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REVIEW

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Platelet-rich plasma, a powerful tool in dermatology

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Abstract

Platelet-rich plasma (PRP), a platelet concentrate contained in a small volume of plasma, has become a promising option in the last decade to treat different diseases related to the skin due to its high concentration of growth factors. When it is of autologous origin, it decreases the probability of suffering adverse reactions and transfusion-transmitted infections, thus it is an optimal and safe therapy for the patient. PRP has been used in the treatment of several dermatological conditions such as acne, alopecia, and skin ulcers. Its use has also extended to other skin conditions such as melasma, hyperpigmentation, and burns, where it stimulates tissue repair and regeneration. The purpose of this article is to review the management and treatment of different dermatological alterations with PRP. Although there are a variety of studies that support the use of PRP, more research is needed to standardise the protocols for obtaining, processing, and applying it as well as understanding the biological and molecular bases of its functioning.

KEYWORDS

acne vulgaris, alopecia, platelet-rich plasma, regenerative medicine, skin manifestations, skin ulcer

1 | INTRODUCTION

Platelet-rich plasma (PRP) has its origins in the 80s, when Helena Matras described the use of fibrin glue as a substance with sealing functions that helped repair tissue in various oral and maxillofacial surgical procedures (Matras, 1982). Later in 1986, Marx incorporated PRP into the gel used in maxillofacial surgery for the placement of bone (Marx et al., 1998). Since these first studies, the PRP has become a growing interest in the clinical and research fields, such as sports medicine, dental specialties, gynaecology, orthopedics, plastic surgery, otorhinolaryngology, and neurosciences, amongst others (Akingboye et al., 2010; Alcaraz-Rubio, Oliver-Iguacel, & Sánchez-López, 2015; Calandruccio & Steiner, 2017; Davenport et al., 2015; Lacci & Dardik, 2010; Whitmann, R, & D, 1997; Wroblewski, Mejia, & Wright, 2010). PRP has a role in the biostimulation of skin fibroblasts where it mimics the coagulation cascade. This is where fibrinogen is converted to fibrin by thrombin, forming the necessary clot to achieve homeostasis, prompting the release of proteins for tissue repair, thus the healing process of injured tissues is accelerated, due to its high concentration of growth factors (GF) (Eppley, Woodell, & Higgins, 2004; Schmitz & Hollinger, 2001).

Platelets are cellular fragments from the megakaryocytes of the bone marrow, characterised by their lack of a nucleus and containing in their cytoplasm organelles and three types of granules: alpha, dense, and lambda. The alpha granules are important for tissue repair because within them are the GF involved in the acceleration of the tissue repair processes, which are released after platelet activation (S-H. Yun, Sim, Goh, Park, & Han, 2016).

The GF is a group of primary messengers of peptidic origin that act in cellular communication by binding to specific membrane receptors of different cell types, triggering cascades of communication in order to develop the specific functions necessary in the process of tissue regeneration. Some of the most studied GF are platelet-derived growth factor, Transforming Growth Factor-Beta, Vascular endothelial growth factor, insulin-like growth factor, and the epidermal Growth factor. These GF interfere in the repair of tissues such as muscles,

tendons, ligaments, cartilages, and nerves exerting a reparative effect by favouring processes such as cell proliferation, angiogenesis, chemotaxis, and cell differentiation (Lacci & Dardik, 2010; Mussano et al., 2016; see Table 1).

2 | OBTAINING PRP

PRP is defined as a platelet concentrate obtained from the blood centrifugation process, where a concentration three to five times more than the basal concentration of platelets is obtained (Lina Andrea Gómez, Escobar, & Peñuela, 2015; Mazzocca et al., 2012). Nowadays there are several methodologies described for obtaining PRP. Published protocols show differences in the methodologies ranging from bleeding technique, rotation force, number and duration of centrifugation, and the types and concentrations of platelet activators. Variables such as the time elapsed between activation and application of PRP may also influence its quality and results (Lina Andrea Gómez et al., 2015; Maghsoudi & Mohammad Abarkar2, 2015).

