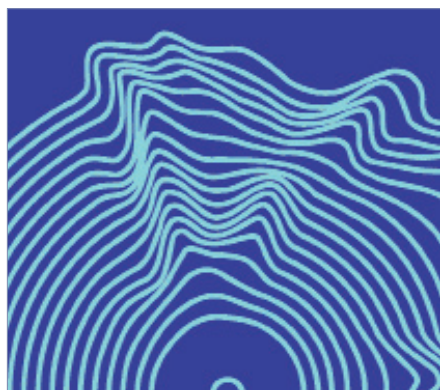




Progress in the Use of Platelet-rich Plasma in Aesthetic and Medical Dermatology

ABSTRACT

Platelet-rich plasma (PRP) has been receiving considerable attention in the field of dermatology since the elucidation of its mechanism and reports of its clinical efficacy. PRP alone or in combination with other therapies has demonstrated benefits for some cosmetic problems and skin diseases. Only a few transient or short-term side effects have been reported with the use of PRP. In this review, we highlight the potential efficacy and benefits of PRP with a focus on its applications in skin rejuvenation, androgenic alopecia, alopecia areata, chronic vitiligo, melasma, inflammatory nail disorders, and psoriasis. We suggest that detailed studies be conducted to standardize PRP preparation and optimize treatment methods in order to further improve its usefulness.

KEY WORDS: Platelet-rich plasma, dermatology, cosmetics, medical

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Platelet-rich plasma (PRP), a biological product, is a portion of the plasma fraction of autologous blood with platelet concentration above the baseline. PRP not only contains a high level of platelets, but also has a full range of clotting factors. Moreover, it is enriched with several growth factors (GFs), chemokines, cytokines, and other plasma proteins.¹

In the preparation of PRP, anticoagulants, such as acid citrate dextrose or sodium citrate, are added to whole blood (10–60mL) to prevent *ex-vivo* coagulation and premature secretion of alpha granules. The anticoagulated blood is subsequently subjected to a soft spin (i.e., slower speed $\pm$ shorter duration) to obtain three layers: a base layer of red blood cells, a central buffy coat layer enriched in white blood cells, and a top plasma layer enriched in platelets while also containing few white blood cells. Different layers of the product are transferred to a fresh tube when pure PRP (P-PRP) and leukocyte-rich PRP (L-PRP) are desired, and these are separately subjected to a hard spin (i.e., higher speed $\pm$ longer duration). When P-PRP is desired, only the most superficial buffy coat with the lower

plasma layer is collected and centrifuged; conversely, when L-PRP is desired, the entire buffy coat with the lower plasma layer is collected and centrifuged. Calcium gluconate, calcium chloride, or thrombin can be added to activate GF secretions before the administration of PRP (Figure 1).^{1–4}

Nonactivated PRP makes use of host dermal collagen and thrombin as endogenous activators. The highest platelet capture efficiency with preserved platelet functions of P-PRP has been reported using the following parameters: $160 \times g$ for 10 minutes in the first spin and $250 \times g$ for 15 minutes in the second spin.^{2,3} There are more than 20 native GFs in PRP, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor 1 (IGF-1). Various types of GFs bind to cell surface receptors and activate cell signaling pathways, resulting in the expression of genes and the synthesis of various proteins required for mitogenesis, for increasing cell numbers, and angiogenesis, for stimulating vascular growth.

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PRP is generally defined as plasma containing 1,000,000 platelets/ μL . Because an individual's baseline platelet count can vary, there can be inconsistencies in quantifying the "fold" increase. Therefore, the absolute number of platelets in PRP and the individual's own platelet count on the day of treatment should be determined and considered.^{4,5} In addition to baseline platelet count, several other variables play a part in preparing the most efficient PRP. There is an intensive ongoing debate regarding these variables, including the terminology used for description, classifications (e.g., four-category, PAW, and DEPA classification), various techniques and preparation systems for PRP (e.g., activators; number, speed, and time of centrifugations; temperature; test tube materials), ideal volume, and technique, site, and frequency of administration.^{4,6,7} We advocate for the four-category classification (P-PRP, L-PRP, P-PRF, and L-PRF; based on leukocyte and fibrin contents) proposed by Dohan et al⁶ for simplified clinical application.

PRP has recently emerged as a treatment choice for a variety of dermatological conditions and concerns. This review aims to highlight the potential efficacy and benefits of PRP in skin rejuvenation, androgenic alopecia (AGA), alopecia areata (AA), chronic vitiligo, melasma, inflammatory nail disorders, and psoriasis.

SKIN REJUVENATION

Skin aging results in wrinkles, coarseness, pigmentation, and loose skin. PRP can induce remodeling of the extracellular matrix (ECM). This increases the expression of matrix metalloproteinases to remove photodamaged ECM components and stimulates the proliferation of dermal fibroblast and synthesis of collagen. However, the PRP-mediated skin rejuvenation is not dose-dependent. Recently, 5% PRP was reported to more strongly induce the production of procollagen Type I carboxy-terminal peptide than 10% PRP.⁸ A similar result was observed in fibroblast proliferation assay *in vitro*, with 5% PRP inducing higher fibroblast proliferation than 10% PRP.⁸ Activin A (ActA) is a member of the TGF- β superfamily. Administration of PRP in irradiated rats exposed to a radiation-delivering cobalt-60 source produced strong ActA/follistatin (FST) signaling on Day 7, parallel with significantly pronounced inflammatory response.⁹ On Day 28 after irradiation, ActA/FST signaling was inhibited and the inflammatory response was

