

REVIEW ARTICLE OPEN ACCESS

Therapeutic Potential of Extracellular Vesicles (Exosomes) Derived From Platelet-Rich Plasma: A Literature Review

Aditya K. Gupta^{1,2}  | Tong Wang²  | Jeffrey A. Rapaport³  | Mesbah Talukder⁴ 

¹Division of Dermatology, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada | ²Mediprobe Research Inc., London, Ontario, Canada | ³Rapaport Hair Institute, Englewood Cliffs, New Jersey, USA | ⁴School of Pharmacy, BRAC University, Dhaka, Bangladesh

Correspondence: Mesbah Talukder (mesbah.talukder@bracu.ac.bd)

Received: 4 September 2024 | **Revised:** 17 November 2024 | **Accepted:** 19 November 2024

Keywords: alopecia | cosmetic dermatology | wound healing

ABSTRACT

Background: There are exciting advances in the field of exosomes research as a potential regenerative therapy. Platelet-rich plasma represents an abundant source of exosomes.

Aim: To present evidence on the use of platelet-rich plasma-derived exosomes in dermatology and discuss current technical limitations.

Methods: A literature search was conducted using Embase (Ovid), Web of Science, and [ClinicalTrials.gov](https://clinicaltrials.gov) in June 2024.

Results: Platelet-rich plasma-derived exosomes contain a myriad of growth factors, genetic materials, and lipids that mediate paracrine signaling. Several preclinical studies have demonstrated their potential in wound healing. This includes faster wound contraction in diabetic animal models, as well as enhanced angiogenesis, increased cell proliferation and migration, and protection against hyperglycemic conditions in vitro. A case study reported a topical platelet-derived exosome product tried successfully in a patient with persistent scalp wounds. In contrast, there is scarce information on the use of platelet-rich plasma-derived exosomes in hair growth and skin rejuvenation. Isolation techniques, activation methods, and methods of delivery have not been optimized, which warrants further research. Novel delivery methods, such as hydrogel-based preparations, may enable the topical application of exosomes.

Conclusion: Exosomes derived from platelet-rich plasma have demonstrated therapeutic potential. More research is needed to standardize its use.

1 | Introduction

Platelet-rich plasma (PRP) is an autologous treatment that entails obtaining a blood sample through venipuncture followed by the separation of plasma enriched in platelets; subsequently, it is administered intradermally or subcutaneously [1]. This procedure has been popularized as a regenerative therapy due to its effects on hair growth [1], stimulation of collagen synthesis [2], wound healing, and anti-inflammatory effects [3]. The therapeutic potential of PRP lies in the platelet production and secretion of growth factors, cytokines, chemokines, and extracellular vesicles (EVs) [4], which can be stimulated using various

activation methods. Despite its popularity, there are significant heterogeneities in how PRP is processed and administered, which limits the comparability between studies [4]. To date, PRP has not been approved by the U.S. FDA; however, several PRP collection systems have received U.S. FDA 510 (k) clearance as medical devices.

Exosomes are acellular, nonreplicative, nanosized EVs that mediate cell-to-cell communication through the delivery of cargos—such as growth factors, signaling lipids, and genetic materials—protected by their lipid bilayer (Figure 1). Despite a surge in research interest, its clinical translation is hampered

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Author(s). *Journal of Cosmetic Dermatology* published by Wiley Periodicals LLC.

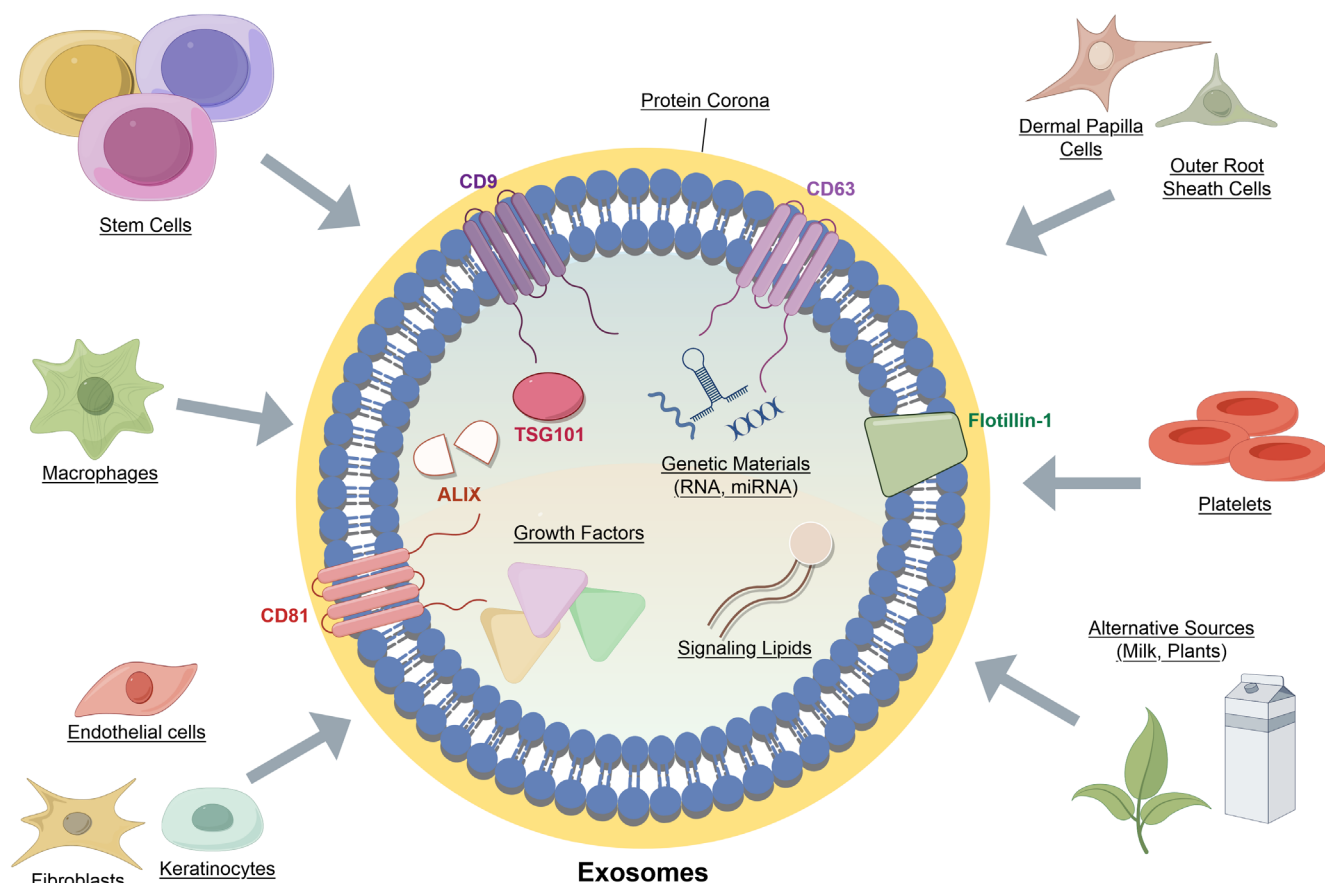


FIGURE 1 | An overview of the biological characteristics of exosomes. Exosomes can be identified through their size (30–150 nm) and molecular markers (CD9, CD63, CD1, flotillin-1, TSG101, Alix) [6]. Exosomes can be extracted from cells, non-cells (platelets), and alternative sources (milk, plant extracts) [6–8]. Exosome cargos include growth factors, genetic materials, and lipids that function in wound-healing, hair growth, collagen synthesis and regulating inflammation [6–8]; the type of cargo contained in exosomes is reflective of their origin. The protein corona—molecules that adhere around exosomes from its environment—also influences their characteristics and function [28]. Illustration created using Figdraw.

