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Current Variants and Latest Trends in PRF : A Systematic Review

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Abstract

Platelet rich fibrin (PRF) a platelet concentrate consisting of a fibrin matrix polymerized in a tetra molecular structure, with incorporation of platelets, leucocytes, cytokines, and circulating stem cells, is known currently for its favourable results in healing. Enormous research is carried out using PRF to assess various aspects such as chemical, mechanical, physical, histological, etc., with alterations in centrifugation protocols, additive factors, medium or chemicals during centrifugation to obtain adjunctive and desirable results for periodontal regeneration. This review aimed to study and describe the current variants and latest advancements of PRF by assessing available literature on PRF. An electronic databases of MEDLINE (PubMed) and Cochrane Database of Systematic Reviews were searched based on few inclusion criteria and exclusion criteria: relevant articles from 2000 till march 2023 were considered. Two reviewers independently screened the titles and abstracts of the search results. Only studies that fulfilled the criteria were further assessed to synthesize the results. 24 articles in total that fulfilled the criteria is mentioned in this article with differing properties obtained, use in different periodontal surgeries, altered centrifugation protocols, the results obtained, etc. This review provides insight into current advances, trends, protocols, techniques, procedures for use of PRF in periodontics. With enormous literature and varied studies on PRF, a vast and promising scope in the future for PRF and its concentrates for its application in field of periodontics is seen by altering few protocols of PRF preparation.

Keywords: Platelet-rich fibrin, Growth factors, Platelet concentrates, Wound healing, Regeneration

Introduction

Periodontal disease (PD) is a common inflammatory oral diseases affecting gingival, cementum, alveolar bone and the teeth. Many techniques are aimed to combat and eliminate this disease and its infectious sources, reducing inflammation to arrest disease progression, which cannot achieve the regeneration of lost periodontal tissues. Over the past few decades, various regenerative periodontal therapies, such as guided tissue regeneration (GTR), enamel matrix derivative, bone grafts, growth factor delivery, blood products and the combination of cells and growth factors with matrix-based scaffolds have been developed to target the restoration of lost tooth-supporting tissues. One such material is Platelet rich fibrin (PRF)[1].

PRF consists of a fibrin matrix polymerized in a tetra molecular structure, with incorporation of platelets, leucocytes, cytokines, and circulating stem cells and is a platelet concentrate containing all the constituents of a blood sample which are favourable to healing and immunity obtained from centrifuged blood without any addition. PRF in the form of a platelet gel can be used in conjunction with bone grafts, which has several advantages, such as promoting wound healing, release of growth factors for bone growth and maturation, wound sealing and haemostasis, and imparting better handling properties to graft materials. It can also be used as a membrane[2].

Although PRF has gained tremendous momentum in recent years as natural blood derived growth factor, enormous research is still in process to obtain different desired properties from PRF in various aspects such as chemical, mechanical, physical, histological, etc. Studies are been carried out by altering its centrifugation protocols, adding other factors, medium or chemicals during centrifugation to obtain adjunctive and desirable results for periodontal regeneration[3]. There exists a great variability in the available literature and protocols on PRF.

Aims and objective

Hence this review article aimed to study and describe the current variants and latest advancements of PRF by assessing available literature on PRF.

Methodology

The electronic databases of MEDLINE (PubMed) and Cochrane Database of Systematic Reviews were searched based on few inclusion criteria discussed below:

1) Relevant articles from 2000 till march 2023;
2) Articles in the English language with full-text digital copies were considered;
3) Search strategy used a combination of the following keywords: “PRF”, “RECENT ADVANCES PRF;
4) Only periodontal literature and articles.

Two reviewers independently screened the titles and abstracts of the search results.

The exclusion criteria:

1) Duplicate articles/ articles repeated;
2) Articles published in other fields such as those from medical literature, oral surgery literature, etc;
3) Articles published before January, 2000;

Only studies that fulfilled the criteria were further assessed to synthesize the results.

Results

After considering the inclusion and exclusion criteria following results were obtained. A comprehensive computer-based search combined the following databases into one search with 24 articles in Pubmed, 0 in Cochrane Database of Systematic Reviews were considered and obtained from a total of 5,186 results in Pubmed , 3 in Cochrane Database of Systematic Reviews .

Figure 1 shows the selection criteria of literature that followed this process.

Table 1 shows the details of the search conducted.

Discussion

The platelet-rich fibrin (PRF) of Choukroun *et al*.[1] is a new step in the therapeutic concept of platelet gel that does not require anticoagulants, thrombin, or any other gelling agent, which makes it no longer than natural blood centrifuged without additives[28,29]. PRF is a second generation platelet concentrate from about four generation of platelet concentration known so far.

The history of PRF evolves around 1970 where first generation platelet concentrate known as PRP (Platelet Rich Plasma) was introduced along with fibrin glue. It was then followed by proposal of second generation platelet concentrate known as PRF (Platelet Rich Fibrin) by **Dr. Joseph Choukron et al, 2001**[31]. Later, A-PRF (Advanced PRF) by **Ghannati,2014**;[32] A-PRF+ by Fujioka-Kobayashi et al.,2016[33], t-PRF (Titanium PRF) by **Tunali et al, 2014**[34];i-PRF (Injectable PRF) by **Mourao et al, 2015**[35] (**figure 2**); PRF lysates and CGF constituted the third generation. The fourth generation focus research on tissue engineering triangle with addition of stem cells. "Platelet-fibrinogen-thrombin mixtures" or "gelatin platelet – gel foam" are various names for the same proposed during 1975-79, no longer used now. The choice of form of PRF to be used is based on its clinical requirement, duration, ergonomics and its availability and its operability[30]. It was found that C-PRF collected specifically from the buffy coat layer following higher centrifugation protocols exhibited an up to a threefold increase in growth factor release when compared with that exhibited by standard i-PRF. This significantly promoted higher gingival fibroblast migration, proliferation, gene expression, and collagen I synthesis[4].

Due to the ability for the clinician to rapidly collect peripheral blood and concentrate blood-derived growth factors following centrifugation, platelet concentrates have long been considered a low-cost and easy-to-obtain source of natural growth factors with continued ongoing research. Numerous factors are known to affect fibrin clot formation and structure include genetic , acquired factors (such as abnormal concentration of thrombin and factor XIII in plasma, blood flow, oxidative stress, platelet activation, hyperglycemia, medications, and cigarette smoking), and other parameters (such as temperature, pH ,microgravity, reducing agents, concentration of chloride and calcium ions, etc) [1].