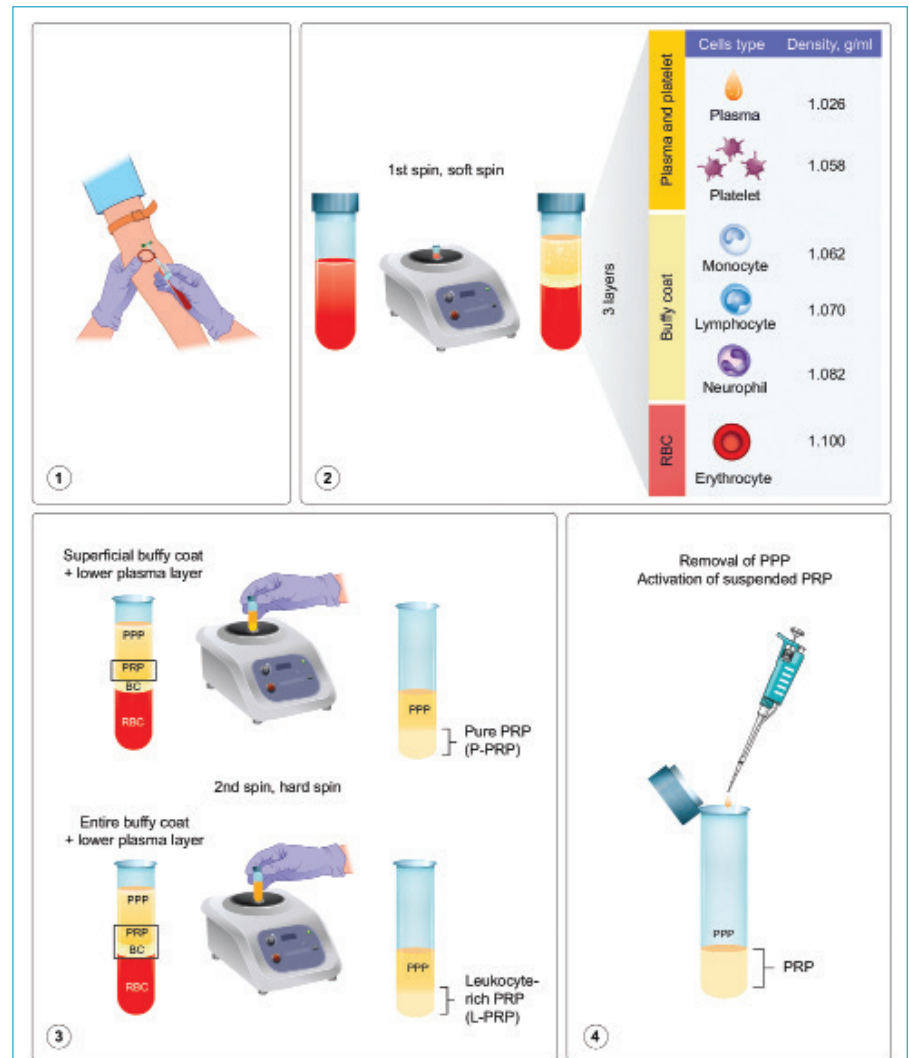


FIGURE 1. The process of platelet-rich plasma (PRP) preparation; (1) The whole blood is drawn in a tube with anticoagulant. (2) After the first spin (i.e., soft spin), the whole blood is separated into three layers. (3) When pure PRP is desired, only the most superficial buffy coat with the lower plasma layer is collected and centrifuged (second spin, hard spin); conversely, when leukocyte-rich PRP is desired, the entire buffy coat with the lower plasma layer is collected and centrifuged (second spin, hard spin). (4) Removal of platelet-poor plasma (PPP); activation of suspended PRP prior to injection.

suppressed, whereas Collagen I expression was highly activated. Histological evaluation results indicated that the morphology was better in the PRP-treated irradiated group on Day 7 than in the non-PRP-treated irradiated group and the epidermal and dermal layers showed organized morphology similar to that in the nonirradiated group on Day 28. To verify the efficacy of PRP rejuvenation on human skin, Abuaf et al¹⁰ performed punch biopsies in the infra-auricular area at three time points: before injection, 28 days after PRP injection (RegenLab[®] kit; Regen Lab SA, Le Mont-sur-Lausanne, Switzerland), and 28

days after saline injection. Collagen fiber bundles in the dermis and the number and thickness of elastic fibers were significantly increased relative to baseline in groups treated with PRP and saline. Furthermore, the density of collagen fibers was significantly higher in the PRP-treated group than in the saline-treated group. The authors concluded that PRP increased dermal collagen levels not only through GFs but also via skin needling (the mesotherapy technique). Moreover, they suggested PRP application to be a safe and effective procedure, even after a single application, for facial skin rejuvenation.¹⁰

TABLE 1. Effect of PRP application on skin rejuvenation evaluated using instruments

STUDY	INSTRUMENT USED	RESULT
Everts et al ¹¹	VISIA-CR (Canfield, Parsippany, New Jersey)	Decrease in brown spot count and brown spot area (-26.3%)
	Optical In Vivo Primos 3D Skin Device (GFMesstechnik GmbH, Berlin, Germany)	Decrease in mean wrinkle count and volume; decrease in true wrinkle count (-37.2%) and volume (-11.5%)
	DermaScan C ultrasound device (Cortex Technology, Hadsund, Denmark)	Decrease in SLEB thickness; increase in SLEB density
	Cutometer dual MPA 580 (C&K)	Increase in skin firmness parameters
	Minolta Chromameter CR-400 (Minolta, Osaka, Japan)	Decrease in skin redness
Cameli et al ¹²	Cutometer dual MPA 580 (C&K)	Increase in skin gross elasticity
	Minolta Chromameter CR-400 (Minolta, Osaka, Japan)	Increase in skin barrier function
	Cutometer MPA 580 (C&K)	Increase in skin capacitance
	Visioscan VC 98 (C&K)	Increase in skin smoothness, scaliness, and kurtosis numeric indexes

PRP: platelet-rich plasma; SLEB: subepidermal low echogenic band; C&K: Courage + Khazaka Electronic, Köln, Germany

Objective assessments of PRP have also demonstrated efficacy for skin rejuvenation. Everts et al¹¹ and Cameli et al¹² administered three regimens of PRP injection at one-month intervals; the results of their studies are presented in Table 1.

Although PRP has been used clinically for skin rejuvenation for several years, the first randomized controlled clinical trial was conducted in 2018 by Alam et al.¹³ PRP and saline were injected in the same subjects on one cheek and the contralateral cheek, respectively. At six-months' follow-up, masked participants rated the conditions and found that the PRP-treated cheek showed significant improvement in skin texture and wrinkles compared to the saline-treated cheek.¹³ Elnehray et al¹⁴ reported that, after a single PRP injection, nasolabial folds responded most favorably to treatment, followed by crow's feet and the transverse forehead lines. There was a significant improvement in fine wrinkles, skin homogeneity, and texture, with notable improvement in the fourth week and the greatest improvement observed in the eighth week after injection. Subjects younger than 40 years of age showed more pronounced improvements in wrinkle appearance than older subjects.¹⁴

Lee et al¹⁵ also administered a single PRP injection on the cheeks and reported that patients were significantly satisfied with the overall facial and cheek appearance based on FACE-Q appearance appraisal scale evaluation. On the FACE-Q postcare scales, the majority of patients reported being pleased with the result (74.2%) and agreed that "it [was] worth the time and effort" (80.0%). However, the majority also

disagreed with that the results were "miraculous" (86.7%) or "fantastic" (70.0%). When the results were evaluated according to the Global Aesthetic Improvement Scale scores, 14 patients had aesthetic improvement and 17 patients experienced no change.