due to technical limitations and a lack of standardized methodologies, as well as the diversity of exosome content reflective of its cellular origin [5]. Exosomes are secreted by all cell types and can be detected in a variety of bodily fluids [6–8]; in particular, allogeneic platelets have been discussed as a preferable source due to the abundance of exosomes, reduced immunogenicity, and ease of sample collection [9, 10], as opposed to the isolation of exosomes from stem cells where an additional ex vivo expansion step may be required to obtain sufficient quantities. Furthermore, standardized protocols and existing infrastructures for platelet isolation are available under the tenets of Good Manufacturing Practice [9], which help minimize safety concerns.

There is an increasing level of recognition of exosomes as a potential treatment for androgenetic alopecia [1, 8], skin aging [11], and wound healing [6, 7]. A review of all potential dermatology applications of EVs was published recently by Novis and colleagues [12]. Navigating the regulatory landscape of exosomes is a challenge due to its inherent complexity (e.g., difficulties in isolation, purification, and quality control; unclear mechanism of action), a wide range of potential clinical applications, and serious safety concerns regarding empirical use (explained further in Section 3.4) [13, 14]. At present, exosomes are not approved by the U.S. Food and Drug Administration (FDA) or the

European Medicines Agency (EMA). The U.S. FDA has granted Investigational New Drug (IND) designations to selected exosome products [15]; however, use of such products in routine care and direct-to-consumer marketing is not allowed.

In this review, we aim to summarize available preclinical and clinical evidence on the therapeutic potential of PRP- or platelet-derived exosomes. New perspectives on addressing the current technical challenges, such as combined isolation methods, the addition of platelet activators, and embedding exosomes in topical hydrogel preparations, are discussed.

2 | Methods

An electronic literature search was conducted using EMBASE (Ovid) and Web of Science in June 2024. The search string included the following terms: “platelet-rich plasma,” “thrombocyte rich plasma,” “dermatology,” “skin,” “hair,” “alopecia,” “face,” “burn,” “wound healing,” “exosome,” “microvesicle,” and “extracellular vesicle.” A search on [ClinicalTrials.gov](https://clinicaltrials.gov) was conducted in June 2024 using the terms “platelet extracellular vesicles” and “platelet exosomes.” The references list of review articles was screened. No date or language restrictions were applied.

The inclusion criteria were full-length articles reporting on the effects of *PRP-derived exosomes* in hair loss, facial rejuvenation, burns, or wound healing. Studies that processed PRP into platelet lysate were considered. Due to the unstandardized nomenclature [16], a study was included if the terms “microvesicle” and “extracellular vesicle” were used with additional molecular characterizations. Articles without full-text availability, preclinical studies that cannot be linked to the aforementioned conditions, reviews, and expert opinions were excluded. The following elements were recorded for data extraction: sample source, platelet concentration, exosome concentration, activation method, exosome diameter, surface markers and cargo, model system, and observed genotypic/phenotypic effects.

Since EV research has mostly remained in the preclinical stage, there are still significant heterogeneities in how EVs or exosomes are isolated and characterized across studies. At present, the International Society for Extracellular Vesicles (ISEV) does not mandate any particular experimental designs for EV research [16]. Quality of reporting was assessed using the EV-Checklist developed by Poupardin et al. [17] in accordance with MISEV (Minimal Information for Studies of Extracellular Vesicles) set by ISEV. The following EV parameters were assessed: source (collection and storage), isolation, characterization, cargo, and function.

3 | Results and Discussion

The literature search yielded 14 preclinical studies on the application of *PRP-derived exosomes* in wound healing ($n=12$), hair growth ($n=2$), and skin rejuvenation ($n=1$), which are summarized in Tables 1 and 2 [18–31]. One case report was identified on the use of a *platelet-derived exosomes* product in wound healing [32]. Platelet concentrations and additional characteristics of exosomes are presented as Supporting Information (Table S1).

3.1 | PRP-Exo in Wound Healing

A multitude of studies have observed favorable wound healing effects of *PRP-derived exosomes* using animal models for diabetes (Table 1). In diabetic patients, hyperglycemia is a significant contributor to the development of chronic wounds characterized by prolonged inflammation, reduced angiogenesis, ulcers, and neuropathy [7]; in animal models, a hyperglycemia condition can be induced through diet, followed by a surgical incision for the evaluation of wound healing effects. Rui et al. [19] obtained platelets using the *apheresis* method, which were then activated using *thrombin and calcium gluconate* to stimulate the production of exosomes. After local injection, diabetic mice treated with *PRP-derived exosomes* exhibited significantly faster wound contraction with complete healing by day 14, which was attributed to the anti-inflammatory effects of miRNA-26b-5p detected in exosomes [19]. Similar results were reported by Chen et al., where an injection of *PRP-derived exosomes*—with *thrombin and calcium gluconate* activation—led to a faster wound closure rate, enhanced angiogenesis (corroborated by the observation of improved endothelial cell viability, migration, and tube formation capacity), and improved re-epithelialization [18]. Authors attributed this effect to a signaling lipid,

sphingosine-1-phosphate, detected in *PRP-derived exosomes* that activates the PI3K/Akt pathway leading to the upregulation of the growth factor VEGF-A [18].

Two studies reported the detection of growth factors in the *PRP-derived exosomes* cargo (b-FGF, PDGF, TGF- β , and VEGF) [25, 29], which may function in proliferating fibroblasts and endothelial cells, regulating the inflammatory immune response, angiogenesis, and tissue remodeling, as well as promoting collagen synthesis and hair growth [10, 33]. Cao et al. [25] treated fibroblasts with *PRP-derived exosomes* containing growth factors and observed an increase in cell viability and migration, as well as an increase in expression of a PDGF receptor that potentiates the JAK2/STAT3 pathway leading to the attenuation of hyperglycemia-induced apoptosis. Similar results were observed by Guo et al., demonstrating an increased cell viability and migration of fibroblasts and endothelial cells. The authors also observed an upregulation of the RhoA/YAP pathway that increases the level of the growth factor CTGF, as well as activation of the PI3K/Akt and Erk1/2 pathways that regulate cell proliferation and angiogenesis [29]. Furthermore, both studies demonstrated wound healing effects in animal models following the administration of *PRP-derived exosomes* in hydrogel preparations [25, 29].

