

# Recent Research Progress of Wound Healing Biomaterials Containing Platelet-Rich Plasma

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**Abstract:** Platelet-Rich Plasma (PRP) is a plasma product obtained by centrifuging autologous blood, containing a high concentration of platelets, white blood cells, and fibrin. PRP is enriched with various growth factors, such as Transforming Growth Factor-beta (TGF- $\beta$ ), Platelet-Derived Growth Factor (PDGF), Epidermal Growth Factor (EGF), Insulin-Like Growth Factor (IGF), and Vascular Endothelial Growth Factor (VEGF), all of which promote tissue growth and repair. Currently, PRP has been widely applied in the clinical field of wound repair and has achieved certain therapeutic effects. Biomaterials, as an important direction in the treatment of wounds, combined with PRP, provide new possibilities to enhance the regenerative repair of wounds by PRP. This article reviews the latest research progress of biomaterials combined with PRP in the treatment of wounds, aiming to provide references for PRP wound treatment, as well as to provide ideas for the development of subsequent medical materials.

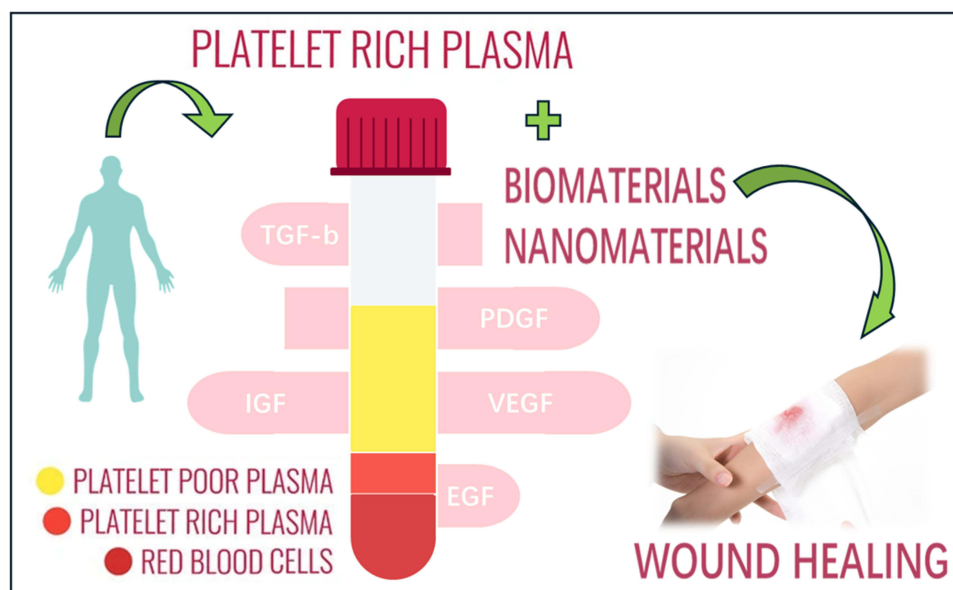
**Keywords:** platelet-rich plasma, prp, wound healing, biomaterials, hydrogel, wound dressing

## Introduction

Trauma is a common issue that is difficult to avoid in production and daily life. Ordinary traumatic wounds can heal through human self-healing capabilities.<sup>1</sup> However, when the severity of a traumatic wound exceeds the body's own healing ability or when the body's healing ability declines, such as in severe burns,<sup>2</sup> pressure sores in malnourished patients,<sup>3</sup> and diabetic wounds<sup>4</sup> often become difficult to heal and continue to have a serious impact on the patient's physiology and psychology. The loss of the skin barrier function not only damages the patient's social functioning but also threatens life if complications such as infection occur. In recent years, the disease spectrum of wound treatment has been constantly changing. With industrial production and the use of electricity and fire becoming more standardized and safer, the number of patients with electric shock injuries and burns has gradually decreased.<sup>5,6</sup> However, the incidence of chronic diseases has increased, the number of diabetes patients continues to grow, and there is a trend towards younger patients. The number of patients troubled by diabetic wounds is also increasing, imposing a serious economic burden on society.<sup>7</sup> Traditional wound treatment includes methods such as debridement, suturing, and skin grafting, but the treatment time is long, and the treatment effect is not satisfactory. Therefore, for wounds that are difficult to heal, how to cure and shorten the patient's healing time and reduce the patient's expenses are urgent issues that need to be resolved in current research.

At present, constructing biomaterials that promote wound healing through tissue engineering is an important and main research field in wound treatment.<sup>8–10</sup> Current experimental studies have shown that combining bio-tissue materials with stem cells,<sup>11</sup> growth factors,<sup>12</sup> and exosomes,<sup>13</sup> and other biological preparations can achieve better wound healing effects. Stem cells have limited sources, are difficult to obtain, and have ethical issues. For wound diseases, clinical application is still a long way off and has great limitations. Although there are exosome products on the market, they are difficult to obtain and expensive. If used clinically, they cannot meet the needs of many patients. Growth factors are currently the most widely used and safe wound healing drugs in clinical practice, with reasonable prices and convenient use. However, the types of growth factor products on the market are single, and the clinical use effect is still not satisfactory. Platelet-rich plasma (PRP) can be

## Graphical Abstract



obtained through autologous blood, the acquisition channel is simple, and there are no ethical issues with other allogeneic biological preparations.<sup>14</sup> The clinical preparation method is also simple, which can be prepared through common centrifugal equipment such as hospital centrifuges and has strong clinical feasibility. It is rich in a variety of the body's own growth factors and has been proven in clinical and scientific research to have great potential in the field of tissue regeneration and repair.

PRP is a plasma product obtained by centrifuging autologous blood, and its platelet concentration is usually 3–7 times higher than that of whole blood.<sup>15</sup> A number of studies have reported that PRP has a promoting effect on the repair of bones, skin, and nerves.<sup>16–19</sup> Many studies have shown that PRP has great potential in the treatment of diabetic wounds.<sup>20,21</sup> In recent years, the application of PRP in wound treatment has achieved preliminary research results. Research on the molecular mechanism of PRP in wound treatment has also made some progress.<sup>22</sup> However, at present, from the application of PRP in clinical practice, researchers' understanding of the mechanism of PRP in wound treatment lacks sufficient depth, which limits the further development of PRP treatment methods. At present, for the treatment of diabetic wounds, hydrogels, artificial dermis, and cell scaffolds are important research directions, which can promote the healing of diabetic wounds.<sup>23–25</sup> They can achieve anti-infection, anti-oxidation, anti-inflammatory, and promote tissue regeneration, and other effects on diabetic wounds by directly combining with various materials and drugs.<sup>26,27</sup> Research combining PRP and these biomaterials has also made certain progress. Therefore, this review summarizes the current research on the mechanism of PRP in wound treatment and the application of biomaterials, sorting out the connections, which is of great importance for guiding the further reasonable development of biomaterials combined with PRP in the treatment of diabetic wounds.

