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REVIEW

Synergistic Innovative Therapies in Dermatology: Integrating Platelet Derivatives, Biomaterials, and Exogenous Bioactive Substances for Enhancing Skin Repair and Regeneration

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Background: The treatment of dermatological diseases has evolved significantly with the advent of advanced therapeutic strategies involving platelet-rich products. These products are rich in morphogens, growth factors, and proteins that play a crucial role in tissue regeneration and wound healing. Their combination with different biomaterials has been engineered to enhance the biomaterials' safety and performance in the context of tissue healing.

Objective: This narrative review aims to explore the current evidence on the biological mechanisms, efficacy, and clinical applications of these combined therapies. Furthermore, we examine the potential advantages of synergistic effects and the challenges associated with optimizing treatment protocols.

Methods: Relevant literature was retrieved through a structured search strategy implemented across PubMed, Scopus, and Google Scholar databases. Studies included investigated co-administration of platelet-rich products with other agents in topical, injectable, or composite formulations for dermatological conditions with no restriction regarding publication date.

Results: The review summarizes in vitro and in vivo biological effects of various biopolymers and active substances combined with platelet-rich products, highlighting diverse application strategies and their effectiveness across dermatological contexts.

Conclusion: Adding platelet-rich products has shown promising results in enhancing therapeutic outcomes for various dermatological conditions, including chronic wounds, burns, scars, and skin aging. Although promising results have been reported, the need for critical thinking regarding the selection of the biomaterial and the platelet-rich products, standardized methodologies, large-scale randomized controlled trials, and long-term follow-up studies is emphasized to fully establish the clinical benefits of these combined treatments in dermatology.

Plain Language Summary: In recent years, there have been major advancements in how skin diseases and injuries are treated. Platelet-rich products are one of the most promising techniques, which are derived from a patient's blood and carry high concentrations of natural growth and repair factors. They stimulate tissue healing and regeneration and, when combined with advanced biomaterials, presumably enhance both efficacy and safety of skin healing processes.

This review gathers current evidence on mechanisms, clinical effectiveness, and dermatological applications of such combination therapies. It highlights their uses in a wide range of disorders—spanning from wounds, burns, and scars to skin aging, autoimmune disorder, and alopecia—and their formulation as creams, injections, or scaffolds.

Evidence has shown that the integration of platelet-rich products with biomaterials or bioactive agents may facilitate quicker healing and improve clinical performance in experimental and clinical studies. Nevertheless, the review highlights the need for stronger studies, standardized protocols, and long-term follow-up to confirm their therapeutic value and facilitate their translation into routine dermatological practice.

Keywords: plasma rich in growth factors, platelet-rich plasma, wound healing, dermatology, biopolymer, bioactive molecules, skin regeneration

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Introduction

Platelet-Rich Preparations in Dermatology

Platelet-rich preparations, including platelet-rich plasma (PRP), plasma rich in growth factors (PRGF-Endoret®, BTI Biotechnology Institute, Vitoria, Spain), and other blood-derived preparations, have become a focal point in the current research and clinical practice in dermatology due to their regenerative and reparative properties. These biologically active autologous substances are rich in growth factors, cytokines, and proteins that are pivotal in the processes of healing, tissue repair, and regeneration.[1] Therefore, these hemoderivatives are increasingly used for a variety of dermatological conditions, including chronic wounds, scars, skin aging, hair loss, and treatment of other aesthetic conditions.[2–4,] However, platelet-rich formulations differ in their structure, composition, growth factors concentrations, and cytokine profile, which critically affects their biological effects.[5] In many cases, variations in therapeutic efficacy could also be attributed to the lack of standardized and reproducible preparation protocols.[6]

In dermatology, platelet concentrates have demonstrated efficacy in promoting wound healing, reducing scarring, and improving skin rejuvenation.[3] Chronic wounds, including diabetic ulcers and pressure ulcers, are challenging to manage and often require advanced therapies.[7] Epithelial tissue regeneration is regulated by cellular metabolic pathways. In diabetes, sustained hyperglycemia induces a significant metabolic dysregulation in epithelial cells, thereby compromising their proliferative and reparative capacity and contributing to impaired wound healing. Growth factors are essential for the activation of epithelial stem and progenitor cells, modulating cellular metabolism and promoting cell proliferation, migration, and tissue repair[8]. Considering the multifaceted cellular and molecular interactions that characterize diabetic wounds, multifunctional hydrogel-based strategies, combining antimicrobial, antioxidant, anti-inflammatory, and blood glucose modulating effects, are increasingly being prioritized as a promising approach for effective therapeutic intervention.[9–11]

Platelet concentrates have shown to accelerate wound closure by promoting epithelialization and collagen synthesis.[12–15] Furthermore, studies have revealed that platelet concentrates can significantly reduce the formation of hypertrophic scars, making them a valuable treatment modality for patients undergoing reconstructive surgery.[16] In the context of aesthetic dermatology, platelet concentrates have gained popularity for their role in combating the effects of skin aging.[17–19] In this sense, PRGF-Endoret® and other platelet concentrates are frequently used in facial rejuvenation treatments, where they stimulate the production of collagen,[20] improving skin tone, texture, and elasticity.[21–23] A growing body of scientific evidence suggests that platelet concentrates can stimulate the proliferation of dermal papilla cells and enhance the vascularization of perifollicular tissue, while also accelerating the transition from telogen to anagen, thereby promoting hair follicle regeneration and minimizing hair loss.[24]

Optimization of Platelet Concentrates

As previously discussed, platelet concentrates offer numerous advantages and considerable therapeutic potential, but also some specific challenges including a relatively fast release of growth factors and cytokines.[25] In order to overcome these limitations, different technologies and manufacturing processes have been developed so far. Many have contributed to significantly enhance the properties of platelet concentrates and their effectiveness for specific uses without introducing exogenous biomaterial or bioactive substances. Indeed, determining precisely the composition of platelet-rich preparations regarding the optimal platelet concentration and the role of leukocytes might be key for their therapeutic efficacy and safety. Many studies with PRGF-Endoret® have reported that a platelet enrichment factor of 2–3 and the absence of leukocytes have resulted in the best outcomes regarding the safety and performance.[26–31]

As a result, the versatility of plasma rich in growth factors (PRG-Endoret®) has culminated in the development of a wide range of formulations with diverging mechanical and biological characteristics, which are applicable in diverse therapeutic scenarios.[29] Figure 1 represents the main differences in preparation methods and the resulting formulations that can be manufactured via PRGF-Endoret® protocol, providing a representative example based on a standardized PRP technique. Liquid platelet-rich formulations, including non-activated PRGF-Endoret®, activated PRGF-Endoret®, and PRGF-Endoret®-released supernatants, are commonly injected or topically applied as eyedrops to provide an immediate supply of a large amount cytokines, growth factors, and other bioactive proteins to damaged tissues.[30,32–34] On the other

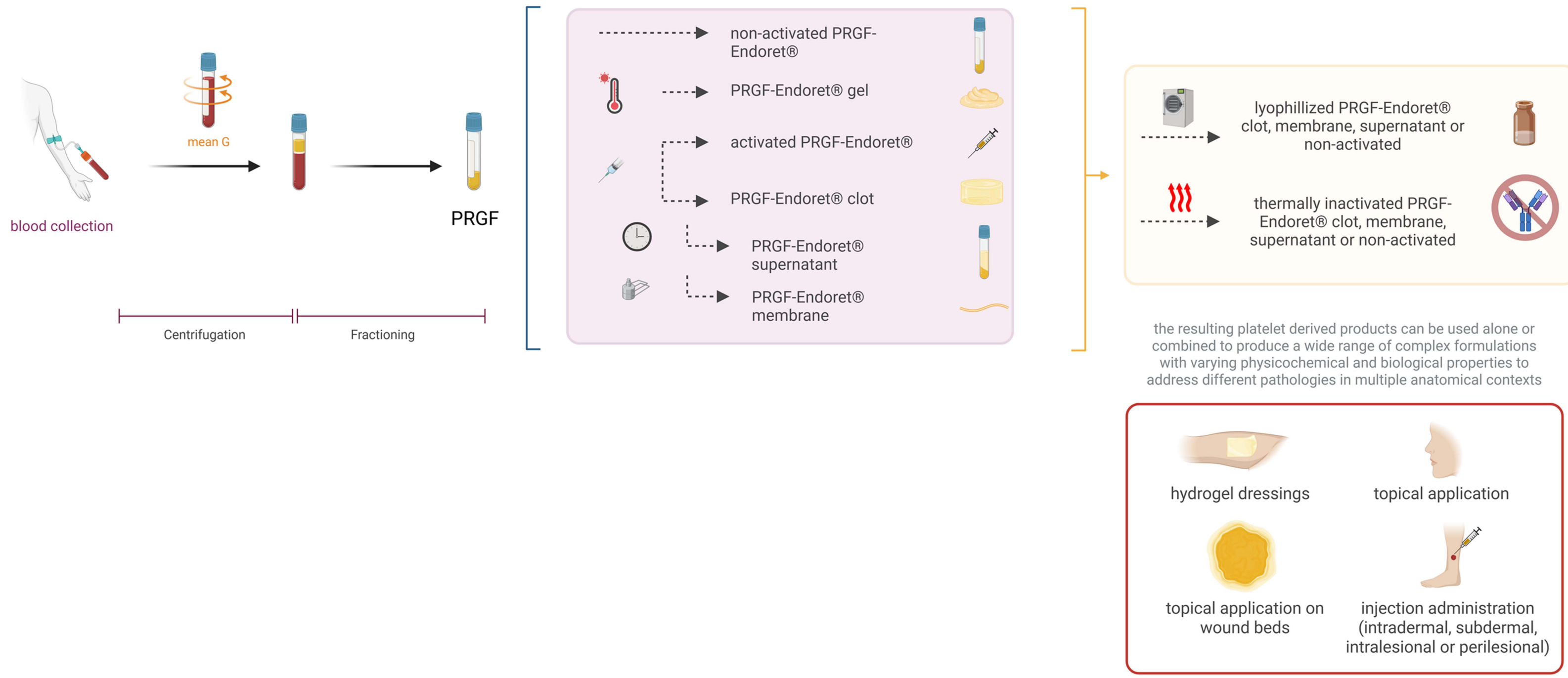

Figure 1 Technical procedures for preparation and administration of PRGF-Endoret® for the treatment of skin pathologies.