In a split-face, double-blind study, PRP and ready-made GFs (MRS FACE, MRS Lift solution; Mesologica, Jakarta Barat, Indonesia) were used for skin rejuvenation every two weeks for a period of three months.¹⁶ Until one month after the last administration, no significant differences in the final epidermal and dermal thicknesses were observed between both groups. However, at six months after the last administration, the PRP group showed sustained improvement, whereas the group given ready-made GFs showed a decrease in both epidermal and dermal thickness. The authors concluded that the PRP group showed sustained effects because GFs and cytokines were naturally induced by PRP, whereas the ready-made GFs applied directly by mesotherapy had shorter life.¹⁶

Sclafani et al¹⁷ used platelet-rich fibrin (PRF) to correct deep nasolabial folds. Immediately after treatment, the average wrinkle assessment scale score was reduced by 2.17 ± 0.56 points. One week after treatment, the reduction was 0.65 ± 0.68 points, which increased to 0.97 ± 0.75 , 1.08 ± 0.59 , and 1.13 ± 0.72 points at two, six, and 12 weeks after treatment, respectively. The authors suggested that PRF could provide long-term diminution of deep nasolabial folds without causing excessive fibrosis, which can result by using foreign materials. In addition, PRF showed a significantly greater ability to induce collagen

matrix synthesis, cell proliferation, fibroblast migration, and messenger RNA expression of TGF- β , collagen 1, and fibronectin relative to PRP.¹⁸

Based on the evidence in the literature, PRP appears to be effective and safe for skin rejuvenation. The adverse effects of PRP, such as burning sensation, erythema, swelling, and ecchymosis, are transient and resolve in less than two weeks. To our knowledge, only one randomized controlled trial (RCT) has been reported. Further RCTs are required to determine the number of optimal sessions, frequency of application, ideal volume, and technique of administering PRP for skin rejuvenation.

PRP FOR ALOPECIA

The mechanism of PRP treatment in relation to hair folliculogenesis and hair cycling has only been partially elucidated. GFs bind to the tyrosine kinase receptors on dermal papilla cells to activate the MAPK/ERK pathway, leading to proliferation, differentiation, and cellular survival; at the same time, these can also activate AKT and Bcl-2 and decrease BAD/BAX, resulting in an antiapoptotic effect.¹⁹ GFs, such as VEGF, EGF, hepatocyte growth factor, fibroblast growth factor, and IGF-1, have angiogenic potential and can increase vascular structures around hair follicles.¹ After reviewing 19 articles published in 2019, Hesseler et al³ concluded that PRP is beneficial for hair growth. To reduce injection pain and minimize subjective bias, such as different depths and volumes, automatic injectors could be an alternative to manual administration.²⁰ Furthermore, topical anesthesia with EMLA (AstraZeneca, Cambridge, United Kingdom), an air-cooling device (Zimmer Biomet, Warsaw, Indiana), and vibratory distracting devices could be helpful for pain relief. However, local anesthesia should be used with caution because it affects the pH of PRP and has been reported to have a negative impact on efficacy.⁴

Androgenic alopecia. The effect of PRP on the yield of follicular units in male baldness surgery was observed for the first time by Uebel et al²¹ in 2006; they reported a significant improvement over conventional techniques. We have reviewed six RCTs on the efficacy of PRP injection for AGA treatment in this study (Table 2).

Several advanced PRP products have been introduced for AGA treatment. Kang et al²⁸ compared the efficacy of interfollicular injections of PRP preparation containing CD34+ cells

TABLE 2. Randomized, controlled trials of PRP in androgenic alopecia treatment

STUDY DESIGN	STUDY GROUPS	PRP PREPARATION	EVALUATION METHODS	OUTCOMES
Lee et al ²²				
- Randomized, controlled study 40 female patients - Grading and staging of AGA was not mentioned	Intraperifollicular injections as follows: 1 injection of PRP followed by 12 injections of PDRN at weekly intervals 12 injections of PDRN at weekly intervals	- SmartPreP2 APC+ system (Harvest Technologies Corp., Plymouth, Massachusetts) was used; 60mL blood obtained from participants was transferred to tubes containing 8mL of 4% sodium citrate solution (Baxter Healthcare Corp., Deerfield, Illinois). The blood was then centrifuged with the SmartPreP2 platelet concentrating system to obtain CD34+ cell-containing, leukocyte-rich PRP 4 mL PRP was prepared 0.05–0.1 mL/cm² injection - Platelet concentration: Not mentioned	- Physical examination - Folioscope (Leed M Corporation, Seoul, Korea)	At 1 week after the final treatment: - PRP + PDRN group showed significant improvement in hair thickness compared with PDRN therapy alone. - No significant difference was observed in mean hair counts between the two groups.
Gentile et al ²³				
- Randomized, placebo-controlled, half-head group study 23 male patients with Norwood–Hamilton Stages IIa–IV	3 interfollicular injections with 1-month interval (1) PRP (2) Saline	- Cascade-Selphyl-Esforax system (Aesthetic Factors, LLC, Wayne, New Jersey) with modifications 1100 × g for 10 min - Platelet-rich Lipotransfert system (CORIOS Soc. Coop, San Giuliano Milanese, Italy) with modifications 1200 rpm for 10 min 9mL PRP include leukocyte 0.1 mL/cm² injection - Platelet concentration: 5.8X	- Global photography, physician's and patient's global assessment scale, phototrichograms (FotoFinder video epiluminescence microscopy; FotoFinder Systems), and TrichoScan digital image analysis (Tricholog GmbH and Dating GmbH) - Histologic evaluation - Immunohistochemistry was performed using mouse monoclonal anti-Ki67 (DakoCytomation; Dako)	At 3 months after the first treatment: - PRP group showed improvement over saline group in terms of hair count, total hair density, and terminal hair density. - PRP increased the epidermis thickness and the number of hair follicles in microscopic evaluation - PRP increased Ki67+ keratinocytes in the epidermis and in hair follicular bulge cells, and a slight increase of small blood vessels around hair follicles
Alves et al ²⁴				
- Double-blind, half-head, and placebo-controlled study 12 male patients and 13 female patients with Hamilton–Norwood stages II–V and Ludwig stages I–III	3 injections with 1-month interval (1) PRP (2) Saline	18mL of peripheral blood was transferred to a tube with 2mL of 3.8% sodium citrate. - Centrifuged at 460 × g for 8 min (OmniGrafter-Proteal, Barcelona, Spain) 3mL pure PRP (leukocyte poor) 0.15mL/cm² injection - Platelet concentration: 3X	- Global photography - Phototrichograms with digital image analysis (FotoFinder; TrichoScan Professional Version)	At 6 months after the first treatment: - PRP showed improvement over saline group in terms of hair density - Significant differences were seen in mean anagen hairs, telogen hairs, total hair density, and terminal hair density in PRP group compared with baseline