Wound healing occurs in three stages, including (1) hemostasis and inflammation, (2) proliferation, and (3) tissue remodeling [3]. Following the formation of a fibrin matrix enabling the infiltration of immune cells, inflammation occurs whereby leukocytes such as neutrophils and macrophages work to clear cellular debris, defend against bacterial infections, as well as secrete growth factors and pro-inflammatory cytokines [3]. In persons with chronic wounds, the inflammation phase is dysregulated—reflected by the excess neutrophils and matrix metalloproteinases (MMPs)—which impedes the transition to the proliferation phase [3]. Rui et al. [19] reported the delivery of miRNA-26b-5p by *PRP-derived exosomes* that inhibited MMP-8, which reduced the number of infiltrating neutrophils forming neutrophil extracellular traps. Similar results were found by Bakadia et al., where a topical application of *PRP-derived exosomes* in hydrogels led to a reduction in the number of macrophages and neutrophil extracellular traps, as well as the downregulation of MMP-9 [24]. Chen et al. also reported the downregulation of inflammatory cytokines and pyroptosis in fibroblasts isolated from patients with diabetic foot ulcers, which was attributed to the upregulation of a long non-coding RNA (MALAT1) and downregulation of miR-374a-5p by *PRP-exosomes* [26].

Two ongoing clinical trials are investigating a *platelet-derived exosomes* product sourced from the *apheresis* method for the treatment of donor site wounds during skin grafting (NCT04664738) and as a treatment for diabetic foot ulcers (NCT06319287). In a case report, this product was used to treat a cancer patient with nonhealing scalp wounds [32]. Four weekly treatment sessions were initially conducted where exosomes were applied topically mixed with a collagen carrier; however, incomplete wound healing and lack of product retention at the wound site led to the switch to a fibrin carrier for four additional weekly sessions [32]. Complete healing of one wound and a 96% contraction of a second wound were observed at follow-up; no adverse reactions were reported [32].

TABLE 1 | Investigations of PRP-derived exosomes for wound healing.

Study	Sample source	Target	Phenotypic/Genotypic effects ^a	Activation	Content
Chen 2023 (1) [18]	Human PRP	Endothelial cells	• Increase cell viability for migration • Increase tube formation capacity	Thrombin and calcium gluconate (10:1)	Sphingosine-1-phosphate
		Wounded diabetic rat	• Faster wound healing • Improve re-epithelialization; no change in collagen deposition • Enhance angiogenesis • Increase levels of FN1, p-AKT, and VEGF-A		
Rui 2024 [19]	Human PRP (apheresis)	Wounded diabetic mice	• Faster wound healing • Reduce number of infiltrating neutrophils forming neutrophil extracellular traps via inhibition of MMP-8 • Reduce number of apoptotic cells	Thrombin and calcium gluconate (10:1)	miRNA-26b-5p
Bakadia 2023 [24]	Rat PRP (cardiac blood)	Endothelial cells ^b and Fibroblasts ^b	• Increase cell viability and migration	Thrombin and calcium gluconate (1:1)	—
		Wounded diabetic rat ^b	• Faster wound healing • Enhance angiogenesis • Formation of granulation tissues • Improve re-epithelialization and collagen deposition • Increase cell proliferation • Decrease in macrophages and neutrophil extracellular traps • Upregulate <i>IGF-1</i>, <i>TGF-β1</i>, <i>EGF</i>, <i>VEGF</i> • Downregulate <i>MMP-9</i>		
Cao 2023 [25]	Human PRP	Fibroblasts	• Increase cell viability and migration • Under a high glucose condition: rescue cell viability and migration, attenuate apoptosis • Increase PDGF receptor • Increase phosphorylation of JAK2 and STAT3 • Upregulate <i>Bcl-2</i> • Downregulate <i>Bax</i>	Thrombin and CaCl ₂	PDGF-BB VEGF b-FGF
		Wounded diabetic rat ^b	• Faster wound healing • Improve re-epithelialization, collagen deposition and arrangement • Enhance angiogenesis		

(Continues)

TABLE 1 | (Continued)

Study	Sample source	Target	Phenotypic/Genotypic effects ^a	Activation	Content
Chen 2023 (2) [26]	Human PRP	Fibroblast cells	• Increase cell viability • Decrease apoptotic cells • Inhibit pyroptosis and pro-inflammatory cytokines • <i>Upregulate MALAT1 and DNMT3A</i> • <i>Downregulate miR-374a-5p</i>	Thrombin and CaCl ₂	—
Lovisolo 2020 [27]	Human PRP	Keratinocytes	• Increase cell migration	CaCl ₂ and Calcimycin	—
Gnomes 2022 [28]	Human platelet lysate	Fibroblastes Skin organoid model (keratinocytes, fibroblasts, epithelial cells) Fibroblast cells	• Support 3D fibroblast spheroid formation • Support 3D organoid formation • Enhance angiogenesis	CaCl ₂	—
Guo 2017 [29]	Human PRP	T cells Endothelial cells and Fibroblasts	• Increase cell migration • Inhibit cell proliferation • Increase cell viability and migration • Increase tube formation capacity • Promote YAP dephosphorylation and upregulates CTGF • Increase phosphorylation of AKT and Erk	None	PDGF-BB TGF-β b-FGF VEGF
Shu 2023 [30]	Human PRP	Wounded diabetic rat ^b Endothelial cells ^b and Fibroblast cells ^b Wounded diabetic rat ^b	• Faster wound healing • Enhance angiogenesis • Improve re-epithelialization, collagen deposition and arrangement • Under a high glucose condition: rescue cell proliferation, maintain autophagy and attenuate apoptosis • Faster wound healing • Improve re-epithelialization, collagen deposition and arrangement • Enhance angiogenesis • Promote autophagy • Inhibit apoptosis	None	—

(Continues)

TABLE 1 | (Continued)

Study	Sample source	Target	Phenotypic/Genotypic effects ^a	Activation	Content
Yi 2023 [31]	Human PRP	Schwann cells	• Increase proliferation and migration • Increase secretion of growth/neurotrophic factors • (NGF, VEGF, GDNF, BDNF) • Upregulate pathways involved in peripheral nerve regeneration and repair • Improve toe mobility • Improve SFI • Recovery of nerve conduction • Nerve regeneration and reversal and muscle atrophy	None	—
Xu 2018 [20]	Human PRP	Rat with sciatic nerve crush injury ^c Wounded diabetic rat	• Faster wound healing • Reduce number of skin ulcers • Increase epidermal thickness • Improve collagen synthesis and deposition • Enhance angiogenesis	—	—

Abbreviations: AKT, protein kinase; B; Bax; Bcl-2, B-cell lymphoma type 2; Bcl-2-associated X protein; BDNF, brain-derived neurotrophic factor; b-FGF, basic fibroblast growth factor; CTGF, connective tissue growth factor; DNMT3A, DNA methyltransferase 3 alpha; EGF, endothelial growth factor; Erk, extracellular signal-regulated kinase; FN1, fibronectin 1; GDNF, glial cell-derive neurotrophic factor; IGF-1, insulin-like growth factor 1; IAK, Janus kinase; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MMP, matrix metalloproteinase; NGF, nerve growth factors; PDGF-BB, platelet-derived growth factor-BB; PRP, platelet-rich plasma; SFI, sciatic functional index; STAT, signal transducer and activator of transcription; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial cell growth factor; YAP, yes-associated protein.

