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Review Article

Emerging Delivery Strategies of Platelet-Rich Plasma with Hydrogels for Wound Healing

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Platelet-rich plasma (PRP), a platelet-rich plasma concentrate obtained from whole blood, has been widely used to treat wounds due to its high contents of growth factors that can not only play a role in the hemostasis, repair, and anti-infection of wounds but also promote cell proliferation, maturation, and angiogenesis. However, after PRP activation, its clinical effect was limited because of burst and uncontrolled release of growth factors and poor mechanical properties of PRP gels. In recent years, increasing attention has been moved to the loading and sustained release of growth factors in PRP by polymeric carriers. Hydrogels, as an interesting carrier, enable controlled delivery of growth factors by structural designs. Moreover, using hydrogels to encapsulate PRP is favorable to controlling the mechanical properties and water maintenance of PRP gels, which can provide a stable and moist wound repair environment to promote coordinated operations of skin tissue cells and cytokines as well as wound healing. In this review, the state of the art of hydrogels that have been used to load PRP for wound treatments is introduced, and further prospects in the research area are proposed.

1. Introduction

As the largest organ of the human body with perception, metabolic, barrier, and other functions, skins are important for maintaining the stability of internal human environments. Extensive destruction of skin integrity due to trauma and diseases can cause severe disability or even death. The healing of skin wounds is divided into orderly and overlapping phases: hemostasis, inflammation, proliferation, and remodeling [1, 2]. They are tightly regulated by a series of external and internal stimuli, such as growth factors and cytokines, resulting in regeneration of the damaged skin [3]. Acute wounds are injuries to skin resulting from abrasion, avulsion, incision, laceration, and puncture [4], while chronic wounds are generally caused by failed or delayed healing as well as accompanying physiological conditions and continuous stimulations (including diabetes [5], elevated and sustained reactive oxygen species (ROS) [6], and infections [7]). Unlike acute wounds that can heal after a relatively short period, chronic wounds tend to heal over a period of 12 weeks or more or even not heal completely.

Wound care consists of wound cleansing, disinfection, closure, if needed, and dressing. Traditional wound dressings (such as gauze, bandages, and plasters) cannot provide a moist healing environment and are also easy to adhere to the wound, which will cause reinjury when the dressing is removed. Many different kinds of temporary skin substitutes have been developed as wound dressings to accelerate wound closure, induce tissue growth, and reduce scar formation, including tissue-engineered skins, aerogel dressings, hydrogel dressings, and foam dressings [8–11]. Tissue-engineered skin substitutes are modern dressings that are cell-containing matrices or acellular matrices that release bioactive molecules to accelerate epithelialization. Aerogel

dressings are generated by the replacement of liquids inside a gel with gas. In comparison to aerogels, hydrogels have many features, including high water content, smoothness, and flexibility and providing a moist environment protecting the wound from drying. Hydrogel dressings can isolate harmful substances and resist microbial infections while maintaining a moist environment around the wound, allowing gas to pass through and absorb exudate. Foam dressings can be used for various wound types due to their strong absorptive capacity. Among them, hydrogels, nanoporous gel structures, are 3-dimensional (3D) hydrophilic polymers designed via gel precursor crosslinking, which can be applied for several uses, such as drug delivery, cell encapsulation, wound healing, and tissue engineering. The difference between hydrogel dressings and other types of dressings is that due to the presence of chemical or physical crosslinks, they are able to swell and retain large amounts of water, which keeps the wound surface moist. Moreover, hydrogels can also offer mechanical improvement as well as biological activity by mimicking the extracellular matrix (ECM) [12–14]. Research on hydrogels as wound dressings has also shown an increasing trend in recent years. Liang et al. [15] prepared a gelatin-grafted dopamine-based CNT-loaded hydrogel, which not only possesses good adhesion performance but also has multiple functions, such as injectable, antibacterial, and antioxidant, showing great potential to promote better healing of infected full-thickness skin wounds. Ma et al. [16] prepared a heat- and pH-sensitive hydroxypropyl chitin/tannin/iron (HPCH/TA/Fe) composite hydrogel using a simple assembly process. The prechilled hydrogel solution can be quickly gelled at a physiological temperature after being injected into wounds. The composite hydrogel showed broad-spectrum antibacterial activity for up to a week. In addition, hydrogels have been applied for bone and muscle as well as cell and drug encapsulation due to their unique features, including high water content, smoothness, flexibility elasticity, and capability to create a moist situation protecting the wound from drying [17, 18].