TABLE 1 Main functions of PRP growth factors (Alcaraz-Rubio et al., 2015; Bava & Barber, 2011; Cross & Mustoe, 2003; Lacci & Dardik, 2010; Yun et al., 2010)

Growth factor	Function
Platelet-derived growth factor (PDGF)	• Angiogenic • Macrophage activator • Mitogen for mesenchymal and neuronal cells • Favours the formation of Type 1 collagen
Transforming growth factor-beta (TGF-β)	• Promotes collagen synthesis • Promotes chemotaxis •Stimulates the proliferation and differentiation of mesenchymal cells
Fibroblast growth factor (FGF)	• Stimulates and regulates mitosis of mesenchymal cells • Promotes chemotaxis • Stimulates cell differentiation
Insulin-like growth factor type 1 (IGF-1)	• Stimulates the differentiation and proliferation of mesenchymal cells • Stimulates the synthesis of osteocalcin, alkaline phosphatase, and Type 1 collagen • Favours the chemotaxis of vascular endothelial cells.
Vascular endothelial growth factor (VEGF)	• Promotes chemotaxis • Stimulates the differentiation of endothelial cells. • Increases the permeability of endothelial cells.
Epidermal growth factor (EGF)	• Promotes chemotaxis • Stimulates the differentiation of epithelial cells • Induces cell migration • Stimulates the formation of granulation tissue

PRP can be obtained by collecting a sample of blood and placing it in a conventional centrifuge in order to separate the PRP from the blood. Another method of obtaining PRP is using an apheresis machine in which the necessary cellular component, in this case the platelets, are separated from the blood returning all other components back to the donor. To avoid coagulation of the blood sample after its extraction, it is necessary to use anticoagulants such as sodium citrate or dextrose citrate in order to prevent platelet activation (van der Meer, 2013).

The next step in procuring PRP is centrifugation, which is a critical step necessary to standardise the methodology; however, several centrifugation methods have been described. These methods can be grouped into two large groups: single centrifugation and double centrifugation, the latter being the most used (Wang & Avila, 2007). For Marx et al, it is essential to make two centrifugation steps in order to have an adequate concentration of platelets. They use a first centrifugation at 5,600 rpm and a second one at 2,400 rpm, achieving an average platelet concentration of 3.3 times (Marx et al., 1998). Pérez et al, did a first centrifugation at 723 rpm for 10 min and the second one at 1,445 rpm for 10 min, achieving a platelet concentration three times higher than basal (Perez et al., 2014).

Gómez et al. suggested making a single centrifugation at 1,500 rpm for 10 min, in order to obtain a platelet concentration between 1.6 to 4.9 times the baseline value as well as lowering the amount of manipulation of the specimen, thus decreasing the risk of PRP contamination and the loss of platelets (Gómez et al., 2015). Anitua et al. also used a single centrifugation method of 1,800 rpm for a duration of 8 min, ultimately obtaining a platelet concentration of 2.67 of the basal value (Anitua, Zalduendo, Troya, Padilla, & Orive, 2015). Finally, Nagata et al. carried out a study in which they compared the two methodologies, observed higher platelet concentrations after double centrifugation. However, they observed alterations in platelet morphology, which may be associated with a decrease in product quality (Nagata et al., 2010). What makes it necessary to standardize the protocols according to the available equipment.

After the centrifugation process, the blood components are arranged by density in the following order, from the base to the mouth of the tube: the red series (highest density), the white series, platelet rich plasma, and platelet-poor plasma (PPP), with a lower density (Figure 1).

If the processing is done manually, the recovery of the PRP must be done in a biological safety cabinet to avoid contaminations. Initially, the platelet-poor plasma is removed, and the next cell layer corresponds to the PRP, which may or may not be activated.

If PRP is activated, chemical substances such as calcium chloride, calcium gluconate, or thrombin (either of animal or human origin), which lead to aggregation and later platelet activation, can be used. Regarding this step, Gómez et al. suggest a ratio of 1:20 (v/v) of calcium chloride 10% solution to activate it (Gómez et al., 2015). However, Marx et al. use a ratio of 1:6 (v/v) of a mixture containing calcium chloride 10% solution and thrombin bovine (Marx et al., 1998). These activating substances can be mixed with the PRP before application or the PRP and the activator can be injected in through separate syringes (Flores, Gallego, & García-Denche, 2012).