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hand, PRGF-Endoret®-derived clots constitute disease-specific bioformulations tailored to the pathoanatomic context underlying the damaged tissue that promote a sustained release of cytokines and growth factors usually prepared via fibrin crosslinking with calcium, thrombin, or collagen.[30,35] Their viscoelastic properties and biodegradability rates could be also modified by mechanical and/or thermal procedures.[36,37]

Plasma gels are also prepared through thermal treatments, where the thermal dose and time-temperature factors play a crucial role in defining the physical and biological characteristics of the resulting hydrogels.[38] Moreover, the mechanical and regenerative properties of the final product can be modified by mixing different proportions of these heat-coagulated albumin gels with other platelet gels or liquid platelet derivatives to address specific therapeutic contexts.[23,36,39] These formulations can be used as soft and hard tissue fillers,[21,38,39] topical agents,[37] and dressings[40] or injection administered prior to clot formation.[37] The identification of optimized centrifugation conditions and the inclusion of additional filtration steps may be used either to enrich the resulting platelet derivatives in selected components or to exclude other blood constituents, thus modifying fibrin architecture and enhancing their regenerative potential,[41] minimizing their immunogenicity,[42] modulating their biodegradability,[43] or improving their optical properties.[44] In addition, thermal treatments have been developed to further reduce the content of soluble components of the immune system (including the complement system and immunoglobulins) in platelet derivatives from patients with systemic immune-mediated disorders.[42,45] Platelet-derived extracellular vesicles are nanoparticles derived from activated platelets that contain growth factors, procoagulants, anti-inflammatory factors, pro-angiogenic factors, nucleic acids (mRNA and miRNA), and mitochondria. The most recent advances conducted to isolate these membrane vesicles with essential roles in homeostasis, osteogenesis, angiogenesis, and tissue regeneration from platelet concentrates involve sequential centrifugation steps at increasing G forces over progressively extended centrifugation intervals.[43] This technological and scientific development has enabled platelet concentration systems suppliers to provide clinicians with an array of medical products, in accordance with European Parliament and Council Directive 2017/745/EC regarding medical devices.[46]

From a regulatory perspective, PRP is classified as a medicinal product and is subject to strict regulation within the European Union.[47,48] The regulatory framework for platelet derivatives is designed to ensure the quality and safety of blood products throughout their preparation, storage, and distribution (European Parliament and Council Directives 2002/98/EC, 2004/33/EC, 2005/62/EC, 2016/1214).[49–52] The core regulation is Directive 2002/98/EC, which governs the quality and safety of blood,[49] while Directive 2005/62/EC as regards Community standards and specifications relating to a quality system for blood establishments and its amendment,[51] Directive 2016/1214, outline the quality system standards for blood establishments.[52] These directives require strict controls on various practices, including blood collection, testing, licensing, qualified personnel, and product traceability. Nevertheless, the implementation of these regulations varies across EU member states, leading to some inconsistencies. This lack of uniformity may prompt EU legislators to step in and standardize the regulatory approach for blood-derived products.[53] In Spain, the Agency of Medicines and Medical Devices (AEMPS) included PRP as a non-industrially produced medicinal product (Report/V1/23052013).[54] Consequently, PRP therapy must be prescribed exclusively by healthcare professionals – doctors, dentists, or podiatrists – within their specific clinical competencies, and not by any other healthcare or non-healthcare professional. Furthermore, prescribing PRP is restricted to professionals with the relevant expertise and qualifications. Moreover, the treatment must be performed using the proper equipment and instruments that are approved for that purpose by regulatory authorities, and PRP may only be utilized in authorized healthcare facilities that adhere to applicable regional government regulations.

Novel Multifunctional Combined Therapies

Leveraging the regenerative potential of PRP to improve biomaterial safety and performance—alongside achieving controlled delivery of platelet-derived morphogens, proteins, and growth factors—has contributed to the development of advanced combined tissue-regeneration strategies.[55] Therefore, therapies that combine tissue-regeneration strategies using platelet derivatives and biomaterials are considered as promising approaches to enhance the stability and durability of platelet-derived therapeutic agents and improve the outcomes of dermatological treatments. In this context, biomaterials, such as composite scaffolds, hydrogels, and synthetic matrices, provide stable mechanical support for the targeted delivery of platelet concentrates, which enable the sustained release of bioactive molecules and protect them from degradation.[56] Furthermore, to enhance the biological effect of platelet derivatives with additional antioxidant, antibacterial, and other biological properties, combining these autologous products with different active ingredients or their mixtures may produce a synergistic action, thus improving the therapeutic impact of the combined therapy.[57,58]

This narrative review aims to consolidate current research on the use of platelet derivatives in combination with other biomaterials, therapeutic agents, or active substances administered simultaneously, regardless of the method of administration, for the treatment of dermatological diseases or aesthetic conditions. By examining the in vitro and in vivo biological effects of different biopolymers and other active substances, the paper summarizes different implementation strategies and evaluates their effectiveness in diverse contexts. Additionally, it highlights deficiencies in the current literature and outlines directions for future research to deepen our understanding of how combining platelet derivatives with other biomaterials and active substances can be used to support and improve skin repair and regeneration.

Methods

A systematic literature search was conducted to identify studies on the use of combination therapy of hemoderivatives and other exogenous elements, molecules, or mixtures (with no restriction regarding their physical state, chemical composition, or biological function) in the treatment of dermatological diseases and aesthetic conditions (including wound/ulcer, burn and scar management, volume restoration, skin ageing, dermatological autoimmune diseases, hair loss, and other conditions affecting the skin). Studies in which platelet derivatives are used as adjuvant therapy for skin reconstruction, tissue regeneration, or soft tissue augmentation surgery based on living tissues, including skin flaps or split thickness skin grafts (STSG) – vascularized or semi-vascularized flaps comprising skin and subcutaneous tissue, mobilized from a donor region to a recipient site during reconstructive or reparative procedures – fat grafts, stromal vascular fraction (SVF), or stem cells were excluded. Only studies in which both agents were administered simultaneously were included, including platelet derivative-loaded hydrogel composites or fibrin-based hydrogels, liquid mixtures of platelet-derivatives and other active substances or topical formulations composed of platelet derivatives, and other biomaterials or therapeutic agents regardless of the method of administration. Accordingly, experimental designs combining hemoderivatives with other therapeutic agents administered separately, including different administration routes or dosing times, were also excluded. The search, with no limitations to language, date or publication status, was carried out using PubMed, Scopus, and Google Scholar databases.

Results

After screening and removing duplicates, the reference list of the preliminary selection was checked to identify additional relevant publications. The details of the literature search and data extraction are provided in a flow diagram (Figure 2). As listed in Table 1, a total of 91 publications reporting in vitro, in vivo, or clinical investigations with the primary or secondary objectives of evaluating the biological effects and/or therapeutic efficacy of different combined therapies involving platelet-derived products and other biomaterials or active principles administered simultaneously for the treatment of skin pathologies and conditions were included in the present review.

Most of the selected studies focused on investigating different combinations of platelet derivatives and polymeric biomaterials, such as hyaluronic acid, chitosan, collagen, gelatin, alginate, or cellulose derivatives mainly for treatment of facial ageing, skin injuries, and wounds. Additionally, a small subset of studies evaluated various combinations of platelet derivatives and other bioactive substances and therapeutic agents, including herbal extracts, phenolic compounds, metals, toxins, or antibiotics to treat chronic wounds and hyperpigmentation. After structuring and extracting relevant information, the selected studies were summarized and discussed below:

Biopolymers

Biopolymers, as naturally sourced polymers derivatives from living organisms, present significant benefits for wound healing, scarring management, and skin rejuvenation. Their biocompatibility, biodegradability, non-immunogenicity, and versatile structural properties position them as excellent candidates for developing drug delivery systems, advanced

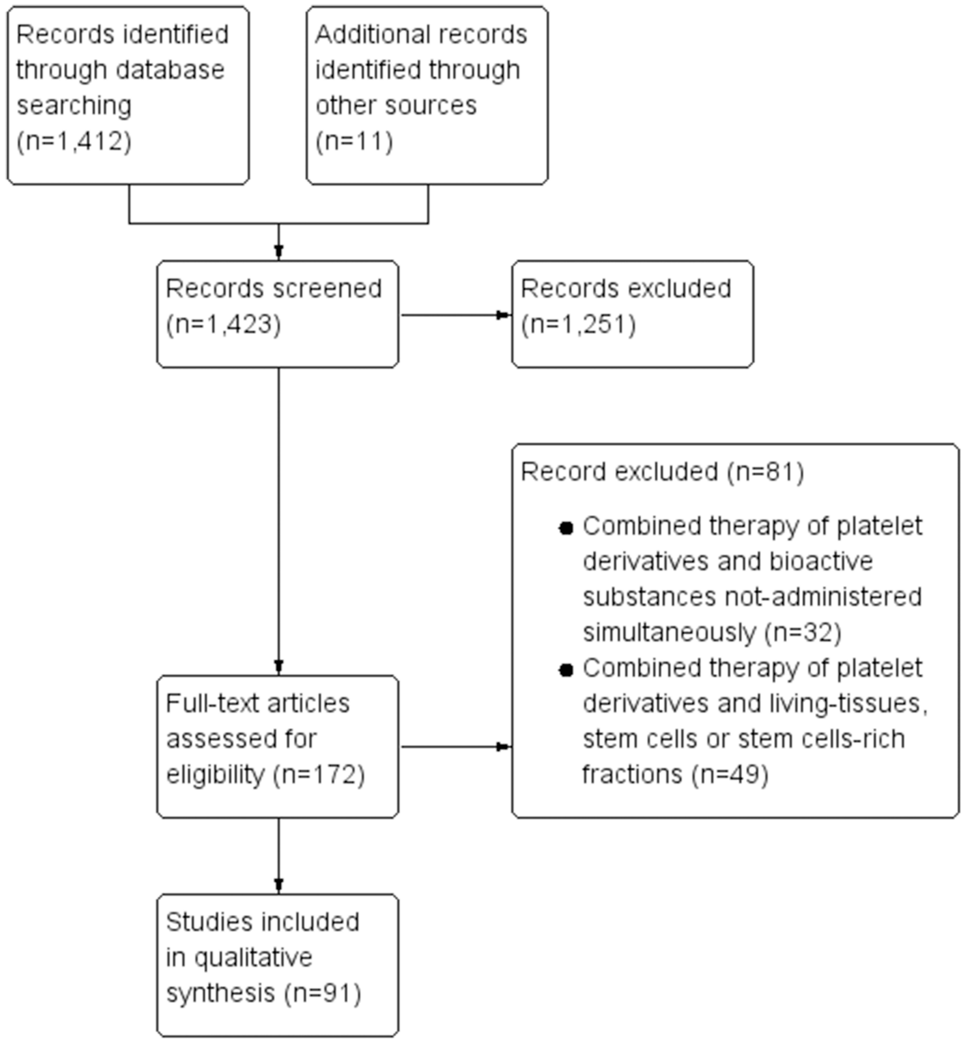

Figure 2 Study flow diagram.

