried out and migration triggered by PRGF and PRF was seen in real-time	Fibroblast proliferation occurred after 24 h in a dose-dependent manner. After 48 h, proliferation occurred but decreased	The migratory ability of fibroblasts is influenced by proliferation factors but not by PRF, but mediators present in blood clots can induce fibroblast proliferation
Wang *et al*. (2020)[41]	L-PRF from rabbits was taken and made into a scaffold for nerve regeneration, Schwann cell proliferation, neurotrophic factor proliferation, as well as anti-inflammatory effects induced by lipopolysaccharide from *Porphyromonas gingivalis*	The growth factor IGF-1 from L-PRF was examined using ELISA. Schwann cell culture was carried out and NGF and GDNF proliferation and secretion were examined using ELISA. Apart from that, RT-qPCR was carried out to see the mRNA expression of NGF and GDNF	The release of 70% IGF-1 occurred on days 1–14, then decreased until day 28 (P<0.001). Schwann cell proliferation was more effective using L-PRF compared to standard culture media (DMEM). The mRNA expression of GDNF and NGF in L-PRF was higher compared with DMEM (P<0.001). There was no difference in GDNF and NGF expression on days 1 and 2 (P>0.1), but there was an increase in expression on day 3 (P<0.01). The expression of IL-1β, IL-6, and TNF-α mRNA and cytokines was significantly lower when pretreated with L-PRF (P<0.05)	L-PRF can increase Schwann cell proliferation and neurotrophic factors *in vitro*, besides that it can suppress the release of inflammatory cytokines (IL-1β, IL-6, TNF-α)
Nagaraja *et al*. (2019)[42]	The blood of 10 healthy subjects was made into PRF and PRFM	The levels of platelets, leukocytes, pH, and histological characteristics of PRF and PRFM were calculated	There was no significant difference in the number of platelets and leukocytes from PRF and PRFM. There was an increase in pH in PRFM, while the pH decreased in PRF. The fibrin network is denser in PRF compared to PRFM	Fibrin matrix formation is determined by the type of preparation performed. In addition, fibrin is important for cell adhesion and proliferation in wound healing
Talebi Ardakani *et al*. (2019)[44]	HGF cultures	Damage to the integrity of HGF cultures was made and the effects of LPRF, PPRF, PRGF, and Emdogain were compared	At 48 h, the percentage of proliferation in the PPRF, Emdogain, and positive control groups was similar (P>0.05). The lowest fibroblast proliferation was in the LPRF group	There was no significant difference between PRGF, PPRF, and Emdogain in fibroblast proliferation and wound healing *in vitro*
Göral *et al*. (2016)[47]	Chopped cartilage from the ears of 9 rabbits	Chopped cartilage from rabbits was divided into control groups, encased in PRF, cellulose, or fascia. The specimen was implanted subcutaneously on the rabbit's back and the sacrifice was carried out at 2 months for histopathological examination	PRF-encapsulated cartilage had better viability than cellulose (P<0.05). There were no differences in inflammation, fibrosis, or vascularization	PRF increases the viability of chopped cartilage grafts and can be considered as a wrapping material for cartilage grafts
Yu *et al*.(2020)[48]	5 mice per group received fat grafts	The treatment group received fat graft + PRF, while the control group only received fat graft. Animals were observed from weeks 1 to 4, and cytokine levels were assessed along with histological examination	The PRF group had better volume and weight retention, increased expression of VEGF-A and PPAR-γ, lower expression of COL1-A1 and BAX, higher vascular density, lower fibrosis, and more viable adipocytes	PRF increases the autocrine function of fat tissue grafts to produce growth factors thereby increasing fat retention through increasing vascularization, adipocyte differentiation, inhibiting apoptosis, and suppressing collagen production

Contd...

Table 1: Contd...