AGA: androgenic alopecia; PDRN: polydeoxyribonucleotide; PRP: platelet-rich plasma

(SmartPreP[®]2 APC+ and SmartPreP[®]2 platelet concentrating systems; Terumo BCT, Lakewood, Colorado) administered twice at three-month intervals with that of placental extract injections (Melsmon[®], Tokyo, Japan) administered at one-week intervals for six months. CD34+ cell-containing PRP treatment showed a significantly higher degree of improvement in hair thickness and overall clinical improvement than placental extract treatment; this was not observed for hair count. The therapeutic use of autologous CD34+ hematopoietic stem cells has been demonstrated to safely promote angiogenesis and vasculogenesis under ischemic conditions. The authors concluded that interfollicular injection of concentrated mobilized CD34+ cells in PRP preparations could have synergistic effects in patients with AGA.

Cole et al²⁹ reported that transplanted grafts resumed growth faster in the presence of platelet lysate (PL; Arthrex Angel[®] system from Arthrex,

Naples, Florida; and Bioruptor Plus[®] sonication device from Diagenode, Denville, New Jersey) than in the presence of a-PRP (Regen[®] Blood Cell Therapy; Regen Lab SA, Le Mont-sur-Lausanne, Switzerland) or saline in male patients with AGA. When PL was injected alone, the patients experienced a 50-percent increase in follicular unit density and 122-percent increase in hair density at seven months after injection. PL generated from a 30-minute sonication of PRP was found to have significantly higher (6- to 8-fold) levels of VEGF, PDGF-BB, and TGF-β1 than a-PRP, which explained the superior follicular regeneration rate of PL-treated grafts.

Ince et al³⁰ compared the efficacy of nonactivated autologous PRP (n-PRP; Young Cell PRP kit), activated autologous PRP (a-PRP; Truecell PRP kit), and homologous PRP (h-PRP, pooled platelets prepared at the blood center) on AGA therapy. They found that h-PRP was most effective for AGA, followed by n-PRP and a-PRP;

however, the reason for this difference was not fully understood. h-PRP had a higher platelet count than autologous PRPs. Autologous PRP has only one individual GF, whereas h-PRP has at least 4 to 5 donor GFs. Low levels of IGF-1 and VEGF after activation in the kit that the authors used might be responsible for the reduced efficacy of a-PRP therapy. Lastly, n-PRP possibly has a more balanced level of GFs.

Stevens et al³¹ reported the positive effect of booster injections with PRP and an adipose-derived stromal vascular fraction, or “platelet-rich stroma,” in male patients with AGA. Hair density significantly increased at six and 12 weeks after injection. Hair-to-hair matching analyses showed that new hair grew from active follicles. Nonfunctioning hair follicles filled with hyperkeratotic plugs also showed new hair growth. Adipose tissue-derived stem cells (ASCs) enable an increase in the proliferation of dermal papilla cells and activation of the anagen phase

TABLE 2 (continued). Randomized, controlled trials of PRP in androgenic alopecia treatment

STUDY DESIGN	STUDY GROUPS	PRP PREPARATION	EVALUATION METHODS	OUTCOMES
Puig et al²⁵				
- Randomized, double-blind, placebo-controlled study 26 female patients with Ludwig stage II	1 subcutaneous injection (1) PRP (2) Saline	- Angel PRP system (CytoMedex) 10mL pure PRP (leukocyte- and erythrocyte-free) - Platelet concentration: 2.75–3.4X	- Hair count (through photography) - Hair mass index (measured using the Cohen hair check system) - Patient survey	At 26 weeks after the treatment, PRP and saline groups showed similar results for hair count and hair mass index
Mapar et al²⁶				
- Prospective, single-blind, randomized, comparative pilot study 17 male patients with Hamilton–Norwood stages IV–VI	2 deep dermis injections with 1-month interval (1) PRP (2) Saline	- Tubex® (Moohan Enterprise, South Korea) 9mL of blood was taken from the participants and mixed with 1mL of acidic citrate dextrose as an anticoagulant 1st spin: 3000 rpm for 6 min 2nd spin: 3300 rpm for 3 min 1.5mL PRP in total 0.1mL of calcium gluconate for every mL of PRP prior to injection - Platelet concentration: 3X	Hair count (using a magnifying glass)	- At 3 and 6 months after treatment: - Terminal hair count and vellus hair count showed no significant difference in both groups when compared with baseline
Tawfik et al²⁷				
- Double-blind randomized placebo-controlled study 20 female patients with Ludwig stages I–III	4 intradermal injections with 1-week interval (1) PRP (2) Saline	10mL of fresh blood was collected from the median cubital vein under sterile conditions into a test tube pre-filled with anticoagulant sodium citrate 1st spin: 1200 × g for 15 min 2nd spin: 2000 × g for 10 min - Activator: calcium gluconate in a 1:9 ratio (0.1mL calcium gluconate per 0.9mL of PRP). - Platelet concentration: not mentioned	- Global photography - Hair pull test - Patient's satisfaction scale - Phototrichograms using Folliscope (Model DLite; STR Company, Felton, California)	- At 6 months after injection: - Hair density and hair thickness measured by folliscope showed significant improvement in PRP group compared with baseline or saline. - The pull test was negative in PRP-injected areas in 25 patients (83%) with average number of three hairs, whereas in placebo-injected areas, the hair pull test remained positive with a mean number of eight hairs. - There was a high overall patient satisfaction in PRP group.

in hair cycles. This stimulates follicle regrowth and modulation of the hair cycle, as well as the production and secretion of GFs. The expression of these GFs allows ASCs to have an angiogenic capacity and the ability to induce tissue neovascularization and a microenvironment with an abundant blood supply for hair cells to regenerate hair follicles. ASCs also exert immunomodulatory and/or immunosuppressive effects via direct cell-to-cell interaction or secreted cytokines.