biological wound dressings, and scaffolds for tissue regeneration.[150] As a consequence, the combination of the bioregenerative potential of PRP with multiple biopolymers or biopolymer-based multifunctional scaffolds has been extensively investigated in aesthetics and medical dermatology:

Chitosan

Chitosan is a bioactive polymer with numerous applications, driven by its functional properties including antibacterial effects, non-toxicity, ease of modification, biocompatibility, and biodegradability.[151] It is the deacetylated form of chitin, a natural copolymer of *N*-acetylglucosamine and glucosamine residues linked by β-1,4-glycosidic bonds synthesized by fungi, crustacean, squids, and cuttlefish.[152] In addition to its excellent mechanical performance, high hydrophilicity and lysozyme degradation properties, chitosan dressings act as strong antimicrobials and procoagulants, enhancing wound healing by creating an optimal environment for cells and beneficial microbiota.[153] Higher amount of growth factors can be released into the plasma by incorporating chitosan with high platelet activation ability to PRP,[65] thus leading to increased proliferation rates in fibroblasts and adipose tissue-derived stromal cells (ASCs).[82] As concluded by Shimojo et al,[73] the performance of in association with porous chitosan outperformed PRP alone, as it delayed the release of growth factors and enhanced stem cell proliferation in vitro. Multiple in vivo studies have also revealed that PRP combined with biodegradable chitosan hydrogels showed positive effects on wound healing and could be recommended for treating different types of wounds in both animals and humans.[78,97,139] Accordingly, 3D wound healing models

Table 1 Characteristics of the Included Studies

Author	Year	Research Methodology[a]	Condition/ Pathology	Platelet Derivative[b]	Combination Therapy	Conclusions
Knox et al[59]	2006	Case report	Wound healing	PRP	PRP + skin substitute	The combination of PRP with a skin substitute shows potential for healing chronic wounds, as demonstrated in a case report
Kakagia et al[60]	2007	RCT	Wound healing	AGF	Protease-modulating matrix + AGF	The synergistic action of a protease-modulating matrix and AGF effectively heals diabetic foot ulcers
Cervelli et al[61]	2010	Retrospective study	Wound healing	PRP	PRP + hyaluronic acid	The combined use of PRP and hyaluronic acid shows promise in treating exposed tendons in the foot and ankle
Hao et al[62]	2010	RCT	Deep II degree burns	PRP gel	PRP + acellular xenogeneic dermal matrix	Autogenous PRP gel combined with acellular xenogeneic dermal matrix is effective for treating deep II degree burns
Cervelli et al[63]	2011	Case series	Wound healing	PRP	PRP + hyaluronic acid	The application of PRP and hyaluronic acid is beneficial for healing wounds involving substance loss with bone exposure
Yang et al[64]	2011	In vivo (murine model)	Wound healing	PRP	Heparin-conjugated fibrin	A sustained release of growth factors contained in PRP significantly enhances skin wound healing
Kutlu et al[65]	2013	In vitro	Tissue engineering	PRP	Chitosan scaffolds	PRP-enriched chitosan scaffolds are promising for tissue engineering applications due to their capacity for controlled and prolonged growth factor release, potentially favoring regeneration
Suzuki et al[66]	2013	In vivo (murine model)	Wound Healing	Platelet-derived growth factors	Gelatin gel	Gelatin gel serves as a suitable carrier for platelet-derived growth factors
Mori et al[67]	2014	In vitro	Wound Healing	PL	Calcium alginate particles and vancomycin hydrochloride	Calcium alginate particles enable the combined and controlled delivery of PL and vancomycin hydrochloride for chronic skin ulcers
Pallotta et al[68]	2014	In vitro	Tissue regeneration	PG	PG + Silk	Characteristics of platelet gels can be effectively combined with silk for biomedical applications
La and Yang[69]	2015	In vivo (murine model)	Wound healing	PRP	PRP-loaded heparin-conjugated poly(lactic-co-glycolic acid) (PLGA) nanospheres	Heparin-conjugated PLGA nanospheres enhance large-wound healing by delivering growth factors in PRP
Morimoto et al[70]	2015	Clinical study protocol	Wound healing	PRP	Gelatin sheet + PRP	A study protocol is proposed for an exploratory clinical trial of combination wound therapy with a gelatin sheet and PRP for chronic skin ulcers
Notodihardjo et al[71]	2015	In vivo (murine model)	Angiogenesis and wound healing	PRP releasate	Gelatin hidrogel + PRP	Gelatin hydrogel impregnated with PRP releasate promotes angiogenesis and wound healing in a murine model
Ramos-Torrecillas et al[72]	2015	Clinical study	Wound healing	PRP	PRP + hyaluronic acid	The combined therapy of PRP and hyaluronic acid emerges as an effective therapeutic option for the management and healing of pressure ulcers
Shimojo et al[73]	2015	In vitro	Tissue regeneration	PRP	PRP + porous chitosan	The combination of PRP with porous chitosan scaffolds represents a promising material for tissue engineering, demonstrating improved tissue regeneration and favorable biocompatibility
Deng et al[74]	2016	Case series	Wound healing	PRP	PRP + bilayered acellular matrix grafting	PRP, bilayered acellular matrix grafting, and negative pressure wound therapy demonstrate efficacy in diabetic foot infection
Gentile et al[75]	2016	Clinical study	Wound healing	PRP	PRP + hyaluronic acid	The combination of PRP and hyaluronic acid is effective in treating complications following Achilles tendon reconstruction

(*Continued*)

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Table 1 (Continued).

Author	Year	Research Methodology[a]	Condition/ Pathology	Platelet Derivative[b]	Combination Therapy	Conclusions
Houdek et al[76]	2016	In vivo (rat model)	Dermal regeneration	PRP	Collagen and PRP scaffold	A collagen and fractionated PRP scaffold is an effective option for dermal regeneration
Lu et al[77]	2016	In vivo (rabbit model)	Wound healing	PRP	Chitosan-gelatin sponge loaded with tannins and PRP	The incorporation of tannins and PRP in chitosan-gelatin sponges represents an effective strategy to enhance skin wound healing
Mohammadi et al[78]	2016	In vivo (rat model)	Wound healing	PRP	PRP + chitosan biodegradable film	The application of PRP together with biodegradable chitosan films substantially improves the full-thickness wound healing process, suggesting a synergistic approach for regenerative medicine
Morimoto et al[79]	2016	Case report	Wound healing	PRP	PRP + gelatin sheet	Easy-to-use preservation and application of freeze-dried PRP in combination with a gelatin sheet is a viable approach for wound therapy
Qiu et al[80]	2016	In vitro *and* in vivo (rat model)	Wound healing	PRP	PRP-laoded poly(d,l-lactide)-Poly(ethylene glycol)-Poly(d,l-lactide) Hydrogel Dressing (PELA)	A PRP-loaded PELA hydrogel dressing promotes full-thickness skin wound healing in a rodent model
Zhang et al[81]	2016	In vitro	Tissue regeneration	PRP	Collagen/PRP scaffold	A novel collagen/PRP scaffold can be successfully prepared, exhibiting favorable growth factor release characteristics
Hattori and Ishihara[82]	2017	In vitro	Tissue regeneration	PRP	Chitosan + PRP	Combining highly platelet-activating chitosan with PRP could be an effective strategy to enhance its therapeutic effects in various medical applications by optimizing growth factor release
Kakudo et al[83]	2017	In vitro *and* in vivo (murine model)	Tissue regeneration	PRP	PRP + gelatin hydrogel granules	PRP combined with gelatin hydrogel granules, and polychromatic light injected into murine subcutis, demonstrates an angiogenic effect
Liu et al[84]	2017	In vivo (rabbit model)	Wound healing	PRP/PPP	PRP/PPP-loaded cocoon scaffold (*Bombyx mori*)	A new cocoon scaffold loaded with PRP (vs PPP) promotes skin wound healing
Park et al[85]	2017	In vivo (murine model) study	Wound healing	PRP	Hydrogel + PRP	Combined treatment with hydrogel and PRP accelerates wound healing
Ulusal[86]	2017	Clinical study	Facial rejuvenation	PRP	PRP + hyaluronic acid	PRP and hyaluronic acid together serve as an efficient biostimulation method for facial rejuvenation
Abdullah et al[87]	2018	In vivo (diabetic murine model)	Wound healing	PRP	PRP + zinc oxide ointment	PRP combined with zinc oxide ointment demonstrates benefits for skin wound healing in diabetic mice
Kshersagar et al[88]	2018	In vitro and in vivo (murine model)	Burns	PRP	Decellularized amnion scaffold + PRP	A decellularized amnion scaffold with activated PRP represents a new paradigm in dressing materials for burn wound healing
Pignatelli et al[89]	2018	In vitro	Tissue regeneration	PL	PL-loaded electrospun silk fibroin fibers	Electrospun silk fibroin fibers are capable of providing controlled release of human PL
Xu et al[90]	2018	In vivo (diabetic rat model)	Diabetic wound healing	PRP exosomes	*Curcuma zedoaria* polysaccharide and chitosan/silk hydrogel sponge + PRP	A *C. zedoaria* polysaccharide with PRP exosomes assembled on a chitosan/silk hydrogel sponge promotes diabetic wound healing
De Angelis et al[91]	2019	In vitro and in vivo	Wound healing	PRP	Hyaluronic acid scaffold + PRP	The combination of hyaluronic acid with PRP represents an effective strategy for treating chronic ulcers, stimulating tissue regeneration and facilitating wound healing
do Amaral et al[92]	2019	In vitro and in vivo	Wound healing	PRP	Collagen-based scaffolds + PRP	Functionalizing collagen-based scaffolds with PRP enhances their potential for skin wound healing
Lei et al[93]	2019	In vivo (murine model)	Wound Healing	PRP	Acellular Dermal Matrix (ADM)/PRP freeze-dried dressing	An ADM/PRP freeze-dried dressing can be prepared and shows positive effects on full-thickness skin defect healing