Growth factors are a class of important bioactive proteins that play an important role in regulating cell function and maintaining tissue homeostasis [19]. Numerous studies have shown that topical treatments such as epidermal growth factor (EGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) enhance wound healing in animal models and clinical trials. Conversely, the absence of relevant cytokines often results in delayed repair or even failure to heal the wound. Among the growth factors, EGF and FGF are the most commonly used factors that can be encapsulated in hydrogel dressings for wound healing to increase their half-lives, which greatly limits the effects of angiogenesis, anti-inflammation, and wound healing [20, 21]. For example, Huang et al. [22] utilized acidic gelatin hydrogel microspheres to control the release of basic fibroblast growth factor (bFGF) in a diabetic mouse skin wound model, inducing the apoptosis of myofibroblasts/fibroblasts and promoting wound healing. VEGF is a multifunctional molecule that has the ability to stimulate the growth of new blood vessels and increase vascular permeability. In recent years, VEGF-encapsulated hydrogel systems have also attracted much attention [23]. In addition, Kim et al. [24] used gelatin hydrogels loaded with matrix-derived factor 1 and sphingosine 1-phosphate agonists to induce aggregations of massive mesenchymal stem cells and macrophages to facilitate wound repair in mouse skin. Although growth factors play an important role in wound healing, their practical applications are restricted due to the short half-life, low stability, and limited effects of a single growth factor [25].

Platelet-rich plasma (PRP) is plasma containing highly concentrated platelets from whole blood produced through the process of gradient density centrifugation, also known as platelet gel or concentrated platelets, and has gained increasing attention in both the scientific literature and the wider media for its potential application in the treatment of traumatic musculoskeletal injury [26–28]. The theoretical benefit of PRP in providing a local environment for tissue regeneration, which is rich in growth factors and other cytokines, has been supported by in vitro and animal studies, which suggest a positive influence on the migration and proliferation of a number of cell types [29, 30]. Recently, PRP has been applied for the repair of various tissues, including bone [31], cartilage [32], skin [33], and soft tissues [34]. Nonhealing chronic wounds and exposed tendons, bones, and joints are very challenging to cure, especially for diabetic patients. Saldamacchia et al. [35] reported the use of PRP for chronic diabetic foot ulcers in 14 patients and found a significantly higher rate of healing after 10 weeks (71% versus 29%). Burgos-Alfonso et al. [36] investigated the curative effects of 40 patients with chronic venous leg ulcers. Compared to conventional therapies (compression and dressing), a significantly improved effect for the ulcer was observed using the post-PRP therapy, that is, reductions in length, width, and area of the ulcer as well as the percentage of change in the ulcer area. Furthermore, Görmeli et al. [37] compared the clinical effect of PRP for osteoarthritis with that of a traditional intra-articular hyaluronic acid injection therapy. Clinical results indicate that intra-articular PRP and hyaluronic acid treatment is recommended for all stages of knee osteoarthritis. For patients with early osteoarthritis, multiple PRP injections have been confirmed to achieve better clinical effects.

In addition to being a source of growth factors, PRP has been utilized for the enhanced delivery of growth factors and/or cells within tissue-engineered constructs, often in combination with biomaterials. Hokugo et al. [38] reported that the combination of PRP with biodegradable gelatin hydrogels showed the potential to enhance bone repair in vivo. Moreover, PRP can be also used as an autologous cell culture additive and cell carrier [39, 40]. It can be administered topically in an inactivated liquid form through infiltration or injection for the treatment of skin, joint, or tendon disorders. In this case, growth factors are released on the application site after platelet activation by endogenous substances such as collagen. Alternatively, PRP can be prepared via exogenous activators, such as bovine thrombin [41], ascorbic acid [42], and thrombin/calcium chloride [43]. PRP can be placed in situ on the affected site after inducing the formation of a clotted/gelatinous material,

Table 1: Some important growth factors secreted by platelets and their functions.

Growth factor	Functions
TGF-β	Promoting angiogenesis, reepithelialization, granulation tissue formation, collagen production, and synthesis of protease inhibitors and inhibiting collagen decomposition
PDGF	Promoting fibroblast proliferation, increasing collagen production, and reshaping extracellular matrix
EGF	Promoting epidermal growth, connective tissue contraction,, and matrix formation
IGF-1	Regulating cell proliferation and differentiation, affecting matrix secretion by osteoblasts, and promoting the synthesis of glycoprotein, collagen, and other proteins
FGF	Stimulating growth and differentiation of chondrocytes and osteoblasts and stimulating expression of collagenase
VEGF	Promoting proliferation, migration, and angiogenesis of endothelial cells

referred to as platelet or PRP gels. Perinelli et al. [44] investigated mechanical properties of PRP gels obtained in the presence of thrombin and different calcium concentrations. The introduction of Ca^{2+} could promote the formation of the internal network structure of PRP gels, enabling high elastic moduli and network stability. Nevertheless, PRP is limited due to burst release and its short half-life; that is, 95% of these growth factors are secreted within an hour, quickly dilute, and decay into the tissue fluid. Despite promoting fibroblast proliferation and angiogenesis, the contribution of growth factors is quite limited [45, 46]. Additionally, pure PRP gels are difficult to separate from activation supernatants, making therapeutic effects for the sinus tract, lacunar space, and epidermal wounds far from requirements.