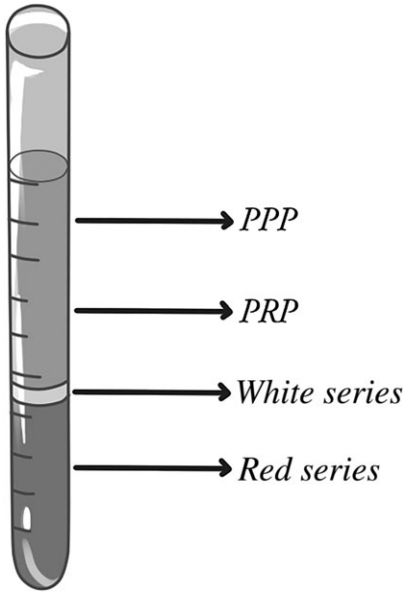

FIGURE 1 Division of cellular components after citrated blood centrifugation

Few studies have evaluated the effect of PRP activation. Vahabi et al. made this comparison using calcium gluconate as an activator, by means of cell proliferation determination (of osteoblasts and fibroblasts *in vitro*). They observed that in the function of time, activated PRP had a higher effect on cell proliferation than nonactivated PRP, although these results were not statistically significant (Vahabi, Yadegari, & Mohammad-Rahimi, 2017).

Additionally, there is no information that establishes the exact time between the activation of the PRP and its subsequent application to ensure the best treatment's effectiveness. Marx says that the PRP can be stable and sterile for 8 hr from its preparation in an anticoagulated state. However, once activated the platelets release 70% of the factors in the first 10 min (Marx, 2001). This suggest that if the PRP is activated, its application should be done as soon as possible. Otherwise, the GF needed in the healing process of the lesion would be lost early, unlike the nonactivated PRP that would allow a longer window of time for its later application.

3 | THE PRP IN DERMATOLOGY

The PRP in dermatology has been successfully used for facial rejuvenation and for the treatment of various dermatological disorders such as acne, scars, ulcers of different aetiology, and alopecia, especially androgenic. In addition, favourable results have been registered in other pathologies such as melasma and burns (Kumaran & Arshdeep, 2014).

3.1 | PRP and acne

Acne is a multifactorial disease that occurs most frequently during puberty, being one of the most common skin conditions, affecting 9.4% of the population worldwide (Tan & Bhate, 2015). It is associated with the excessive proliferation of *Propionibacterium acnes* and it is characterised by being a chronic pathology of the pilosebaceous follicle. The clinical signs include papules, pustules, comedones, macules, nodules, cysts, abscesses, and lesions that can sometimes leave scars. It is common to see this condition in people from 11 to 30 years of age in areas with a high concentration of pilosebaceous glands and with a certain sensitivity to androgens, because acne patients produced higher rates of androgens (Makrantonaki, Ganceviciene, & Zouboulis, 2011; Purdy & de Berker, 2011).

Atrophic scars are the most worrisome complication of acne, because they are permanent lesions that develop due to the poor resolution of these inflammatory lesions. Because of their frequent location in the facial area, they lead to problems of low self-esteem. However, most of these scars can be preventable with a proper treatment (Asif, Kanodia, & Singh, 2016; Chawla, 2014; Lina Andrea Gómez et al., 2015).

There are currently multiple therapeutic options for the management of acne. Amongst the topical management options there are different alternatives, depending on the magnitude of the area affected by acne. They include monotherapies as well as combined therapies. The most used topical medications are retinoids and antimicrobials, which show efficacy for cases of mild acne and are sometimes used together with the systemic treatment. However, such treatments tend to have a limited therapeutic effect and multiple adverse effects such as irritation with erythema, desquamation, dryness of the skin, microbial resistance, and photosensitivity (Bienenfeld, Nagler, & Orlow, 2017; Chawla, 2014; Kosmadaki & Katsambas, 2017; Toquero & Ocampo Candiani, 2009). The systemic management of acne is used when it does not respond to topical management (cases of moderate to severe acne) and consists of the administration of oral antibiotics such as tetracycline hydrochloride, doxycycline, minocycline, azithromycin, tripetropim-sulfamethoxasol, and dapsone. Although these therapeutic options are effective in some cases, it entails undesirable side effects for the patient, such as photosensitivity, gastrointestinal disorders, hepatic dysfunction (in severe cases), hypersensitivity reactions, and increases in bacterial resistance (Bienenfeld et al., 2017; Chawla, 2014; Toquero & Ocampo Candiani, 2009).

These reasons support the need to develop minimally invasive strategies, with no risk of toxicity, which are safe and do not generate adverse effects for skin healing. The use of PRP as a single therapy or with another concomitant treatment (microneedling, oral or topical antibiotics, and laser) has been proposed with satisfactory results (Abdel Aal, Ibrahim, Sami, & Abdel Kareem, 2018; Abuaf et al., 2016; Asif et al., 2016; Chawla, 2014).