Author(s)	Subjects	Methods	Results	Conclusions
Wang *et al*. (2019)[43]	Mesenchymal stem cell culture from rabbit bone marrow	PRF, L-PRF, and bone marrow from rabbits were taken. Bone marrow culture was carried out and growth factors, proliferation ability, and differentiation were measured	L-PRF releases growth factors that support proliferation and differentiation *in vitro*. The combination of L-PRF and stem cell fragments enabled bone tissue regeneration *in vivo* without significant differences between PRF and L-PRF (P=0.24)	The combination of L-PRF and stem cells can be useful in creating artificial bone tissue
Xu *et al*. (2016)[45]	Human breast adipose tissue stem cells, 20 mice	Scaffolds were made from collagen and some groups were added with Ginsenoside Rg1, PRF, or both. Stem cell culture was carried out and the effects of ginsenoside Rg1 and PRF extract were observed. Next, the cell culture was implanted in mice to observe its effect on cell growth	The group that received ginsenoside Rg1 and PRF were higher than controls (P<0.001). The combination of ginsenoside Rg1 and PRF increased adipogenesis significantly (P<0.01). At implantation, small vessel density was significantly greater in the treatment group (P<0.01). In addition, the expression of PPARγ, HIF-1α, and VEGF increased in the treatment group (P=0.01)	Stem cells placed on scaffolds containing ginsenoside Rg1 or PRF had better neovascularization and adipogenesis than controls
Bayer *et al*. (2020)[46]	Human keratinocyte culture	Human keratinocyte culture was carried out using PRF and PRGF. Next, RNA sequencing, RT-PCR, and ELISA were carried out for TGFβ1, FN1, MMP9, TGM2, FERMT1, COL1A1, and COL22A1. ELISA is carried out to see the protein expression of the gene in question	There was an increase in the expression of the factors studied as an effect of PRGF through EGFR blockade	*In vitro*, it is suspected that the tissue repair observed through administration of PRF occurs due to the effects of PRGF

PRF: Platelet-rich fibrin, PRFM: PRF matrix, HAp: Hydroxyapatite, PPP: Platelet-poor plasma, CGF: Concentrated growth factor, ABH: Alveolar bone height, ABW: Alveolar bone width, CT: Computed tomography, RCT: Randomized controlled trial, LLLT: Low-level diode laser radiation, L-PRF: Leukocyte- and PRF, AgNP: Silver nanoparticle, CSBC: Calcium silicate-based cement, PRFr: PRF releasate, RT-qPCR: Reverse transcription-quantitative polymerase chain reaction, C-PRF: Concentrated PRF, PRP: Platelet-rich plasma, ABC: Alveolar blood clot, CGF: Concentrated growth factor, ALP: Alkaline phosphatase, WBC: White blood cell, CRP: C-reactive protein, MD: Mean difference, CI: Confidence interval, CM: Collagen membrane, ABB: Anorganic bovine bone, A-PRF: Advanced PRF, DMEM: Dubelco's modified eagle medium, ELISA: Enzyme-linked immunoassay, PLGA: Poly(lactic-co-glycolic acid), SD: Sprague-dawley

Is platelet-rich fibrin as good as it is?

Although majority of studies showed beneficial effects of PRF, Blatt *et al*. showed that PRF did not bring the expected result after mandibular osteonecrosis debridement.[32] Similarly, Waldner *et al*. showed that PRF had a similar performance with fibrin glue (BrokerF) for enzymatic debridement after burn injury.[33] Reksodiputro *et al*. have utilized PRF in injection laryngoplasty after vocal cord paralysis, but the result showed no significant differences in MDVP and maximum phonation time with microlobular fat use only ($P > 0.1$).[34] A comparison of PRF with *Unna's paste* for chronic venous ulcer showed no significant differences after 3 weeks of treatment.[35] Further, Dandekar *et al*. (2019) showed poorer outcomes of PRF in comparison to chorionic membrane when used in gingival reconstruction.[36]

Action of platelet-rich fibrin is mediated by balance of inflammation and proliferation

As a biomaterial, concentrated PRF has been studied *in vitro* to measure sustained TGF-β activity in gingival fibroblasts culture. Kargarpour *et al*. in 2020 proved induction of Smad2/3 translocation and Smad3 phosphorylation in PRF-treated culture. In addition, PRF improved IL-11 and NADPH-oxidase 4 expression.[37] Yi *et al*. studied a combination of PRF, alginate, and gelatin as a scaffold for gingival fibroblast culture. Marked degradation of scaffold was observed in the first week, but matrices held up until the 6th week. PRF matrices nevertheless showed prolonged and sustained release of PDGF, VEGF, EGF, fibroblast growth factor, and TGF-β1, sustaining fibroblast proliferation.[38] Espitia-Quiroz *et al*. in 2022 showed improved fibroblast adhesion and proliferation in cellular culture when PLG-hydroxyapatite scaffold was used in conjunction with PRF.[39] Bucur *et al*. (2019) observed PRF effect on fibroblast L929 cell culture. Fibroblast migration was not related to PRF administration, but alveolar blood clots induced fibroblast proliferation and migration by PRGF.[40]