Notodihardjo et al[94]	2019	In vivo (murine model)	Wound Healing	PL	Gelatin Hydrogel impregnated with PL	Gelatin hydrogel impregnated with concentrated platelet lysate shows efficacy in murine wound healing.
Pirrello et al[95]	2019	Open-label clinical study	Scleroderma	PRP	Hyaluronic acid + PRP	Hyaluronic acid and PRP offer a new therapeutic alternative for scleroderma patients
Carney et al[96]	2020	In vitro *and* in vivo (murine model)	Re-epithelialization	PRP	PRP + inorganic polyphosphate	Inorganic polyphosphate in PRP accelerates re-epithelialization both in vitro and in vivo
Farjah et al[97]	2020	In vivo (rat model)	*Candida albicans*-infected partial burns	PRP	PRP + chitosan	The combined topical application of PRP and chitosan is an effective strategy to enhance the healing of infected burns, showing synergistic antimicrobial and regenerative properties
Han et al[98]	2020	In vivo (rat model)	Wound healing	PRP	Chitosan/silk fibroin and PRP wound dressing	This novel composite dressing of chitosan, silk fibroin, and PRP shows great potential as a hemostatic material for wound treatment, combining rapid bleeding control with a favorable environment for healing
Qian et al[99]	2020	In vitro and in vivo (rat model)	Wound healing	PRP	Injectable and self-healing hidrogel composite of chitosan and silk fibroin loaded with PRP	The hydrogel loaded with PRP represents a promising strategy for treating chronic diabetic wounds, offering controlled growth factor release
Bhatnagar et al[100]	2021	In vitro	Wound healing	PL	PL- loaded chitosan reinforced with kenaf nanocrystalline cellulose	The use of chitosan reinforced with Kenaf nanocrystalline cellulose as a platelet lysate delivery system is a promising strategy for accelerating wound healing due to its mechanical properties and ability to release bioactive factors
Hersant et al[101]	2021	RCT	Facial rejuvenation	PRP	PRP +hyaluronic acid	Autologous PRP and hyaluronic acid injections demonstrate synergistic effects in facial skin rejuvenation
Kartika et al[102]	2021	RCT	Wound healing	PRF	PRF + hyaluronic acid	Combined use of PRF and hyaluronic acid shows promise for wound healing in diabetic foot ulcer patients compared to PRF with placebo
Shi et al[103]	2021	In vitro and in vivo (rat model)	Infected wound healing	PRP	Gelatin microspheres (GMs) loading gentamycin sulphate (GS) and PRP	These innovative dual-release antibiotic and PRP dressings are highly promising for treating infected wounds by combining antimicrobial effects with stimulation of tissue regeneration
Wei et al[104]	2021	In vitro and in vivo (diabetic murine model)	Infected wound healing	PRP	Oxidized dextran (ODEX) and antimicrobial peptide-modified hyaluronic acid (HA-AMP) composite hydrogel + PRP	A composite hydrogel co-delivering antimicrobial peptides and PRP significantly enhances the healing of infected diabetic wounds
Zheng et al[105]	2021	In vitro and in vivo (murine model)	Skin repair	PRP	Polydopamine-modified collagen sponge scaffold + PRP	A polydopamine-modified collagen sponge scaffold with sustained PRP release provides a one-step strategy for accelerating skin repair
Zhou et al[106]	2021	In vitro and in vivo (rat model)	Wound healing	PRP	Nanosilver doped carboxymethyl chitosan-polyamideamine alginate composite dressing + PRP	The development of this composite dressing with silver nanoparticles offers a multifunctional material for wound treatment, effectively combining antimicrobial and regenerative properties
Biazar et al[107]	2022	In vivo (rat model)	Full-thickness skin defects	PRGF	Acellular fish skin + PRGF	Acellular fish skin combined with PRGF factor effectively heals full-thickness skin defects
Chen et al[108]	2022	In vitro and in vivo (rat model)	Wound healing	CGF	CGF-loaded sponge scaffold consisting of polydopamine nanospheres (PDA-NPS) incorporated into a network of acellular dermal matrix (ADM) and chitosan	The innovative multifunctional composite scaffold exhibits strong compatibility with biological tissues and effectively supports wound healing and skin regeneration when activated by near-infrared (NIR) stimulation

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Table 1 (Continued).

Author	Year	Research Methodology[a]	Condition/ Pathology	Platelet Derivative[b]	Combination Therapy	Conclusions
Diaz-Gomez et al[109]	2022	Material engineering and in vitro study	Wound healing	AGF	AGF-loaded 3D printed carboxymethyl cellulose scaffolds	3D printed carboxymethyl cellulose scaffolds serve as effective carriers for autologous growth factors in wound healing
Foffa et al[110]	2022	Pilot clinical study	Chronic wound management	CBPG	Carboxymethyl Cellulose-Based Hydrogel Film + CBPG	A carboxymethyl cellulose-based hydrogel film combined with umbilical CBPG is an innovative tool for chronic wound management
Garcia-Orue et al[111]	2022	In vitro and in vivo (diabetic murine model)	Wound healing	PRP	PRP fibrin matrix oxidized alginate hydrogel	A bioactive and degradable hydrogel based on human PRP fibrin matrix combined with oxidized alginate promotes diabetic wound healing
Guo et al[112]	2022	Case report	Hyaluronic acid embolic cutaneous necrosis and alopecia	PRP	PRP + botulinum toxin A	The combination of PRP with botulinum toxin A is effective in treating hyaluronic acid embolic cutaneous necrosis and alopecia
Koyuncu et al[113]	2022	In vitro	Wound healing	PRP	PRP-loaded hitosan/gelatin scaffolds	The combined use of PRP and polychromatic light on chitosan/ gelatin scaffolds can enhance fibroblast activity and, therefore, improve wound healing processes
Li et al[114]	2022	In vitro and in vivo (rat model)	Skin regeneration	PRP	PRP-loaded self-healing hyaluronic acid nanocomposite hydrogel based on aldehyde-modified sodium hyaluronate (AHA), hydrazide-modified sodium hyaluronate (ADA), and aldehyde-modified cellulose nanocrystals (oxi-CNC)	Self-healing hyaluronic acid nanocomposite hydrogels impregnated with PRP are effective for promoting skin regeneration
Ma et al[115]	2022	In vitro	Wound healing	PRP	Chitosan, polyethylene glycol (PEG) and lyophilized PRP gel	The development of this novel chitosan, PEG, and lyophilized PRP-based gel offers a promising solution for wound treatment, combining hemostatic capacity with antimicrobial properties
Marinescu et al[116]	2022	In vivo (rat model)	Skin defects	PRP	PRP + hyaluronic acid	Histological analysis in a rat model confirms that PRP enriched with hyaluronic acid significantly improves the treatment of skin defects
Rao et al[117]	2022	In vitro and in vivo (diabetic murine model)	Wound healing	PRP	PRP + hyaluronic acid	Hyaluronic acid prolongs growth factor release from platelets, enhancing proliferation and collagen deposition, thus accelerating wound healing in diabetic mice
Tang et al[118]	2022	In vitro and in vivo (porcine model)	Wound healing	PRP	Thermosensitive decellularized adipose tissue/PRP hydrogel (IPN)	A thermosensitive decellularized adipose tissue/PRP interpenetrating polymer network hydrogel shows promise for wound healing
Tekam and Belgaumkar[119]	2022	Self-controlled clinical study	Melasma	PRP	PRP + hydroquinone 4%	The combination of autologous PRP and hydroquinone 4% is more effective than hydroquinone alone in treating melasma
Alinezhad et al[120]	2023	Material engineering and in vivo (animal model) study	Skin regeneration	PRP	Multifunctional injectable hydrogel containing alginate (ALG), gelatin (GT), PRP and polydopamine (PDA)	A PRP-based multifunctional injectable hydrogel with photothermal, antibacterial, and antioxidant properties is effectively engineered for skin regeneration
Bakadia et al[121]	2023	In vitro and in vivo (rat model)	Wound healing	PRP, PRP-derived exosomes	PRP/PRP-derived exosomes-loaded dual-crosslinked hydrogels based on silk protein (SP) (sericin and fibroin)	Engineering dual-crosslinked hydrogels based on homologous PRP, PRP-derived exosomes, and MSC-derived exosomes creates bioactive diabetic wound dressings
Cai et al[122]	2023	In vitro and in vivo (rat model)	Wound healing	PRP	Hybrid organohydrogel consisting of cellulose and PRP into a poly-N-(tris[hydroxymethyl]methyl)acrylamide (THMA)/ N-acryloyl aspartic acid (AASP)	A PRP composite organohydrogel with water-locking and anti-freezing properties accelerates wound healing

