Platelet Rich Plasma: from Basic Science to Its Dermatological Indications

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ABSTRACT

There is no strong evidence that platelet-rich plasma (PRP) can be used to treat different types of dermatological illnesses, despite the rising trend in this direction. This inspired us to evaluate the basic science and dermatological uses of it.

Keywords: Scar, growth factors, and platelet-rich plasma (PRP).

Introduction:

A plasma fraction of autologous blood generated from the patient's blood that has a platelet content above baseline is called platelet-rich plasma, also known as platelet-enriched plasma, platelet-rich concentrate, and autologous platelet gel **(1).**

Although PRP's platelet count is still not at its best, the concentrate should have a platelet count that is four to five times higher than the baseline. This treatment approach comprises a wealth of autologous growth factors and proteins that, when activated, take part in a variety of tissue healing phases, including collagen synthesis, tissue granulation, and angiogenesis **(2).**

PRP has recently been employed in the field of dermatology to aid in the healing of wounds, as an adjuvant therapy for rejuvenation, and even as a post-laser treatment. PRP is being used for dermatological disorders other than just skin rejuvenation therapy for patients with face aging, with success rates for conditions like alopecia and skin ulcers. Dermatologists must improve their understanding of the underlying biological effects and their capacity to evaluate PRP critically since there is a requirement for empirical evidence of its efficacy **(3).**

Platelet Origin, contents and function:

1) Platelets, a type of white blood cell made up of the cytoplasmic fragments of megakaryocytes, are created in the bone marrow. The tiniest blood cells are round

or oval in form and have a diameter of about 2 m. a bilayer of phospholipids and cholesterol that is covered, sporadically interspersed with, and penetrable by a trilaminar cell membrane with a glycoprotein receptor surface is visible under electron microscopy. They are made up of granules, microtubules, and organelles like mitochondria. The latter can be categorized into three groups:

2) 2) Delta or dense granules, which contain the powerful agonists or platelet-activators ADP, ATP, and serotonin.

3) 3. Lambda granules, which are lysosomes that aid in dissolving the clot after it has completed its task.

4) Alpha granules.

Despite lacking a nucleus and DNA, it has been noted that platelets possess copies of roughly one-third of the known proteins in the human genome, a system for protein synthesis, and the ability to process mRNA, and the capacity to correctly translate a variety of proteins. These discoveries have altered how platelets are perceived **(5).**

The abundance of growth factors found in platelet granules, as well as their capacity for de novo protein synthesis, antimicrobial action, and inflammatory modulation, all encourage extracellular matrix synthesis and cell growth, which in turn promotes healing, wound repair, and the repair of various tissue defects. Due to these characteristics, the use of autologous PRP for tissue regeneration and repair has been suggested **(6).**

In the bone marrow, platelets are made. They are the initial component to reach the site of tissue damage. They contain granules made up of different materials (**Figure 1**), which are released when the platelets activate, **(7).** Growth factors (GF), cytokines, adhesion molecules, integrin, and coagulation proteins are some of the key chemicals secreted from these granules **(8).**