In vitro studies have shown that PRP can inhibit the growth of *Propionobacterium acnes* (Intravia et al., 2014). And also, the inflammation provoked at the time of inoculation of the PRP, triggers a cellular stimulus that will contribute to the production of collagen that subsequently will result in improvement of the skin appearance (Abuaf et al., 2016; L A Gómez, Casas, & Merchán, 2017).

Currently, there are some studies with favourable results regarding the treatment of acne using PRP either as the only treatment or combined with other therapeutic options. For a span of 3 months, Gómez

and collaborators applied three doses of PRP, one every month, to a patient that had acne for 3 years. They observed a significant decrease in both the inflammatory lesions and the scars generated by acne (Gómez et al., 2017). Asif and collaborators used PRP with microneedling (a roller with multiple small needles), to treat a group of patients with atrophic scars secondary to acne. As a control, they had a group treated with distilled water and microneedling, finding that the PRP combined with the microneedle technique is more effective in the treatment of atrophic acne scars than only microneedling (Asif et al., 2016). Abdel and colleagues observed that the use of intradermal PRP potentiates the effects of CO_2 laser therapy in the treatment of scars secondary to acne (Abdel Aal et al., 2018).

Although there are reports available, the data they yield is still limited. Reports with a larger number of patients, for example, are needed in order to get higher-quality evidence.

3.2 | PRP in the treatment of alopecia

Alopecia is defined as the progressive loss of hair. There are two types of alopecia: scarring (also known as cicatricial alopecia) and nonscarring. The latter type of alopecia has a better prognosis because the hair follicles have not been completely lost, within which androgenic alopecia and alopecia areata are included amongst others (Gordon & Tosti, 2011). Androgenetic alopecia (AA) affects both men and women, which is associate with a high rate of presentation worldwide and whose main presentation factor is genetic and causes problems of self-esteem and depression. Usually, the hair on the scalp grows in the absence of androgens, whereas the growth of body hair depends on the presence of androgens. This explains the relationship between the presence of androgens, the failure to lose body hair and AA (Lolli et al., 2017). In women, it is known as female pattern alopecia, which occurs in 6% to 12% of women between 20 and 30 years of age and in 40% of women in their 70s. In men, it is known as male androgenic alopecia, occurring in more than 45% of men over 40 years and in 80% of men over 70 years of age (Hoffmann & Happle, 2000; Kaufman, 2002).

Currently, there are only two treatments for alopecia approved by the Food and Drug Administration: Minoxidil Topical, a vasodilator, which prolongs the anagen phase (or growth phase) of the hair and increases the size of the follicles. Its mechanism of action is apparently related to the modulation of prostaglandin levels. The other medication is Finasteride oral, a drug that inhibits Type 2 5α-reductase, whose activity is markedly increased in men that develop AA by preventing the conversion of testosterone to dihydrotestosterone (Gordon & Tosti, 2011). In addition, to the existence of few therapeutic options, these treatments have several adverse effects such as headaches and hypertrichosis associated with Minoxidil and decreased libido associated with finasteride, a treatment only tested in men (Qi & Garza, 2014).

Nowadays, new treatment strategies are being developed in search of good tolerance and greater efficacy, such as PRP, which has been used in several studies as a treatment for non-scarring alopecia with positive results reported, such as the emergence of new hair, root resistance, and increase in hair thickness (Khatu, More, Gokhale, Chavhan, & Bendsure, 2014; Singh, 2015). Gkini and colleagues treated patients with androgenic alopecia by means of three injections of PRP every 20 days and a final boost at 6 months, finding from the first 3 months a decrease in hair loss and an increase in hair density, without finding adverse effects (Gkini, Kouskoukis, Tripsianis, Rigopoulos, & Kouskoukis, 2014). Ho Antony and colleagues treated 24 patients suffering androgenic alopecia by means of four PRP sessions, one each month and reinforcements every 3 or 6 months, in combination with antiandrogen medications. The results show that there was an increase in hair density (Ho, Sukhdeo, Lo Sicco, & Shapiro, 2018). In addition, the effectiveness of PRP has also been tested against alopecia areata, Singh treated 20 patients suffering from alopecia areata, with no response to previous treatments, who improved significantly according to follow-up clinical evaluations performed 1 year later (Singh, 2015).