Gierek et al[123]	2023	Comparative retrospective study	Hidradenitis Suppurativa (surgical treatment)	PRP	PRP + Acellular Dermal Matrix (ADM)	PRP combined with ADM is a valuable approach in the surgical treatment of Hidradenitis Suppurativa
Huang et al[124]	2023	In vitro and in vivo	Wound healing	PRP	PRP-loaded chitosan@sodium alginate@gelatin shell-core fibrous hydrogels	These PRP-loaded hydrogels offer a promising solution for treating diabetic ulcers, facilitating sustained growth factor release and promoting more effective healing
Lin et al[125]	2023	Clinical study	Wound healing	PRF	PRF + Silver Nanoparticle Dressing	PRF combined with silver nanoparticle dressing positively impacts healing time and therapeutic efficacy of chronic refractory wounds
Lin et al[126]	2023	In vivo (diabetic rat model)	Wound healing	PRP	Ultrasound-Assisted-Digested Formic Acid-Decellularized Extracellular Matrix and Sacchachitin Nanofibers composite hydrogels + PRP	Composite hydrogels of decellularized extracellular matrix and sacchachitin nanofibers with PRP are effective for diabetic wound treatment
Shu et al[127]	2023	Material engineering and in vivo (animal model) study	Wound healing	PRP-derived exosomes	PRP-loaded fiber-reinforced gelatin/β-cyclodextrin hydrogels	Fiber-reinforced gelatin/β-cyclodextrin hydrogels loaded with PRP-derived exosomes are effective for diabetic wound healing
Tang et al[128]	2023	In vitro and in vivo (murine model)	Wound healing	PRP	Carboxymethyl chitosan/poly-γ-glutamic acid and PRP bio-sponge	The studied composite bio-sponges offer an effective and biocompatible platform for rapid hemostasis and wound healing
Wang et al[129]	2023	Case series	Female androgenetic alopecia (FAGA)	PRP	PRP + non-cross-linked hyaluronic acid compound	PRP combined with non-cross-linked hyaluronic acid shows efficacy in treating FAGA
Wang et al[130]	2023	In vitro and in vivo (rat model)	Wound healing	PRP	Sodium alginate hydrogel + PRP	Sodium alginate hydrogels containing PRP are effective for promoting wound healing
Xu et al[131]	2023	In vitro and in vivo (murine model)	Wound healing	PRP	PRP-loaded multifunctional hydrogel composed of PRP, dopamine (DA) grafted alginate (Alg-DA), and 6-aminobenzo[c][1,2] oxaborol-1(3H)-ol (ABO) conjugated hyaluronic acid (HA-ABO)	A PRP-loaded multifunctional hydrogel effectively accelerates diabetic wound healing by regulating abnormal microenvironments
Yang et al[132]	2023	In vitro and in vivo (rat model)	Infected wound healing	PRP	PRP + β-lactams	Combining the dual antibacterial and regenerative activities of PRP with β-lactams is effective in mitigating MRSA-infected skin wounds
Zhang et al[133]	2023	In vivo (rat model)	Wound healing	PRP	Injectable bioactive dressing based on PRP and laponite	The bioactive dressing based on PRP and nanoclay provides sustained deferoxamine release to accelerate wound healing
Chen et al[134]	2024	In vivo (rat model)	Wound healing	PRP	PRP-loaded graphene oxide/alginate gel	Slow-sculpting graphene oxide/alginate gel loaded with PRP effectively promotes wound healing in rats
Darwish et al[135]	2024	RCT	Skin deflects	PRP	Dermal substitute + PRP	Using PRP with dermal substitutes offers benefits for treating skin defects
Duan et al[136]	2024	In vitro and in vivo	Wound healing	PRP	Adhesive wound dressings (HA-DA/PRP) composed of PRP and dopamine-modified-hyaluronic acid (HA-DA)	Injectable hyaluronic acid-based hydrogels with anchored PRP effectively accelerate diabetic wound healing
Gomaa et al[137]	2024	In vivo (rabbit model)	Wound healing	PRP	PRP-loaded gelatin	Gelatin loaded with PRP effectively promotes full-thickness wound healing
Gomaa et al[138]	2024	In vitro and in vivo	Wound healing	PRP	PRP integrated into a gelatin scaffold with titanium dioxide (TiO_2) (P25)/single-walled carbon nanotubes (SWCNTs)/Ag and P25/ reduced graphene oxide (rGO)/Ag	Nanocomposites within a PRP-gelatin scaffold demonstrate synergistic antimicrobial activity and accelerate wound healing

(*Continued*)

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Table 1 (Continued).

Author	Year	Research Methodology[a]	Condition/ Pathology	Platelet Derivative[b]	Combination Therapy	Conclusions
He et al[139]	2024	In vitro and in vivo	Wound healing	PRP	PRP-loaded carboxymethyl chitosan (CMCS), oxidized dextran (Odex) and oligomeric procyanidins (OPC) hydrogels	The creation of ROS/pH-sensitive chitosan hydrogels loaded with PRP offers a promising platform for targeted growth factor delivery
Heydari et al[140]	2024	In vitro	Wound healing	PRP	Poly glycerol sebacate (PGS)/poly lactide acid (PLA) fiber dressing + PRP	A PGS/PLA fiber dressing containing PRP enhances wound regeneration
Karas et al[141]	2024	In vitro and in vivo (diabetic murine model)	Wound healing	PRP	Selenium nanoparticles + PRP	A novel therapeutic combination of selenium nanoparticles and PRP accelerates wound healing
Li et al[142]	2024	In vivo (porcine model)	Wound healing	PRP	Highly concentrated collagen/chondroitin sulfate scaffold + PRP	A highly concentrated collagen/chondroitin sulfate scaffold with PRP significantly promotes bone-exposed wound healing
Liu et al[143]	2024	In vitro and in vivo (rat model)	Wound healing	PRP	Chitosan-based wound dressing hydrogel with β-glycerophosphate (GP), hydroxy propyl cellulose (HPC), graphene oxide (GO) and PRP	An injectable and thermosensitive hydrogel loaded with PRP enhances the biotherapy of skin wound healing
Liu et al[144]	2024	In vitro	Infected wound healing	PRP	Dynamic polysaccharide hydrogels composed of antimicrobial polysaccharide, carboxymethyl chitosan, and PRP	The combination of dynamic polysaccharide hydrogels with PRP presents an innovative and effective strategy for managing infected wounds by providing both antimicrobial effects and regenerative stimuli
Roohaninasab et al[145]	2024	RCT	Burn scars	PRP	PRP + non-cross-linked hyaluronic acid	PRP, non-cross-linked hyaluronic acid, and their combination demonstrate varying but generally positive efficacy, safety, and satisfaction rates in treating burn scars with fractional CO2 laser
Yan et al[146]	2024	In vitro	Infected wound healing	PRP	Methacrylated gelatin hydrogel conjugated with ε-polylysine + PRP	Methacrylated gelatin hydrogel conjugated with ε-polylysine and enriched with PRP shows promise for treating chronically infected wounds
Zhao et al[147]	2024	In vitro and in vivo	Infected wound healing	PRP	Injectable hydrogel based on PRP, pullulan polysaccharide and metal-phenol network nanoparticles	An injectable and self-healable hydrogel containing PRP and metal-phenol network nanoparticles effectively treats infectious wounds
Zheng et al[148]	2024	In vitro and in vivo (murine model)	Wound healing	PRP	Molybdenum selenide-based carboxymethyl chitosan/polyvinyl pyrrolidone and PRP composite antioxidant hydrogels	The design of these composite hydrogels, which combine the antioxidant properties of molybdenum selenide with the regenerative capacity of PRP and the characteristics of chitosan, offers an advanced approach for effective wound healing
Back et al[149]	2025	In vitro and in vivo (rat model)	Wound healing	Platelet Extracellular Vesicles (EVs)	PRP-loaded gelatin hydrogel	Platelet EVs-loaded gelatin hydrogels are a promising solution for advanced wound care

Abbreviations: RCT, Randomized Controlled Trial; AGF, Autologous Growth Factors; CBPG, Cord Blood Platelet Gel; CGF, Concentrated Growth Factors; PRGF, Plasma Rich in Growth Factors; PRP, Platelet-Rich Plasma; PG, Platelet Gel; PL, Platelet Lysate.

revealed that fibroblasts were stimulated, extracellular matrix formation was enhanced and oxidative stress levels decreased in chitosan/gelatin scaffolds loaded with PRP.[113] Moreover, PRP loaded shell-core fibrous hydrogels consisting of chitosan, alginate, and gelatin have proven to reduce inflammation and accelerate the growth of granulation tissue and angiogenesis, stimulate the formation of dense hair follicles, and promote the development of a dense and well-organized collagen fiber network.[124] Similar pro-healing and pro-hemostatic effects have been observed for hydrogels manufactured with PRP and highly absorbent bio-sponges based on carboxymethyl chitosan/poly-γ-glutamic acid in a murine wound model.[128] In the same line, chitosan-gelatin sponges crosslinked with tannic acid and loaded with PRP demonstrated strong antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* with low cytotoxicity, and also promoted a rapid healing when applied as wound dressings.[77]

In vivo experiments developed by Shi et al[103] showed that gelatin microspheres (GMs) loading gentamycin sulfate (GS) and PRP and covalently bond to carboxymethyl chitosan (CMC) dressings could accelerate the healing of full-thickness wounds infected with *E. coli* and *S. aureus*, promoting re-epithelialization, collagen deposition, and angiogenesis, inhibiting bacterial growth, and modulating the expression of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and anti-inflammatory growth factors (TGF-β1). Other variants, including PRP-loaded hydrogels based on chitosan and PEG have been identified as excellent hemostatic material for superficial wounds with antibacterial and wound healing effects as revealed by in vitro and in vivo experiments,[114] whereas CMCS/polyvinyl pyrrolidone (PVP)/Molybdenum (IV) Selenide (MoSe2), and platelet-rich plasma (PRP) (CMCS/PVP/MoSe2/PRP) based antioxidant hydrogels can prevent inflammatory storms by neutralizing free radicals at the wound site and inhibiting the release of inflammatory factors.[148] On the other hand, PRP-chitosan/silk fibroin composite dressings could function as effective wound dressings that facilitate rapid hemostasis and accelerates the healing process.[98,99] Multifunctional platforms have been also constructed by mixing PRP and alginate-based dressing containing nano silver (Ag)-doped carboxymethyl chitosan grafted polyamide-amine cationic polymers with strong antiinflammatory, antibacterial, and proangiogenic properties.[106] In vitro and in vivo experiments conducted by Liu et al[144] concluded that a thermosensitive chitosan-based wound dressing hydrogel containing β-glycerophosphate (GP), hydroxy propyl cellulose (HPC), graphene oxide (GO), and PRP for the treatment of skin wounds exhibited antibacterial properties against *Pseudomonas aeruginosa* and ability to stimulate cell proliferation and migration along with reduced inflammation levels. Finally, according to Bhatnagar et al,[100] chitosan (CS) and kenaf nanocrystalline cellulose (NCC) hydrogel composites loaded with platelet lysate (PL) could increase fibroblast proliferation in vitro and enhance wound closure.