## The Functions of PRP on Wound Healing

The capacity of Platelet-Rich Plasma (PRP) to enhance wound healing is largely attributed to platelets, anucleate blood components that are about 3  $\mu\text{m}$  in diameter and play a pivotal role in hemostasis and thrombus formation at wounds.<sup>28</sup> During the wound repair process, platelets become activated and change shape, altering the conformation of the glycoprotein IIb/IIIa complex on the platelet cell membrane and translocating functional proteins such as P-selectin. These substances rapidly bind to the extracellular surface of cells in grafts, flaps, or wounds through transmembrane receptors present on mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells, and epidermal cells.<sup>29</sup> They

mediate a variety of cellular functions, including cell migration, differentiation, cell cycle, apoptosis, metabolism, and proliferation.<sup>30,31</sup> The molecules released include growth factors (GFs) and cytokines, predominantly located in the  $\alpha$ -granules of platelets.<sup>32</sup> Key factors in these granules include Transforming Growth Factor (TGF- $\beta$ 1), Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), and Vascular Endothelial Growth Factor (VEGF), these factors play very important roles in the healing of wounds and can effectively promote wound healing. Besides these platelet-activated compounds, PRP in plasma also contains significant bioactive factors, such as Hepatocyte Growth Factor (HGF) or Insulin-Like Growth Factor (IGF-1), which originate more from the liver than from platelets,<sup>33,34</sup> and are involved in the regulation of cell chemotaxis, cell differentiation, and mitosis.<sup>35</sup> These abundant growth factors stimulate mesenchymal and epithelial cells to promote the synthesis of collagen and matrix, facilitating the formation of fibrous connective tissue and scar tissue. In addition to growth factors, structures like micro-vesicles and exosomes are also present in the plasma and play a crucial role in cell communication and signal transduction processes.<sup>36</sup>

## Progress in the Extraction and Application of PRP

Reports on the extraction of PRP emerged in the late 1990s, and over the following decade, numerous different preparation methods were reported, all of which involved centrifugation and platelet activation.<sup>14</sup> There is no unified and complete standard for the preparation and use of PRP, and after nearly two decades of development, PRP remains very popular in clinical settings. Traditional PRP preparation methods have certain limitations in terms of collection volume, platelet concentration, and consistency. Nowadays, many innovative preparation methods are continuously emerging and are being improved based on PRP.

PRP can be frozen for storage to achieve a longer shelf life, more efficient inventory management, and more suitable transportation conditions to overcome the limitations in clinical application storage management, which has practical application advantages.<sup>37</sup> However, biologically active components in PRP such as platelets, growth factors, and micro-vesicles will inevitably suffer a loss of biological activity during freezing storage and the subsequent thawing process when used. The research results of Su et al (2024) indicate that frozen PRP has stable biological activity and shows significant regulatory capabilities in key wound healing processes, such as macrophage polarization, fibroblast proliferation, and endothelial cell function.<sup>38</sup>

## Rotary Evaporation Plasma Concentration Method

Jon Mercader Ruiz et al (2024), based on previous research and component analysis of PRP, inferred that in addition to platelets and their derived growth factors, other components in the plasma are important and should not be ignored in the therapeutic effects of PRP.<sup>39</sup> Therefore, they improved the extraction method of PRP by using a rotary evaporator with a water evaporation method. After obtaining standard PRP (sPRP) through traditional centrifugation, a rotary evaporator is used to remove half the volume of water in the plasma to obtain concentrated PRP (nPRP). The study found no significant difference in protein concentration between blood and sPRP ( $p < 0.0001$ ), but the protein concentration in nPRP almost doubled. Obviously, the method of water evaporation can inevitably increase the concentration of platelets and growth factors. However, the concentration of various ions will also increase accordingly, and the environment of ions that is most suitable for the human body is disrupted. The most direct result is that the pH of nPRP increased to 8.4, and its coagulation time was extended. Therefore, it is necessary to adjust the pH by adding HCl and CaCl<sub>2</sub>.<sup>40</sup> PRP obtained by this method has also been verified in cellular experiments for its stronger ability to promote proliferation.

## Lyophilized Platelet-Rich Plasma

Using lyophilization to preserve PRP can achieve a longer storage time. However, PRP must still have sufficient biological activity when used after lyophilization. Nakajima et al (2024) reported a lyophilization method for PRP, and PRP lyophilized by this method still has good anti-inflammatory effects after one year of storage, and the level of biological activity is not affected.<sup>41</sup> Lyophilization for preserving PRP greatly extends its storage time, and it does not require stringent storage conditions, facilitating the clinical use and preservation of PRP.

## Autologous Platelet and Leukocyte-Rich Fibrin Material

Autologous platelet and leukocyte-rich fibrin material (L-PRF) are also a plasma enrichment product. It only requires a single centrifugation cycle for the blood sample without the need for anticoagulants and activators, making the preparation faster and cheaper, and eliminating potential risks associated with the use of bovine thrombin or other activators.<sup>42</sup> Compared with PRP, L-PRF has a higher concentration of leukocytes, which helps immune and antibacterial responses.<sup>43</sup> The extracted L-PRF clot is composed of a dense fibrin matrix forming a complex three-dimensional scaffold containing platelets, leukocytes, growth factors, and fibronectin.<sup>44</sup> It is reported that one of the advantages of L-PRF over PRP is that its high-density fibrin network is conducive to the slow and gradual release of growth factors.

## Autologous Platelet Plasma-Derived Fibrin Scaffold

The autologous platelet plasma-derived protein fibrin scaffold (ABDPS) has been used in wound treatment for many years and is also prepared from autologous blood.<sup>45</sup> ABDPS can be locally injected in a liquid state or serve as a matrix for scaffolds. Current research indicates that the main therapeutic components are platelet and plasma-derived growth factors, microvesicles and exosome-like substances, and fibrin.<sup>46</sup>

The components and mechanisms of action of ABDPS and PRP are similar, but ABDPS is produced from blood through a more complex production process than PRP into an injectable gel or wound dressing application form. For open wounds, wound dressings are the main application form. However, the structure of the wound dressing made from ABDPS is loose, with insufficient strength and support, easy deformation, and poor adhesion and absorption capacity for wounds. Chronic non-healing wounds have variable shapes and depths, and ABDPS as a wound dressing cannot meet the mechanical property requirements of wound healing materials.<sup>47</sup> Therefore, the current research direction is to improve the mechanical properties of pure PRP dressings by incorporating PRP into bio-tissue engineering materials while retaining the healing-promoting ability of PRP.<sup>48</sup>

## Clinical Research on Autologous PRP for Wound Healing

Since ancient times, wound healing has been a challenge for humanity. With the changing disease spectrum, chronic non-healing wounds have gradually become a clinical treatment dilemma. Taking diabetic foot as an example, studies have reported that the median healing time for diabetic foot ulcers without surgery is 12 weeks,<sup>49</sup> 20% of patients cannot heal within a year, and the probability of recurrence within the same year is 40%.<sup>50</sup> Existing treatment measures cannot effectively solve the problem of wound healing. Therefore, in the clinic, researchers have been continuously exploring new methods for wound treatment.