In recent years, PRP has been successfully encapsulated into biodegradable but mechanically stable hydrogel materials. For example, chitosan scaffolds were proposed for PRP encapsulation and controlled release of growth factors [47]. Similarly, PRP-loaded scaffolds of hyaluronic acid/gelatin or gelatin were investigated for bone healing [48]. Growney et al. [49] designed injectable alginate hydrogels loaded with PRP through chemical bonding to saccharide backbones with carbodiimide chemistry. Censi et al. [50] investigated the chemical encapsulation of PRP and the controlled release of growth factors with vinyl sulfone bearing hyaluronic acid/poly (hydroxypropyl methacrylamide lactate)-polyethylene glycol hydrogels. The loading of PRP with the hydrogel via Michael addition enabled an increase in G', suggesting the formation of PRP-involving crosslinked networks. Jain et al. [51] also used Michael addition to prepare degradable PEG hydrogels for the sustained release of PRP. From the in vitro investigations, the PEG hydrogel sustained the release of different PRP growth factors until gel degradation but still exhibited a burst release with up to 40% of protein released in 1 h. An additional 30%-40% release was observed at 10-24 h, with the remaining protein being released at complete gel degradation. Moreover, Notodihardjo et al. [52] used gelatin hydrogels as a sustained-release system for delivering platelet-rich plasma release (PRPr) and evaluated the wound healing effect in murine skin defects. After impregnation with PRPr (PRPrG), gelatin hydrogels significantly accelerated the reduction in the wound area, epithelial formation from the marginal wound, and capillary formation of the wound bed and prevented wound contraction after 21 days compared with the control, gelatin, and PRPr groups. In addition, PRPrG provided a moist environment for wound healing and showed efficacy in wound healing compared with the single application of PRP. In conclusion, hydrogels are employed as carriers to achieve controlled transport of growth factors and improve the mechanical properties of PRP gels. When neat PRP gels are applied to wounds, the gels are easily separated from wound surfaces with wound necrosis and exudation, losing anti-inflammatory and repair effects. In comparison, PRP-loaded hydrogels can provide moist environments conducive to wound healing and absorb excess exudates. Additionally, hydrogels working as dressings can provide a stable and moist wound repair environment for damaged skin tissues and promote the coordinated operation of skin tissue cells and cytokines [53]. This review will introduce the latest research progress on hydrogels for the controlled delivery of PRP and healing of skin wounds.

2. Mechanism of PRP in Promoting Wound Healing

PRP participates in various stages of wound healing. After wound formation, platelets in the PRP gather to form a primary thrombus. Then, thrombin is activated by platelets, catalytic conversion of fibrinogen to fibrin, fibrin network, and finally blood clots. Moreover, blood clots are strengthened by platelet contractions, acting as a secondary hemostatic effect. PRP exerts immune effects by secreting platelet basic proteins and fibrin peptides, mediating inflammatory responses by expressing Fc and complement receptors [54, 55]. Soluble fibrinogens in PRP can regulate major inflammatory cells at injury sites, mediating transitions of inflammatory responses to proliferative repair phases during wound healing. The formed constructed fibrin networks further act as carriers for active platelet components, facilitating the aggregation and functionalization of leukocytes and platelets [56]. PRP contains not only antimicrobial peptides but also catecholamines, serotonin, osteonectin, proaccelerin, and other substances that are beneficial for adjusting the local microenvironments of

Table 2: Applications of PRP-loaded hydrogels for wound healing.

Composing materials of hydrogels	Types of wounds	Functions	Ref.
D,L-Lactide, PEG, and stannous octoate	Full-thickness skin wound/rat	Better wound healing performances, greater angiogenesis	[64]
Citrate, sildenafil	Nonsplinted excision skin wound model/rat	Regeneration of the epidermis tissue, supporting the collagen formation, reducing the expression of proinflammatory factors (IL-1β, IL-6, TNF-α, and CRP)	[65]
Gelatin	Full-thickness wound/mice	Better wound contraction, the formation of new blood capillaries	[52]
Sodium alginate	Full-thickness wound model/mice Full-thickness wound model/porcine	Upregulation of growth factors levels and promotion of reepithelialization and angiogenesis, accelerated healing of wounds	[66]
Soleucine-lysine-valine-alanine-valine and arginine-glycine-aspartic acid (RGD)	Full-thickness excision skin wound/mice	Encourage angiogenesis, fibroblast propagation in vitro and scar-free wound healing in vivo	[67]
Curcuma zedoaria polysaccharide	Full-thickness for diabetic/mice	Promotion of wound contraction, enhanced angiogenesis, collagen synthesis, and deposition in treated wounds	[68]
Chitosan and silk fibroin	Skin full-thickness for diabetic/mice	Enhanced angiogenesis, nerve repair, and collagen synthesis and deposition	[69]
Oxidized dextran, hyaluronic acid, and antimicrobial peptide	Skin full thickness for diabetic wound infection model/mice	Regulation of inflammation, suppressed the expression the proinflammatory cytokines (TNF-α, IL-1α, and IL-6), enhancing the formation of granulation tissue, promoting angiogenesis, and facilitating collagen deposition	[70]
Carboxymethyl chitosan, sodium alginate, and nanosilver	Round wound infection model/rat	Faster wound healing, anti-inflammatory, and proangiogenic effects	[71]