The mechanism of action of PRP used to treat alopecia is not very clear, despite that the function of several GF has been described in this field. The Fibroblastic growth factor stimulates the proliferation of the papilla cells, leading to the lengthening of the hair. Other GF that have been reported as useful in the treatment of alopecia are PDGF, EGF, and VEGF. These GF seem to act in the bulb of the follicle joining to primitive stem cell receptors to activate the proliferative phase of the hair, originating a new follicular unit, maybe through the extracellular signal-regulated kinase pathway. Additionally, human dermal papilla cells increased their growth rate when they were cultured with PRP, therefore PRP may be involved in the stimulation of cell growth in the hair follicle (Gkini et al., 2014; Khatu et al., 2014) (Strazzulla, Avila, Lo Sicco, & Shapiro, 2018).

3.3 | PRP and skin ulcers

An ulcer is a lesion caused spontaneously or because a trauma or a base disease, which generates a defect in the skin, usually occur in the lower extremities and are considered chronic when they persist for more than 6 weeks, even after receiving adequate treatment. These lesions, independent of their origin (venous, arterial, diabetic, and pressure), have a great importance because in most cases they can compromise mobility, resulting in loss of labor productivity and in high costs in health care. Most of these injuries tend to be chronic, compromising the quality of life of the person affected (Jones, 2013). Skin ulcers are a relatively common condition amongst adults. It is believed that the incidence of these injuries are related to ageing, because these injuries usually affect the 0.6%–3% of people over the age of 60 years, and up to 5% of those over 80 years. However, ulcers are not only closely related to ageing, because there are some factors that increase the risk of developing an ulcer such as atherosclerotic occlusion, obesity, and diabetes (Agale, 2013).

The management of this type of lesion must involve a strategic and early approach to develop the appropriate treatment option

according to the type of ulcer presented, in order to guarantee an adequate approach and an effective healing result. The basic principles of the management of skin ulcers are to treat the underlying cause, and thus, allow adequate functionality of the affected area. Current treatments include surgery, sclerotherapy, conventional therapy (debridement, bandages, moisturizing dressings, topical antibiotics), and adjuvant pharmacotherapy. The aim of the treatment for these injuries is to close the wound in the shortest time possible, in order to avoid possible complications and prevent the wound from becoming chronic (Moreno-Giménez, Galán-Gutiérrez, & Jiménez-Puya, 2005).

Nevertheless, despite the treatment, there are ulcers that do not heal properly and persist for months and even years, and may reappear after healing. These lesions deteriorate the affected area that increase the probability of becoming cases of amputation (Health Quality Ontario, 2009; Suthar, Gupta, Bukhari, & Ponemone, 2017).

As alternative healing methods and new treatment options have been sought, methods such as PRP represent the advancements made in treatment options due to its demonstration that it stimulates and accelerates the healing of soft tissues, creating an environment more conducive to the restoration of affected tissue (San Sebastian et al., 2014; Suthar et al., 2017). Several studies have demonstrated the advantages and effectiveness of PRP as a treatment option for skin ulcers, because in addition to helping to control the infection, there have been no adverse reactions to its use (Crovetti et al., 2004; Kim et al., 2012; Martinez et al., 2013). This postulates PRP as a technique that guarantees efficacy and safety for the patient improving their quality of life.

The use of PRP has been published for the treatment of several types of cutaneous ulcers with satisfactory results. For example, in one of the first studies reported for the treatment of chronic cutaneous ulcers with PRP, it was reported that after 8 weeks with the treatment, there was about a 73% of wound area reduction (Anitua et al., 2008). In a case report, the pressure ulcer of an elderly woman was treated with PRP, which had 4 months of evolution, and its total closure was obtained after 57 days of treatment (Ramos-Torrecillas, De Luna-Bertos, García-Martínez, Díaz-Rodríguez, & Ruiz, 2013). Moreover, in other case report that included 12 patients, with an average age of 33.5 years, 17 varicose ulcers were treated and an improvement of more than 94% was determined in the area of the ulcers (Sarvajnamurthy, Suryanarayan, Budamakuntala, & Suresh, 2013). Suthar team used PRP topically (gel) and injected it on 24 patients, having a 90% of reduction in the wound area on 70.8% of their patients (Suthar et al., 2017). Another study compared the efficacy of PRP versus conventional topical antibiotic treatment in 56 patients with diabetic foot ulcers, obtaining a cure rate of 86% in the group treated with PRP and only 68% in the control group (Ahmed, Reffat, Hassan, & Eskander, 2017).