In recent clinical studies, there have been many positive reports on the use of PRP for wound treatment. As early as 2019, Tasmania et al concluded that the use of PRP in diabetic foot ulcers can promote wound healing, reduce the volume of ulcers, shorten the time for complete wound healing, reduce the incidence of adverse events, and there is no difference in the probability of wound complications.<sup>51</sup> In Grant et al' 2021 clinical study, it was found that mixing PRP with fat for the treatment of diabetic foot wounds can increase the survival rate of fat grafts and promote early wound vascularization.<sup>52</sup>

However, at the same time, Ajay et al clinical study involving 60 patients showed that the application of PRP had no significant effect on promoting ulcer healing.<sup>53</sup> Napit et al (2024) conducted a clinical controlled study on 130 patients with neuropathic leprosy ulcers, and the results were not sufficient to prove their routine use in the treatment of neuropathic ulcers of leprosy.<sup>54</sup> From the current numerous clinical studies and meta-analyses of these clinical studies, PRP treatment for wounds is effective.<sup>55</sup> The results obtained by Ajay et al may be related to the extraction method and treatment method of PRP. This indicates that PRP for wound treatment currently lacks a systematic, stable, and promotable treatment plan. Therefore, summarizing the latest research progress of PRP in wound treatment helps to establish an effective plan for the application of PRP.

Although scar formation is the ultimate way of wound healing, excessive scar formation affects aesthetics, and pathological scar formation can also affect patient health. Studies have shown that PRP also has an improvement effect on wound scar formation.<sup>56</sup> Zawadzki et al (2024) conducted a clinical study on patients who underwent breast segmentectomy and found

that using PRP for postoperative injection at the incision can improve postoperative scars.<sup>57</sup> This method only requires one blood drawing and causes minimal harm to the patient. PRP wound injection is clinically feasible for patients who have aesthetic appearance requirements after surgery and for those who have undergone suture after facial trauma. However, injecting through a needle over the wound range also needs to consider whether it will aggravate the damage, so it would be a better research direction if PRP can be used to design non-invasive scar repair materials.

## Combination of PRP With Bio-Tissue Engineering Materials for Wound Healing

Bio-tissue engineering materials play an important role in wound treatment, such as artificial dermis,<sup>58</sup> acellular allogeneic dermis,<sup>59</sup> acellular xenogeneic dermis,<sup>60</sup> and various wound dressings.<sup>61–64</sup> However, current bio-tissue engineering materials still cannot meet clinical needs. Moreover, materials like acellular allogeneic dermis, although they have good clinical effects, are expensive, and many patients cannot afford the cost of treatment, and the material sources are scarce.<sup>65</sup> One characteristic of current bio-tissue engineering materials is the lack of growth-promoting factors. In the clinic, exogenous growth factor drugs are mainly applied to wounds, but there are many shortcomings to this direct application, such as short action time and uneven action.<sup>66</sup> The types and effects of growth factors used in the clinic are single, while wound healing is the result of the common growth and regeneration of various cells.<sup>67</sup> Many studies have combined growth factors with wound dressing bio-tissue engineering materials and found that it can achieve the effect of drug sustained release, which can better promote wound healing.<sup>68,69</sup> However, if this method is applied to actual clinical practice, the evaluation of materials must be according to drug standards to ensure that the production process, storage, and effective performance meet clinical needs. At present, there are no similar products in the clinic. PRP is extracted from autologous sources, has high safety, can be obtained on demand, and all medical institutions have conditions for preparation, which meets the conditions for clinical use. Moreover, PRP has a rich content of growth factors, and if an appropriate method can be found to combine with bio-tissue engineering materials, it will inevitably play a better role. In recent years, studies on the combination of PRP and bio-tissue engineering materials for wound treatment have been continuously reported as shown in Table 1, but it will take many years for their materials to truly enter clinical applications. However, their latest design ideas, principles, and mechanisms are of great reference significance for clinical applications.

**Table 1** The Bio-Tissue Engineering Materials Combined With PRP

Biomaterial	Substance	Innovation	Effects	Ref
Se NPs-PRP	Se NPs and PRP	Leveraging the antioxidant and antimicrobial properties of Se NPs and the growth factor-rich nature of PRP to accelerate wound healing.	Anti-bacteria and accelerate wound healing	[66]
ADAC Hydrogel	AHA, ADA, oxi-CNC, PRP	Self-healing hydrogel with improved strength and PRP impregnation for synergistic skin wound healing	Promotion of granulation tissue, collagen deposition, re-epithelialization, and neovascularization	[67]
NFC hydrogel	NFC, PRP, cellulase	Use of NFC hydrogel as a carrier for PRP, with cellulase assisting in the release of PRP at the wound site	Enhanced re-epithelialization, collagen deposition, and angiogenesis	[68]
CP-PRP sponge	CMCS, $\gamma$ -PGA, PRP	Preparation of a hydrogel through crosslinking of CMCS with $\gamma$ -PGA and enzymatic coagulation of PRP, followed by freeze-drying into a sponge	Enhanced hemostasis effect and promotion of wound healing by releasing EGF and VEGF	[69]
Slow-Sculpting GO/Alginate Gel	GO, alginate, PRP	Slow-sculpting gel with excellent plasticity and PRP loading for wound healing	Promotion of wound collagen synthesis and angiogenesis to accelerate wound healing	[70]

(Continued)

**Table 1** (Continued).

Biomaterial	Substance	Innovation	Effects	Ref
CS/GP/HPC–GO–PRP hydrogel	CS, $\beta$ -GP, HPC, GO, PRP	A thermosensitive chitosan-based wound dressing hydrogel incorporating GP, HPC, GO, and PRP with antibacterial properties and repair promotion	Reduction of wound infection, promotion of epithelial repair and collagen deposition	[71]
NF	NF derived from inguinal subcutaneous adipose tissue, PRP	Use of nanofat to accelerate vascularization, lymphatic drainage, and wound healing	Accelerated wound closure, improved vascularization, and lymphatic drainage	[72]
ODEX/HA-AMP/PRP hydrogel	ODEX, HA-AMP, PRP	The together use of antimicrobial peptides and PRP	Promotion of effective wound healing in chronic infected wounds	[73]
Shell-Core Fibrous Hydrogels	CS, sodium alginate, gelatin, PRP	Design of PRP-loaded multi-layer shell-core fibrous hydrogels for sustained release of growth factors	Promotion of diabetic foot ulcer healing through reduced inflammation, enhanced granulation tissue growth, angiogenesis, and collagen fiber network formation	[74]
HA-DA/PRP	HA-DA and PRP	Combination of HA-DA with PRP for enhanced wound healing	Tissue adhesiveness, rapid self-healing, shape adaptability, antibacterial, antioxidant, and anti-inflammatory properties	[75]
Injectable Dual-Network Hydrogel	HAMA, PVA, PRP	Locational activation of PRP within the uterine cavity for sustained growth factor release	Endometrial regeneration, promotion of cell proliferation, pro-angiogenic effects, and suppression of endometrial fibrosis	[76]

**Abbreviations:** PRP, Platelet-Rich Plasma; Se NPs, Selenium nanoparticles; AHA, Aldehyde-modified sodium hyaluronate; ADA, hydrazide-modified sodium hyaluronate; oxi-CNC, aldehyde-modified cellulose nanocrystals; NFC, Nanofibrillated cellulose; CMCS, Carboxymethyl chitosan;  $\gamma$ -PGA, poly- $\gamma$ -glutamic acid; GO, Graphene oxide; CS, Chitosan; GP,  $\beta$ -glycerophosphate; HPC, hydroxy propyl cellulose; NF, Nanofat; ODEX, Oxidized dextran; HA-AMP, antimicrobial peptide-modified hyaluronic acid; HA-DA, Dopamine-modified hyaluronic acid; HAMA, Phenylboronic acid-modified hyaluronic acid; PVA, polyvinyl alcohol.