wounds. Attili et al. [57] evaluated antibacterial properties of PRP with an agar gel diffusion method and the inhibition effect of PRP against the growth of *Staphylococcus aureus* and *Escherichia coli*. Smith et al. [58] also reported the in vitro bacteriostatic effect of PRP on the *S aureus* and *S. epidermidis*. Furthermore, the full array of potential bioactive growth factors and chemokines released upon platelet activation is becoming well defined [59]. These include transforming growth factor (TGF-β1 and TGF-β2), platelet-derived growth factor (PDGF), VEGF, FGF, insulin growth factor (IGF-1), and EGF, which promote local angiogenesis, cell migration, proliferation, and differentiation coupled with the deposition of proteins such as collagen, which play a key role in enabling the restoration of normal tissue structure and function [60, 61] (Table 1). The stable release of growth factors at wounds, together with signal transduction after interacting with cells, is particularly important for the proliferation and differentiation of cells and the formation and remodeling of the ECM.

3. Applications of PRP-Loaded Hydrogels in Wound Healing

Wound healing follows a complex process involving a variety of cells and cytokines. Growth factors in PRP play an important role through different pathways in wound repair; however, how to significantly enhance their maintenance at wound sites, on the premise of maintaining the activities of exogenous cells and various cytokines, remains a major challenge. Therefore, recent works have focused on the controlled and sustained release of growth factors with advanced hydrogels. In recent years, to improve the delivery efficiency and realize the controlled delivery of growth factors, natural polymer-based hydrogels, such as alginate and silk fibroin, have been explored as potential carriers to induce angiogenesis, reduce inflammatory responses, regulate the expression of active factors, and accelerate skin repair [62, 63] (Table 2).

Qiu and coworkers [64] prepared a poly (D,L-lactide)-poly (ethyleneglycol)-poly (D,L-lactide) hydrogel as a delivery vehicle for PRP growth factors. From the factor release assay, a sustained release of PDGF-BB for 14 days was realized by the hydrogel, which promoted angiogenesis and accelerated healing in rodents. As a potent stimulator of angiogenesis, sildenafil was also used together with PRP for enhanced wound healing. Gad et al. [65] studied the effectiveness of topical application of PRP and/or sildenafil citrate hydrogel (SCH) in a nonsplinted excision skin wound model. PRP and/or SCH topical treatments caused an enhancement of wound healing parameters, including a rapid switch from the inflammatory phase to the connective tissue stage, as evidenced by less systemic hematological changes and decreased values of interleukin-6 (IL-6), tumor necrosis factor (TNF-α), interleukin (IL-1β), and C-reactive protein (CRP) on the 7th or 14th day. The results suggest that the combined therapy of PRP and sildenafil has higher efficiency in wound healing in terms of anti-inflammation, collagen remodeling, and epithelization. Furthermore, Zhang et al.'s group [66] proposed an engineered PRP dual-network (DN) hydrogel based on sodium alginate constructed through a simple "one-step" activation process. Inside the DN hydrogel, fibrin networks were formed, followed by the activation of PRP. On the other hand, Ca^{2+}