Advanced Platelet-Rich Fibrin (A-PRF+), Leukocyte Platelet-Rich Fibrin (L-PRF), and injectable Platelet-Rich Fibrin (i-PRF) when compared invitro was interpreted to have capacity to increase the osteogenic potential of osteoblast-like cells. A-PRF+ seems to have the highest potential for mineralization, while i-PRF seems to have the potential to enhance early cell differentiation. A-PRF+ and i-PRF could inhibit the growth of Aggregatibacter actinomycetemcomitans, more by i-PRF in chronic periodontitis patients. All plasma preparations inhibited *Aa* growth in the first 12 h after application, and i-PRF exhibited a significantly greater antimicrobial effect than A-PRF + at each time point[20]. Results from the previous studies have also shown that T-PRF contained the maximum tensile strength (404.61 ± 5.92 MPa) and modulus of elasticity (151.9 ± 6.92 MPa) however, A-PRF is the most favourable form of platelet concentrate in regenerative periodontal therapy as it has a sustained release of growth factors over time [15].

PRF is a known periodontal treatment entity in various procedures that includes periodontal regeneration[1], guided alveolar bone regeneration[21], ridge (bone)

augmentation before implant placement sinus augmentation[26,] Miller's class I and II gingival recession defects/ root coverage procedures [22,24,27], sinus augmentation[9], etc. Also recent studies have recommended the use of PRF membranes for the treatment of gingival recession as an alternative to SCTGs[27]. Results obtained from few studies showed that the successful clinical and radiographic results using A-PRF and i-PRF can be beneficial for bone augmentation of the alveolar ridge before implant placement. CAF is a predictable treatment for isolated Miller's class I and II recession defects[26]. The addition of PRF membrane with CAF provides superior root coverage with additional benefits of gain in CAL and WKG at 6 months postoperatively[27]. Studies have also shown that Polycaprolactone/Keratin/0.5Platelet-rich fibrin (PCL/Kr/PRF) fibrous scaffold fabricated through electrospinning process could be used for wound healing and skin regeneration and hence may be considered as wound dressing agent[7].

Differing and conflicting results were also seen where no significant differences was seen The presence or absence of A-PRF showed in gingival fibroblast cells and osteosarcoma cells adhesion when PRF was compared with alloderm and mucograft membranes[6].

The highest reported growth factor released from platelet concentrates was PDGF-AA followed by PDGF-BB, TGFB1, VEGF, and PDGF-AB. After 15–60 min incubation, PRP released significantly higher growth factors when compared to PRF and A-PRF, however A-PRF released the highest total growth factors and protein at later time points up to 10 days[12]. Also studies have been performed using variations and different protocols to obtain PRF and showed that PRF clots obtained by utilizing the low-speed centrifugation speeds (~ 200 g for 8 min) produce clots that contained a higher concentration of evenly distributed platelets, secreted higher concentrations of growth factors over 10 day period and were smaller in size, irrespective of the centrifugation device utilized, whereas in silica-coated tubes platelet distribution was commonly more diffusive than in glass tubes. Interestingly, compared to centrifugation devices utilized, the centrifugation tubes used had a much greater impact on the final size outcome of PRF clots. It was found that the process for PRF tubes produced significantly greater-sized clots when compared to other commercially available tubes. The Salvin Dental tubes also produced significantly greater PRF clots when compared to the IntraLock tubes on each of the tested centrifugation devices[3]. Therefore, both blood-collection tube types and centrifugal conditions appeared to influence platelet distribution in the PRF matrix. However, better growth factor retention and release was contributed by platelets distributed in the deep regions of the PRF matrix[3]. Protocols of greater than 8 min at 400g led to no leukocyte accumulation in the upper PRF layers (found specifically within the buffy coat). Protocols at or below 200g were unable to effectively accumulate platelets/leukocytes. The optimal centrifugation speed and time for solid-PRF ranged between 400 and 700g for 8 min. Within the investigated ranges, a protocol of 700g for 8 min presented the highest yield of platelets/leukocytes evenly distributed throughout the upper PRF layers[17].

One study demonstrated that cooling of liquid-PRF is able to extend the working properties by over 90 min and may represent as a useful clinical strategy[16]. Recently, evaluation of the centrifugation angle revealed greater entrapment of large cells, such as red blood cells, when centrifugation was changed from a fixed to a horizontal angle[16]. Also a study revealed that the

presence of fibrin nano-fiber structures as a constituent can provide a good substrate for cell attachments[19].

With such heterogeneity present in literature pertaining to PRF and its actions, more studies should be focused to set a standard protocol to obtain a desired uniform result. More studies should be promoted and carried out to find the best results of PRF in the field of periodontics.

Conclusion

With enormous literature and varied studies on PRF, research is still ongoing to find advances in PRF. However, a vast and promising scope in the future for PRF and its concentrates for its application in field of periodontics is still seen. Future research should be focused on incorporating various advances such as laser, stem cell therapy, nanotechnology, robotics, artificial intelliegence etc with PRF concentrates and examining its property. A universally accepted and uniform PRF concentrate that serves as the miracle drug for periodontal regenerative procedure can hence be obtained.