## Combination of Platelet-Rich Plasma With Selenium Nanoparticles

Selenium nanoparticles (Se NPs) have been proven to be a multifunctional drug with higher bioavailability and lower toxicity.<sup>77</sup> Selenium (Se) is an essential trace element in almost all physiological processes of the human body, but it is necessary to control the Se concentration to achieve an effective concentration without exceeding unsafe concentrations.<sup>70</sup> Se NPs have all the physiological functions of Se, with low toxicity and high bioactivity. These characteristics make them an ideal choice to solve the safety problem of Se concentration.<sup>14</sup> Studies have found that Se NPs have certain antibacterial abilities, and antibacterial research has not found bacterial drug resistance, making Se NPs an ideal candidate for the treatment of infectious and chronic wounds.<sup>78</sup> Karas et al combined Se NPs with PRP, hoping that the advantages of both in treating diabetic wounds can be combined while solving the instability of PRP.<sup>71</sup> In this study, Se NPs were synthesized by reducing sodium selenite with ascorbic acid in the presence of polyvinylpyrrolidone (PVP) and cetyltrimethylammonium chloride (CTAC), resulting in the formation of orange-colored elemental selenium nanoparticles. The study found that Se NPs have nano-sized particle diameter and a large surface area, have good free radical scavenging ability, can regulate the wound microenvironment, and play a good anti-inflammatory effect. While promoting cell proliferation with PRP, it also regulates inflammatory factors such as interleukin-17A and interleukin-1 $\beta$ . The two regulate wound inflammation in different ways and can play a better role.

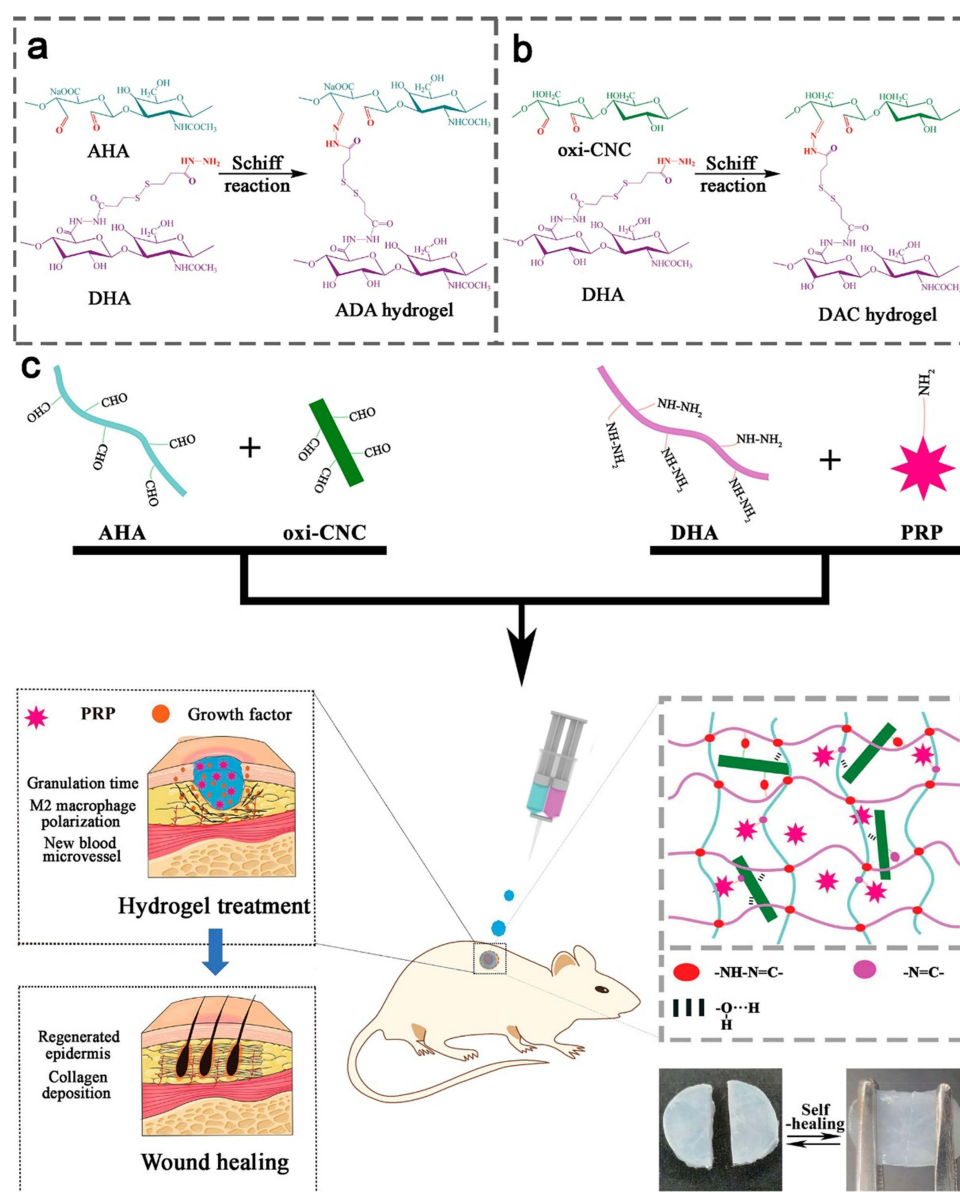
## Combination of Diverse Hydrogels and Platelet-Rich Plasma

Hydrogel dressings are currently the main research direction for wound treatment and have great application prospects. The effect of combining PRP with hydrogels is naturally an indispensable study. After hydrogels and PRP are mixed to make new wound dressings, the stable release ability of PRP and maintaining the bioactivity of various factors in PRP are important indicators for evaluating the effect of PRP in the material. To improve the effectiveness and stability of PRP, appropriate hydrogel materials



should be used to allow bioactive substances to be released through diffusion or material degradation. Plain hydrogels may lack necessary adhesion, injectability, antioxidant properties, and antibacterial properties, and cannot fully meet the treatment requirements of complex diabetic wounds. Li et al (2022) showed that PRP-based hydrogels significantly promote skin wound healing by promoting granulation tissue formation, promoting collagen deposition, and accelerating re-epithelialization and neovascularization (Figure 1).<sup>79</sup> Koivunotko et al (2024) combined PRP with nanocellulose hydrogels, the hydrogel slowly degrades and releases PRP during the treatment process, and the two work together to promote wound healing.<sup>80</sup> These studies show that PRP has a strong combination ability and application prospects with various hydrogels.