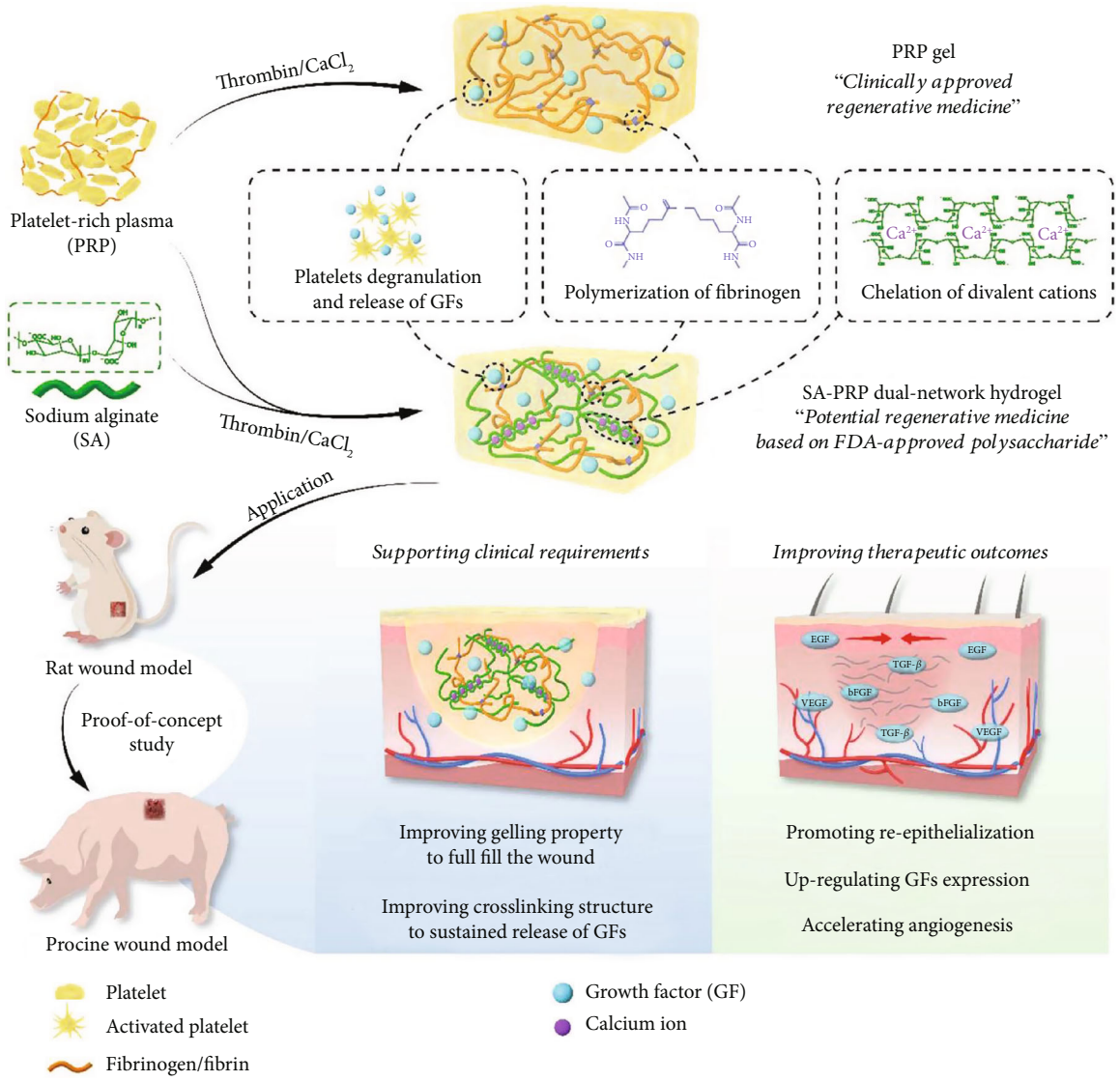

Figure 1: Schematic illustration of the preparation of sodium alginate-based PRP dual-network hydrogels and their application as a wound dressing [66].

ions were able to interact with the carboxylic groups of the alginate backbone, forming "egg-box" ionic cross-linked networks. Compared to the PRP gel, the DN hydrogel showed an order of magnitude increase in G', indicating the contribution of the dual networks to mechanical properties. From in vivo measurements, the EGF production in the presence of the DN hydrogel showed a relatively high expression during the entire healing process, which promotes the reepithelialization process by activating epithelial cells to migrate into the wounded region and deposit basement membrane components. This superior bioactivity could be attributed to substantial improvement in the temporal release by the DN hydrogel, thereby effectively stimulating fibroblasts and keratinocytes to proliferate and secrete autologous EGF during the proliferation and remodeling of wound healing. Furthermore, expression levels of VEGF-A and TGF-β1 in the DN gel-treated groups were significantly higher than those in the other groups on day 2. This indicated that DN gel can quickly activate angiogenesis and promote the deposition and organization of a new ECM, thus contributing to the accelerated wound healing process. Moreover, the DN hydrogel also showed a high healing efficiency in a wound model of a Bama miniature pig (Figure 1). The PRP-based hydrogel delivery system, combined with hydrogel and PRP properties, can sustain the release of growth factors to the wound and promote wound healing (Table 3). Therefore, it may become a treatment for wounds and skin regeneration in the future.

4. Applications of PRP-Loaded Hydrogels in Chronic Wound Healing

Chronic wounds involve numerous problems, such as excessive inflammatory responses, impaired fibroblast migration and proliferation, abnormal collagen formation and deposition, obstructed wound vascularization, and reepithelialization. Hydrogel dressings loaded with cells or cytokines can

Table 3: Evaluation of PRP hydrogel performance.

Load content	Delivery systems	Characteristic	Ref.
PRP	Polyethylene glycol (PEG) hydrogel	Controllable released growth factors	[51]
Platelet-rich plasma release (PRPr)	Gelatin hydrogel	Sustained released of growth factors, providing a good moist environment	[52]
PRP	PLEL hydrogel	Sustained released growth factors up to 14 days, excellent biocompatibility, a good moist environment	[64]
PRP	p(HPMAm-lac)-PEG-based hydrogel	Injectable and thermosensitive hydrogels, interpenetrating polymer networks	[50]
Platelet-rich plasma exosomes (PRP-Exos)	ZWP hydrogel	Sustained released of growth factors, excellent biocompatibility	[68]
PRP	Dual-network hydrogel	Bioactive multifunctional properties (injectability, self-healing, sustained release property)	[66]
PRP and antimicrobial peptides (AMP)	ODEX/HA-AMP/PRP hydrogel	Anti-inflammatory and antioxidant, sustained release of AMP and PRP, antibacterial properties	[70]
PRP	CBPGCTS–SF@PRP	Bioactive injectable hydrogels, good self-healing ability, excellent and controlled release ability	[69]
PRP and nanosilver (Ag)	Alg/1.0Ag@CMC-PAMAM/PRP	Highly effective antibacterial activity	[71]
PRP and tigecycline nanoparticles	tg-ChNPs-ChPRP hydrogel	Good antibacterial activity, injectable multifunctional hydrogel	[75]