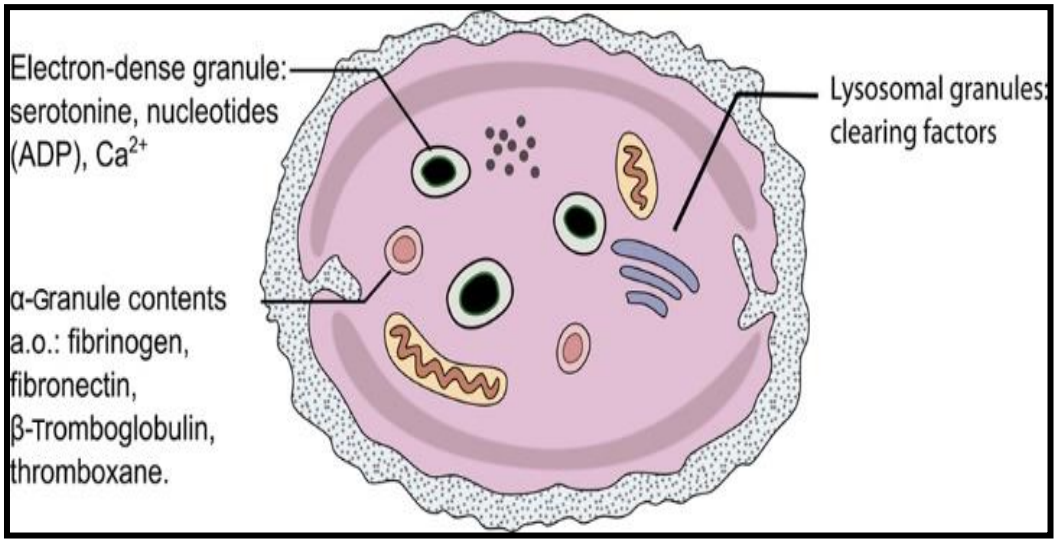

Figure (1): Schematic drawing of a single platelet and its contents **(7)**

By adhering to cell membranes, platelets aid in aggregation, clot formation, homeostasis, and the release of chemicals that aid in tissue healing. Additionally, they affect blood cell types involved in inflammation, angiogenesis, and regeneration as well as the reactivity of blood vessels **(9).**

The average platelet life span is They circulate in the blood in their resting condition for 7 to 9 days. When linked to exposed endothelium or triggered by agonists, they change their shape and release the contents of the granules (including ADP, fibrinogen, and serotonin), which is followed by platelet aggregation **(10).**

Collagen, fibronectin, von Willebrand factor, and laminin are only a few of the molecules on a damaged endothelium that platelets adhere to in order to get activated. Other physiological agonists include Collagen, thromboxane A2, thrombin, ADP, and the platelet activating factors **(11).**

Platelets discharge following activation, release their granular contents into the environment. a variety of growth elements required to initiate and sustain the healing response are found in large quantities in the platelets' alpha granules **(12).**

Depending on the platelet separation device and process employed, the amount of plasma, erythrocytes, white blood cells, and platelets in PRP can change. To consider rich PRP, the platelet concentration needs to be raised above the entire blood concentration. Compared to baseline values for the total blood, it must have at least five times as many platelets **(13)**.

As doctors started to use PRP in many different areas of medicine and started to see clinical results from concentrating a patient's own blood factors, its popularity grew. PRP has

demonstrated efficacy in gingival regeneration in odontology. It is employed in orthopedics to speed the healing of bone fractures and to restore articular cartilage. PRP is also used to treat muscle strain injuries, and intriguing outcomes when treating patients with complicated injuries and the treatment of osteodegenerative disorders have been documented. PRP efficiently cured ulcer reconstruction, especially in diabetic patients **(14).**

Mechanism of action of PRP:

According to reports, platelet-rich plasma can speed up tissue healing in a variety of ways. This is probably because it releases a large number of bioactive chemicals and encourages cell growth **(Figure 2)**. Basic fibroblastic growth factor, platelet-derived growth factor (PDGF), transforming growth factor alpha and beta (TGF-), epidermal growth factor (EGF), and vascular endothelial growth factor are all secreted by activated platelets as intracellular granules. These elements are known to control numerous procedures, including cell adhesion, proliferation, and differentiation **(15)**.