Chronic wounds, due to the loss of skin barrier function, and bacterial infection are almost an inevitable issue. How to deal with bacteria on wounds and prevent bacterial infection is an aspect that wound dressing design must consider. Bactericidal through photothermal effect is a popular antibacterial method at present. The photothermal effect kills bacteria by quickly converting light energy into heat energy through near-infrared light irradiation, causing a rapid increase in temperature. PRP,

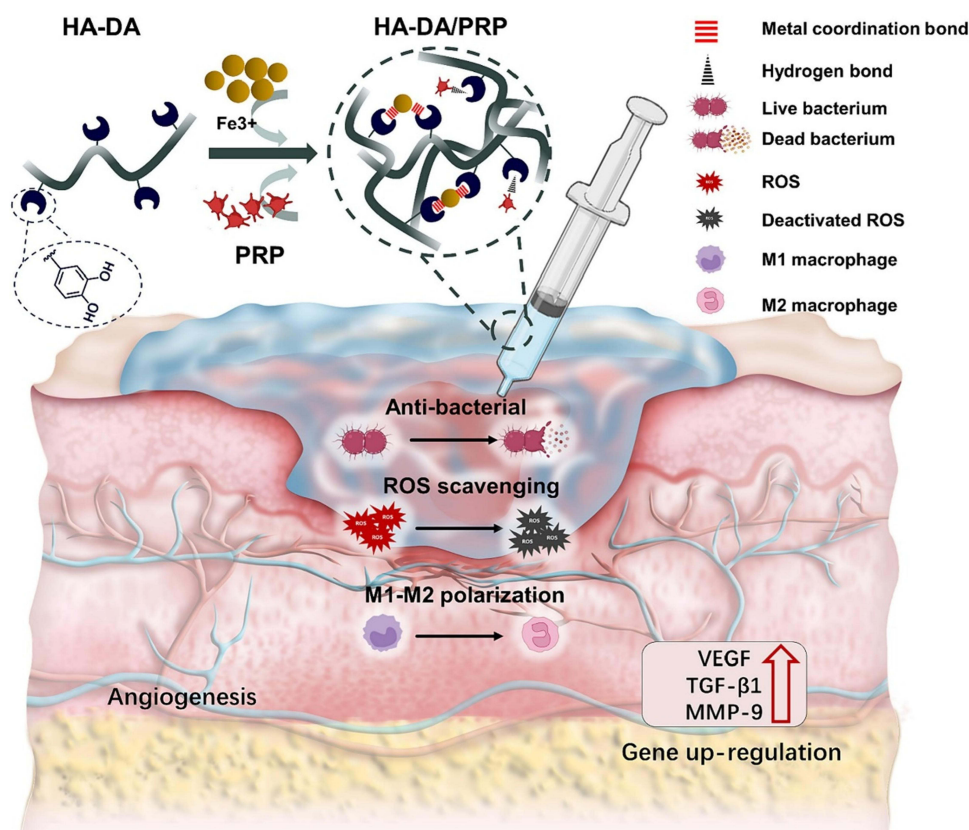


**Figure 1** Schematic illustrations of self-healing hyaluronic acid nanocomposite hydrogels with PRP impregnated for skin regeneration. (a and b) Preparation of hyaluronic acid nanocomposite hydrogels with PRP impregnated. (c) Injection of the hyaluronic acid nanocomposite hydrogels with PRP impregnated into a wound area in situ for skin regeneration. Reproduced with permission from Li S, Dong Q, Peng X, et al. Self-healing hyaluronic acid nanocomposite hydrogels with platelet-rich plasma impregnated for skin regeneration. *ACS Nano*. 2022;16(7):11346–11359. Copyright (2022) American Chemical Society.<sup>79</sup>

extracted from human plasma, usually needs to be stored under cold conditions to maintain its activity. In hydrogels with photothermal effects, it is unknown whether PRP can still exert its biological activity when the temperature rises rapidly. Many growth factors in PRP are biologically active proteins, and temperature changes are likely to affect them. Liu et al published a study in 2024 that combined PRP with hydrogel dressings with photothermal effects.<sup>81</sup> They used chitosan and hydroxypropyl cellulose to form the hydrogel matrix, using graphene oxide as a light-to-heat converter. This hydrogel can quickly raise the temperature by 16 degrees Celsius within 8 minutes under near-infrared light irradiation, with the highest temperature controlled around 43 degrees Celsius. The experimental results in animals also showed that the hydrogel with photothermal effect was better than the hydrogel without photothermal effect. Although the gel contained PRP in the experiment and promoted healing compared to the control group, each experimental group in the experiment contained PRP, so it cannot be concluded that the photothermal effect would affect the activity of PRP, and it is even uncertain whether PRP played a role in the in vitro experiments.

An important issue faced by PRP hydrogels in practical applications is the lack of adhesiveness, leading to the rapid loss of PRP at the wound site and a decrease in its effectiveness.<sup>82</sup> Increasing the stability of PRP and its action time at the wound undoubtedly can enhance its therapeutic effect on diabetic wound healing.<sup>72</sup> In addition, PRP lacks the ability to regulate oxidative stress, inflammation, and infection at diabetic wounds. Dopamine (DA) happens to supplement this missing capability of PRP. Hydrogels combined with DA not only exhibit wet adhesion to various surfaces but also demonstrate antioxidant and anti-inflammatory properties.<sup>83</sup> The two can achieve a variety of healing effects by simply combining them in the same biomaterial.

Duan et al (2024) combined dopamine-modified hyaluronic acid (HA-DA) hydrogels with PRP to construct a series of sticky wound dressings, aiming to achieve the goal of diabetic wound repair through anti-inflammatory, antibacterial, antioxidant, and regenerative promotion as shown in Figure 2.<sup>84</sup> To provide injectability to DA-derived hydrogels, they