Wang *et al*. in 2020 proved that L-PRF increased Schwann cell proliferation *in vitro* due to increased secretion of neurotrophic factors (IGF-1, glial cell-derived neurotrophic factor, and nerve growth factor) and reduction of inflammatory cytokine (IL-1β, IL-6, and TNF-α) secretion.[41] Nagaraja *et al*. in 2019 used A-PRF and L-PRF in HGF, showing PRF ability to improve HGF viability and migration in the first 48 h in comparison to standard culture medium.[42] The use of L-PRF and PRF in rabbit mesenchymal stem cell culture has been studied by Wang *et al*. in 2019 with positive result. The L-PRF and PRF improved the release of growth factors necessary for proliferation and differentiation, and the combination of

Table 2: Risk of bias assessment

Author (s)	1. Randomization	2. Deviations	3. Missing outcomes	4. Measurements of outcomes	5. Selections of results	Overall bias
Akyildiz *et al*.[7]	Low	Low	Low	Low	Low	Low
Ondur *et al*.[8]	Some concerns	Low	Low	Low	Low	Some concerns
Bölükbaşı *et al*.[9]	Some concerns	Low	Low	Low	Low	Some concerns
Salih *et al*.[10]	Low	Low	Low	Low	Low	Low
Tayşi *et al*.[11]	Some concerns	Low	Low	Low	Low	Some concerns
Li *et al*.[15]	Low	Low	Low	Low	Low	Low
Shanei *et al*.[16]	Low	Low	Low	Low	Low	Low
Demirel *et al*.[17]	Low	Low	Low	Low	Low	Low
Wong *et al*.[22]	Some concerns	Low	Low	Low	Low	Some concerns
Dietrich *et al*.[23]	Low	Low	Low	Low	Low	Low
Chuang *et al*.[24]	Low	Low	Low	Low	Low	Low
Kornsuthisopon *et al*.[25]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Ensari *et al*.[50]	Low	Low	Low	Low	Low	Low
Wang *et al*.[27]	Low	Low	Low	Low	Low	Low
Nica *et al*.[30]	Low	Low	Low	Low	Low	Low
Duan *et al*.[31]	Low	Low	Low	Low	Low	Low
Singh *et al*.[20]	Low	Low	Low	Low	Low	Low
Revathy *et al*.[21]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Eid *et al*.[22]	Low	Low	Low	Low	Low	Low
Sari *et al*.[23]	Low	Low	Low	Low	Low	Low
Mahajan *et al*.[28]	Low	Low	Low	Low	Low	Low
Dutta *et al*.[29]	Low	Low	Low	Low	Low	Low
Singampalli *et al*.[11]	Low	Low	Low	Low	Some concerns	Some concerns
Xue *et al*.[13]	Low	Low	Low	Some concerns	Low	Some concerns
Kartika *et al*.[14]	Low	Some concerns	Low	Low	Low	Some concerns
Blatt *et al*.[32]	Low	Low	Low	Low	Low	Low
Waldner *et al*.[33]	Low	Low	Low	Low	Low	Low
Reksodiputro *et al*.[34]	Low	Low	Low	Some concerns	Low	Some concerns
Yuvasri and Rai[35]	Low	Low	Low	Low	Low	Low
Dandekar *et al*.[36]	Low	Low	Low	Low	Low	Low
Kargarpour *et al*.[37]	Low	Low	Low	Low	Low	Low
Yi *et al*.[38]	Low	Low	Low	Low	Low	Low
Espitia-Quiroz *et al*.[39]	Low	Low	Low	Low	Low	Low
Bucur *et al*.[40]	Low	Low	Low	Low	Low	Low
Wang *et al*.[41]	Low	Low	Low	Low	Low	Low
Nagaraja *et al*.[42]	Low	Low	Low	Low	Low	Low
Wang *et al*.[27]	Low	Low	Low	Low	Low	Low
Talebi Ardakani *et al*.[44]	Low	Low	Low	Low	Low	Low
Xu *et al*.[45]	Some concerns	Low	Low	Low	Low	Some concerns
Bayer *et al*.[46]	Low	Low	Low	Low	Low	Low
Göral *et al*.[47]	Low	Low	Low	Low	Low	Low
Yu *et al*.[48]	Low	Low	Low	Low	Low	Low
Wang *et al*.[43]	Low	Low	Low	Low	Low	Low