Although these reports suggest that PRP can become a safe, economical, and effective therapeutic alternative for the treatment of chronic nonhealing ulcers, there are reports no clear about the PRP effectiveness in healing of chronic wounds, and even where complications are evident (Martinez-Zapata et al., 2016). For these reasons, double blind and randomised studies are needed to improve the quality of the current evidence.

3.4 | Use of PRP in skin rejuvenation

Ageing is commonly defined as a progressive loss of the homeostatic capacity of the skin. It is a complex process that occurs as a consequence of extrinsic factors like UV radiation, environmental pollutants, and exposure to chemicals, amongst others (Helfrich, Sachs, & Voorhees, 2008). One of the most important factors is solar radiation, which generates free radicals that increase the activity of collagenase by activating the degradation of collagen and decreasing the concentration of the TGF, as well as reducing the formation of collagen fibres (Amaro-Ortiz, Yan, & D'Orazio, 2014). Regarding intrinsic factors like hormone levels, genetic regulation, and inflammatory factors that generate molecular changes at the cellular as well as histological levels. These are the most visible at the anatomical level: wrinkles, benign neoplasms, decrease the basal keratinocytes amount, and decrease in the aqueous content of the tissues as time passes, and altering the state of hydration of the skin. All these changes not only affect physical appearance, but also have physiological implications as the skin, in an ageing state, does not adequately fulfil its function as a protective barrier (Farage, Miller, Elsner, & Maibach, 2008).

The main treatment to combat skin photoageing is the prevention of sun exposure. However, there are currently other secondary prevention options, such as retinoid preparations (tretinoin and tazarotene), antioxidants (topical vitamin C, coenzyme Q10, oral supplements), oral estrogens, and even tertiary prevention options such as chemical peels, laser, botulinum toxin, dermal, and subdermal fillers (Helfrich et al., 2008). However, none of these alternatives is a natural, autologous, and chemical-free strategy.

Biostimulation is a restitutive treatment that consists in restoring the metabolism and the proper functioning of the skin, based on the use of PRP in order to biologically activate the anabolic functions of the fibroblast as well as the production of Collagen 3 and 4, elastin, and hyaluronic acid (Ramírez, Ríos, Gómez, Rojas, & J, 2015). One of the main advantages of biostimulation with PRP is that it can be applied at any age, preferably from the age of 30 years, which is when the visible changes due to photo-ageing begin to appear.

The PRP, thanks to the GF, biological mediators that modulate cell turnover and regeneration, exerts an effect on the target cells and on the extracellular matrix, thus achieving the stimulation of the repair and tissue regeneration. Different studies have shown that PRP produces remarkable changes on aged skin by restoring vitality, increasing dermal collagen levels, recovering elastic consistency, improving vascular inflow, and stimulating smoothness, tone, and appearance (Abuaf et al., 2016; Díaz-Ley et al., 2015; Yuksel, Sahin, Aydin, Senturk, & Turanli, 2014). In addition, these changes can be observed from the first injection (Elnehrawy, Ibrahim, Eltoukhy, & Nagy, 2017).

Furthermore, PRP has been used in combination with other typical ageing treatments with satisfactory results. Ulusal et al, used an

average of three sessions of PRP plus hyaluronic acid in 94 women with different degrees of facial ageing. They observed that from the second application, there was an improvement of fine wrinkles and skin tone; and at the end of the sessions, it was observed that most of the wrinkles had disappeared and there was facial restoration (Ulusal, 2017). Moreover, it was shown that the combination of PRP and ultra-pulsed fractional CO_2 laser shortened the duration of laser side effects and improved the efficacy of the treatment after 3 months (Hui, Chang, Guo, Zhang, & Tao, 2017).

One of the most important manifestations of cutaneous photoageing is the appearance of wrinkles. The application of GF, either as monotherapy or concomitant with other substances, leads to the activation of cellular regeneration of the skin. This is specifically seen with keratinocytes of the basal layer and fibroblasts, and the GF also stimulate the production of glycosaminoglycans, essential collagen fibres to repair and restore the damaged structures (Díaz-Ley et al., 2015). Although there are several publications supporting the use of PRP in facial rejuvenation, it is still necessary to standardise its preparation method and application procedure as well as understand the PRP mechanism of action in the field of skin rejuvenation.