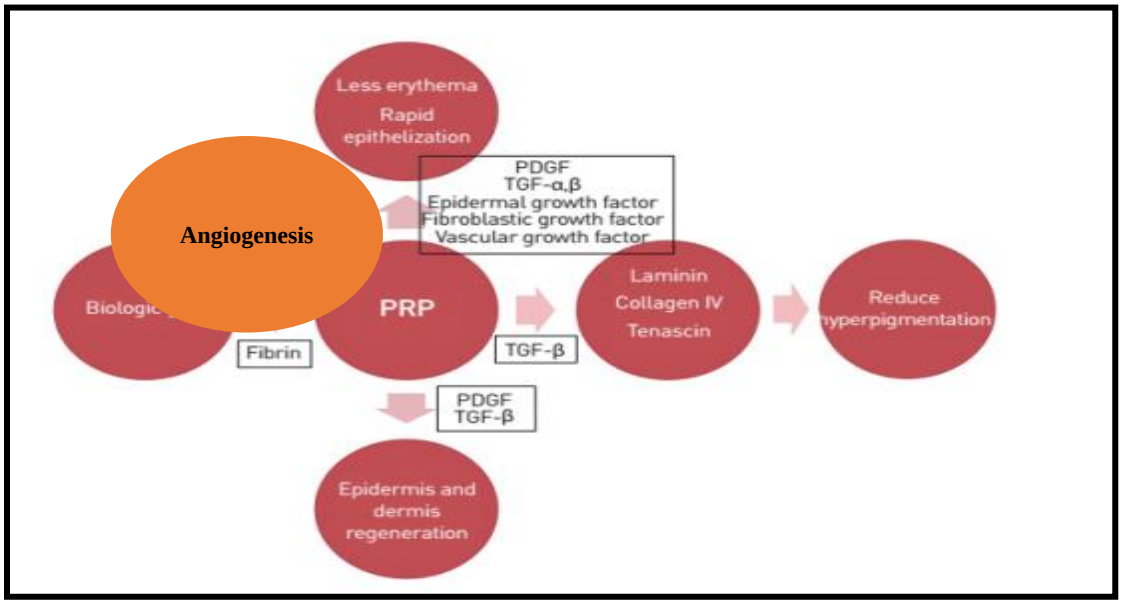

Figure (2): Schematic figure demonstrates actions of PRP and its bioactive molecules **(15).**

Growth factors:

1) Platelet Derived Growth Factor (PDGF):

Human PDGF was initially shown to be a disulfide-linked dimer of two different polypeptide chains, A and B. The three proteins that made up its founding family were PDGF-AA, PDGFAB, and PDGF-BB, all of which were encoded by the two PDGF-A and PDGF-B genes. Two additional PDGF genes and proteins, PDGF-C and PDGF-D, were found via later research. The PDGFs are crucial for the growth of the kidney, lung, and central nervous system.

Modeling has been done to determine how platelet-derived growth factors (PDGFs) and their receptors work as growth factors and receptor tyrosine kinases. Blood vessel development, early hematopoiesis, and the promotion of fibroblast and smooth muscle cell proliferation are all impacted by PDGF receptor signaling in culture have been identified **(16).**

2) The Epidermal Growth Factor (EGF) family:

The EGF family of growth factors includes the Transforming Growth Factor-alpha (TGF-), Heparin Binding EGF-Like Growth Factor, Amphiregulin, Betacellulin, Epiregulin, Epigen, and Neuregulins. The EGF family is the collective name for the ErbB family, which consists of ErbB1 (also known as EGF receptors), ErbB2, ErbB3, and ErbB4. EGF family when members connect to their receptors, they initiate an intracellular signaling cascade **(17).**

By regulating the rate of DNA synthesis in the outer root sheath and hair bulb cells, studies have shown that the growth factor receptor ErbB1 is essential for regulating the growth cycle of hair follicles **(18, 19).**

3) Transforming Growth Factor-β (TGF-β):

The various TGF- isoforms, the nodals, activins and inhibins, anti-mullerian hormone, and a large number of other structurally related substances are all included in the super family of TGF-.There are three members of the TGF-family: TGF-β1,TGF-β2 and TGF-β3 **(20).**

Numerous biological processes, such as cell division, the production of extracellular matrix, angiogenesis, an immunological response, and differentiation, are regulated by transforming growth factor-isoforms **(21).**

4) Hepatocyte Growth Factor:

This substance is initially described as a potent hepatocyte mitogen and an inducer of epithelial cell dissociation **(22).**

5) Keratinocyte Growth Factor (KGF):

Keratinocyte Growth Factor (KGF) is a member of the FGF-7 family of fibroblast growth factors. KGF is a potent mitogen of epithelial cells **(23).** Mesenchymal cells release a paracrine growth factor that especially encourages the proliferation of epithelial cells. The KGF Receptor, which has only been discovered on the surface of epithelial cells, is assumed to be largely released in the stroma by fibroblasts **(24).**

6) Insulin-like Growth Factor (IGF):

Insulin-like growth factor (IGF) I and II, also known as somatomedin C and somatomedin A, are peptides with mitogenic and insulin-like properties. IGF-I binds to IGF-I receptors to regulate cell proliferation, differentiation, and survival. Numerous IGFR-l molecules have been discovered in the granulosa cells of the germinal layer of the outer root sheath and the stromal mother cell of the hair bulb close to the dermal papilla according to studies **(25, 26).**

In vivo tests revealed that IGF-1 injections into the skin, either systemically or locally, were necessary help keep the hair growing, particularly in the early stages of the hair cycle. This might stop hair follicles from prematurely entering the catagen cycle **(27).**

7) Vascular Endothelial Growth Factor (VEGF):