Thus, irrespective of whether PRP is administered alone or in combination with other agents, it seems to be a promising treatment for AGA. It should be noted that two RCTs conducted by Mapar et al²⁶ and Puig et al³² showed no positive effect of PRP on AGA. Possible causes for the unfavorable results in these two studies include the following: (1) advanced stage of AGA; (2) low number of PRP injections (one injection in Puig et al and two injections Mapar et al); (3) injections were too deep (subcutaneous in Puig et al and deep dermis in Mapar et al); and (4) use of a subjective evaluation method only, whereas other studies used a folliscope as an objective evaluation method.

Alopecia areata (AA). Our review of published clinical trials revealed that PRP administered either alone or in combination with triamcinolone acetonide (TrA) effectively improved AA. The data of studies using PRP for AA treatment is presented in Table 3.

AA is considered an organ-specific autoimmune disease and affects self-esteem; it results in the loss of the immune privilege of hair follicles. Conventional therapies are mostly immunosuppressive in nature and have significant relapse rates and side effects. For instance, relapse rates of 29 percent and 72 percent were reported for intralesional corticosteroids in limited AA and alopecia totalis, respectively; moreover, relapse rates of 37 percent to 63 percent, 25 percent to 41 percent, more than 50 percent, and 100 percent were reported for topical steroids, oral steroids, methotrexate, and cyclosporine, respectively.³⁶ For chronic AA, the relapse rate was significantly lower after intralesional PRP injections (5%–31%) than after intralesional TrA injections (25%–71%). The improvement in chronic AA showed no significant difference between PRP and TrA in two studies, but PRP showed significantly better results

than TrA in one study. Mood changes associated with systemic corticosteroid administration are not uncommon. A high prevalence of mood disorders, such as major depressive disorder and anxiety, was observed in patients with AA.³⁷ The mechanism of PRP in AA treatment remains unclear, but is likely the result of combination effects of proliferation and differentiation, anti-inflammatory effects, and immunomodulatory mechanisms induced by GFs.³³ Apart from pain, no other side effects of PRP were reported in AA treatment. Further RCTs are required to validate the efficacy of PRP for AA by conducting long-term follow-up and evaluating the relapse rate and benefits of PRP for those who experience mood changes with steroids.

Cicatricial alopecia. Two biopsy-proven cases of primary scarring alopecia caused by cicatricial alopecia and lichen planopilaris were reported.⁴⁰ Both cases showed no response to conventional therapies, but responded well after three injections of PRP administered at four-week intervals. Six months after treatment, hair loss resumed in both patients, indicating the need for maintenance therapy. For cicatricial alopecia, anti-inflammatory effects of GFs, as well as their

TABLE 3. Studies using PRP for alopecia areata treatment

STUDY DESIGN	STUDY GROUPS	PRP PREPARATION	OUTCOMES
Trink et al ³³			
- Randomized, double-blind, placebo- and active-controlled, half-head, parallel-group study 45 AA patients with chronic, recurring disease of at least 2 years' duration, and having between four and six symmetrically distributed patches of hair loss	3 injections at 1-month intervals: - PRP - TrA: 2.5 mg/mL - Distilled water	36 mL of peripheral blood - Centrifuged at $70 \times g$ for 8 min - The PRP fraction was separated and suspended in calcium gluconate. - Platelet concentration: $3.5 \times$	At 1 year poststudy: - Complete remission rate: PRP (60%) > TrA (27%) - Regrowth of fully pigmented hair: PRP (96%) > TrA (25%) - Relapse rate: PRP (31%) < TrA (71%) - The number of dystrophic hairs by dermoscopic photomicrographs decrease - Burning or itching sensation decrease - Ki-67 increase
Albalat et al ³⁴			
- Randomized double-blind study 80 patients	3 to 5 subfollicular injections at 2-week intervals - PRP - TrA: 5 mg/mL	15mL of venous blood was collected in five special 3mL sterile tubes containing an anticoagulant (sodium citrate 3.8%). 1st spin: $150 \times g$ for 10 min 2nd spin 1500 to $2000 \times g$ for 10 min - Activator: calcium chloride (0.1 mL of CaCl_2 per 0.9mL of PRP) 3mL of PRP in total	- Hair regrowth with improvement: PRP = TrA - Relapse rate: PRP (5%) < TrA (25%) at 6 months after treatment
Shumez et al ³⁵			
- Nonrandomized controlled study 74 patients (48 TrA, 26 PRP)	3 injections at 3-week intervals: - PRP - TrA: 10mg/mL	20 mL of blood was drawn 1st spin: 5,000 rpm for 15 min 2nd spin: 2000 rpm for 5–10 min - Activator: 10% calcium chloride (0.3 mL per 1 mL of PRP)	Overall improvement: PRP = TrA (100% in the 9th week and on the 3rd month for all patients)

AA: alopecia areata; PRP: platelet-rich plasma; TrA: triamcinolone acetonide

PRP > TrA: PRP group showed significantly greater improvement than TrA group; PRP < TrA: PRP group showed significantly lesser improvement than TrA group; PRP = TrA: There was no significant difference between the PRP group and TrA group

ability to remodel collagen and the ECM, might contribute to their potential success. Although the results of this limited case series are encouraging, further studies are required to understand the possible role of this treatment.