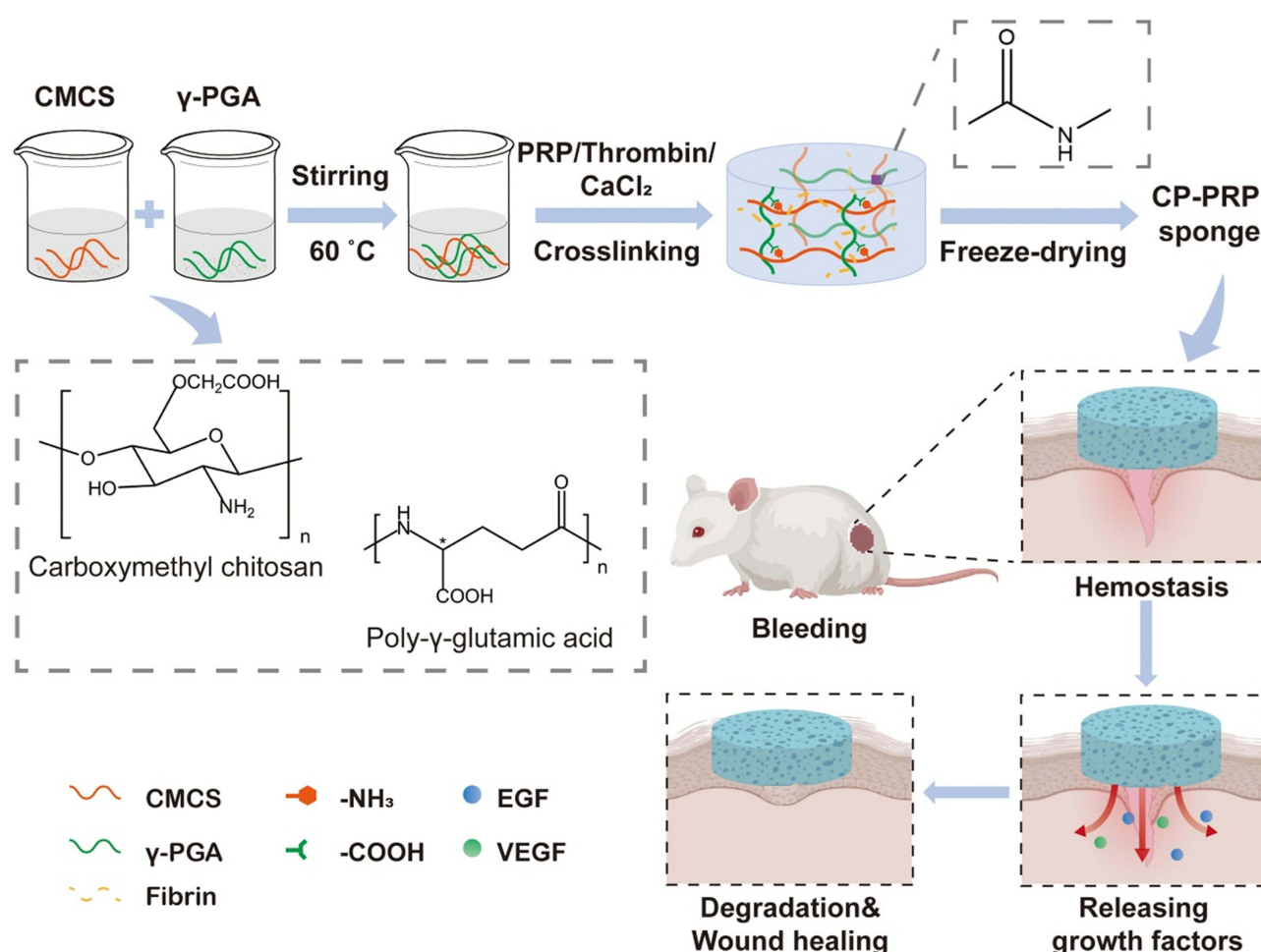
**Figure 2** Scheme of the preparation of HA-DA/PRP adhesives and their applications on diabetic SD rats with infected full-thickness skin defect. The preparation of the designed HA-DA/PRP adhesive required only one step by mixing the solution of HA-DA and the solution of  $\text{FeCl}_3$  with PRP. PRP is anchored in this network due to the hydrogen bonds between PRP protein and DOPA. By applying HA-DA/PRP adhesive on the wound site, the adhesives serve as a microenvironment regulator for infected diabetic wound healing. Reprinted from *Carbohydr Polym.* Volume 337. Duan W, Jin X, Zhao Y, et al. Engineering injectable hyaluronic acid-based adhesive hydrogels with anchored PRP to pattern the micro-environment to accelerate diabetic wound healing. 122146, copyright 2024, with permission from Elsevier.<sup>84</sup>



introduced  $\text{Fe}^{3+}$  chelating agents into the system. The other advantage of  $\text{Fe}^{3+}$  is its potential antibacterial ability based on iron. Through the interaction between catechol groups and PRP proteins, PRP is incorporated and anchored in the HA-DA adhesive network. Therefore, just a few simple ingredients can obtain the urgently needed anti-inflammatory, antioxidant, antibacterial, and regenerative capabilities for wound healing. In Duan et al's hydrogel, the important photothermal effect characteristic of DA was overlooked. The photothermal effect has been proven to be of great significance for the healing of diabetic wounds. DA has proven to have good near-infrared light conversion ability, and the photothermal conversion ability after combining DA and HA was not verified in this experiment. If it also has photothermal conversion effects, the material's ability to promote the healing of diabetic wounds will be greatly enhanced.

## Combination of Wound Sponge Dressing With Platelet-Rich Plasma

Lyophilized sponge dressings have a porous structure and are highly absorbent products that can absorb a large amount of PRP to exert its effects in clinical use. Tang et al (2023) used carboxymethyl chitosan and poly- $\gamma$ -glutamic acid as the base materials for lyophilized sponges, and added calcium ions and thrombin as PRP and activators as shown in Figure 3.<sup>73</sup> PRP was added and then lyophilized to construct lyophilized sponge materials. The platelets in PRP can play a role in wound coagulation and hemostasis, while growth factors can be responsible for promoting wound growth. Although this method of simultaneously lyophilizing PRP and materials to obtain lyophilized sponges is feasible in experimental research, there are obstacles in real clinical applications. As an autologous plasma product, if PRP is