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Legend Tables and Figures

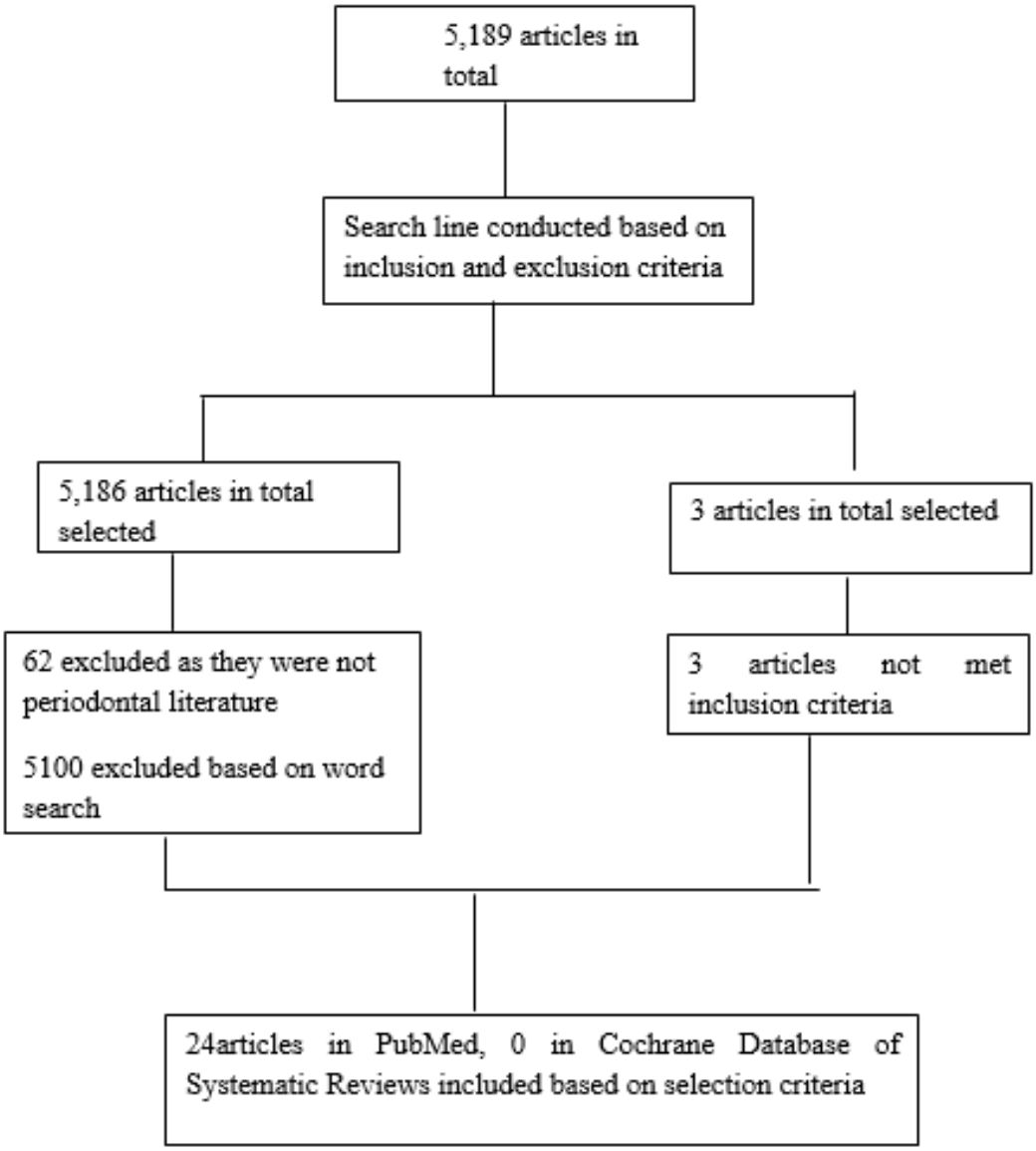

Figure 1: Selection process PRISMA flow chart

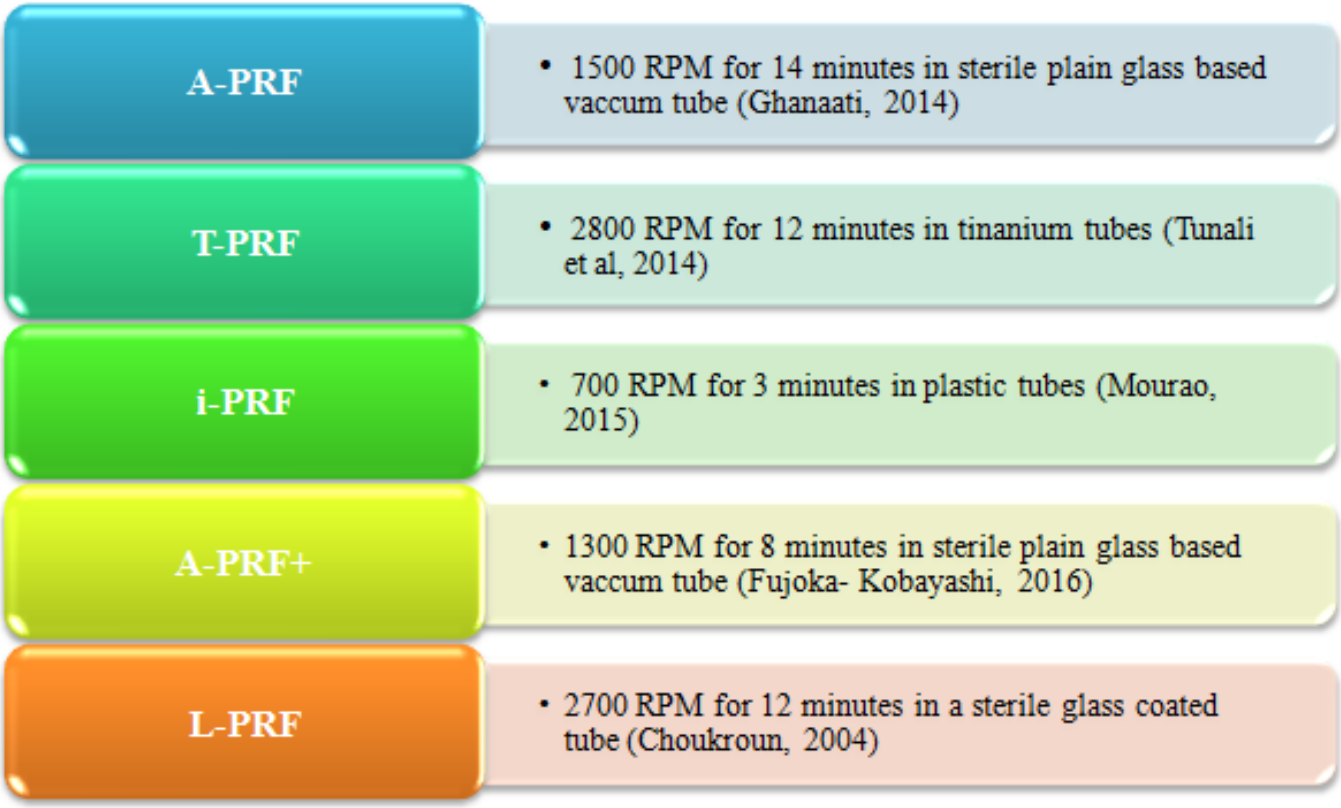

Figure 2: Various forms of platelet rich fibrin and its protocol

Sn.	Author	Title	Objective	Methodology	Results	Conclusion
1	Dos Santos RF et al, 2023.[18]	Advances in separation methods for the use of platelet-rich fibrin in tissue repair: an integrative review	This study sought to perform an integrative literature review to compile the available data on different protocols for generating plasma preparations and their	A descriptive research method was adopted for assessing the literature on processes for obtaining PRF, and articles indexed in the MEDLINE database were searched.	plasma preparations originating from the centrifugation of blood samples, such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF), have proven useful for the treatment of gingival recession due to their rich concentration of cells and cytokines fundamental in the mechanisms of both soft tissue and hard tissue repair.	The evolution in protocols has resulted in various forms of PRF with different components: (1) a membrane that aggregates platelets and leukocytes (L-PRF); (2) a PRF rich in growth factors and cytokines, known as advanced PRF (A-PRF); (3) a liquid phase called injectable PRF (I-PRF) that shows greater cell accumulation than L-PRF; (4) A-PRF plus (A-PDF+), which improved the release of