L-PRF and stem cells improved bone regeneration, showing further promise in artificial tissue engineering.[43] Meanwhile, Talebi Ardakani *et al*. compared L-PRF, P-PRF, PRGF, and Emdogain for HGF culture but found no significant difference in fibroblast proliferation.[44]

The use of PRF in xenograft of human adipose stem cell culture has been studied by Xu *et al*. in 2016. Scaffolding of stem cells in ginsenoside Rg1 or PRF matrices improved neovascularization and adipogenesis when compared to negative control.[45] Similarly, Bayer *et al*. cultured human keratinocytes and showed increased *TGFβ1*, *FN1*, *MMP9*, *TGM2*, *FERMT1*, *COL1A1*, and *COL22A1* expression. The effect of PRF came from PRGF action to block EGFR, thus improving tissue repair.[46]

Göral *et al*. (2016) utilized PRF, cellulose, and fascia for grafting rabbit diced cartilage. Diced cartilage survived better in PRF than cellulose, with no marked difference in inflammation, fibrosis, or vascularization.[47] Yu *et al*. used PRF

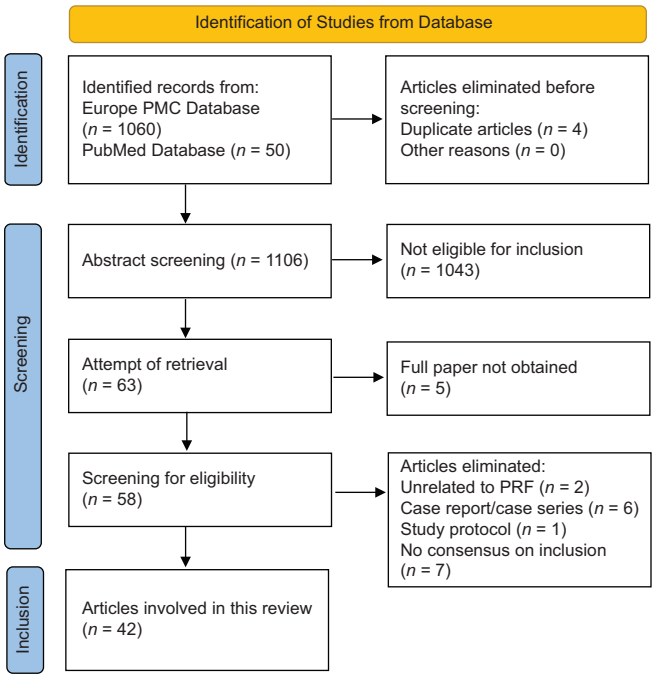

Figure 1: PRISMA flow diagram[49]

as an adjuvant for rat fat graft, showing that PRF improved graft autocrine function to secrete VEGF-A and PPAR-γ. The use of PRF juga reduced apoptosis via decreased expression of COL1-A1 and BAX.[48]

This study is limited with lack of homogeneity between studies preventing us to commit meta-analyses. Furthermore, limited full publications available to obtain reduced available publications to review. Additional studies are required to better understand the implications of PRF applications.

Conclusions

PRF action probably comes from increased proliferation and differentiation due to the effect of growth factors and cytokines. PRF may also reduce inflammatory cell proliferation and associated inflammation and fibrosis by inhibition of fibroblast. Through balancing proinflammatory activity and enhancing proliferation and differentiation, PRF may improve tissue healing, graft integration, and bone repair. Although majority of the studies yielded positive results, some contradictory studies exist. Further researches are still needed to better elucidate the impact of PRF on inflammation and tissue healing, particularly in clinical settings to improve tissue healing after injury.

Author contribution

PZ conceptualized the study, reviewed all publications, and prepared the main manuscript. IS reviewed all publications, prepared algorithm for searches, and reviewed the manuscript. KM reviewed all publications, prepared risk of bias assessment, and reviewed the manuscript. IAL reviewed all publications and reviewed the manuscript.

Ethics approval

Ethical exemption has been obtained from Sriwijaya University Faculty of Medicine Institutional Review Board (No. 011-2023), approved on January 12, 2024.

Data availability statement

All relevant publications have been provided in this review.

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Conflicts of interest

There are no conflicts of interest.

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