Hyaluronic Acid

Hyaluronic acid (HA) is a natural glycosaminoglycan present in the extracellular matrix of skin, cartilage, bone, and brain, among other tissues. It plays a crucial role in wound healing and tissue repair by creating a humid environment that promotes tissue regeneration, while also modulating the release of growth factors and cellular components and stimulating the movement of different cells that are essential for the healing process.[154] During the last decades, several studies have concluded that the combination of PRP and HA may benefit from its synergistic biological effects, supporting the activity of signaling molecules such as inflammatory mediators, catabolic enzymes, cytokines, and growth factors, which could improve the treatment of different skin conditions.[72,91,117] In addition to its volumizing and moisturizing effect, it has been concluded that HA sustains platelet stability and induces a prolonged release of growth factors from PRP.[155] Moreover, the rheological behavior of HA is especially relevant in the field of dermatology and aesthetic medicine for improving wound healing and skin rejuvenation. In this sense, due to its ability to exhibit both elastic and viscous properties, it is considered as an effective carrier for both topical and transdermal applications, showing high biodegradability and biocompatibility, and low immunogenicity.[156]

According to Rao et al,[117] topical hydrogels manufactured with PRP and HA can accelerate wound healing in mice since they retain their biological activity over extended periods and ensure a continuous release of morphogens to the wound. In line with these findings, both macroscopic and microscopic observations in a rat model revealed that the mean healing period was reduced by 7 days (approximately 33%) in lesions treated with PRP enriched with HA.[116] More complex combinations of PRP, HA, and other biopolymers have been also demonstrated remarkable healing properties. For example, Li et al[114] developed a self-healing nanocomposite hydrogel (ADAC) based on aldehyde-modified sodium

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hyaluronate (AHA), hydrazide-modified sodium hyaluronate (ADA), and aldehyde-modified cellulose nanocrystals (oxi-CNC) loaded with PRP with promising mechanical and biological characteristics. As revealed by in vivo models, ADAC hydrogel enhanced full-thickness skin wound repair by stimulating granulation tissue formation, collagen deposition, re-epithelialization, and neovascularization. On the other hand, Wei et al[104] constructed a hydrogel by incorporating Schiff base linkages between oxidized dextran (ODEX), antimicrobial peptide-modified hyaluronic acid (HA-AMP), and PRP under physiological conditions. This hydrogel exhibited an initial rapid release of growth factors and antimicrobial peptides (AMP), followed by a sustained long-term release over more than 120 hours. Moreover, in vivo studies revealed that the hydrogel significantly promoted wound healing in diabetic mice with infections by modulating inflammation and enhancing collagen synthesis and angiogenesis. Additionally, the hydrogel displayed notable antibacterial properties against *S. aureus* and *P. aeruginosa*, reduced proinflammatory cytokines (TNF-α, IL-1β, and IL-6), and increased the levels of anti-inflammatory factor TGF-β1 and VEGF. Recently, Duan et al[136] concluded that injectable adhesive wound dressings (HA-DA/PRP) composed of PRP and dopamine-modified-hyaluronic-acid (HADA) also accelerated in vivo healing of diabetic ulcers by inhibiting bacterial growth, enhancing regenerative and angiogenic processes, promoting collagen deposition, and modulating inflammation through M1→M2 polarization.

Clinical data also support the use of PRP enriched in HA for the treatment of wounds. An observational study involving 364 patients conducted by De Angelis et al[91] confirmed the strong regenerative potential of PRP and HA combined in relation to epidermal growth and dermal remodeling. A randomized controlled trial involving 100 participants focused on evaluating the effectiveness of plasma rich in growth factors (PRGF-Endoret®) and HA for the treatment and care of pressure ulcers was published by Ramos-Torrecillas et al.[72] As revealed by clinical data, the greatest mean reduction in pressure-ulcer area (80.4% vs baseline) was obtained with the PRGF-Endoret® plus HA regimen. In the same line, Cervelli et al[61,63] also concluded that PRP dressings combined with HA are able to stimulate the regeneration of the lower-extremity complex soft- and hard-tissue wounds. As concluded by Gentile et al,[75] PRP gel combined with HA resulted in accelerated and uncomplicated effective wound closure, a good cutaneous elasticity and a notable aesthetic improvement in the treatment of complications derived from Achilles tendon reconstruction. A randomized controlled trial published by Roohaninasab et al[145] also supported the effectiveness of PRP and non-cross-linked HA injections in patients with burn scars treated with fractional CO_2 laser. Similarly, Kartika et al[102] observed increased angiogenesis and reduced inflammation in diabetic foot ulcers treated with platelet-rich fibrin and HA after conducting an open-label randomized controlled trial.

In reference to facial rejuvenation, Ulusal et al[86] detected a statistically significant improvement in general appearance and also in skin firmness and texture after intradermal applications of platelet-rich plasma combined with HA. These results were confirmed by a randomized controlled prospective study involving 93 patients and published by Hersant et al,[101] who concluded that combining platelet-rich plasma and HA could be regarded as a promising treatment for facial rejuvenation, showing highly significant improvements in facial appearance and skin elasticity compared with conventional therapies or PRP alone. Similar approaches have demonstrated to be an efficient therapeutic alternative for patients affected by other skin pathologies. For example, it has been reported that platelet-rich plasma combined with non-cross-linked HA significantly improved hair loss and hair count evaluated at the 3-month follow-up relative to baseline in patients suffering female androgenic alopecia.[129] Moreover, Pirrello et al[95] concluded that filler injections of HA and PRP constitute an effective strategy to increase skin elasticity, mouth's opening, and upper lip's thickness in patients affected by scleroderma.

Alginate

Alginate is a naturally sourced biopolymer derived mainly from brown marine algae and certain bacterial taxa that Is widely integrated into biomedical practices due to its desirable physicochemical, mechanical, and biological properties, such as biocompatibility, non-toxicity, affordability, biodegradability, absorbability, and non-immunogenicity.[157] It has been widely used to manufacture different variants of wound dressings, including hydrogels, films, wafers, foams, nanofibers, and in topical formulations.[158] As revealed by multiple studies, PRP combined with alginate could be considered an effective strategy to accelerate wound healing. In vitro studies on human fibroblasts and keratinocytes demonstrated that a degradable hydrogel composed of alginate and PRP is non-cytotoxic and promotes cell adhesion and proliferation.[111] Alginate-based particles are also able to load and release platelet lysate and vancomycin hydrochloride, thus enhancing fibroblast proliferation in the context of chronic skin ulcers.[67] According to Wang et al,[130] a dual-network hydrogel incorporating sodium alginate (SA) and PRP could stimulate cell proliferation and vascular regeneration and showed a high wound closure effectiveness in rats. Nevertheless, most studies focus on multifunctional hydrogels providing an array of beneficial properties, including antibacterial and antioxidant activities, bioadhesion, and optimized mechanical characteristics. For example, Alinezhad et al[120] engineered a calcium-crosslinked PRP-based injectable hydrogel by mixing alginate (Alg), gelatin (GT), polydopamine (PDA), and PRP that exhibited promising photothermal, antibacterial, and antioxidant properties for skin regeneration. A multifunctional hydrogel prepared with PRP, dopamine (DA)-grafted alginate (Alg-DA), and 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol (ABO)-conjugated hyaluronic acid (HA-ABO) through ionic interactions, hydrogen bonds, and boronate ester bonds induce beneficial changes for diabetic wound healing, including rapid anti-inflammatory effects, and also promoted macrophage polarization toward the M2 phenotype, accelerated angiogenesis, increased migration and enhanced proliferation of fibroblasts.[131] Similar wound healing promoting results have been obtained using different hydrogels based on platelet-rich plasma and alginate, such as platelet rich plasma-loaded slow-sculpting graphene oxide (GO)/alginate gel[134] or PRP-loaded alginate/ carboxymethyl-cellulose hydrogels.[85]

Collagens and Gelatin

Collagens are the most prevalent proteins in the human body. The widespread presence of collagen in animal systems, especially fibrillar collagen type I, is mainly due to its distinct mechanical and physiological properties, such as thermal and chemical stability, mechanical strength, and its ability to interact physiologically.[159] During wound healing, fibroblasts and other cells produce these collagens, which are then transformed into complex structures. The collagen superfamily comprises 28 distinct types, which are categorized into eight subfamilies. Most of these collagen types fall under the fibril-forming subfamily, which includes type I, type II, type III, or type V collagen. These two types are the primary components of the extracellular matrix (ECM) in the dermis.[160] Collagen plays a critical role in modulating inflammation, angiogenesis, and ECM remodeling, providing valuable support in wound healing therapy. Collagen-based biomaterials are commonly used in wound dressings due to their biocompatibility, low immunogenicity, and ability to attract key wound healing cells such as macrophages and fibroblasts.[161] It has been concluded that collagen-induced platelet activation results in sustained release of growth factors and anabolic cytokines.[162–164] As demonstrated by do Amaral et al,[92] porous collagen-glycosaminoglycan (collagen-GAG) scaffolds functionalized with PRP stimulated the release of key regenerative growth factors for wound healing and vascularization (FGF, TGFβ, VEGF, and PDGF) for up to 14 days, enhanced cell-proliferation and migration in vitro, and also demonstrated increased angiogenic and vascularization potential in vivo. Other collagen-based PRP loaded candidate scaffolds for wound healing and tissue repair include collagen/chondroitin sulfate scaffolds with platelet-rich plasma.[142] In the same line, a hydrogel scaffold developed through combination of type I collagen and PRP recruited more stem cells from skin tissue in vivo compared to collagen hydrogels alone at both the 4- and 8-week time points. Additionally, fractionated PRP-enriched hydrogels stimulated wound healing, angiogenesis, and the formation of hair and sweat glands, ultimately leading to the regeneration of dermis-like tissue.[76] According to Zheng et al,[105] a polydopamine (pDA)-modified collagen sponge scaffold loaded with PRP stimulated in vitro proliferation, adhesion, and migration of keratinocytes and endothelial cells. Moreover, histological results confirmed that wound healing was accelerated in pDA-CSS@PRP scaffolds with less scar formation via rapid angiogenesis and the deposition of more mature and well-organized collagen.