^aGenotypic effects are shown in italics.

^bExosomes were embedded in a hydrogel preparation to achieve a slow, steady rate of release.

^cExosomes were delivered using ultrasound-assisted microbubble destruction.

TABLE 2 | Investigations of PRP-derived exosomes for hair growth and skin aging.

Study	Sample source	Target	Phenotypic/Genotypic effects ^a	Activation	Content
<i>Hair growth</i>					
Nilforoushzadeh 2020 [21]	Human PL (cord blood)	DPCs	• No or minimal change in cell proliferation and migration • No or minimal change in hair follicle inductivity markers	None	—
Nilforoushzadeh 2021 [22]	Human PRP (cord blood)	DPCs	• No or minimal change in cell proliferation • No or minimal change in hair follicle inductivity markers	None	—
<i>Skin Aging</i>					
Rosmarwati 2023 [23]	Human PL	IRM	• Improve collagen deposition • Decrease MMP-1 levels	None	—

Abbreviations: DPC, dermal papilla cell; IRM, intrinsic aging rat model; MMP-1, metalloproteinase-1; PL, platelet lysate; PRP, platelet-rich plasma.

^aGenotypic effects are shown in italics.

3.2 | PRP-Derived Exo in Hair Growth and Skin Rejuvenation

The dermal papilla, composed of mesenchymal cells, plays a critical role during hair follicle morphogenesis as a mediator of signaling pathways (e.g., Wnt/ β -catenin pathway) [33]; during the anagen phase of the hair growth cycle, the interaction between dermal papilla cells and the hair bulge stem cells leads to the formation of a new hair fiber [33]. In androgenetic alopecia, hair follicle miniaturization is linked to a shrinking dermal papilla with reduced hair follicle inductivity [34]. Exosomes, through its role as a paracrine regulator, may restore the dermal papilla and induce hair growth [33]. In two studies, the in vitro effects of *PRP- or platelet lysate-derived exosomes* (sourced from *human cord blood*) were investigated in dermal papilla cells and compared against exosomes derived from other sources (Table 2) [21, 22]. Their results indicate that exosomes were less effective in promoting cell proliferation and in inducing the inductivity of dermal papilla cells [21, 22].

Considering that *platelet-derived EVs including exosomes* represent the majority of EVs detected in blood [35], and that PRP has been recognized as a valuable treatment option for androgenetic alopecia [1], further studies may be warranted to confirm these findings. This should include studies assessing the effects of *PRP-derived exosomes* from healthy adult donors obtained with or without activation in dermal papilla cells and in ex vivo hair follicle models, with detailed biological characterizations including the cargo.

One hallmark of the aging skin is the collapse of the collagen matrix mediated by MMPs, which creates an unfavorable micro-environment that compromises the function of fibroblasts [36]. Without stretch or mechanical tension, fragmented collagen causes fibroblast collapse, resulting in reduced collagen production and increased levels of MMPs degrading collagens [36]; this chain of events generates a negative feedback loop that furthers the aging process. Thus, treatments that induce new collagen production can aid in restoring fibroblast function, thereby

attenuating the effects of aging. In a study by Rosmarwati et al. (Table 2) [23], *platelet lysate-derived exosomes* were delivered by injection to a rat model with features of intrinsic aging. The results showed an increased level of collagen deposition in the dermis with reduced levels of MMP-1 [23], which supports *PRP-derived exosomes* as a potential antiaging treatment.

3.3 | Technical Challenges

Limitations to the use of *PRP-derived exosomes* include donor-to-donor variabilities, as well as non-standardized activation methods and isolation protocols, that will impact the exosome cargo with varying therapeutic effects [9]. For instance, exosomes isolated from diabetic subjects exhibit qualitative differences from those of healthy donors [37]; PRP obtained from older individuals also appeared less effective [38]. What exactly defines an “active” component of exosomes or cargoes (i.e., proteins, genetic materials) responsible for the genotypic/phenotypic changes in recipient cells remains unclear [39]. In order to establish standards for quality control, the exosome content, in addition to its quantity and size, should be validated. As well, contamination of exosomes with plasma lipoproteins and viruses due to similar sizes is another concern [9]. An overview of the current obstacles in the clinical translation of exosomes is presented in Figure 2.

ISEV has recently published their position on the minimal information recommended for reporting of EV studies [16]. Exosomes represent a subset of EVs with diameters < 200 nm; however, the all-encompassing term “EV” is preferred over “exosomes” unless an endosomal subcellular origin is proven [16]. Reporting recommendations include descriptions and characterizations of the sample source, storage conditions pre- and post-isolation, assessments of the depletion of cells or other co-isolates, and implementation of quality controls [16]. For blood-derived EVs, it is recommended to report donor characteristics, as well as detailing the collection and processing procedures, including the use of anticoagulants and