3.5 | PRP and other dermatological conditions

The role that PRP plays has been seen in several dermatological conditions.

3.5.1 | Melasma

This dermatosis is a pigmentary disorder that is usually chronic. Its diagnosis is made through clinical evaluation, which reveals areas of symmetrical hyperpigmentation, usually brown or grey on areas of the facial surface that have been or are exposed to the sun (forehead, nose, malar, and mandibular region). The aetiology of this disease is multifactorial, some of the causes are the increased synthesis of melanin, genetic factors, and ultraviolet radiation (Ogbechie-Godec & Elbuluk, 2017).

The management of melasma remains a challenge for medical personnel; the treatment has been focused on identifying the key factors in the synthesis of melanin. Some of the treatments for this disease include topical alternatives such the use of retinoids, hydroquinone, azelaic acid, arbutin, kojic acid, ascorbic acid, and corticosteroids, all of which can cause skin irritation as a side effect. Oral alternatives such tranexamic acid and glutathione are also used, which can lead to abdominal distension, disturbances of the menstrual cycle, headache, and even deep vein thrombosis (Ogbechie-Godec & Elbuluk, 2017; Rodrigues & Pandya, 2015). Recent studies show that the use of therapies such as chemical peels, therapies based on laser technology, and microdermabrasion can be effective, but they can have side effects ranging from erythema to burns (Ogbechie-Godec & Elbuluk, 2017).

The use of PRP is proposed as an alternative treatment, which shows minimal side effects that are mainly associated with its injection (transient marks after injection). PDGF is related to the positive results obtained with the PRP treatment, because it plays an important role in angiogenesis, synthesis of collagen, and extracellular matrix components. Therefore, the effect of PRP achieves the repair of tissues by acting on the different types of cells that are located in the skin, promoting their proliferation and differentiation (Cayırlı, Calışkan, Açıkgöz, Erbil, & Ertürk, 2014).

Few studies have been reported on the use of PRP as a treatment in melasma, Cayırlı et al. reported a case of a 27-year-old woman, who achieved an 80% reduction in melasma after three PRP sessions with 15-day intervals (Cayırlı et al., 2014). Similarly, a study led by Adel evaluated the clinical efficacy of PRP as a treatment in melasma and the role of intense pulsed light as an activator for PRP. In this study, 20 women with facial melasma were treated on one side of the face with PRP plus intense pulsed light, and on the other side of the face only with PRP, although the results showed no statistically significant difference between both study groups (Adel, 2017).

3.5.2 | Periorbital hyperpigmentation

In this condition, there is a darker shade on the eyelids, which is a significant aesthetic problem for many who suffer from it. Its prevalence is higher in people with dark skin and usually affects different age groups and both genders. Its causes seem to be multifactorial, involving both intrinsic and extrinsic factors, and the presence of melanin pigment in the affected area is a specific feature of the aetiology and pathogenesis thereof (Sarkar et al., 2016).

For the treatment of this dermatosis, several options have been proposed that include the topical application of depigmenting products such as hydroquinone, kojic acid, and retinoids. Even though, they can cause dermal irritation. Physical therapies that include chemical peels, dermabrasion, cryosurgery, and laser have also been used. However, there are not many studies in the literature that demonstrate their efficacy and long-term tolerability (Sarkar et al., 2016). For this reason, the use of PRP is proposed as an option for the management of periorbital hyperpigmentation. Although it does not have the same ethiopathogenesis of melasma, both share the characteristic of hyperpigmentation in the affected area and both appear to respond positively to treatment with PRP.

One study demonstrated the efficacy of PRP in the treatment of periorbital hyperpigmentation, where after three sessions in 50 patients, significant changes were obtained in all patients (Salah Hashim Al-Shami, 2014). Mehryan et al. treated 10 patients with PRP intradermal injections, the results show improvement in infraorbital colour homogeneity from the first session (Mehryan, Zartab, Rajabi, Pazhoohi, & Firooz, 2014). On the other hand, 30 patients were treated with seven intradermal injections of PRP on the left area every 2 weeks, and carboxytherapy on the right area every week. Although 10 patients refused to complete all PRP sessions, due to bad tolerance to the pain of the injections, both treatments showed a comparable efficacy at the end of the study (Nofal et al., 2018).