Vascular Endothelial Growth Factor (VEGF), a homodimeric glycoprotein, promotes endothelial cell migration and proliferation which binds to heparin. Four different isoforms of it have been created through alternative splicing. Both VEGF receptor types 1 and 2 bind to VEGF. Biologically active VEGF is secreted by epidermal keratinocytes in vitro, whereas epidermal sheets grown in vast quantities also produce VEGF **(28).**

Mei-Dan et al. (29) identified the primary cytokines in platelets as IL1, IL6, and TNF alpha, which are critical for cell division, chemotaxis, proliferation, and regeneration. These endogenous cytokines are all present in PRP in "normal" physiologic ratios, which is one of its unique benefits. A clot that includes fibronectin, fibrin, and vitronectin as well as other cell adhesion molecules is used to distribute the platelets in PRP. These cell adhesion molecules contribute to the possible biologic activity of PRP since they are involved in cell migration. **(30).**

The thick granules of platelets also contain bioactive substances. The thick granules contain serotonin, histamine, dopamine, calcium, and adenosine **(table 1),** The biologic features of wound healing are fundamentally affected by those non-growth factors **(31).**

Table (1): Growth factors and cytokines in PRP and their different mechanisms **(29)**

Mechanisms	Growth factors and cytokines	Function
Pro inflammatory cytokines	IL1, IL6, and TNF-alpha	Important role in the early responses of tissue repair.

Growth factors	(PDGF), (TGF)beta, (PDEGF), (PDAF), (IGF-1), and platelet factor 4 (PF-4), (VEGF), (EGF)	Help the regeneration of tissues with low healing potential.
Angiogenesis factors	Vascular growth factor (VGF), VEGF, platelet derived membrane microparticles (PMP), and peripheral blood mononuclear cells (PBMNCs)	Promote angiogenesis.
Factors in other mechanisms of PRP	Serotonin, histamine, dopamine, calcium, and adenosine	In the dense granules in platelets and have fundamental effects on the biologic aspects of wound healing

When coagulation factors make contact with particular receptors on cell surfaces, platelets are activated inherently.Some intracellular processes that boost angiogenesis, cell migration, and differentiation, as well as extracellular matrix (ECM) accumulation and tissue regeneration are activated **(32).**

The study by **Cho et al., (33)** demonstrated that the expression of MMP-1 and MMP-3 protein is increased by PRP (activated PRP) **(table 2).** PRP may therefore encourage the removal of photodamaged ECM components and trigger the production of new collagen by fibroblasts, which in turn stimulates their growth. They can help with dermis regeneration by eliminating collagen fragments that harm the dermal connective tissue and provide as a suitable foundation for the deposition of new collagen **(34).**

Table (2): Mechanism of action of PRP in skin rejuvenation **(33).**

Increased proliferation of human dermal fibroblasts
Increased expression of MMP* - 1 and MMP – 3 --- removal of photo damaged ECM
Increased production of procollagen type I peptide and expression of collagen type I, alpha-I ---- Synthesis of new collagen
Increases expression of G1 cell cycle regulators ---- accelerates wound healing

*MMP: Matrix Metalloproteinase

Subsets of PRP:

According to **Najafipour et al. (35)** four platelet concentration preparation categories are found

1- Pure PRP or leukocyte poor:

Leukocyte-free formulations with a weak fibrin network after activation. These products are mostly utilized in sports medicine injuries and come in gel or liquid solution form.

2-Leukocyte PRP:

Low-density fibrin network and leukocytes are present in this preparation.

3-Pure platelet rich fibrin

that lacks leukocytes yet has a fibrin network with great density.

4-Leukocyte and platelet rich fibrin

High-density fibrin and leukocyte productions are the only two be found as strong activated gel. **(36, 37)**

Preparation of PRP:

After receiving proper consent and in an environment that strictly adheres to aseptic procedures, a sample of the patient's blood is taken at the time of therapy. Depending on the patient's initial platelet count, the instrument used, and the procedure used, a 10 cc vein will produce 3-5 cc of PRP. A blood sample is taken while an anticoagulant, such as citrate dextrose, is also added. The procedure used to prepare PRP is called as differential centrifugation; it takes around 15 minutes, and the finished product is then prepared for injection.According to a distinct specific gravity, the acceleration force is changed in this procedure to sediment specific cellular components **(38)**.