Gelatin is a commonly used natural biopolymer derived from natural collagen with excellent biocompatibility, biodegradability, and non-immunogenicity.[165] Additionally, it exhibits other physicochemical characteristics that attained strong interest in the biomedical research such as rheological stability within a pH range of 5 to 9, water solubility, high-viscosity, and temperature sensitivity. As a consequence, gelatin-based biomaterials support wound repair and regeneration due to its adhesive, anti-inflammatory, antibacterial, angiogenic, and regenerative properties.[166] As highlighted in multiple studies, platelet-rich plasma combined with gelatin hydrogel granules can promote angiogenenesis in vivo.[66,70,71,79,83,94] Clinical trials have also been designed investigate the efficacy and safety profile of PRP covered with a gelatin sheet as dressing for the treatment of chronic wounds.[70] Preliminary data suggest that gelatin combined with PRP is a valuable option in the treatment of non-healing wounds.[79] Enhanced antimicrobial effects and in vitro HUVEC proliferation promoting properties were observed in methacrylated gelatin hydrogels conjugated with ε-polylysine and enriched with PRP.[146] Fiber-reinforced gelatin (GEL)/β-cyclodextrin (β-CD) therapeutic hydrogels loaded with PRP-derived exosomes significantly induced autophagic activity and reduced apoptotic processes in HUVECs and human skin fibroblasts (HSFs), thus stimulating microvascular network creation, collagen synthesis, and re-epithelialization in a diabetic rat wound healing model.[127] Accordingly, Gomaa et al[138] revealed that PRP integrated into a gelatin (GLT) combined with nanocomposites of titanium dioxide (TiO2) (P25)/single-walled carbon nanotubes (SWCNTs)/Ag and P25/reduced graphene oxide (rGO)/Ag showed superior antioxidant activity, enhanced antimicrobial properties, and enhancer tissue repair. Recently, gelatine-based hydrogel (PAH-G) foams loaded with platelet-derived extracellular vesicles (pEVs) demonstrated reduced inflammation in vivo and wound closure after 14 days.[149] The in vivo biological effects of combing platelet-rich plasma with synthetic collagen-based skin substitutes[59] or acellular human or animal tissues for wound healing and skin repair, including amnion,[88] dermis,[62,74,93,123,135] fish skin,[107] or decellularized extracellular matrix[108,126] have also been extensively assessed.

Cellulose Derivatives

Cellulose is a highly biocompatible, non-toxic, and biodegradable polysaccharide composed of glucose units linked by β-1,4-glycosidic bonds, which is commonly regarded as the most abundant natural biopolymer on Earth.[167] Though cellulose is best known as a plant structural molecule, it is also synthesized by various non-plant organisms, including bacteria, oomycetes, algae, slime molds, and the only known cellulose-producing animals: urochordates.[168] As a result from its mechanical strength, structural stability exceptional, water absorption capacity, and the capability of cellulose derivatives to create thermally responsive hydrogel systems, it has gained a considerable attention in hydrogel development during the last decades, and different chemical methods, such as oxidation, etherification, and esterification, have been proposed to overcome the poor solubility of cellulose in water and most organic solvents.[169] Cellulose derivatives include cellulose dialdehyde (DAC), cellulose dicarboxylic acid (DCC), and 2,2,6,6-tetramethylpiperidine-1-oxyl-oxidized cellulose nanofibrils (TOCNF), ethylcellulose (EC), methylcellulose (MC), carboxymethylcellulose (CMC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), cellulose acetate (CA), nitrocellulose (CN), cellulose sulfate (CS), cellulose acetobutyrate (CAB), and hydroxypropylmethylcellulose phthalate (HPMCP). Cellulose-based biomaterials have been utilized in wound healing or tissue engineering applications to mimic skin, accelerate the regeneration of skin cells, and reduce scarring.[170]

Both in vitro and in vivo models confirmed that carboxymethyl cellulose (CMC) scaffolds loaded with PRP sustained the release of growth factors, stimulated angiogenesis, stem cell migration, and facilitated re-epithelialization, granulation, and angiogenesis in full-thickness skin defects of diabetic wounds.[109] A pilot study that investigated the clinical performance of a hydrogel consisting of umbilical cord blood platelet gel (CBPG) and CMC revealed that this dressing demonstrated efficacy in promoting faster regeneration of chronic wounds with no observed adverse effects.[110] Cellulose derivatives are commonly included into multifunctional formulations.[100,143] As published by Cai et al,[122] a composite adhesive organohydrogel manufactured via introduction of bacterial cellulose and PRP into a poly-N-(tris[hydroxymethyl]methyl)acrylamide (THMA)/N-acryloyl aspartic acid (AASP) hybrid organohydrogel stimulated angiogenesis and collagen deposition in vivo, thus accelerating the wound healing process. A randomized controlled trial published by Kakagia et al[60] reported that a significant three-dimensional reduction of diabetic foot ulcers was achieved in individuals treated with a combination of oxidized regenerated cellulose/collagen biomaterial and PRP compared to both cellulose/collagen or PRP alone.

Other Biopolymers

The mechanical and biological performance of PRP combined with a wide range of biopolymers has been explored. Yang et al[64] observed enhanced angiogenesis and epidermal regeneration in vivo after treating wounds with PRP and heparin-conjugated fibrin (HCF). Platelet-rich formulations have also been combined to treat refractory wounds, with significant reductions in wound area and duration.[171] Cocoon composites derived from the silkworm *Bombyx mori* have demonstrated improved water absorption and retention capacities. After loading with PRP, these composites stimulated cell growth in vitro and enhanced the wound healing process in a rabbit wound healing model.[84] The combination of platelet-rich plasma-based gels with silk fibroin gel have proven to augment both the compressive stiffness and rheological properties of PRP-based gels, and promoted cell infiltration and blood vessel neoformation when injected in nude rats.[68] Similar results were obtained by Pignatelli et al[89] after combining silk fibroin fibers with platelet lysate (PL). As revealed by in vitro and in vivo experiments, PRP-loaded dual-crosslinked silk protein-based hydrogel systems (SP) (sericin and fibroin) stimulated diabetic wound healing more effectively than platelet-rich plasma and SP by increasing the expression of growth factors, inhibiting matrix metalloproteinase-9 (MMP-9) expression, and promoting anti-NETotic activity, angiogenesis, and re-epithelialization.[121] On the other hand, the application of combined treatment consisting of *Curcuma zedoaria* polysaccharides with PRP-derived exosomes assembled on chitosan/silk hydrogel sponge in wounded diabetic rats resulted in a significant reduction of ulcer size and an increase of epidermal thickness.[90] Zhao and Yuan et al[147] proposed a multifunctional hydrogel backbone composed of pullulan polysaccharide derivatives (OPD), poly-lysine derivatives (EPL-BA) with encapsulated tea polyphenols (TP), gallic acid (GA), and metal ions (Cu^{2+}) loaded with PRP with antibacterial, anti-inflammatory, regenerative, and pro-angiogenic properties to treat infected wounds. Regenerative properties have also been described for lactic acid and glycolic acid-based hydrogels loaded with PRP.[69,80,140]

Plant-Derived Extracts

To date, the incorporation of plant products as additives or adjuvants in platelet derivatives has been little explored. In this sense, the deleterious effect of many plant secondary metabolites on platelet functionality could be considered as a significant limitation to the development of mixed formulations, since they could lead to impaired clot formation and altered release of growth factors. For example, several studies have concluded that the phenolic fraction derived from olive oil effectively reduces platelet aggregation and eicosanoid formation in vitro.[172–174] Similarly, sea buckthorn berry oil, *Vitis vinifera* or *Arachis hypogaea* seed oils have also demonstrated to suppress or reduce platelet function.[175,176] In the same line, the inhibition of platelet aggregation by plant aqueous or ethanolic extracts has been widely described.[177–181] Nevertheless, the treatment of skin diseases in humans has long benefited from plants, which offer a wide array of bioactive molecules with therapeutic properties.[182] In a novel study, Rastegar et al[58] concluded that the combination of herbal extracts derived from the fruits of *Persea americana*, flowers of *Althaea officinalis, Chamaemelum nobile, Thymus vulgaris*, and leaves of *Rosmarinus officinalis, Urtica dioica* and PRP was shown to significantly promote the proliferation of human dermal papilla cells (DPCs) through G1 cell cycle progression at concentrations between 1.5% and 4.5%. This study demonstrated that ERK phosphorylation and phosphorylated Akt expression increased dose-dependently following treatment with herbal extracts in the presence of PRP. In this sense and despite the field remains largely unexplored, the authors consider that the incorporation of phytochemicals as bioactive molecules in platelet derivative-based formulations constitutes a promising direction for future regenerative dermatological applications. As highlighted by Zhou et al,[183] a wide range of plant-based bioactive molecules, such as polyphenols, terpenes, alkaloids, and carotenoids, are easily obtained, inexpensive, mostly safe, and reliable, and have also demonstrated multiple biological properties including anti-inflammatory, antibacterial, antioxidant activity, proangiogenic behavior, and ability to promote stem cell differentiation.