Despite the existence of some research about the effect of PRP in periorbital hyperpigmentation, it is not substantial, and more

studies are needed to establish the efficacy of PRP in this dermal condition and its mechanism of action.

3.5.3 | Burns

The injuries generated by burns are an important cause of trauma and have a high degree of mortality, due to the fact that 69% of patients have burns that cover more than 70% of the bodily surface (Pavoni, Gianesello, Paparella, Buoninsegni, & Barboni, 2010). In these types of injuries, there is a decrease in the local blood flow and lymphatic flow due to the edema that is generated in the affected area. This compromises the platelet adhesion necessary for cellular repair. At the same time, microcirculatory stasis accompanied by microvascular thrombosis occurs. These phenomena intervene in the supply of nutrients and oxygen to the injured area, which in turn, generates the production of both aesthetic and functional sequelae. In addition to this, burns are associated with infectious processes, increasing the morbidity and mortality rates in patients. They also show physical and psychological alterations leading to a decrease in the quality of life of patients (Pavoni et al., 2010). The standard burn treatment includes two main phases: the first one is the excision, which must be performed within the first 48 hr, which reduces the risk of bleeding, infections, as well as the associated morbidity and mortality. The second one is the graft, used in accelerating the healing and minimizing scars (Rowan et al., 2015). Although with these measures, the mortality rate from burns has decreased, complications and obstacles still exist when treating injuries, because both secondary infections and long periods of healing continue to be a challenge.

When PRP is applied to burns, it could favour the acceleration of cell repair. Ozcelik et al. published a study in which burns were induced in 10 rats on which PRP was subsequently applied, and 7 days after the injury they were sacrificed to study the histological changes and establish the amount of hydroxyproline (amino acid component of collagen important in tissue regeneration processes). They determined that hydroxyproline levels were higher and found a lower infiltration of inflammatory cells in rats treated with PRP compared with the control group, which did not have any treatment. However, the authors did not find significant differences regarding the development of fibroblasts and vessels as well as epithelialization (Ozcelik et al., 2016). In another study, PRP was used topically in rats suffering from both deep epidermal lesions of the second degree and associated with diabetes mellitus, or third degree burns. They showed that the PRP accelerated the healing process by favouring the formation of granulation tissue and new epidermis in both, although it was less effective for third-degree burns (Venter, Marques, dos Santos, & Monte-Alto-Costa, 2016). Finally, Huang et al., described that subcutaneous PRP injection can mitigate neuropathic pain in rats with burn-induced neuropathic pain (Huang et al., 2018).

In regards to humans, Mark and colleagues investigated the effect of PRP on wound healing in 52 patients suffering several areas of burns and who required meshed split skin graft surgery, using intrapatient controls. Although PRP shows a better epithelialization rate, there was not a significant difference in scar quality between the PRP and standard treatment after 1 year (Marck et al., 2016).

Although there is little evidence in the literature that shows the effectiveness of PRP as an effective treatment in the management of burns, it has been shown that PRP is safe and can be an effective treatment option.

4 | DISCUSSION

The PRP, a bioactive agent that has been used in recent decades as a new therapeutic option in several dermatological disorders, used as the only treatment, and in other cases, as an adjuvant tool, showing positive effects on tissue repair at structural and also at functional levels. Although, to obtain the PRP, several protocols have been created, it is clear that factors such as the strength and number of centrifugations and the method used to activate platelets influence the quality of PRP, which may be related to the variety of results obtained.

Several studies demonstrate the potential role of PRP in the dermatology field. The results allow us to conclude that this treatment leads to a faster rate of tissue repair, and also proliferation of keratinocytes and fibroblasts as well as a better collagen and elastin production and generation of granulation tissue, with few adverse effects because it is well-tolerated.

Despite this, more studies are needed to standardise the PRP preparation that allow one to obtain quality PRP as well as its injection method, number of doses, and duration of the treatment for each dermatological alteration, together with evaluation of the long-term efficacy in a greater number of controlled clinical studies. Thus, it would be possible to have more consolidated results to finally acquire better knowledge about its biology and mechanisms of action, which will develop a quality therapeutic strategy that responds to the needs of doctors and patients and, above all, improving their quality of life.

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CONFLICTS OF INTEREST

The authors report that they have no conflicts of interest in the authorship and publication of this article.

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