PIGMENTARY DISORDERS

Vitiligo. PRP treatment can improve vitiligo by several possible mechanisms:

1. Growth factors: the stimulation of melanocyte regeneration is very important for vitiligo treatment. Basic fibroblast growth factor (bFGF) in PRP can significantly enhance the migration of melanocytes and the proliferation of keratinocytes and fibroblasts. Stem cell factor and bFGF are also essential for cell survival. Serum TGF- β levels are reduced in patients with nonsegmental vitiligo. Parambath et al⁴¹ proposed that TGF- β present in PRP leads to better response for stable vitiligo. Moreover, PRP could stimulate the undifferentiated stem cells.
2. Anti-inflammatory effect: PRP exhibits anti-inflammatory effects and can suppress the release of cytokines, such as interleukin-1, interferon- γ , and tumor necrosis factor- α . This, in turn, benefits

the interaction between melanocytes and keratinocytes.^{41–46}

3. Matrix proteins: PRP containing fibrin, fibronectin, and vitronectin enhances cell adhesions between keratinocytes, fibroblasts, and melanocytes.⁴⁶

In a double-blind RCT, stable vitiligo was treated with autologous transplantation of noncultured epidermal cell suspension (NECS). The results indicated that NECS in PRP resulted in significantly greater mean repigmentation and patient satisfaction compared to that when using phosphate-buffered saline.⁴¹ Mahajan et al⁴² showed that treatment with intralesional PRP injections, consisting of six injections at two-week intervals, was an effective therapy for chronic localized vitiligo patients who did not respond to traditional therapies. As for the treatment of stable nonsegmental vitiligo lesions, the combination of fractional CO₂ laser with intralesional PRP injection resulted in superior repigmentation to either the combination of fractional CO₂ laser with narrowband ultraviolet B (NB-UVB), or fractional CO₂ laser alone, or PRP injection alone.^{45,46} Another study also revealed that the combination of intralesional PRP injection with NB-UVB led to better repigmentation than NB-UVB alone.⁴⁷ Vitiligo

stability is crucial for the planning of treatment strategy. Ejjiyar et al⁴³ reported the development of facial vitiligo in a female patient after PRP injections (Koebner phenomenon).

The desired content and possible role of leukocytes in PRP products have not been elucidated in previous studies. Against the presence of leukocytes in PRP, some research groups have advocated that it might have negative therapeutic outcomes due to the potential risk of stimulating the inflammatory process.⁶ In contrast, other groups insist that some leukocytes are required to increase GF production.⁶ Moreover, because the pathogenesis of vitiligo involves autoimmune-mediated destruction of melanocytes, the inhibition of autoimmunity could be considered as a vitiligo treatment, and P-PRP or L-PRP can be used by dermatologists for its treatment.

Melasma. Cayırlı et al⁴⁸ used the RegenKit® for three sessions at 15-day intervals and Garg et al⁴⁹ used the two-spin centrifugation method for six sessions to administer PRP injections for the treatment of melasma. Both of these studies found significant melasma reductions upon PRP injection. TGF- β 1 and PDGF present in PRP could have led to melasma reduction. TGF- β 1 decreases melanogenesis via delayed extracellular signal-

TABLE 3 (continued). Studies using PRP for alopecia areata treatment

STUDY DESIGN	STUDY GROUPS	PRP PREPARATION	OUTCOMES
Singh et al ³⁶			
- Prospective study 20 patients with longer than 2-year duration	6 subfollicular PRP injections at 4-week intervals	25mL of blood was drawn and the PRP solution obtained from the lab was used within 30 min of its preparation	Only one patient had a relapse at the end of 1 year
Donovan et al ³⁷			
- Case report - Ophiasis-type AA with corticosteroid-resistant and bipolar disorder	PRP injection	- Arthrex Angel System (Arthrex Inc., Naples, FL) at a concentration 3.5 times above baseline using a 2% hematocrit setting 120mL of blood was drawn	Hair regrowth was noted by 1 month with robust regrowth of hairs measuring 2.8cm by 3 months
Thamer Mukki ³⁸			
- Case report - A patient with chronic diffuse AA for more than 5 years	- Right half of scalp: 4 PRP injections alternated with 4 TrA injection at 2-week intervals - Left half of scalp: 4 TrA injections at 4-week intervals; TrA (2.5 mg/mL, total of 4mL); PRP (2–3mL)	- Pure PRP System, Seoul, Korea) containing ACD-A (trisodium citrate, citric acid, and dextrose) 18mL of blood was drawn - centrifuged at 1500 × g for 4 min - The PRP fraction was separated and suspended with calcium chloride	The half head treated with the combined therapy showed more hair regrowth (+16% vs. +12%) and larger hair fiber diameter (+35% vs. -4%)
El Taieb et al ³⁹			
- Randomized controlled study 90 patients were randomized into three groups (30 patients per group)	- Topical 5% minoxidil twice daily (six puffs/ time) 3 PRP injections at 1-month intervals - Placebo cream	10mL of blood was drawn and placed in two test tubes (5mL each) - Centrifuged at 3000 rpm for 10 min - The PRP fraction was separated and suspended in calcium gluconate 4mL PRP was used	- Patients treated with PRP had an earlier response for hair regrowth, reduction in short vellus hair percentage, and dystrophic hair, as compared with patients treated with minoxidil and control. - PRP resulted in significant improvements in cases of patchy AA, lesser for alopecia universalis, but not effective for alopecia totalis - PRP was more effective in AA treatment than topical minoxidil (5%) in clinical evaluation and dermoscopic findings

AA: alopecia areata; PRP: platelet-rich plasma; TrA: triamcinolone acetone

PRP>TrA: PRP group showed significantly greater improvement than TrA group; PRP<TrA: PRP group showed significantly lesser improvement than TrA group; PRP=TrA: There was no significant difference between the PRP group and TrA group

regulated kinase activation and therefore inhibits melanin synthesis in a concentration-dependent manner. PDGF could accelerate neogenesis, collagen synthesis, and ECM formation, leading to a favorable microenvironment in the dermis.