			indications, benefits, and results.		The literature review showed that changes in the PRF protocols for obtaining blood concentrates have led to better isolation of cells and growth factors and more promising results in tissue repair.	growth factors for a period of 10 days; and (5) concentrated PRF (C-PRF) obtained by progressive pipetting, which has the greatest cell accumulation among all of the types of platelet aggregates. Subsequently, the observation that the speed of centrifugation influenced the acquisition of specific cells resulted in the development of the low-speed centrifugation concept. Then, it was determined that reduction of the relative centrifugation forces significantly increased the number of platelets, leukocytes, and growth factors. Recently, evaluation of the centrifugation angle revealed greater entrapment of large cells, such as red blood cells, when centrifugation was changed from a fixed to a horizontal angle. Tissue bioengineering studies are allowing for significant advances in the process of obtaining blood components and enabling

						their use for tissue repair with greater predictability and less morbidity.
2	Kosmidis K et al, 2023 [20]	An in vitro study into three different PRF preparations for osteogenesis potential.	To investigate the effect of Advanced Platelet-Rich Fibrin (A-PRF+), Leukocyte Platelet-Rich Fibrin (L-PRF), and injectable Platelet-Rich Fibrin (i-PRF) on osteogenesis of a human osteoblast-like cell line in vitro.	A-PRF+, L-PRF, and i-PRF were prepared from six male donors and pre-cultured with 10 mL culture medium for 6 days. 5 x 10^3 cells/ml osteoblasts from the osteoblast cell line (U2OS) were seeded and cultured either with conditioned medium derived from the different PRF conditions or with regular culture medium. At five different time points (0, 7, 14, 21, 28 days), the osteogenic capacity of the cells was assessed with Alizarin Red S to visualize mineralization. Also in these cells, the calcium concentration and alkaline phosphatase activity were investigated. Using qPCR, the expression of alkaline phosphatase,	In osteoblast-like cells cultured with conditioned medium, the A-PRF+ conditioned medium induced more mineralization and calcium production after 28 days of culturing compared with the control ($p < .05$). No significant differences were found in the extent of cell proliferation between the different conditions. RUNX-2 and osteonectin mRNA expression in the cells were lower in all PRF-stimulated cultures compared with control at different time points. The i-PRF-conditioned medium induced more ALP activity ($p < .05$) compared with control and osteoblasts-like cells differentiated more compared with	The three PRF preparations seem to have the capacity to increase the osteogenic potential of osteoblast-like cells. A-PRF+ seems to have the highest potential for mineralization, while i-PRF seems to have the potential to enhance early cell differentiation.

				osteocalcin, osteonectin, ICAM-1, RUNX-2, and collagen 1a was assessed.	osteoblasts cultured with L-PRF.	
3	Pham TAVet al, 2023.[23]	Antimicrobial effect against *Aggregatibacter actinomycetemcomitans* of advanced and injectable platelet-rich fibrin from patients with periodontal diseases versus periodontally healthy subjects.	. This study aimed to compare the antimicrobial effects of these PRF materials against the periodontal pathogenic bacterium *Aggregatibacter actinomycetemcomitans* (*Aa*) in patients with different periodontal conditions.	Blood samples were collected from periodontally healthy individuals, patients with gingivitis, or patients with periodontitis to prepare A-PRF+ and i-PRF. The antibacterial capacity of these materials was evaluated through antibiofilm formation, biofilm susceptibility, and the time-kill assay over a 48-h period.	A-PRF+ and i-PRF from each patient groups interfered with *Aa*'s ability to form biofilm on the test tube surface, and the effect of i-PRF was significantly different among the patient groups. In contrast, these plasma preparation had a weak impact on mature biofilm. For products from the gingivitis and periodontitis groups, these effects were significantly stronger for i-PRF than A-PRF+ . All plasma preparations inhibited *Aa* growth in the first 12 h after application, and i-PRF exhibited a significantly greater antimicrobial effect than A-PRF + at each time point.	A-PRF+ and i-PRF in all three patient groups could inhibit the growth of Aa *in vitro*, and i-PRF from patients with periodontitis exhibited a more significant effect than PRF from the other groups.
4	Miron	Extending	first aim of	In total, 30	The findings from	Cooling of blood

	RJ et al, 2022.[16]	the working properties of liquid platelet-rich fibrin using chemically modified PET tubes and the Bio-Cool device	the present study was to investigate the liquid consistency of liquid-PRF utilizing both standard and chemically modified PET plastic tubes. This study also investigated for the first time the use of a cooling device (Bio-Cool) to extend the liquid working properties of liquid-PRF.	participants enrolled in this study. From each patient, four tubes of liquid-PRF were drawn, two standard white Vacuette tubes and two blue chemically modified hydrophobic tubes. Following centrifugation at 700 RCF-max for 8 min in a Bio-PRF horizontal centrifuge, one white and one blue tube were kept upright at room temperature, while the other white and blue tube were placed within the cooling device. Thereafter, the liquid-PRF layers were monitored over time until clotting occurred. Patient gender, age, and altitude above sea level (+ 5000 ft) were recorded and compared for clotting times.	the present study demonstrated that the chemically modified PET tubes performed 37% better than the control tubes (extended the working properties of liquid-PRF by over 20 min). Most surprisingly, tubes kept in the cooling device demonstrated an average of 90 min greater working time (270% improvement). While patients living at altitude did significantly improve the clotting ability of liquid-PRF, no differences were observed when comparing male vs female or younger vs older patients in liquid-PRF clotting times.	following centrifugation represented a 270% improvement in working properties of liquid-PRF. Optimization of liquid-PRF tubes utilizing chemically modified hydrophobic PET tubes also delayed the clotting process by 37%. Patient gender and age had little relevance on liquid-PRF. **Clinical relevance:** The present findings demonstrate for the first time that cooling of liquid-PRF is able to extend the working properties of liquid-PRF by over 90 min. Thus for clinicians performing longer clinical procedures, the cooling of blood may represent a viable strategy to improve the working time of liquid-PRF in clinical practice.
5	Mirhaj M et al,	Platelet rich fibrin containin	to evaluate the wound healing	A range of techniques were utilized to fully characterize the	by the addition of only 0.5%w/v PRF to PCL/Kr sample, the	Overall, the data presented in this study greatly suggest that the