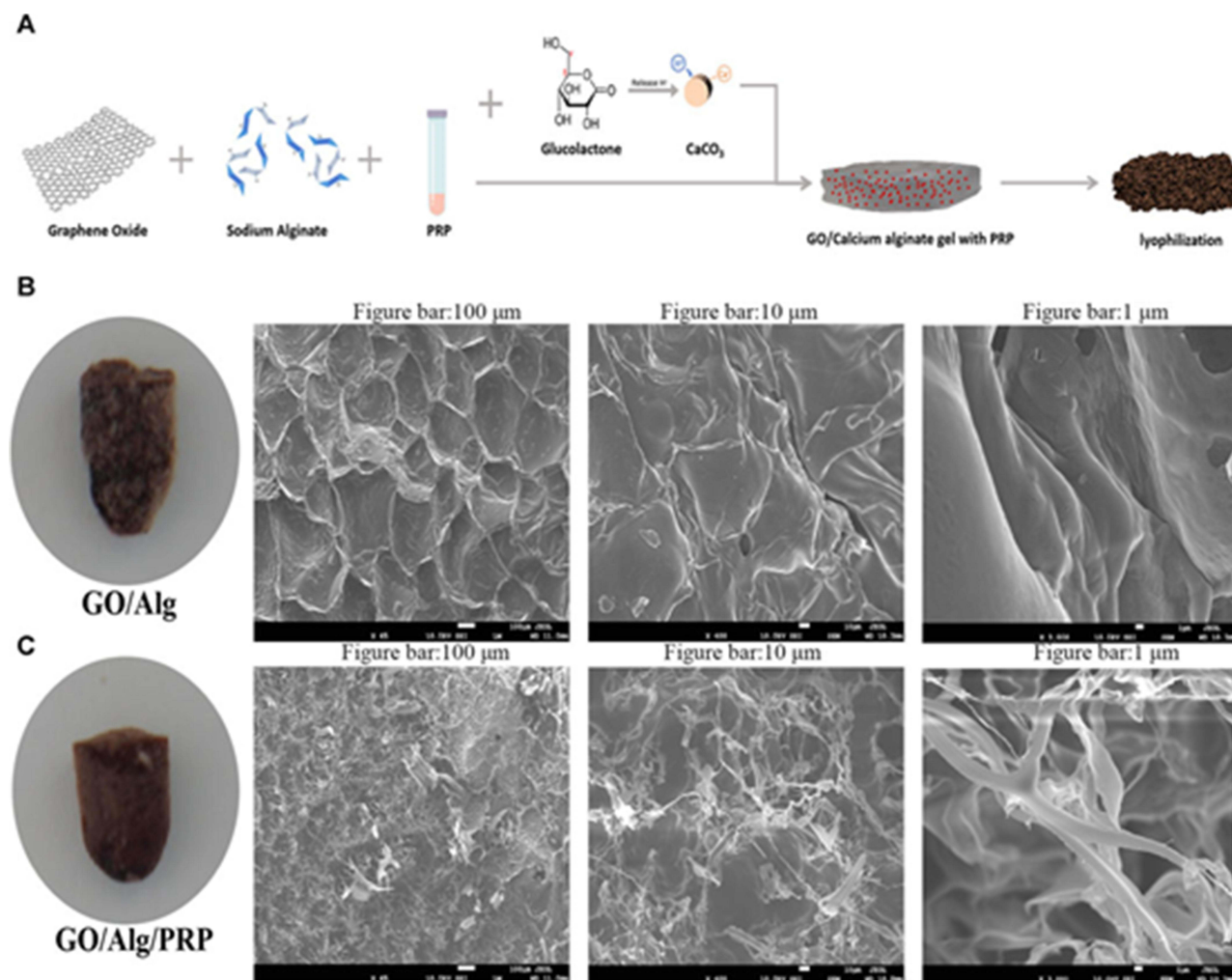


**Figure 3** A brief presentation for preparation, microstructure, and mechanism of CP-PRP for hemostasis and wound healing. Reprinted from *Int J Biol Macromol*. Volume: 247. Tang J, Yi W, Yan J, et al. Highly absorbent bio-sponge based on carboxymethyl chitosan/poly- $\gamma$ -glutamic acid/platelet-rich plasma for hemostasis and wound healing. 125754. Copyright 2023, with permission from Elsevier.<sup>73</sup>

extracted and then made into sponge dressings by medical device companies, it increases the production process and is not conducive to clinical application. However, wound sponge dressings can adsorb PRP on their own without the need to incorporate PRP into the material and then lyophilize together. The activators of PRP and the base materials of the dressing can be lyophilized together, and PRP can be added on the spot when used in the clinic, making such materials versatile.

## Combination of Graphene Oxide With Platelet-Rich Plasma

Graphene oxide, as a new type of material, has the advantages of high specific surface area, great thermal stability, special physicochemical properties, good electrical conductivity, and amazing mechanical strength, and can play a synergistic effect with other materials.<sup>74</sup> Chen et al incorporated PRP into a graphene oxide-reinforced alginate hydrogel to construct a wound dressing as shown in Figure 4.<sup>85</sup> Graphene oxide surfaces contain a variety of oxygen-containing functional groups, have richer surface activity, good hydrophilicity, and biocompatibility, which not only play its role in the hydrogel's good biocompatibility and moisturizing effect, promoting wound healing, but also have antibacterial properties.<sup>75</sup> Although the material showed good results, it is a pity that the study did not further explore whether there were any interactions between the graphene oxide material and PRP.



**Figure 4** Preparation and characterization of the GO/Alg/PRP. Preparation route of the GO/Alg/PRP (A). Gross appearance and SEM image of GO/Alg, GO/Alg/PRP at indicated magnification scale, and their porous structure (B and C). Reprinted from *Front Bioeng Biotechnol*. Volume: 12. Chen N, Li M, Yang J, Wang P, Song G, Wang H. Slow-sculpting graphene oxide/alginate gel loaded with platelet-rich plasma to promote wound healing in rats. 1334087, Creative Commons.<sup>85</sup>

## Autologous Fat Components Combined With Platelet-Rich Plasma

Components derived from autologous fat, such as adipose-derived mesenchymal stem cells and Nanofat (NF), have been proven to play an important role in tissue regeneration and repair. NF is an autologous fat derivative obtained through mechanical emulsification and filtration to form a liquid suspension.<sup>86</sup> NF is widely used in the fields of regenerative and aesthetic medicine, such as facial rejuvenation, fat filling, scar repair, burn management, and hair loss treatment.<sup>87</sup> Like PRP, NF can also be extracted from the patient's own body. NF contains a high concentration of extracellular matrix, growth factors, adipose tissue-derived stem cells, and microvascular fragments.<sup>76</sup> All of these individual components have been proven to promote tissue formation and the development of new blood perfusion microvascular networks.<sup>88</sup> Limido et al (2024) mixed NF with PRP for the treatment of full-thickness wounds in mice and found the effect to be better than using NF alone.<sup>89</sup> Using PRP on the wound can stabilize NF and significantly accelerate and improve tissue regeneration. Both NF and PRP have been widely used in the clinic, and their combination is therefore rational and feasible in clinical applications. However, the extraction of NF requires the removal of a certain amount of autologous fat tissue from the patient's fat layer, which is highly traumatic to the patient. For patients suffering from chronic diseases, it is uncertain whether such an operation will cause another chronic non-healing wound, and more clinical studies are needed to determine safety. The mechanical and physical properties of both autologous NF and PRP materials are not ideal, with high fluidity. As a dressing, it is possible to consider improving its mechanical properties for clinical use.

Iseki et al (2024) combined adipose-derived mesenchymal stem cells, photo-curable hydrogels, and PRP to create an injectable cartilage repair hydrogel.<sup>90</sup> Hydrogel can provide sufficient mechanical support for the dressing and also support the growth of encapsulated adipose-derived mesenchymal stem cells. The growth factors rich in PRP can also protect mesenchymal stem cells and promote their differentiation.<sup>91</sup> The interaction of adipose-derived mesenchymal stem cells, hydrogels, and PRP constitutes a closely connected repair system. The same system is also referential in the repair of diabetic wounds.