Psoriasis. Nuclear factor kappa B (NF- κ B), which plays a regulatory role in inflammation, could also be a crucial mediator in the pathogenesis of psoriasis. PRP exerts inhibitory effect on NF- κ B through enhanced cellular I κ B α expression, which results in the retention of NF- κ B-p65 subunit within cytosol and prevents its nucleocytoplasmic shuttling. PRP reduces chemotaxis by inhibiting chemokine transactivation and CXCR4 receptor expression, possibly controlling local inflammation. Patients with chronic plaque psoriasis treated with PRP and methotrexate showed a significant improvement in erythema, induration, and desquamation at each visit compared to patients treated with methotrexate alone.⁵⁰ At Week 16, all patients in the combination therapy group achieved a Psoriasis Area Severity Index (PASI) score of 50, 10 of 16 (62.5%) achieved PASI 75,

and 2 of 16 (12.5%) achieved PASI 90. None of the patients in the monotherapy group achieved PASI 50, although they showed a 35 percent to 40 percent improvement relative to baseline PASI.⁵⁰

Inflammatory nail disorder. Kaur et al⁵¹ reported intramatrix PRP injection to be a safe and effective alternative in refractory nail disorder. They reported one case with lichen striatus who was nonresponsive to six-week topical corticosteroid treatment and developed onychoschizia and leukonychia after two intramatrix steroid injections. Another case with idiopathic trachyonychia showed no improvement after eight-week topical corticosteroid treatment. Both cases showed significant improvement after two PRP injections administered at three-week intervals. The authors proposed that PRP improved inflammatory nail disorders by decreasing the inflammatory factors, thereby normalizing the nail matrix kinetics (both proliferation and keratinization) and promoting regeneration through the release of GFs.⁵¹

CONCLUSION

With the unveiling of its mechanisms and clinical efficacy in recent years, PRP seems to be a promising therapeutic modality in the field of dermatology. PRP, used alone or in combination with other therapies, showed beneficial effects in terms of cosmetic improvements and for some skin diseases. Only transient or short-term side effects were noted in some cases. Currently, there are no standardized PRP preparations, which are essential for optimizing this treatment. The role of leukocytes in PRP products for autoimmune diseases, including AA, vitiligo, and psoriasis, remains unclear and should be further explored and verified. Lastly, because PRP as a treatment option has become popular, more studies are required to elucidate its benefits and limitations.

REFERENCES

- Alves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. *Skin Appendage Disord.* 2018;4(1): 18–24.
- Dohan Ehrenfest DM, Rasmussen L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leukocyte- and platelet-rich fibrin (L-PRF).