Other Adjuvants

A combination of PRP and botulinum toxin A has been explored for the treatment of hyaluronic acid embolic cutaneous necrosis and alopecia that has yielded positive and encouraging outcomes.[112] In reference to therapeutic drugs, a combination therapy based on platelet-rich plasma and hydroquinone exhibited a higher effectiveness than hydroquinone alone in treatment of melasma.[119] Regarding inorganic molecules, Lin et al[125] concluded that platelet-rich fibrin (PRF) with nano silver (AgNP) dressing effectively reduces pain and local inflammation in patients with chronic refractory wounds, enhances the wound healing rate, accelerates recovery time, and reduces the risk of complications. In vivo experiments have also demonstrated that platelet-rich plasma combined with zinc oxide ointments applied subcutaneously could be effective in accelerating wound healing.[87] In the same line, Karas et al[141] recently demonstrated that the synergistic interaction between selenium nanoparticles (SeNPs) and PRP significantly improved wound repair in diabetic murine models, with selenium's antibacterial characteristics playing a pivotal role. An injectable bioactive dressing based on PRP and the nano-clay laponite (DPLG) has shown to accelerate wound healing through promotion of macrophage polarization and angiogenesis in a full-thickness skin defect model in both type I diabetic and normal rats.[133] According to Carney et al,[96] inorganic polyphosphate in PRP can also stimulate re-epithelization process in vivo and in vitro. The regenerative properties of PRP have been also combined with antibiotics to treat infected wounds. For example, Yang et al[132] evaluated the antimicrobial and wound healing potential the combination or PRP with β-lactams (ampicillin and/or oxacillin) for the administration on methicillin-resistant *Staphylococcus aureus* (MRSA)-infected skin. The results of this study concluded that the combination of platelet-rich plasma and β-lactam antibiotics demonstrated a synergistic effect, reducing wound area by 39%, as PRP enhanced keratinocyte proliferation and suppressed macrophage infiltration at the wound site, leading to a shorter inflammatory phase and an accelerated activation of the proliferative phase.

In spite of the heterogeneity observed across the included studies regarding experimental designs, combination therapies, and pathological conditions, no significant adverse events associated with combined therapies of platelet derivatives and biomaterials, active agents, or adjuvants were reported. The autologous origin of platelet derivatives inherently minimizes immunogenicity, with any observed reactions generally confined to mild, local, and transient responses associated with the injection procedure. Provided that standardized preparation and administration procedures are implemented, these therapies can be considered to have a low overall risk, excluding potential contributions from co-delivered biomaterials, active molecules, or adjuvants. Future in vivo and clinical studies should focus on the systematic evaluation of potential side effects, assessing both individual biomaterial, active agents, or adjuvants and their combined formulations. In this sense, transparent and standardized reporting of such events will be essential to strengthen the evidence base, inform safer and more effective clinical application, and ultimately improve patient-centered outcomes.

Decision Making Process

PRP, PRGF-Endoret,® and other platelet-rich formulations have been shown to be effective in treating several dermatological conditions including hair loss, dermatological disorders (lichen planus and melasma, among others), wound healing, scar revision, vitiligo, facial rejuvenation, and aesthetics.[184–190] The development of a wide arrange of therapeutic formulations (Figure 1) have allowed platelet-rich derivatives such as PRGF-Endoret® to be used as a stand-alone therapy in most of these applications. Through the modulation of the immune response and tissue formation, these hemoderivatives can affect the clinical progress of the postoperative recovery by achieving less pain, less inflammation, better quality of life, and accelerated tissue formation.[191,192] Their clinical use should be based on the understanding of the physiology of tissue healing, through the phases of hemostasis, inflammation, proliferation and remodeling, and the clinical condition to treat.[193] This understanding will determine the specific objectives to achieve through the implementation of a combined regenerative approach that requires the design and execution of a strategic plan to assess its effectiveness.

Different approaches are being developed within regenerative dermatology to target delivery of bioactive molecules to localized wounds, enhancing repair and accelerating regeneration.[194] Basic and clinical research should complement each other within the framework of providing evidence-driven translation from laboratory research to clinical application, confirming safety and performance. Moreover, such a combined strategy should be tailored to clinical procedures and be cost-effective. As highlighted in the review, the integration of growth factors and appropriate biomaterials, via physical or chemical interactions, facilitates sustained local delivery at effective doses, thereby improving tissue regeneration and the performance of biopolymers in skin repair.[191,192]

Commonly used biopolymers include hyaluronic acid, chitosan, collagen, gelatin, alginate, and cellulose derivatives. The selection of PRP as source of growth factors is justified by the fact that the healing process is orchestrated by multiple growth factors and cytokines that induce adequate cellular response and cell–cell communication during its progress.[43,195] Additionally, the gluing properties of fibrin (the product of activating the coagulation cascade in PRP) would improve the handling and delivery of the biomaterials.[196] The core of the PRP is the enrichment with platelets and the preparation protocols are designed for that purpose.[197,198] In addition, platelets play a dual role in hemostasis and immunomodulation to facilitate healing. They are reservoirs for many growth factors, proteins, and cytokines that mediate tissue healing after an injury. To have them available it is very important to activate the platelet to induce cytoplasmic changes and the attachment of granules to the plasma membrane and subsequent degranulation. This occurs concurrently with the conversion of fibrinogen to fibrin giving rise to 3D-structure.[199] The fibrin matrix is transformed into a collagen-rich extracellular matrix that eventually matures into functional tissue. However, their mechanical stability is determined by the relatively fast degradation of fibrin and thus they will need support for the treatment of critical-size defects or when there is a demand on better mechanical properties like the case of correcting tissue defects[200,201] In these cases, combination with other biomaterials would leverage their use in the clinical setting.

Thus, it is important to assess the effect of PRP on the physical and chemical properties of the biopolymer as well as the effect of that biopolymer on the platelet activation and the formation of the fibrin.[191,192] Furthermore, tailoring the incorporation method is essential to produce scaffolds aligned with specific clinical requirements. For example, distribution of the PRP within the biomaterial and the susceptibility to degradation, erosion, or swelling would be expected to condition the biological performance. Moreover, the type of PRP should be selected in the quest of achieving optimized biomaterial performance.[193] This aspect has received little attention in the reviewed literature. There are a wide variety of protocols to obtain PRP that yields different products in terms of cellular composition and the final volume of PRP[26,27,31] Accordingly, differences in platelet and leukocyte content lead to variability in the biological outcomes derived from platelet-rich plasma administration. When selecting a specific type of PRP, it would be helpful to critically assess the available basic and clinical evidence of the performance of that product in regenerative dermatology. The availability of standardized protocols of the selected PRP products would also ensure the comparability of the different studies assessing that specific formulation.

From a regulatory perspective, PRP is a medicinal product and its combination with biopolymers has an important impact on the route to achieve marketing authorization of the combined product. In the scenario where he combined product is released as an independent product, the combination may be subject to oversight from two distinct regulatory environments. If the use of PRP is ancillary to the medical device (biopolymers), then it will be, according to the Article 1 first and second paragraph of the medical device regulation (MDR) an integral product which is a medical device incorporates one or more substances which, if used separately, would be considered a medicinal product, including medicinal products derived from human blood or plasma, non-viable tissues, or cells of human origin or their derivatives as an integral part, within the meaning of 1 MDR, if and only if, the device and the substance form an integral product, when placed on the market or put into service. Under this scenario, the combined device will be under the scope of the MDR (Medical Device Coordination Group).[202] However, if the action of the PRP is principal, then it will be governed by the Directive 2001/83/EC[203] or by Regulation (EC) No 726/2004,[204] but the relevant general safety and performance requirements of Annex I to the MDR shall apply as far as the safety and performance-related device features are concerned.

However, if the biopolymer use is intended to administer the PRP at the injured site, then the combined product will be a single integral product which is a device intended to administer a medicinal product and the respective medicinal product form a single integral product, within the meaning of Article 1 of MDR,[202] if and only if the device and the medicinal product form an integral entity when placed on the market and, furthermore, the product is intended exclusively for use in the given combination and which is not reusable.

Thus, a single integral product consists of at least two constituent parts, one of which is a device and the other a medicinal product, which are combined in such a manner that they are not intended to be separated prior to administration.

Within this framework, the integral product is governed by the Directive 2001/83/EC[203] or by Regulation (EC) No 726/2004.[204] However, the relevant general safety and performance requirements outlined in Annex I of the MDR shall apply with respect to the device's safety and performance-related features. Another possibility that reflects the clinical reality is that the two products are authorized independently and their combination (the PRP and the biopolymer) is performed by the clinicians according to the clinical evaluation of the patient needs. Therefore, a systematic approach needs to be implemented in the integration of PRP with biomaterials in regenerative dermatology. This is important as this topic is attracting growing scientific interest and building conclusive scientific evidence is needed. Such a combination not only could enhance the preparation, handling, and application of conventional biomaterials, but more critically, it could significantly improve their biological and therapeutic effectiveness.

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Figure 3 Synthesis of potential therapeutic benefits of combining the biological properties of platelet derivatives with exogenous elements, molecules, or mixtures.

Conclusions

The use of PRGF-Endoret® and other platelet derivatives in dermatology is rapidly expanding, with numerous studies demonstrating their ability to promote wound healing, tissue regeneration, and aesthetic improvements. When combined with biopolymers and other adjuvants, including therapeutic agents, antibiotics, or other bioactive molecules, platelet-derived products can provide synergistic effects that significantly enhance clinical outcomes. As reviewed, the potential therapeutic benefits of combining the biological properties of platelet derivatives with exogenous elements, molecules, or mixtures are summarized in Figure 3. Despite the promising results, further research is needed, including large-scale randomized controlled trials and long-term follow-up studies, to optimize treatment protocols, understand the underlying mechanisms, and determine the most effective combinations for different dermatological pathologies and aesthetic conditions. As technology and our understanding of these biological products continue to advance, the clinical applications of platelet derivatives will likely expand, offering novel and effective treatments for a wide range of skin disorders.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics/Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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