## Summary and Perspective

### PRP Has High Feasibility in the Clinical Treatment of Wounds

The model of extracting PRP from patients and then applying it to diabetic wounds has clinical feasibility. Firstly, the source of PRP is stable PRP can be obtained by centrifuging a harmless amount of blood drawn from the patient, and the existing equipment in the hospital's laboratory can meet its preparation requirements. The amount obtained is sufficient for small-area wounds commonly seen in clinical practice, such as diabetic foot ulcers. However, for large area burns and other wounds, the source of PRP is still not abundant enough.

PRP is easy to preserve. PRP can be preserved by freezing in common freezers in hospitals.<sup>38</sup> Chronic wounds still require a long recovery time even after debridement and skin grafting. During this period, supplementing the wound with growth factors and other substances can promote the growth of granulation tissue, providing a good environment for skin grafting and facilitating the survival of the transplanted skin. PRP can be obtained from the body at one time, preserved by freezing, and used multiple times. Chronic wounds are recurrent and have a high risk of recurrence, and PRP can be preserved by lyophilization for a longer storage time, which can be applied to multiple treatments.

### PRP Requires a Standardized Protocol in Wound Treatment to Ensure Effectiveness

At present, there is no standardized guide for the use of PRP in wound treatment, which has led to different hospitals relying more on empirical treatments, resulting in unstable effectiveness. Firstly, there is no unified standard for the source of PRP. There is no standard plan for extracting PRP. The methods of extracting PRP in literature are diverse, and the effectiveness of different methods in the clinic has not been certified. Secondly, there is no screening mechanism for patients suitable for PRP treatment. Most patients with chronic wounds are older and have other underlying diseases. It is uncertain whether the blood extracted from patients can be prepared into qualified PRP. There are no standards for the effectiveness of prepared PRP. The content of key components such as platelets and growth factors in the extracted PRP should meet what standards to be qualified PRP has no standards. Secondly, there are no standards for the use of PRP. The dosage and frequency of PRP use are the basis for its effectiveness. Too little PRP will lead to its ineffectiveness,

and too much will cause waste. There are no standards for how to use PRP. The methods used in current research include injection, application within the wound, and combination with wound dressings.

A 2024 review and meta-analysis of 10 randomized controlled trials concluded that PRP treatment for ulcers significantly improved the healing rate and time for diabetic foot patients compared to traditional treatment.<sup>92</sup> However, a 2021 clinical study found no improvement in healing rate and time between PRP-containing dressings and regular dressings.<sup>53</sup> The main reason for these different conclusions from various studies is the different application methods of PRP. Platelet drugs, food, blood sugar, hypertension, dyslipidemia, and stress levels can all affect the quality and effectiveness of PRP samples.<sup>93</sup> Moreover, the method of using PRP also has an important impact on its effectiveness.

Therefore, establishing a complete set of PRP usage standards is of great significance to ensure the effectiveness of its treatment. The first step is to determine the effectiveness of the source of PRP and establish a screening mechanism for patients suitable for PRP treatment. For obtained PRP, screening standards should be established, such as testing platelet content and growth factor content to avoid applying ineffective PRP to patients. Establish reasonable clinical usage standards for PRP to regulate its dosage, frequency, and method of use. The method of using RPR may be the key to its effectiveness. The reason why ordinary PRP dressings are ineffective may be due to incorrect usage methods, which fail to exert their effectiveness. The growth factor substances in PRP are more similar to growth factor drugs used in the clinic. Ordinary gauze dressings do not have enough drug-controlled release capacity and cannot help them exert their effectiveness. There are also a variety of materials used for skin regeneration in the clinic, and a reasonable combination of PRP with these materials can better exert the function of PRP.

## Materials Combined With PRP Need to Consider Versatility

PRP, as an autologous transplant material, can only be used on the person from whom it is extracted in clinical use and is directional. Therefore, biomaterials containing PRP must also be usable only by the patient from whom the plasma was extracted. However, current medical device production and PRP extraction are not completed by the same entity. Current experimental research, design, and production are all completed by the same laboratory, and the experimental product contains both PRP and biomaterials. The application of experimental animals as subjects does not consider the unity of PRP extraction and usage. These two situations are different from the actual clinical use. In clinical use, hospitals have the ability to extract and produce PRP but do not have the ability to produce wound dressings. Wound dressings are usually produced by medical device companies. Therefore, the most suitable materials for clinical use should be versatile materials produced by medical device companies that can be used in conjunction with PRP when applied.

## PRP Has the Ability to Combine With a Variety of Hydrogel Materials

Hydrogel dressings are an important research area in biomaterials for wound treatment today. They can promote wound healing and also provide a platform for many wound treatment drugs. The combination of drugs that promote wound healing with hydrogels is also an important design strategy for wound dressings today. If the drug is combined with the hydrogel and cannot be released, it will inevitably greatly reduce its effectiveness. Many studies have shown that PRP can be combined with a variety of hydrogel materials, such as methacrylated hyaluronic acid hydrogel,<sup>94</sup> dopamine-modified hyaluronic acid hydrogel,<sup>84</sup> methacrylate gelatin hydrogel,<sup>90</sup> bacterial cellulose hydrogel,<sup>95</sup> and alginate hydrogel.<sup>96</sup> These studies have also proven that PRP can be combined with hydrogels, which can help PRP act on the wound for a longer time and increase the healing ability of hydrogels.

## The Effect of Hydrogels With Photothermal Effect Combined With PRP Needs Further Study

Hydrogels with photothermal effects can quickly convert near-infrared light into heat, achieving the effect of wound sterilization and promoting healing. PRP is extracted from the human body and contains platelets and a variety of growth factors. When the wound temperature rises rapidly and exceeds the normal human body temperature, whether the



effective components will denature and whether the effectiveness will decrease is not yet deeply studied. If the rapid increase in temperature causes PRP to become ineffective, then the combination of the two would be detrimental. All current studies have not considered this point. If you want to verify whether PRP is effective under photothermal action, you need to set up control groups with and without PRP under near-infrared light irradiation to observe the effect of PRP after temperature change.

If PRP is still effective after the temperature rises in hydrogels with photothermal effects, then its application range will be greatly expanded. Dopamine is also an excellent photothermal conversion material. There have been studies combining PRP with dopamine-containing hydrogels, but there has been no research on its photothermal effect.

## Conclusion

In summary, the application of PRP in wound healing has demonstrated significant potential, particularly in the context of diabetic and chronic wounds. The integration of PRP with various biomaterials, such as hydrogels and sponge dressings, has shown promise in enhancing the regenerative process by leveraging the natural growth factors present in PRP. While the clinical application of PRP has been met with variable success, the development of standardized protocols for PRP extraction, application, and combination with biomaterials is crucial for ensuring consistent therapeutic outcomes. Furthermore, the exploration of PRP's synergistic effects with novel materials like graphene oxide and selenium nanoparticles holds great potential for advancing wound care. Despite the challenges in optimizing PRP's stability and activity, especially in innovative dressings with photothermal properties, the future of PRP in wound healing appears bright. As research continues to address the variability in PRP preparation and application methods, the field moves closer to realizing PRP's full potential in transforming wound care and enhancing patient recovery.

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## Declaration

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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