	2022.[7]	g nanofibrous dressing for wound healing application: Fabrication, characterization and biological evaluations	process using Polycaprolactone/Keratin/Platelet-rich fibrin (PCL/Kr/PRF) fibrous scaffold fabricated through electrospinning process.	chemical, physical and biological properties of the resultant structure.	fibers diameter decreased from 193.93 ± 64.80 nm to 65.98 ± 14.03 nm, and the stress at break demonstrated a 18.27% increase in comparison to the PCL sample. The PCL/Kr/0.5PRF scaffold showed more antibacterial activity against gram-positive and gram-negative bacteria than PCL/Kr sample. Based on enzyme-linked immunosorbent assays, the PCL/Kr/0.5PRF sample revealed an independent release of VEGF and PDGF for 7 days. Cell viability studies demonstrated non-cytotoxic nature of PRF-containing dressings. Also, chorioallantoic membrane (CAM) assay was performed to evaluate the angiogenic potential of the wound	PCL/Kr/0.5PRF wound dressing could be a suitable candidate for wound healing and skin regeneration.

					dressings. The in vivo assessments also showed that PCL/Kr/0.5PRF accelerated the wound healing process in terms of collagen deposition and the formation of skin appendages which was comparable to the normal skin.	
6	Haripr asad R et al, 2021.[8]	Assessme nt of Growth Factors with Three Different Platelet Preparatio ns, Namely Platelet-Rich Fibrin, Platelet-Rich Plasma, and Lyophiliz ed Platelet: An *In vitro* Stud	at investigati ng the levels of growth factors in three different platelet preparation s namely platelet rich plasma (PRP), platelet rich fibrin (PRF) and lyophilized platelets.	Autologous blood for preparing the platelet preparations was obtained from healthy donors aged between 25 to 35 years. The samples were then divided into three experimental groups. The preparation of PRP was done with the addition of anticoagulant and the PRF is prepared without adding it. The platelet counts in the blood were analyzed and the growth factors were quantitatively measured using ELISA reader. The statistical analysis	Results In the quantitative analysis of growth factors LPL showed significant increase of the liberation of growth factors compared to PRP and PRF.	With the various recent advances in technologies for preparing these platelet concentrates this can be widely used in clinical practice more accurate in the future.

		y		was performed by using the Chi square test.		
7	Pavlovic V, Ciric M et al, 2021.[14]	Platelet-rich fibrin: Basics of biological actions and protocol modifications.	The current article intends to clarify the relevant advances about physiological role of certain PRF components and to provide insight into the new developmental approach.			It summarizes the evolution of platelet concentrates and biologic properties of different modifications of PRF procedure.
8	Reisie BH et. al, 2021.[6]	Evaluation and comparison number of gingival fibroblast and osteosarcoma cell (MG-63 cell line) adhesive	to evaluate the effect of A-PRF on the adhesion of gingival fibroblast cells and osteosarcoma cells to different membranes.	In this experimental *in vitro* study, three collagen, alloderm, and mucograft membranes were studied, which were cut into four 5 mm × 5 mm pieces and placed in the bottom of a 24-well culture medium. One milliliter of A-PRF	In the presence of A-PRF, there was a significant higher osteoblast adhesion to collagen membrane compared to alloderm and mucograft membranes ($P < 0.001$). In the absence of A-PRF, adhesion of osteoblasts to	A-PRF was effective on fibroblast adhesion to the collagen membrane, which is similar to its absence. A-PRF was also found to be very effective on the adhesion of fibroblast cells to the collagen membrane, and in its absence, even less adhesion was observed compared to the other membranes. The presence

		to mocugraft, alloderm, and collagen membrane with or without advanced platelet-rich fibrin		was added to two wells from each group and the other two wells remained without A-PRF. The gingival fibroblasts and osteosarcoma cells were individually added to each well. The cell adhesion was studied using an electron microscope after 24 h. The data were analyzed by independent *t*-test, one-way analysis of variance, and least significant difference test.	collagen membrane was significantly higher than alloderm and mucograft (P = 0.019). Moreover, in the presence of A-PRF, fibroblast adhesion to collagen membrane was significantly higher than alloderm and mucograft membranes (P < 0.001). Furthermore, in the absence of A-PRF, no significant difference was found among the study groups (P = 0.830).	or absence of A-PRF showed no significant differences in both cells' adhesion for alloderm and mucograft membranes.
9	Castro AB et al, 2021[10]		This in-vitro study aimed to compare the biological and physical characteristics of three types of PRF membranes using two different centrifuges	Release of growth factors, macroscopic dimensions, cellular content and mechanical properties of the respective membranes, prepared from blood of the same individual were explored. Furthermore, the impact of timing (blood draw-centrifugation and centrifugation-membrane	No statistically significant differences amongst the three PRF modifications could be observed, neither in their release of growth factors or the cellular content, nor in clot/membrane dimensions. The difference between both centrifuges were negligible when the same g-force was used. A lower g-	Timing in the preparation process had a significant impact. Adaptation of RCF only had a minimal impact on the final characteristics of PRF membranes.

			with adapted relative centrifugal forces (RCF): leucocyte- and platelet-rich fibrin, advanced platelet-rich fibrin, and advanced platelet-rich fibrin+.	preparation) was assessed morphologically as well as by electron microscopy scanning.	force, however, reduced membrane tensile strength.	
10	Farmani AR, et al, 2021[19]	Application of Platelet Rich Fibrin in Tissue Engineering: Focus on Bone Regeneration.	This study attempts to review the history, structure, and biology of platelet-rich fibrin (PRF) as well as *in vitro*, pre-clinical, and clinical studies on the use of PRF for		Bone tissue engineering (BTE) is a strategy for reconstructing bone lesions, which is rapidly developing in response to higher demands for bone repairing. Recently, this method, along with the emergence of functionally graded, biocompatible and biodegradable materials, has been expanded. Moreover, scaffolds with	The most important reason for using platelet-rich formulations in bone regeneration is based on releasing growth factors from alpha granules in platelets, which can induce osteogenesis. Moreover, the presence of fibrin nano-fiber structures as a constituent can provide a good substrate for cell attachments.