facilitate wound healing and tissue reconstruction [72]. Due to the growth factors in PRP, PRP-loaded hydrogels have shown significant importance in the clinical treatment of chronic wounds, such as diabetes and bedsores. Therefore, the release of anti-inflammatory drugs and growth factors must be guaranteed for a certain time, and compared with aerogels, hydrogels with water in network structures are favorable to wound healing. Zhang et al. [67] assessed the combined efficacy of shortened poly-N-acetyl glucosamine (sNAG) hydrogels and PRP in the treatment of wound healing. The results indicated that sNAG hydrogels loaded with PRP showed curative efficacy during wound healing in mice. The combination of PRP and sNAG hydrogels promotes wound healing through increased proliferation and the prevention of fibroblast apoptosis through adenosine A2A receptor activation. In addition, Xu et al. [68] evaluated the effect of one kind of purified polysaccharide from *C. zedoaria* alone or in combination with PRP-Exos on chitosan/silk hydrogel dressing in the repair of cutaneous lesions in diabetic mice. Overall, separate or combined treatments significantly accelerated wound contraction, reepithelialization, collagen synthesis, and deposition, along with dermal angiogenesis in diabetic rats, thus resulting in faster healing of diabetic wounds. However, the use of PRP-Exos and ZWP combination therapy was more successful for wound healing. Qian et al. [69] fabricated a self-healing and injectable hydrogel with chitosan, silk fibroin, and PRP (CBPGCTS-SF@PRP) to promote diabetic wound healing. After cyclic step strains, G' and G'' could quickly recover at a low shear strain of 1%, indicating the self-healing property of the CBPGCTS-SF@PRP hydrogel. Moreover, the hydrogel could protect PRP from enzymatic hydrolysis; that is, biological activities of extracellular vesicles derived from PRP could be preserved after the enzymatic degradation for 72 h. Hence, a sustained release of bioactive molecules in PRP was achieved for up to 14 days. The in vitro results showed that CBPGCTS-SF@PRP could enhance the chemotaxis of mesenchymal stem cells and promote the proliferation of repairing cells. Moreover, it enhanced wound healing by expediting collagen deposition, angiogenesis, and nerve repair in a type 2 diabetic rat model and a rat skin defect model (Figure 2). This multifunctional hydrogel wound dressing may open vistas in chronic wound management and guide diabetes treatment in clinical applications.

The inhibition of wound infections is a clinical challenge in skin wound repair. Infections can induce a local excessive inflammatory reaction of wounds and prolong healing times. More seriously, tissue necrosis and fatal sepsis may be concomitantly caused. In clinical treatments, the effects of antibiotics are unsatisfactory due to insufficient local blood supply of wounds, and there may be risks of adverse antibiotic reactions and bacterial drug resistance. Therefore, infectious wounds usually need to be simultaneously treated with antibiotics and growth factors. To prolong the duration of drugs and reduce the administration frequency, both antibiotics and growth factors were encapsulated into hydrogels by physical loading and chemical conjugation. The release of the biologically active substances was adjusted by controlling hydrogel degradation behaviors [73]. Wei et al. [70] used Schiff base linkages to construct a hydrogel from oxidized dextran (ODEX), antimicrobial peptide-modified hyaluronic acid (HA-AMP), and PRP under physiological conditions. Such hydrogels had an initial burst release of GFs and AMP followed by a sustained release for over 120 h. More importantly, in vivo experiments demonstrated that the prepared hydrogels could significantly improve wound healing in a diabetic mouse infection by regulating inflammation