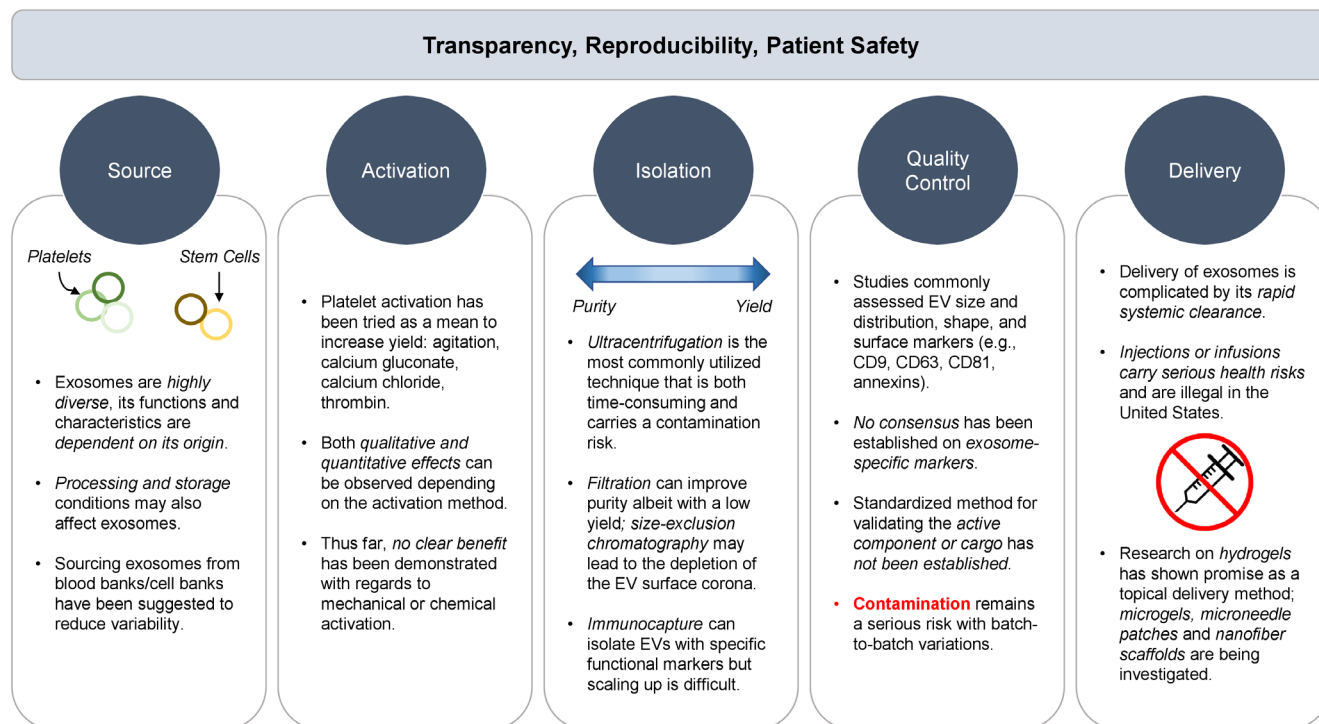


FIGURE 2 | Clinical translation challenges of PRP-derived exosomes.

centrifugation settings [16]. Special considerations include the removal of blood cells by centrifugation while preventing hemolysis and the removal of lipoproteins and other soluble proteins that can be co-isolated with EVs. If samples were pooled from multiple donors, then the number of individual samples should be reported along with matching demographic information and volumes [16]. For studies utilizing ultracentrifugation, details such as the type of rotor and tube, speed, time, temperature, as well as acceleration/deceleration settings should be reported [16]. Recommended EV characterizations, include quantity, size, morphology, protein components, and detection of co-isolates [16]. In Japan, the Science Board of the Pharmaceuticals and Medical Devices Agency (PMDA) published a review on the quality and safety standards of EVs [39]. To minimize variabilities across studies, the establishment of cell banks was suggested alongside quality control measures for contamination sources. For upscaling exosome production, ultrafiltration, column chromatography, or a combination method may be preferred over ultracentrifugation [39]. In cases where an active exosome component has been identified, an antibody-based affinity purification/immunocapture method may be considered [39]. Lastly, a public repository for EV research protocols has been established to improve transparency and facilitate standardization (EV-TRACK) [40].

The EV-Checklist was used to assess the quality of reporting of the included preclinical studies (see [Supporting Information](#)) [17]. In studies where PRP was obtained from human donors, donor characteristics (e.g., medical histories) were frequently not reported. Although freeze–thaw cycles may affect the characteristics of exosomes [16], the thawing procedure, after storing EV preparations at -80°C , was not reported. Quality control measures such as the detection of hemolysis during blood separation or detection of co-isolates, including lipoproteins or viruses,

were also not reported. Nine studies did not report the number of particles (exosomes/mL) [18, 20–22, 25–27, 29, 30]. One study did not report methods for exosome isolation and characterization [20]. For isolation (Table S1), most studies employed combinational methods of ultracentrifugation with ultrafiltration (e.g., a separate filtration step following ultracentrifugation or ultracentrifugation with a filtered unit). Two studies added a precipitation step [26, 31], two studies utilized size-exclusion chromatography [23, 28], and one study utilized tangential-flow filtration [28].

Although ultracentrifugation is commonly employed for the isolation of exosomes, this method can be limited due to time and sample volume requirements and contamination risk [10]. Thus, the combined use of size-exclusion chromatography or filtration methods has been suggested to improve the isolation of exosomes [10]. In a study by Gnomes et al. (Table 1) [28], a comparison was made between two fractions of CaCl_2 -activated, platelet lysate-derived EVs that were isolated using either tangential-flow filtration alone or tangential-flow filtration followed by size-exclusion chromatography. When examining the ability of platelet-derived EVs in aiding the formation of human skin organoids, the filtrated fraction—without undergoing size-exclusion chromatography—was found to be significantly more effective [28]; this fraction was also more effective in inducing fibroblast migration and inhibiting T-cells. The authors have attributed this difference to the depletion of the EV surface corona by the size-exclusion chromatography method [28], which are plasma proteins adsorbed around EV surfaces that partially determine its biological activity (Figure 1) [41]. In the absence of the protein corona, platelet-derived EVs exhibited a higher net negative surface charge, affecting their stability and function; re-introducing the protein corona allowed for the partial recovery of their functions [28].

Activation of platelets leading to the stimulated release of exosomes can be achieved through mechanical means such as agitation causing membrane disruption, as well as by the addition of calcium salts, calcium ionophores, or thrombin that increases exosome secretion through the accumulation of calcium ions in the cytoplasmic space [9]. A study comparing activation methods found a significantly higher quantity of exosomes released from PRP using *calcium gluconate* ($23.4 \pm 2.9 \times 10^8/\text{mL}$) compared to *thrombin* ($2.1 \pm 0.7 \times 10^8/\text{mL}$) [42]. Besides increasing the quantity, activation methods may also alter the functional profile of exosomes; for instance, Saumell-Esnaola et al. found that *platelet-derived exosomes* activated by CaCl_2 exhibited a different protein signature than exosomes without activation [43], whereas Goetzl et al. [44] reported an increased level of chemokines and high-mobility group box 1 in *platelet-derived exosomes* following *thrombin* activation. To date, no consensus has been established on the benefits of using activation methods. For wound healing (Table 1), we identified varying activation methods utilized across studies (i.e., *thrombin* and *calcium gluconate*, *thrombin* and CaCl_2 , CaCl_2 and *Calcimycin*) with positive effects; however, similar results were also reported in studies where no activation methods were used [29, 30]. In contrast, none of the studies assessing hair growth and skin aging employed an activation method (Table 2).