			bone regeneration.		chemical, physical and external patterns have induced bone regeneration. However, the maintenance of healthy bone and its regeneration in the human body needs a series of complex and accurate processes. Hence, many studies have been accompanied for reconstructing bone by using blood-derived biomaterials, especially platelet-rich fabricates.	
11	Alexandru BC et al, 2021[21].	Bone Morphogenetic Protein 7 Expression in Alveolar Bone Addition With Autologous Blood, Lyophilized Plasma.	to evaluate alveolar bone addition and bone morphogenetic protein 7 (BMP7) expression using an improved autologous and xenogeneic biomaterial.	Chronic marginal periodontitis was induced in sheep; the intervention group received bone addition as periodontal therapy, using a composite system with lyophilized bovine bone enriched with atelocollagen type 1, platelet-rich plasma and advanced platelet-rich fibrin (A-PRF). Six weeks after the intervention,	The untreated sheep showed inflammation, periodontal ligament destruction, remnants of calculus and bacterial plaque as well as foreign bodies in the desmodontal space, without sings of repair. In the treated sheep, fibroblasts/fibrosis, cartilage and/or new bone, cellular cementum and	The current composite system meets all the necessary conditions for promising guided alveolar bone regeneration.

				the dentoalveolar structures were evaluated using hematoxylin-eosin and immunohistochemical staining, to evaluate bone addition and BMP7 expression.	desmodontium, along with remnants of biomaterial with various degrees of cellularity were observed. In the untreated group, the presence of BMP7 was found in osteoblasts and osteocytes while in the treated group, it was mainly found in the biomaterial remnants, while immunohistochemical staining was less intense in the newly formed osteo-periodontal tissues. Quantitative analysis using the Mann-Whitney U-test showed highly statistically significant differences between the groups.	
12	Collins JR, et al, 2021 [22]	Connective Tissue Graft vs Platelet-rich Fibrin in the Treatment	The aim of this study was to evaluate the outcome of PRF combined	Ten healthy patients exhibiting mandibular or maxillary Miller class I and II were treated with PRF + CAF or DeCTG + CAF. GR, probing depth (PD), and	GR, PD, and GT differences between the test and control groups at 28 weeks were not statistically significant. GR was 3.30 ± 1.25 mm and 3.00 ± 1.63 mm	Within the limitations of the present study, it can be concluded that localized gingival recessions could be successfully treated with CAF + PRF or CAF + DeCTG.

		of Gingival Recessions: A Randomized Split-mouth Case Series.	with a CAF (test) compared to de-epithelialized connective tissue graft (DeCTG) + CAF (control) for GR coverage.	gingival thickness (GT) were evaluated at baseline, 6 weeks, and 28 weeks postoperatively.	(control vs test) group (baseline) and -0.10 ± 0.32 vs -0.20 ± 0.42 mm (7 months), respectively.	**Clinical significance:** This study suggests that PRF membrane may be an alternative and valid graft material for treating localized gingival recessions Miller class I and II.
13	Miron RJ et al, 2020[17]	Evaluation of 24 protocols for the production of platelet-rich fibrin.	The aim of this study was to evaluate 24 protocols for the production of platelet rich fibrin (PRF) produced via horizontal centrifugation to better understand cell separation following protocols at various times and	All protocols were compared utilizing a recent method to quantify cells in PRF in 1 mL sequential layers pipetted from the upper layer downwards until all 10 mL were harvested. In total, 960 complete blood counts (CBCs) were investigated. Both solid and liquid-based PRF protocols were investigated following 24 protocols involving 6 relative centrifugal force (RCF) values (100, 200, 400, 700, 1000 and 1200g) at 4 centrifugation times	In general, platelets could more easily accumulate in the upper 4 layers when compared to leukocytes owing to their lower cellular density. Protocol time seemed to have a greater impact on the final cell layer separation when compared to the effect of speed. Protocols of greater than 8 min at 400g led to no leukocyte accumulation in the upper PRF layers (found specifically within the buffy coat). Protocols at or below 200g were	Within the investigated ranges, a protocol of 700g for 8 min presented the highest yield of platelets/leukocytes evenly distributed throughout the upper PRF layers.

			speeds.	(3, 5, 8 and 12 min).	unable to effectively accumulate platelets/leukocytes. The optimal centrifugation speed and time for solid-PRF ranged between 400 and 700g for 8 min. It was noted that variability in patient baseline platelet/leukocyte/erythrocyte counts (hematocrit) significantly affected cell layer separation. This finding was more pronounced at lower centrifugation speeds.	
14	Ravi S, et al, 2020[15]	Mechanical, chemical, structural analysis and comparative release of PDGF-AA from L-PRF, A-PRF and T-PRF - an in vitro study.	to correlate the release profile of PDGF-AA from various forms of platelet concentrates (L-PRF, A-PRF, T-PRF) based on their mechanical	Blood samples were drawn from 2 male and 3 female systemically healthy patients between 20 and 25 years of age who were about to undergo periodontal regeneration for PRF preparation. The blood sample was immediately centrifuged using a table top centrifuge (Remi R4C) at 1060 rpm (208 x g) for 14	On comparing the three PRF membranes, it was found that T-PRF contained the maximum tensile strength (404.61 ± 5.92 MPa) and modulus of elasticity (151.9 ± 6.92 MPa). Statistically significant differences between the three groups were found on comparing the groups for their	Results from the present study indicate that A-PRF is the most favourable form of platelet concentrate in regenerative periodontal therapy as it has a sustained release of growth factors over time.

			and chemical properties.	min for A-PRF preparation, 1960 rpm (708 x g) for 12 min for L-PRF preparation and 1960 rpm (708 x g) for 12 min in titanium tubes for T-PRF preparation. Tensile test was performed using universal testing machine. The in vitro degradation test of the prepared PRF membranes were conducted by placing the PRF membrane in 10 ml of pH 7.4 PBS on an orbital shaker set at 50 rpm. SEM evaluation of the PRF membrane was done under both low and high magnification. In order to determine the amount of released growth factor PDGF-AA at 15 min, 60 min, 8 h, 1 day, 3 days, and 10 days, samples were placed into a shaking incubator at 37 °C to allow for growth factor release into the culture media.	mechanical properties. In the degradation test, it was found that the maximum amount of degradation was found in L-PRF (85.75%), followed by A-PRF (84.18%) and the least was found in T-PRF (82.27%). T-PRF released the highest amount of PDGF-AA (6060.4 pg/ml) at early time points when compared to A-PRF (5935.3 pg/ml). While T-PRF had rapid release of PDGF-AA, A-PRF had a sustained release of growth factors released at later time points.	