In the differential centrifugation method, the first spin of the centrifuge was used to separate The second spin was used to concentrate platelets and red blood cells (RBC) **(figure 3)**, which are suspended in the smallest final plasma volume **(35).**

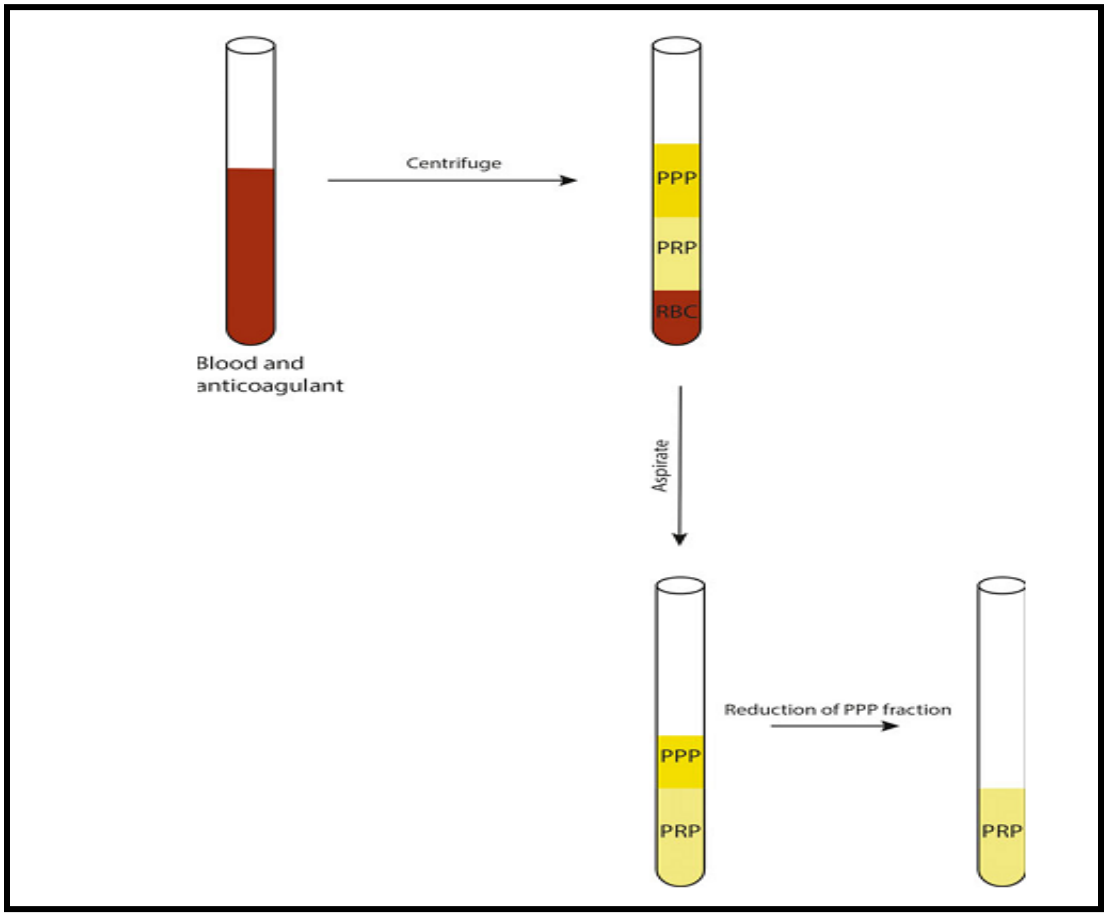

Figure (3): Platelet-rich plasma preparation **(38)**

PRP is activated using platelet activators like Thrombin or calcium chloride.Over the course of seven days, growth factors are trapped and released by a loose fibrin matrix made by the addition of CaCl2 and centrifugation. It is used more frequently during procedures like fat grafting or soft tissue augmentation due to the slower secretion over a longer time period **(39).**

Injection of PRP:

The fact that clotting results in platelet activation, which in turn causes Degranulation, or the release of growth factors from alpha granules, is crucial. Within 10 minutes, roughly 70% of the growth factors that have been stored are released, and within an hour, nearly 100% are. PRP needs to be applied 10 minutes after activation. The platelet may continue to produce a For the remainder of its (1 week) life, a small amount of growth factors **(40).**

Safety of PRP:

Infiltration is a safe and tolerable procedure since platelet rich plasma is an autologous preparation Rarely can it cause post-puncture infection or minor localized inflammation. It

carries no chance of HIV, hepatitis B, or other infections spreading. It doesn't affect the nucleus, hence it has no mutagenic effects **(3).**

Dermatological indications:

1) Peri-orbital hyperpigmentation:

Patients with peri-orbital hyperpigmentation who received Both wrinkles and skin texture were improved with platelet rich plasma skin tone. When PRP is either topically or directly injected into the skin, the ECM is remodeled and fibroblasts are stimulated to create new collagen. However, PRP produces greater results for face and neck regeneration. In order to increase skin remodeling by causing modest inflammatory reactions, microneedles and lasers have been used to improve peri-orbital area vascularity and appearance **(38).**

2) Androgenetic alopecia (AGA):

The most common type of baldness is androgenetic alopecia, although there are now just a few mildly effective treatments available. In order to develop possible therapies that promote hair development, researchers are working in order to comprehend the molecular mechanisms and cellular processes involved in the pathophysiology of alopecia **(41).**

The growth of hair stem is induced by fibroblast growth factor and epidermal growth factor cells, cause them to transdifferentiate, produce new follicular units, beta-FGF and beta-catenin, and encourage the anagen phase of papilla cells, all of which are essential for lengthening the hair shaft **(42).**

Blood flow surrounding hair follicles is improved by platelet rich plasma, which also affects angiogenesis.By having It has mitogenic and antiapoptotic properties that prolong dermal papillae's lifespan **(12, 43)**.

In order to improve the survival probability following implantation, it is often utilized as an adjuvant in hair transplantation. PRP therapy prior to transplanting of follicular units has increased hair growth and density.Prior to implantation and following the PRP is injected into the scalp of the hair follicles in the donor and recipient locations for 15 minutes to encourage wound healing and minimize scarring **(44).**

3) Skin Rejuvenation:

Ageing of the skin is a natural, unavoidable process that is impacted by both internal and external influences. The intrinsic variables that contribute to skin aging, such as ROS-activated MMP, reflect several physiological and pathological processes. The ECM continues to deteriorate due to the buildup of fragmented collagen fibrils, which hinders neocollagenesis **(38).**

PRP works by accelerating the generation of hyaluronic acid to rejuvenate the skin. The hyaluronic acid matrix swells after hyaluronic acid absorbs water, increasing skin volume and turgor. Additionally, it encourages the production of extracellular matrix and collagen fibers, as well as cell proliferation. Overall, it might improve the suppleness of skin. Through PRP, all of these procedures as well as some unidentified ones help to rejuvenate tissue **(33, 45, 46).**

4) Scars and Contour Defects:

Scars on the face can affect a person psychologically and cosmetically. Though they have had mixed results, procedures There have been experiments with fillers, lasers, fat grafting, chemical peeling, and dermabrasion. Due to (PRP's) success in promoting wound healing, in addition to other treatment techniques, it is used to cure depressed face scars. PRP combined with fractional laser or LED phototherapy has resulted in significant improvement, good cosmetic outcomes, and skin renewal **(47).**

Deep nasolabial folds have been effectively treated using platelet-rich fibrin, the second generation of platelet concentrate **(48)**. PRP has a stimulating impact on fat grafts in addition to having rejuvenating properties, hence it is used as an adjuvant in procedures requiring autologous fat transfer. PRP growth factors help the skin recover from laser injury and speed up tissue remodeling by increasing collagen synthesis. Consequently, PRP holds promise for soft tissue augmentation. **(12, 49)**.

5) Acute and Chronic Ulcers:

The treatment of diabetic foot ulcers is quite challenging. PRP is employed to treat diabetic ulcers after recombinant PDGF- bp (becaplermin) gel proved effective in treating these ulcers **(50).**

PRP is used topically or intraperitoneally by injections. A viscous fibrin meshwork Platelet-rich fibrin is a substance that is high in growth factors matrix promotes reepithelization and speeds up recovery **(51).**

6) Striae Distensae:

Striae distensae (striae Alba) is a challenging aesthetic condition issue, and current treatment options have had mixed success. PRP and higher energy fluencies were directly injected into the dermis using a radiofrequency device. PRP accelerates wound healing while bipolar radiofrequency heat energy denatures elastic fibers and collagen bundles, resulting in synergistic advantages and favorable cosmetic outcomes **(12, 52, 53).**