Lastly, exosomes delivered through injections are subjected to a high rate of clearance, limiting their therapeutic effects; hence novel application methods such as embedding exosomes in hydrogels have been investigated [7]. Hydrogels are a network of polymers that expand in volume upon contact with water, with adjustable features that can mimic the conditions of an extracellular matrix [28]. This material can be administered either topically or by injection to improve the pharmacokinetics of exosomes; moreover, some hydrogel preparations can augment the effects of exosomes through wound healing effects [25], antibacterial properties [24], promoting cell proliferation [30], and reducing the levels of reactive oxygen species [7]. Bakadia et al. developed a silk protein-based hydrogel that delivered *PRP-derived exosomes* through a controlled, sustained rate of release rather than in bursts (Table 1) [24]; this preparation, either alone or in combination with exosomes, also demonstrated inhibitory activities on bacterial growth [24]. Similar results were observed in other studies applying *PRP-derived exosomes* topically using hydrogels (Table 1) [29, 30], this opens the door to eliminating the need for local injections, which could help address current safety concerns. Other methods for exosome delivery being investigated include microgels, microneedle patches, and nanofiber scaffolds [7]. These applications could be extended further to investigate the effects of *PRP-derived exosomes* in hair growth and skin aging.

3.4 | Regulatory Perspectives and Concerns

Exosomes remain an investigational treatment that is classified as a biologic drug overseen by the Center for Biologics Evaluation and Research (CBER) as part of the U.S. FDA [13, 14], which categorizes exosome products into naïve exosomes (e.g., *PRP-derived exosomes*) from unmodified or modified sources, modified exosomes from genetically manipulated sources, and naïve

exosomes from unmodified sources with synthetic content [13]. The EMA regulates exosomes depending on their cargo [14]. In case if the cargo has a gene regulation effect (e.g., miRNA), then the exosome product will be given the Genetic Therapy Medicine Products (GTMP) designation by the Committee for Advanced Therapies (CAT), otherwise, it will be classified as biologics [14].

During the global SARS-CoV-2 pandemic, an uptick in commercial activities making unsubstantiated claims about exosome products—mostly concentrated in the United States and Mexico targeting individuals with long COVID symptoms—was reported [45]. The finding includes businesses offering exosomes via intravenous injections, often marketed directly to consumers on social media platforms, with costs ranging from \$4000 to \$15000 [45]. This trend raises serious concerns about patient safety and well-being, prompting responses from national regulatory bodies.

The U.S. FDA has issued a consumer alert [46], as well as warning letters to businesses (7 warning letters as of November 2024), related to exosome products. Notable violations include a contaminated facility with a lack of good laboratory practice/aseptic techniques resulting in serious adverse events and bacterial infections [47], as well as the marketing of an IND exosome product without a biologics license [48]. Manufacturing of exosomes should adhere to the tenets of the Pharmaceutical Inspection Convention and Current Good Manufacturing Practices (cGMP) or Cooperation Scheme Good Manufacturing Practices (PIC/S GMP) [14]. In the United States, clinical investigations of exosomes have now been restricted to topical administrations only [49]; injections or infusions, either intradermal, intramuscular, or subcutaneous, are illegal [49].

4 | Conclusions

As opposed to the current use of autologous PRP, *exosomes derived from allogeneic PRP* pooled from healthy donors with well-defined biological characteristics have the potential to limit interstudy variabilities and may allow for a clearer path to clinical validation. Exosomes are considered as biologics and are currently not approved by any regulatory body worldwide. There is ample preclinical evidence on the use of *PRP-derived exosomes* for wound healing; however, despite the wide use of PRP among dermatologists, evidence is scarce on the application of *PRP-derived exosomes* in hair growth and skin rejuvenation. Given the ongoing challenges encompassing the nomenclature, isolation and purification methods, quality control, and clinical translation, further research on exosomes should be centered on transparency, reproducibility, and patient safety. Healthcare providers are cautioned against administering exosomes until more research is done and a clear regulatory framework is developed.