15	Fujioka-Kobayashi Met. Al,2020.[4]	Improved growth factor delivery and cellular activity using concentrated platelet-rich fibrin (C-PRF) when compared with traditional injectable (i-PRF) protocols	Due to these previous findings, a novel harvesting technique was recently developed to collect higher concentrations of platelets/leukocytes specifically from the buffy coat layer (C-PRF) following faster centrifugation protocols. The aim of this study was to investigate the regenerative properties and effects on growth	The upper 1-ml layer collected through standard i-PRF protocols at low centrifugation speeds was compared with 1 mL of C-PRF collected from the buffy coat layer following high centrifugation protocols (3000×g for 8 min on a horizontal centrifuge) to specifically concentrate cells within the platelet/leukocyte-rich buffy coat layer. Thereafter, the expression of seven different growth factors, including PDGF-AA, PDGF-AB, PDGF-BB, TGF-β1, VEGF, IGF-1, and EGF, was characterized for up to 10 days. Then, gingival fibroblast biocompatibility was investigated at 24 h (live/dead assay); migration was investigated at 24 h; proliferation was	At all time periods, a significant increase in growth factor release was observed in C-PRF. In particular, the release of PDGF-AA, TGF-β1, and EGF exhibited the highest increases when compared with that in i-PRF. While both i-PRF and C-PRF exhibited high biocompatibility and induced significantly higher fibroblast migration and proliferation when compared with that of the control tissue culture plastic group, C-PRF showed the greatest potential for cell migration and proliferation. Furthermore, C-PRF induced significantly higher mRNA levels of TGF-β and PDGF levels at 3 days and greater collagen 1 staining when compared with induced by i-PRF.	It was found that C-PRF collected specifically from the buffy coat layer following higher centrifugation protocols exhibited an up to a threefold increase in growth factor release when compared with that exhibited by standard i-PRF. This significantly promoted higher gingival fibroblast migration, proliferation, gene expression, and collagen I synthesis. **Clinical relevance:** The findings of the present study demonstrate that a more potent formulation of liquid platelet concentrate than that obtained from the upper plasma layer following a short and slow centrifugation protocol (i-PRF protocol) can be obtained for clinical use by specifically harvesting cells in the platelet- and leukocyte-rich buffy coat layer following an 8-min 3000×g centrifugation protocol (C-PRF protocol).

			factor release and cellular activity of PRF collected through this novel harvesting technique compared to standard i-PRF protocols.	investigated at 1, 3, and 5 days; and the expression of PDGF and TGF-β was investigated at 3 days. Collagen 1 immunostaining was also quantified at 14 days		
16	Miron RJ et. al, 2020 .[5]	Comparison of platelet-rich fibrin (PRF) produced using 3 commercially available centrifuges at both high (~ 700 g) and low (~ 200 g) relative centrifugation forces	Owing to its widespread use, many companies have commercialized various centrifugation devices with various proposed protocols. The aim of the present study was to compare 3 different commercially	PRF was produced on three commercially available centrifuges including the IntraSpin Device (IntraLock), the Duo Quattro (Process for PRF), and Salvin (Salvin Dental). Two separate protocols were tested on each machine including the original leukocyte and platelet-rich fibrin (L-PRF) protocol (~ 700 RCF max (~ 400 RCF clot) for 12 min) as well as the advanced platelet-rich fibrin (A-PRF+) protocol (~ 200 g RCF max (~ 130 g	PRF clots produced utilizing the low-speed centrifugation speeds (~ 200 g for 8 min) produce clots that (1) contained a higher concentration of evenly distributed platelets, (2) secreted higher concentrations of growth factors over a 10 day period, and (3) were smaller in size. This was irrespective of the centrifugation device utilized and consistently observed on all 3 devices. The greatest impact was found between the protocols utilized (up	The present study demonstrated the reproducibility of a scientific concept (reduction in RCF produces PRF clots with more evenly distributed cells and growth factors) utilizing different devices. Furthermore, (and until now overlooked), it was revealed for the first time that the centrifugation tubes are central to the quality production of PRF. Future research investigating tube characteristics thus becomes critically important for the future optimization of PRF. **Clinical relevance:** This

			available centrifuges at both high and low g-force protocols.	RCF clot) for 8 min). Each of the tested groups was compared for cell numbers, growth factor release, scanning electron microscopy (SEM) for morphological differences, and clot size (both weight and length/width).	to a 200%). Interestingly, it was further revealed that the centrifugation tubes used had a much greater impact on the final size outcome of PRF clots when compared to centrifugation devices. It was found that, in general, the Process for PRF tubes produced significantly greater-sized clots when compared to other commercially available tubes. The Salvin Dental tubes also produced significantly greater PRF clots when compared to the IntraLock tubes on each of the tested centrifugation devices.	is the first study to reveal the marked impact of centrifugation tubes on the final production of PRF. Future study thus becomes markedly important to further optimize the quality of PRF-based matrices. It was further found that little variability existed between the centrifugation devices if optimized centrifugation protocols (lower centrifugation speeds) were utilized.
17	Dandekar SA et al, . 2019[24].	Comparative evaluation of human chorion membrane and platelet-	, the aim of the study was evaluation and comparison of the efficacy of	This was a randomized controlled clinical study. Totally 30 sites with Miller's Class I and Class II recession were taken and randomly allocated to	Significant differences were seen from baseline to 6 months in test group regarding gain in CAL ($P <$ 0.001), reduction in REC-HT ($P <$ 0.001), decrease	Both are effective materials in root coverage, but chorion membrane showed better and more stable results at the end of 6 months as compared to PRF membrane in treating

		rich fibrin membrane with coronally advanced flap in treatment of Miller's class I and II recession defects: A randomized controlled study.	chorion membrane and PRF membrane in the treatment of Miller's Class I and Class II recession defects.	chorion membrane (test) PRF membrane (control) group. The clinical parameters recorded were clinical attachment level (CAL), recession height (REC-HT), recession width (REC-WD), width of keratinized gingiva (WKG) and gingival tissue thickness (GTH).	in REC-WD (P = 0.02), increase in WKG (P < 0.001), and increase in GTH (P < 0.001). In the control group also, significant difference was noted at the end of 6 months i regarding gain in CAL (P < 0.001), reduction in REC-HT (P < 0.001), decrease in REC-WD (P = 0.029), increase in WKG (P < 0.001), and increase in GTH (P < 0.001). Intergroup analysis showed significant differences between test and control groups at the end of 6 months, with CAL, REC-HT, WKG, and GTH showing statistically significant differences with P = 0.002, 0.001, 0.001, and 0.026, respectively. No significant difference was seen regarding REC-WD (P = 0.39).	gingival recession.
18	Gutiér	Root	The			