7) Vitiligo:

The Koebner phenomenon may be explained by the intrinsic hypothesis of vitiligo, which states that melanocytes need constant stimulation from keratinocyte-derived c-Kit to remain active. Therefore, passive melanocyte death may occur as a result of weak keratinocyte-derived factor expression, such as stem cell factor **(54).**

PRP's precise mode of operation in vitiligo is yet unclear. According to various reports, keratinocytes and fibroblasts as well as melanocytes play some roles in the etiology of vitiligo. Lack of unidentified growth elements like fibroblast growth factor and keratinocyte growth factor may impair melanocyte attachment and cause transepidermal elimination and chronic melanocytorrhea **(55).**

These growth factors encourage keratinocyte and fibroblast growth, which enhances their interaction with melanocytes and causes the stability of melanocytes, which may explain the favorable effect of PRP in vitiligo. Additionally, it was discovered that PRP treatment led to accelerated fibroblast proliferation and migration via upregulation of CDK4, which is essential for cell migration and proliferation, and cyclin E **(56)**.

Additionally, it is believed that the presence of numerous growth factors, including matrix metalloproteinase-2, platelets-derived growth factor, epidermal growth factor, basic fibroblast growth factor, and platelets-derived growth factor, is what causes the beneficial benefits of autologous PRP on repigmentation, which bind to the transmembrane receptors of the target cells and activate intracellular signal proteins and gene sequences, causing cellular proliferation and the formation of new matrix **(57).** This process may also affect vitilagenous lesions and perilesional skin contain keratinocytes and fibroblasts, improving their interactions with melanocytes and assuring the stabilization of melanocytes, it was proposed **(58)**.

The fundamental justification for combining various forms of therapy with NB-UVB therapy to reduce treatment time is the latter's lengthy duration. Intradermal PRP therapy may be utilized to lower the total UVB radiation exposure and enhance the results of repigmentation. For social, financial, and health reasons, many patients may find it more convenient as a result **(59)**.

The combination of PRP with NB-UVB in the treatment of vitiligo may increase the effectiveness because NB-UVB activates the dopa-negative, amelanotic melanocytes in the outer hair root sheaths, which are encouraged to multiply and spread outward to neighboring depigmented skinof NB-UVB. **(60)** , While PRP promotes the interaction of keratinocytes, fibroblasts, and melanocytes, aiding in the stabilization of melanocytes **(58)**.

PRP has the potential to lower the risk of cancer-related with long-term NB-UVB exposure since its growth factors never reach cells or their nuclei, making them non-mutagenic

and acting by speeding up natural repair. As a result, PRP cannot cause the development of tumors **(61)**.

8) Other Dermatological Conditions:

There are few effective treatments for the widespread autoimmune disorder alopecia areata, which causes inflammatory hair loss. In alopecia areata, platelet-rich plasma has been reported to help in hair growth. Isolated case studies demonstrate the potential of PRP in the treatment of persistent skin conditions, such as persistent lipodermatosclerosis and lichen sclerosus of vulva **(62, 63).**

Complications of PRP:

Following PRP injection, there may be a sharp pain or soreness where the injection was made, some pain, mild swelling, or skin redness. As the PRP is injected into the skin with a needle, bruising is another potential side effect. Despite meticulous sterilization protocols, infection is a small but real risk with any injection-based therapy. Rarely, a patient will experience an allergic reaction where their body rejects their own serum and responds poorly to the medication. Based on bruising history, discoloration Although the area around the skin where a PRP injection site may look bruised may be normal (**40, 64).**

Contraindications to PRP:

In individuals who have been carefully chosen, autologous PRP therapy is typically regarded as safe. Before receiving PRP therapy, eligible patients should have a hematologic assessment to rule out any coagulopathies and platelet function issues (**65).**

Platelet dysfunction syndrome, anemia, thrombocytopenia, hemodynamic instability, severe hypovolemia, unstable angina, and treatment with anticoagulants or fibrinolytics septicemia, and local infection at the surgery site are absolute contraindications **(66)**.

NSAID use on a regular basis smoking, recent fever or illness, malignancy, especially hematological or bone cancer, within 48 hours of the surgery, corticosteroid injections at the treatment site within a month, systemic use of corticosteroids within two weeks, and are relative contraindications HGB < 10 g/dl and platelet count < 105 **(67).**

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