- Trends Biotechnol.* 2009;27(3):158–167.
3. Hessler MJ, Shyam N. Platelet-rich plasma and its utilities in alopecia: a systematic review. *Dermatol Surg.* 2019;81(3):834–846.
 4. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. *Arthroscopy.* 2012;28(7):998–1009.
 5. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent.* 2001;10(4):225–228.
 6. Dohan Ehrenfest DM, Andia I, Zumstein MA, et al. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. *Muscles Ligaments Tendons J.* 2014;4(1):3–9.
 7. Magalon J, Chateau AL, Bertrand B, et al. DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices. *BMJ Open Sport Exerc Med.* 2016;2(1):e000060.
 8. Kim DH, Je YJ, Kim CD, et al. Can platelet-rich plasma be used for skin rejuvenation? Evaluation of effects of platelet-rich plasma on human dermal fibroblast. *Ann Dermatol.* 2011;23(4):424–431.
 9. Omar NN, Rashed RR, El-Hazek RM, et al. Platelet-rich plasma-induced feedback inhibition of activin A/follistatin signaling: a mechanism for tumor-low risk skin rejuvenation in irradiated rats. *J Photochem Photobiol B.* 2018;180:17–24.
 10. Abuaf OK, Yildiz H, Baloglu H, et al. Histologic evidence of new collagen formulation using platelet rich plasma in skin rejuvenation: a prospective controlled clinical study. *Ann Dermatol.* 2016;28(6):718–724.
 11. Everts PA, Pinto PC, Girão L. Autologous pure platelet-rich plasma injections for facial skin rejuvenation: Biometric instrumental evaluations and patient-reported outcomes to support antiaging effects. *J Cosmet Dermatol.* 2019;18(4):985–995.
 12. Cameli N, Mariano M, Cordone I, et al. Autologous pure platelet-rich plasma dermal injections for facial skin rejuvenation: clinical, instrumental, and flow cytometry assessment. *Dermatol Surg.* 2017;43(6):826–835.
 13. Alam M, Hughart R, Champlain A, et al. Effect of platelet-rich plasma injection for rejuvenation of photoaged facial skin: a randomized clinical trial. *JAMA Dermatol.* 2018;154(12):1447–1452.
 14. Elnehray NY, Ibrahim ZA, Eltouky AM, Nagy HM. Assessment of the efficacy and safety of single platelet-rich plasma injection on different types and grades of facial wrinkles. *J Cosmet Dermatol.* 2017;16(1):103–111.
 15. Lee ZH, Sinno S, Poudrier G, et al. Platelet rich plasma for photodamaged skin: a pilot study. *J Cosmet Dermatol.* 2019;18(1):77–83.
 16. Gawdat HI, Tawdy AM, Hegazy RA, et al. Autologous platelet-rich plasma versus readymade growth factors in skin rejuvenation: a split face study. *J Cosmet Dermatol.* 2017;16(2):258–264.
 17. Sciafani AP. Platelet-rich fibrin matrix for improvement of deep nasolabial folds. *J Cosmet Dermatol.* 2010;9(1):66–71.
 18. Wang X, Yang Y, Zhang Y, Miron RJ. Fluid platelet-rich fibrin stimulates greater dermal skin fibroblast cell migration, proliferation, and collagen synthesis when compared to platelet-rich plasma. *J Cosmet Dermatol.* 2019;18(6):2004–2010.
 19. Singh B, Goldberg LJ. Autologous platelet-rich plasma for the treatment of pattern hair loss. *Am J Clin Dermatol.* 2016;17(4):359–367.
 20. Gentile P, Garcovich S, Scioli MG, et al. Mechanical and controlled PRP injections in patients affected by androgenetic alopecia. *J Vis Exp.* 2018;131:56406.
 21. Uebel CO, da Silva JB, Cantarelli D, Martins P. The role of platelet plasma growth factors in male pattern baldness surgery. *Plast Reconstr Surg.* 2006;118(6):1458–1466.
 22. Lee SH, Zheng Z, Kang JS, et al. Therapeutic efficacy of autologous platelet-rich plasma and polydeoxyribonucleotide on female pattern hair loss. *Wound Repair Regen.* 2015;23(1):30–36.
 23. Gentile P, Garcovich S, Bielli A, et al. The effect of platelet-rich plasma in hair regrowth: A randomized placebo-controlled trial. *Stem Cells Transl Med.* 2015;4(11):1317–1323.
 24. Alves R, Grimalt R. Double-blind, placebo-controlled pilot study on the use of platelet-rich plasma in women with female androgenetic alopecia. *Dermatol Surg.* 2018;44(1):132–133.
 25. Puig CJ, Reese R, Peters M. Double-blind, placebo-controlled pilot study on the use of platelet-rich plasma in women with female androgenetic alopecia. *Dermatol Surg.* 2016;42(11):1243–1247.
 26. Mapar MA, Shahriari S, Haghighizadeh MH. Efficacy of platelet-rich plasma in the treatment of androgenetic (male-patterned) alopecia: A pilot randomized controlled trial. *J Cosmet Laser Ther.* 2016;18(8):452–455.
 27. Tawfik AA, Osman MAR. The effect of autologous activated platelet-rich plasma injection on female pattern hair loss: a randomized placebo-controlled study. *J Cosmet Dermatol.* 2018;17(1):47–53.
 28. Kang JS, Zheng Z, Choi MJ, et al. The effect of CD34+ cell-containing autologous platelet-rich plasma injection on pattern hair loss: a preliminary study. *J Eur Acad Dermatol Venereol.* 2014;28(1):72–79.
 29. Cole JP, Cole MA, Insalaco C, et al. Alopecia and platelet-derived therapies. *Stem Cell Investig.* 2017;4:88.
 30. Ince B, Yildirim MEC, Dadaci M, et al. Comparison of the efficacy of homologous and autologous platelet-rich plasma (PRP) for treating androgenic alopecia. *Aesthetic Plast Surg.* 2018;42(1):297–303.
 31. Stevens HP, Donners S, de Bruijn J. Introducing platelet-rich stroma: Platelet-rich plasma (prp) and stromal vascular fraction (svf) combined for the treatment of androgenetic alopecia. *Aesthet Surg J.* 2018;38(8):811–822.
 32. Puig CJ, Reese R, Peters M. Double-blind, placebo-controlled pilot study on the use of platelet-rich plasma in women with female androgenetic alopecia. *Dermatol Surg.* 2016;42(11):1243–1247.
 33. Trink A, Sorbellini E, Bezzola P, et al. A randomized, double-blind, placebo- and active-controlled, half-head study to evaluate the effects of platelet-rich plasma on alopecia areata. *Br J Dermatol.* 2013;169(3):690–694.
 34. Albalat W, Ebrahim HM. Evaluation of platelet-rich plasma vs intraleisional steroid in treatment of alopecia areata. *J Cosmet Dermatol.* 2019 May 10. Epub ahead of print.
 35. Shumez H, Prasad PVS, Kaviarasan P, Deepika R. Intraleisional platelet rich plasma vs intraleisional triamcinolone in the treatment of alopecia areata: a comparative study. *Int J Med Res Heal Sci.* 2015;4(1):118–122.
 36. Singh S. Role of platelet-rich plasma in chronic alopecia areata: Our centre experience. *Indian J Plast Surg.* 2015;48(1):57–59.
 37. Donovan J. Successful treatment of corticosteroid-resistant ophiasis-type alopecia areata (AA) with platelet-rich plasma (PRP). *JAAD Case Rep.* 2015;1(5):305–307.
 38. Thamer Mubki. Platelet-rich plasma combined with intraleisional triamcinolone acetonide for the treatment of alopecia areata: a case report. *J Dermatol Dermatol Surg.* 2016;20(1):87–90.
 39. El Taieb MA, Ibrahim H, Nada EA, Seif Al-Din M. Platelets rich plasma versus minoxidil 5% in treatment of alopecia areata: a trichoscopic evaluation. *Dermatol Ther.* 2017;30(1):e12437.
 40. Finney R. Commentary on use of platelet-rich plasma in cicatricial alopecia. *Dermatol Surg.* 2019;45(7):982–983.
 41. Parambath N, Sharma VK, Parihar AS, et al. Use of platelet-rich plasma to suspend noncultured epidermal cell suspension improves repigmentation after autologous transplantation in stable vitiligo: a double-blind randomized controlled trial. *Int J Dermatol.* 2019;58(4):472–476.
 42. Mahajan R, Ninama K, Shah H, Bilimoria F. Effect of intraleisional platelet rich plasma in chronic localized vitiligo. *Int J Res Dermatol.* 2018;4(4):550–555.
 43. Ejjiyar M, Sahibi M, El Gueouatri M, et al. [Vitiligo and Koebner phenomenon following platelet-rich plasma injections]. *Pan Afr Med J.* 2019;32:58. Article in French.
 44. Garg S, Dosapathy N, Arora AK. Laser ablation of the recipient area with platelet-rich plasma-enriched epidermal suspension transplant in vitiligo surgery: a pilot study. *Dermatol Surg.* 2019;45(1):83–89.
 45. Abdelghani R, Ahmed NA, Darwish HM. Combined treatment with fractional carbon dioxide laser, autologous platelet-rich plasma, and narrow band ultraviolet B for vitiligo in different body sites: a prospective, randomized comparative trial. *J Cosmet Dermatol.* 2018;17(3):365–372.
 46. Kadry M, Tawfik A, Abdallah N, et al. Platelet-rich plasma versus combined fractional carbon dioxide laser with platelet-rich plasma in the treatment of vitiligo: a comparative study. *Clin Cosmet Investig Dermatol.* 2018;11:551–559.
 47. Ibrahim ZA, El-Ashmawy AA, El-Tatary RA, Sallam FA. The effect of platelet-rich plasma on the outcome of short-term narrowband-ultraviolet B phototherapy in the treatment of vitiligo: a pilot study. *J Cosmet Dermatol.* 2016;15(2):108–116.
 48. Cayirli M, Caliskan E, Acikgöz G, et al. Regression of melasma with platelet-rich plasma treatment. *Ann Dermatol.* 2014;26(3):401–402.
 49. Garg S, Khillan K, Bharija SC. Platelet-rich plasma therapy in the treatment of recalcitrant melasma. *Dermatol Surg.* 2019;45(3):482–484.
 50. Chakravdhanula U, Anbarasu K, Verma VK, Beevi SS. Clinical efficacy of platelet rich plasma in combination with methotrexate in chronic plaque psoriatic patients. *Dermatol Ther.* 2016;29(6): 446–450.
 51. Kaur I, Jakhar D. Intramatrix platelet-rich plasma therapy: A novel treatment modality in refractory nail disorders. *Dermatol Ther.* 2019;32(2):e12831. **JCAD**