	rez et al.. 2019 [25]	Coverage with Platelet-Rich Fibrin in Miller's Class I, III, and IV Gingival Retractions	purpose of this report is to present a case of multiple Miller's Class III and IV GR treated with CAF and PRF where the potential of PRF to increase gingival thickness and clinical attachment level, and improve soft-tissue healing and clinical appearance was corroborated.			
19	Tsujino T et. al, and 2019.[11]	Striking Differences in Platelet Distributi	It was recently demonstrated that centrifugat	prepared PRF matrices using various types of blood-collection tubes (plain glass	Using low-speed centrifugation, platelets were distributed homogeneously	Therefore, both blood-collection tube types and centrifugal conditions appeared to influence platelet distribution in the

		on between Advanced -Platelet-Rich Fibrin and Concentrated Growth Factors: Effects of Silica-Containing Plastic Tubes	ion conditions influence the composition of PRF and that silica microparticles from silica-coated plastic tubes can enter the PRF matrix. These factors may also modify platelet distribution and was hence studied	tubes and silica-containing plastic tubes) and different centrifugation speeds. The protocols of concentrated growth factors and advanced-PRF represented high- and low-speed centrifugation, respectively. Platelet distribution in the PRF matrix was examined immunohistochemically.	within the PRF matrix regardless of tube types. In high-speed centrifugation, platelets were distributed mainly on one surface region of the PRF matrix in glass tubes, whereas in silica-coated tubes, platelet distribution was commonly more diffusive than in glass tubes.	PRF matrix. Platelets distributed in the deep regions of the PRF matrix may contribute to better growth factor retention and release. However, clinicians should be careful in using silica-coated tubes because their silica microparticles may be a health hazard.

20	Miron RJ et al, 2018 [9]	Sinus Augmentation Using Platelet-Rich Fibrin With or Without a Bone Graft: What Is the Consensus?	The use of PRF for the repair of Schneiderian membrane perforations and as a barrier membrane for lateral window closure is discussed.		This article highlights the biological and clinical advantages of using PRF with or without a bone grafting material for sinus augmentation procedures and provides guidelines detailing when, where, and why to use PRF alone versus in combination with a bone graft.	
21	Agrawal AA et al, 2017.[13]	Evolution, current status and advances in application of platelet concentrate in periodontics and implantology.	This review intends to clarify all these confusion by briefing the exact evolution of PC, their preparation techniques, recent advances and their various clinical and technical			

			aspects and applications.			
22	Chenchev et al,. 2017 [26]	Application of Platelet-Rich Fibrin and Injectable Platelet-Rich Fibrin in Combination of Bone Substitute Material for Alveolar Ridge Augmentation - a Case Report	The aim of this case report was to assess the possibility for augmentation of the alveolar ridge in the frontal region of the upper jaw, utilizing a combination of bone graft material, injectable platelet-rich-fibrin (i-PRF) and advanced platelet-rich fibrin (A-PRF).	An 18 year-old male with expulsion of tooth 11 and partial fracture of the alveolar ridge was treated with augmentation of the alveolar ridge using bone graft material, injectable platelet-rich-fibrin(i-PRF) and advanced platelet-rich-fibrin (A-PRF). Clinical results were reviewed 4 months after the augmentation and a dental implant was placed.	The postoperative period was uneventful. The control CBCT scan showed good organization of new bone allowing placement of a dental implant.	The successful clinical and radiographic results of the case suggest that using A-PRF and i-PRF can be beneficial for bone augmentation of the alveolar ridge before implant placement.
23	Kobayashi E, et al.,	Comparative release of	to compare growth factor	Eighteen blood samples were collected from six	The highest reported growth factor released from platelet	The study indicated that the various platelet concentrates have quite

	2016 [12]	growth factors from PRP, PRF, and advanced-PRF.	release over time from platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and a modernized protocol for PRF, advanced-PRF (A-PRF).	donors (3 samples each for PRP, PRF, and A-PRF). Following preparation, samples were incubated in a plate shaker and assessed for growth factor release at 15 min, 60 min, 8 h, 1 day, 3 days, and 10 days. Thereafter, growth factor release of PDGF-AA, PDGF-AB, PDGF-BB, TGFB1, VEGF, EGF, and IGF was quantified using ELISA.	concentrates was PDGF-AA followed by PDGF-BB, TGFB1, VEGF, and PDGF-AB. In general, following 15-60 min incubation, PRP released significantly higher growth factors when compared to PRF and A-PRF. At later time points up to 10 days, it was routinely found that A-PRF released the highest total growth factors. Furthermore, A-PRF released significantly higher total protein accumulated over a 10-day period when compared to PRP or PRF.	different release kinetics. The advantage of PRP is the release of significantly higher proteins at earlier time points whereas PRF displayed a continual and steady release of growth factors over a 10-day period. The new formulation of PRF (A-PRF) released significantly higher total quantities of growth factors when compared to traditional PRF. **Clinical relevance:** PRP can be recommended for fast delivery of growth factors whereas A-PRF is better-suited for long-term release.
24	Padma R et al,.. 2013 [27]	A split mouth randomized controlled study to evaluate the adjunctive effect of platelet-	the present research was undertaken to study the additional benefits of PRF when used along with	Total of 15 systemically healthy subjects presenting bilateral isolated Miller's class I and II recession were enrolled into the study. Each patient was randomly treated with a combination of CAF along with a	Mean percentage root coverage in the test group after 1, 3, and 6 months was 34.58, 70.73, and 100, respectively. Differences between the control and test groups were statistically significant. This	CAF is a predictable treatment for isolated Miller's class I and II recession defects. The addition of PRF membrane with CAF provides superior root coverage with additional benefits of gain in CAL and WKG at 6 months postoperatively.

		rich fibrin to coronally advanced flap in Miller's class-I and II recession defects	coronally advanced flap (CAF).	platelet-rich fibrin (PRF) membrane on the test site and CAF alone on the control site. Recession depth, clinical attachment level (CAL), and width of keratinized gingiva (WKG) were compared with baseline at 1, 3, and 6 months between test and control sites.	study also showed a statistically significant increase in WKG in the test group (2.94 ± 0.77 at baseline to 5.38 ± 1.67 at 6 months).	