Author Contributions

Conceptualization, A.K.G., J.A.R., M.T. investigation, T.W. methodology, T.W. resources, A.K.G. visualization, T.W. writing – original draft preparation, T.W. writing – review and editing, A.K.G., J.A.R., M.T.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. S. Devjani, O. Ezemma, K. J. Kelley, E. Stratton, and M. Senna, "Androgenetic Alopecia: Therapy Update," *Drugs* 83, no. 8 (2023): 701–715, <https://doi.org/10.1007/s40265-023-01880-x>.
2. O. K. Abuaf, H. Yildiz, H. Baloglu, M. E. Bilgili, H. A. Simsek, and B. Dogan, "Histologic Evidence of New Collagen Formulation Using Platelet Rich Plasma in Skin Rejuvenation: A Prospective Controlled Clinical Study," *Annals of Dermatology* 28, no. 6 (2016): 718–724, <https://doi.org/10.5021/ad.2016.28.6.718>.
3. K. Mehdipour Chari, S. E. Enderami, R. N. Mansour, et al., "Applications of Blood Plasma Derivatives for Cutaneous Wound Healing: A Mini-Review of Clinical Studies," *Regenerative Therapy* 27 (2024): 251–258, <https://doi.org/10.1016/j.reth.2024.02.011>.
4. A. K. Gupta and J. Carviel, "A Mechanistic Model of Platelet-Rich Plasma Treatment for Androgenetic Alopecia," *Dermatologic Surgery* 42, no. 12 (2016): 1335–1339, <https://doi.org/10.1097/DSS.0000000000000901>.
5. E. Anitua, M. Troya, J. M. Falcon-Pérez, S. López-Sarrio, E. González, and M. H. Alkhraisat, "Advances in Platelet Rich Plasma-Derived Extracellular Vesicles for Regenerative Medicine: A Systematic-Narrative Review," *International Journal of Molecular Sciences* 24, no. 17 (2023): 13043, <https://doi.org/10.3390/ijms241713043>.
6. L. Yu, J. Qin, J. Xing, et al., "The Mechanisms of Exosomes in Diabetic Foot Ulcers Healing: A Detailed Review," *Journal of Molecular Medicine* 101, no. 10 (2023): 1209–1228, <https://doi.org/10.1007/s00109-023-02357-w>.
7. L. Shi, D. Song, C. Meng, Y. Cheng, B. Wang, and Z. Yang, "Opportunities and Challenges of Engineered Exosomes for Diabetic Wound Healing," *Giant* 18 (2024): 100251, <https://doi.org/10.1016/j.giant.2024.100251>.
8. A. K. Gupta, T. Wang, and J. A. Rapaport, "Systematic Review of Exosome Treatment in Hair Restoration: Preliminary Evidence, Safety, and Future Directions," *Journal of Cosmetic Dermatology* 22, no. 9 (2023): 2424–2433, <https://doi.org/10.1111/jocd.15869>.
9. T. Burnouf, M. L. Chou, D. J. Lundy, E. Y. Chuang, C. L. Tseng, and H. Goubran, "Expanding Applications of Allogeneic Platelets, Platelet Lysates, and Platelet Extracellular Vesicles in Cell Therapy, Regenerative Medicine, and Targeted Drug Delivery," *Journal of Biomedical Science* 30, no. 1 (2023): 79, <https://doi.org/10.1186/s12929-023-00972-w>.
10. C. Puricelli, E. Boggio, C. L. Gigliotti, et al., "Platelets, Protean Cells With All-Around Functions and Multifaceted Pharmacological Applications," *International Journal of Molecular Sciences* 24, no. 5 (2023): 4565, <https://doi.org/10.3390/ijms24054565>.
11. F. G. Fedok and J. G. Lighthall, "Evaluation and Treatment Planning for the Aging Face Patient," *Facial Plastic Surgery Clinics of North America* 30, no. 3 (2022): 277–290, <https://doi.org/10.1016/j.fsc.2022.03.002>.
12. T. Novis, A. H. Gomes Menezes, L. C. Vilaça Lima, J. Lötvall, I. J. Borges do Nascimento, and C. Maeda Takiya, "The Therapeutic, Diagnostic, and Prognostic Values of Extracellular Vesicles (Exosomes) in Dermatology: A Systematic Review," *Journal of the American Academy of Dermatology* 1 (2024): 135–174, <https://doi.org/10.1016/j.jdrv.2024.06.006>.
13. D. Jaalouk, A. Prasai, D. J. Goldberg, and J. Y. Yoo, "Regulatory Aspects of Regenerative Medicine in the United States and Abroad," *Dermatological Reviews* 5, no. 4 (2024): e244, <https://doi.org/10.1002/der2.244>.
14. C. K. Wang, T. H. Tsai, and C. H. Lee, "Regulation of Exosomes as Biologic Medicines: Regulatory Challenges Faced in Exosome Development and Manufacturing Processes," *Clinical and Translational Science* 17, no. 8 (2024): e13904, <https://doi.org/10.1111/cts.13904>.
15. K. Cheng and R. Kalluri, "Guidelines for Clinical Translation and Commercialization of Extracellular Vesicles and Exosomes Based Therapeutics," *Extracellular Vesicle* 2 (2023): 100029, <https://doi.org/10.1016/j.jvesic.2023.100029>.
16. J. A. Welsh, D. C. I. Goberdhan, L. O'Driscoll, et al., "Minimal Information for Studies of Extracellular Vesicles (MISEV2023): From Basic to Advanced Approaches," *Journal of Extracellular Vesicles* 13, no. 2 (2024): e12404, <https://doi.org/10.1002/jev2.12404>.
17. R. Poupardin, M. Wolf, N. Maeding, G. Fuhrmann, and D. Strunk, "EV-Checklist: A fast Documentation Tool for Enhancing Transparency and Accessibility in Extracellular Vesicle Research," (2024), *bioRxiv*, <https://doi.org/10.1101/2024.05.17.594642>.
18. T. Chen, P. Song, M. He, et al., "Sphingosine-1-Phosphate Derived From PRP-Exos Promotes Angiogenesis in Diabetic Wound Healing via the S1PR1/AKT/FN1 Signalling Pathway," *Burns and Trauma* 11 (2023): 11, <https://doi.org/10.1093/burnst/tkad003>.
19. S. Rui, L. Dai, X. Zhang, et al., "Exosomal miRNA-26b-5p From PRP Suppresses NETs by Targeting MMP-8 to Promote Diabetic Wound Healing," *Journal of Controlled Release* 372 (2024): 221–233, <https://doi.org/10.1016/j.jconrel.2024.06.050>.
20. N. Xu, L. Wang, J. Guan, et al., "Wound Healing Effects of a *Curcuma zedoaria* Polysaccharide With Platelet-Rich Plasma Exosomes Assembled on Chitosan/Silk Hydrogel Sponge in a Diabetic Rat Model," *International Journal of Biological Macromolecules* 117 (2018): 102–107, <https://doi.org/10.1016/j.ijbiomac.2018.05.066>.
21. M. A. Nilfroushzadeh, N. Aghdami, and E. Taghiabadi, "Human Hair Outer Root Sheath Cells and Platelet-Lysis Exosomes Promote Hair Inductivity of Dermal Papilla Cell," *Tissue Engineering and Regenerative Medicine* 17, no. 4 (2020): 525–536, <https://doi.org/10.1007/s13770-020-00266-4>.
22. M. A. Nilfroushzadeh, N. Aghdami, and E. Taghiabadi, "Effects of Adipose-Derived Stem Cells and Platelet-Rich Plasma Exosomes on the Inductivity of Hair Dermal Papilla Cells," *Cell Journal* 23, no. 5 (2021): 576–583, <https://doi.org/10.22074/cellj.2021.7352>.
23. E. Rosmarwati, E. Y. Ellistasari, A. Kusumawardani, et al., "Human Platelet Lysate-Derived Exosomes Are Superior to the Lysate at Increasing Collagen Deposition in a Rat Model of Intrinsic Aging," *Journal of Applied Pharmaceutical Science* 13, no. 6 (2023): 211–216, <https://doi.org/10.7324/JAPS.2023.125707>.
24. B. M. Bakadia, A. A. Qaed Ahmed, L. Lamboni, et al., "Engineering Homologous Platelet-Rich Plasma, Platelet-Rich Plasma-Derived Exosomes, and Mesenchymal Stem Cell-Derived Exosomes-Based Dual-Crosslinked Hydrogels as Bioactive Diabetic Wound Dressings," *Bioactive Materials* 28 (2023): 74–94, <https://doi.org/10.1016/j.bioactmat.2023.05.002>.
25. W. Cao, X. Meng, F. Cao, J. Wang, and M. Yang, "Exosomes Derived From Platelet-Rich Plasma Promote Diabetic Wound Healing via the JAK2/STAT3 Pathway," *iScience* 26, no. 11 (2023): 108236, <https://doi.org/10.1016/j.isci.2023.108236>.
26. C. Chen, Q. Wang, D. Li, Z. Qi, Y. Chen, and S. Wang, "MALAT1 Participates in the Role of Platelet-Rich Plasma Exosomes in Promoting Wound Healing of Diabetic Foot Ulcer," *International Journal of*