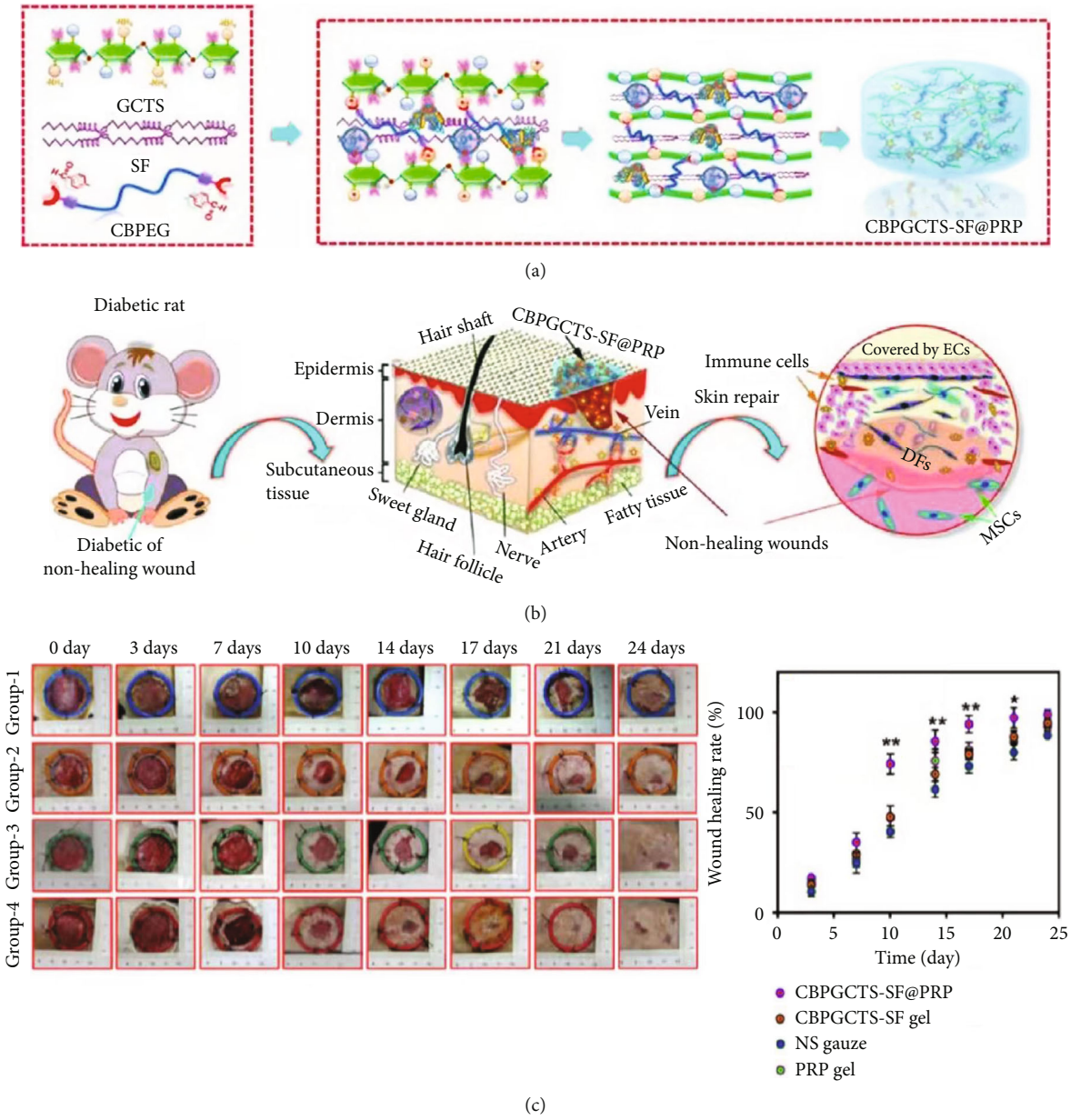

Figure 2: Schematic illustration of (a) preparation of CBPGCTS-SF@PRP hydrogels and (b) diabetic wound healing with the participation of dermal fibroblasts, endothelial cells, and mesenchymal stem cells in tissue repair and (c) their effects on wound healing in diabetic rats [69].

and accelerating collagen deposition and angiogenesis. In addition, the prepared hydrogel showed significant antibacterial activity against *S. aureus* and *P. aeruginosa*, inhibited proinflammatory factors (TNF-α, IL-1β, and IL-6), and enhanced anti-inflammatory factor (TGF-β1) and VEGF production (Figure 3).

In addition to PRP, some metal and polymeric nanoparticles have also been introduced into hydrogels to enhance anti-infection properties, mechanical properties, and healing effects [74]. Silver nanoparticles are one of the most important antibacterial materials because of their high and broad-spectrum antibacterial activity. Zhou et al. [71] prepared a multifunctional platform (Alg/1.0Ag@CMC-PAMAM/PRP) as wound dressings by mixing PRP with sodium alginate- (Alg-) based dressings containing nanosilver- (Ag-) doped carboxymethyl chitosan-grafted polyamideamine (Ag@CMC-PAMAM) cationic polymers. The results showed that the components of Ag@CMC-PAMAM nanoparticles endow them with excellent antibacterial performance, while the incorporation of PRP promotes the effect of anti-inflammatory and angiogenesis by upregulating the relative expression of TGF-β1, CD31, and α-SMA and downregulating inflammatory-related genes, including TNF-α, IL-6, and IL-1β, all of which promote wound closure and produce a healing effect superior to that of the commercial AQUACEL Ag group. Moreover, there are few studies of

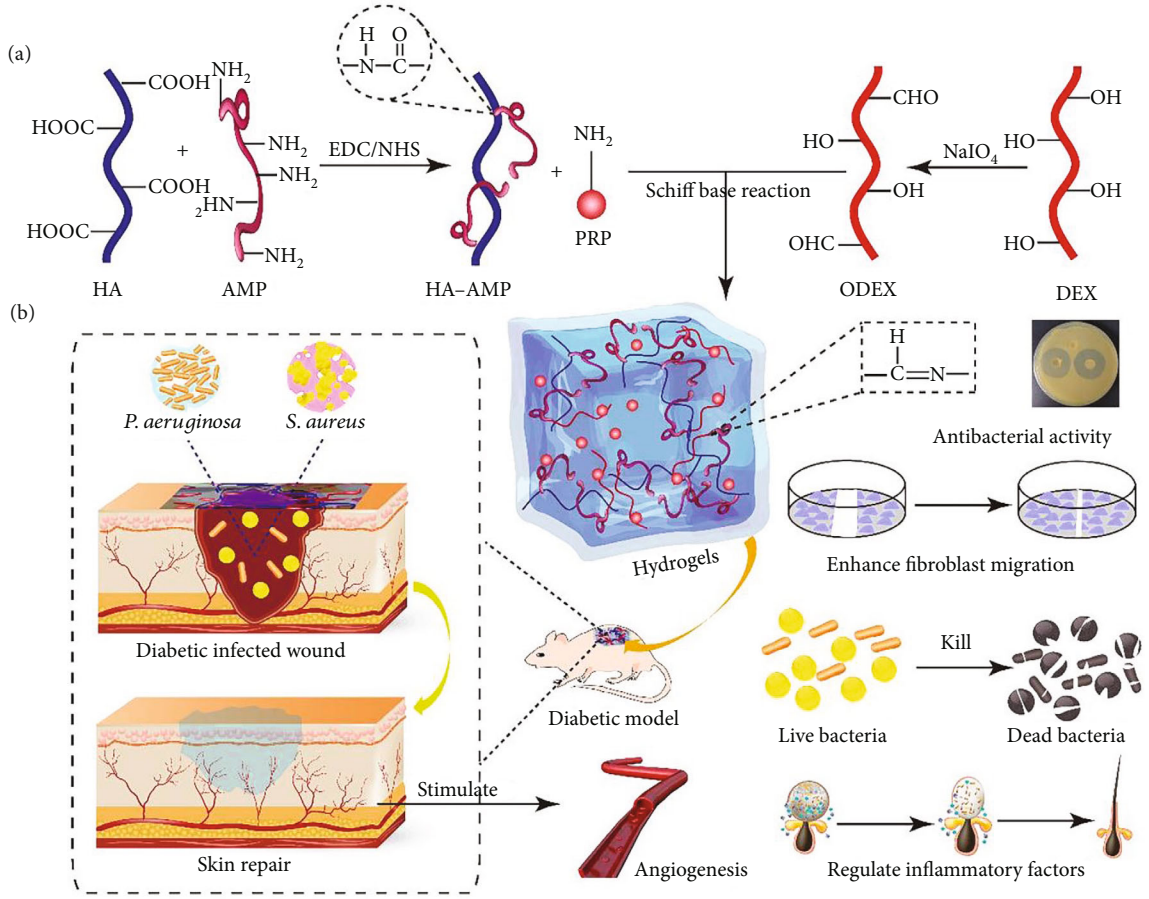

FIGURE 3: Schematic illustration of (a) preparation and (b) wound healing effect of ODEX/HA-AMP/PRP hydrogels for skin reconstruction of diabetic infection [74].

hydrogels as injectable hydrogels and the treatment of chronic wounds. Nimal et al. [75] introduced tigecycline nanoparticles into chitosan-PRP hydrogel (tg-ChNPs-ChPRPgel). Rheology studies have confirmed the shear thinning property and thermal stability of the prepared gel systems. The tigecycline release study confirmed that tigecycline release from tg-ChNPs-ChPRP gel is slower and more sustained, which is ideal for effective infection control. The sustained antibiotic release can decrease the chance of invasion of bacteria into the wound and thereby decrease the frequency of wound dressing. In addition, this nanoparticle/hydrogel composite can be injected through a syringe, suggesting that these biodegradable materials may have potential applications in biomedical antimicrobial and injectable formulations.

5. Conclusions and Perspectives

In conclusion, ideal wound dressings for wound management should not only have high biocompatibility, tissue-like water contents, and three-dimensional porous network structures similar to the natural extracellular matrix but also possess excellent physicochemical properties. The state of the art has realized suitable mechanical strengths and pore sizes of hydrogels, efficient encapsulation, and sustained release of PRP and corresponding growth factors. The progress has overcome the limitations of the mechanical properties of PRP gel, provided a stable and moist wound healing environment for damaged skin tissues, and promoted synergistic effects of skin tissue cells and cytokines on wound healing.

Despite the great potential of PRP-loaded hydrogels in wound healing, there are still many challenges for further applications in clinical treatments. It may be more attractive to develop intelligent multifunctional PRP-based drug delivery hydrogel systems with integrated sensors (such as pathogen infection detectors) for simultaneous real-time wound monitoring and treatments. Using biomacromolecules, such chitosan, dextran, sodium alginate, and hyaluronic acid, to construct biocompatible PRP-loaded hydrogels has demonstrated efficient wound healing performances. Regarding the complex wound environments, the development of hydrogels with high mechanical properties and some new functions, including self-healing, antioxidant, antibacterial, extracellular matrix-mimicking, and tissue adhesion, will become a new focus. In addition, it is worth noting that the inactivation of PRP generally occurs within 48 h after isolation; thus, the "autologous supply" mode is basically adopted in clinical trials, which brings much inconvenience to the preparation and application of PRP-loaded dressings. Therefore, developing a class of PRP hydrogels that can be

stored for a long time will be highly promising; this is highly expected to advance their applications. With gradual in-depth investigations of the complex dynamics of biological systems and structure-property-function relationships, the development and application of PRP-based therapy will usher in a new era.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Ya Zhang and Zi-Lin Wang contributed equally to this work.

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