- Biological Macromolecules* 238 (2023): 124170, <https://doi.org/10.1016/j.jbiomac.2023.124170>.
27. F. Lovisolo, F. Carton, S. Gino, M. Migliario, and F. Renò, "Platelet Rich Plasma-Derived Microvesicles Increased In Vitro Wound Healing," *European Review for Medical and Pharmacological Sciences* 24, no. 18 (2020): 9658–9664, https://doi.org/10.26355/eurrev_202009_23055.
 28. F. G. Gomes, A. C. Andrade, M. Wolf, et al., "Synergy of Human Platelet-Derived Extracellular Vesicles With Secretome Proteins Promotes Regenerative Functions," *Biomedicine* 10, no. 2 (2022): 238, <https://doi.org/10.3390/biomedicines10020238>.
 29. S. C. Guo, S. C. Tao, W. J. Yin, X. Qi, T. Yuan, and C. Q. Zhang, "Exosomes Derived From Platelet-Rich Plasma Promote the Re-Epithelization of Chronic Cutaneous Wounds via Activation of YAP in a Diabetic Rat Model," *Theranostics* 7, no. 1 (2017): 81–96, <https://doi.org/10.7150/thno.16803>.
 30. Q. H. Shu, R. T. Zuo, M. Chu, et al., "Fiber-Reinforced Gelatin/ β -Cyclodextrin Hydrogels Loaded With Platelet-Rich Plasma-Derived Exosomes for Diabetic Wound Healing," *Biomaterials Advances* 154 (2023): 213640, <https://doi.org/10.1016/j.bioadv.2023.213640>.
 31. D. Yi, Y. Zhang, M. Li, et al., "Ultrasound-Targeted Microbubble Destruction Assisted Delivery of Platelet-Rich Plasma-Derived Exosomes Promoting Peripheral Nerve Regeneration," *Tissue Engineering Parts A* 29, no. 23–24 (2023): 645–662, <https://doi.org/10.1089/ten.tea.2023.0133>.
 32. A. D. Pumford, K. L. Staricha, E. T. Kunkel, M. F. Armstrong, A. Behfar, and K. M. Van Abel, "Exosome Therapy for a Nonhealing Scalp Wound Following Chemoradiation and Surgical Therapy," *Mayo Clinic Proceedings* 99, no. 6 (2024): 1006–1012, <https://doi.org/10.1016/j.mayocp.2024.04.011>.
 33. E. Taghiabadi, M. A. Nilforoushzadeh, and N. Aghdami, "Maintaining Hair Inductivity in Human Dermal Papilla Cells: A Review of Effective Methods," *Skin Pharmacology and Physiology* 33, no. 5 (2020): 280–292, <https://doi.org/10.1159/000510152>.
 34. D. A. Whiting, "Possible Mechanisms of Miniaturization During Androgenetic Alopecia or Pattern Hair Loss," *Journal of the American Academy of Dermatology* 45, no. 3 Suppl (2001): S81–S86, <https://doi.org/10.1067/mjd.2001.117428>.
 35. Y. Hou, X. Wen, L. Zhou, and X. Fang, "The Value of Platelet-Rich Plasma-Derived Extracellular Vesicles in Modern Medicine," *Annals of Medicine* 55, no. 2 (2023): 2287705, <https://doi.org/10.1080/07853890.2023.2287705>.
 36. G. J. Fisher, J. Varani, and J. J. Voorhees, "Looking Older: Fibroblast Collapse and Therapeutic Implications," *Archives of Dermatology* 144, no. 5 (2008): 666–672, <https://doi.org/10.1001/archderm.144.5.666>.
 37. P. R. Guda, A. Sharma, A. J. Anthony, et al., "Nanoscopic and Functional Characterization of Keratinocyte-Originating Exosomes in the Wound Fluid of Non-Diabetic and Diabetic Chronic Wound Patients," *Nano Today* 52 (2023): 52, <https://doi.org/10.1016/j.nantod.2023.101954>.
 38. K. Chowdhary, A. Sahu, H. Iijima, S. Shinde, J. Borg-Stein, and F. Ambrosio, "Aging Affects the Efficacy of Platelet-Rich Plasma Treatment for Osteoarthritis," *American Journal of Physical Medicine & Rehabilitation* 102, no. 7 (2023): 597–604, <https://doi.org/10.1097/PHM.0000000000002161>.
 39. Y. Takakura, R. Hanayama, K. Akiyoshi, et al., "Quality and Safety Considerations for Therapeutic Products Based on Extracellular Vesicles," *Pharmaceutical Research* 41, no. 8 (2024): 1573–1594, <https://doi.org/10.1007/s11095-024-03757-4>.
 40. EV-TRACK Consortium, J. Van Deun, P. Mestdagh, et al., "EV-TRACK: Transparent Reporting and Centralizing Knowledge in Extracellular Vesicle Research," *Nature Methods* 14, no. 3 (2017): 228–232, <https://doi.org/10.1038/nmeth.4185>.
 41. M. Heidarzadeh, A. Zarebkohan, R. Rahbarghazi, and E. Sokullu, "Protein Corona and Exosomes: New Challenges and Prospects," *Cell Communication and Signaling* 21, no. 1 (2023): 64, <https://doi.org/10.1186/s12964-023-01089-1>.
 42. Y. Yang, W. Zhang, and B. Cheng, "Experimental Research on the Effects of Different Activators on the Formation of Platelet-Rich Gel and the Release of Bioactive Substances in Human Platelet-Rich Plasma," *Zhonghua Shao Shang Za Zhi* 33, no. 1 (2017): 12–17, <https://doi.org/10.3760/cma.j.issn.1009-2587.2017.01.004>.
 43. M. Saumell-Esnaola, D. Delgado, G. García del Caño, et al., "Isolation of Platelet-Derived Exosomes From Human Platelet-Rich Plasma: Biochemical and Morphological Characterization," *International Journal of Molecular Sciences* 23, no. 5 (2022): 2861, <https://doi.org/10.3390/ijms23052861>.
 44. E. J. Goetzl, L. Goetzl, J. S. Karliner, N. Tang, and L. Pulliam, "Human Plasma Platelet-Derived Exosomes: Effects of Aspirin," *FASEB Journal* 30, no. 5 (2016): 2058–2063, <https://doi.org/10.1096/fj.20150150R>.
 45. L. Turner, J. R. Martinez, S. Najjar, T. Rajapaksha Arachchilage, and J. C. Wang, "Businesses Marketing Purported Stem Cell Treatments and Exosome Therapies for COVID-19: An Analysis of Direct-to-Consumer Online Advertising Claims," *Stem Cell Reports* 18, no. 11 (2023): 2010–2015, <https://doi.org/10.1016/j.stemcr.2023.09.015>.
 46. The U.S. Food and Drug Administration, "Consumer Alert on Regenerative Medicine Products Including Stem Cells and Exosomes," 2020, <https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/consumer-alert-regenerative-medicine-products-including-stem-cells-and-exosomes>.
 47. The U.S. Food and Drug Administration, "Warning Letter: EUCYT Laboratories LLC," 2020, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/eucyt-laboratories-llc-607182-06042020>.
 48. The U.S. Food and Drug Administration, "Warning Letter: Kimera Labs Inc," (2024), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/kimera-labs-inc-649343-09012023>.
 49. N. Singh, A. N. Brown, and M. H. Gold, "PRP, Exosomes, and Stem Cells: An International Perspective," *Dermatological Reviews* 5, no. 5 (2024): e70000, <https://doi.org/10.1002/der2.70000>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.