

Advances in the Applications of Extracellular Vesicle for the Treatment of Skin Photoaging: A Comprehensive Review

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Abstract: Skin photoaging is a complex biological process characterized by the accumulation of oxidative damage and structural changes in the skin, resulting from chronic exposure to ultraviolet (UV) radiation. Despite the growing demand for effective treatments, current therapeutic options for skin photoaging remain limited. However, emerging research has highlighted the potential of extracellular vesicles (EVs), including exosomes, micro-vesicles, apoptotic bodies and liposomes, as promising therapeutic agents in skin rejuvenation. EVs are involved in intercellular communication and can deliver bioactive molecules, including proteins, nucleic acids, and lipids, to recipient cells, thereby influencing various cellular processes. This comprehensive review aims to summarize the current research progress in the application of EVs for the treatment of skin photoaging, including their isolation and characterization methods, roles in skin homeostasis, therapeutic potential and clinical applications for skin photoaging. Additionally, challenges and future directions in EVs-based therapies for skin rejuvenation are discussed.

Keywords: extracellular vesicles, exosomes, liposomes, stem cells, skin photoaging, skin rejuvenation

Introduction

Skin, being the largest barrier organ, is susceptible to various injuries caused by genetic factors, lifestyle choices, nutrition, solar radiation, and environmental factors.¹⁻³ Skin aging and diseases impose a significant burden, encompassing mental, social, and financial consequences for individuals, families, and society.^{4,5} Skin photoaging, a prominent manifestation of cutaneous aging, is primarily induced by chronic exposure to UV radiation.^{6,7} It is characterized by the appearance of fine lines, wrinkles, pigmentation irregularities, and loss of skin elasticity.⁸ Photoaged skin exhibits structural alterations, such as the degradation of collagen fibers, the accumulation of abnormal elastic fibers, and the disruption of the epidermal barrier function.⁹⁻¹² Despite the widespread prevalence and significant socioeconomic impact of skin photoaging, effective treatment modalities are still limited.¹³ Conventional approaches, such as topical retinoids,¹⁴⁻¹⁶ antioxidants,^{17,18} and laser therapies,¹⁹⁻²¹ often provide modest and transient results, necessitating the exploration of novel therapeutic strategies.

In recent years, EVs have gained significant attention due to their crucial role in intercellular communication and their potential as therapeutic agents for various diseases, including skin disorders.^{22,23} EVs comprise a diverse group of membrane-bound vesicles, including exosomes, micro-vesicles, apoptotic bodies and liposomes, which are released by various cell types.^{24,25} These vesicles, excluding liposomes that are artificially synthesized, encapsulate a cargo of bioactive molecules derived from their parent cells.²⁴ This cargo includes a wide range of bioactive molecules, such as proteins, nucleic acids, lipids, and signaling molecules (Figure 1).²⁶ Through the transfer of these bioactive molecules, EVs play a crucial role in mediating intercellular communication and regulating various physiological and pathological processes, such as proliferation, migration, and differentiation, thus influencing tissue homeostasis and repair.²⁷⁻²⁹

Graphical Abstract

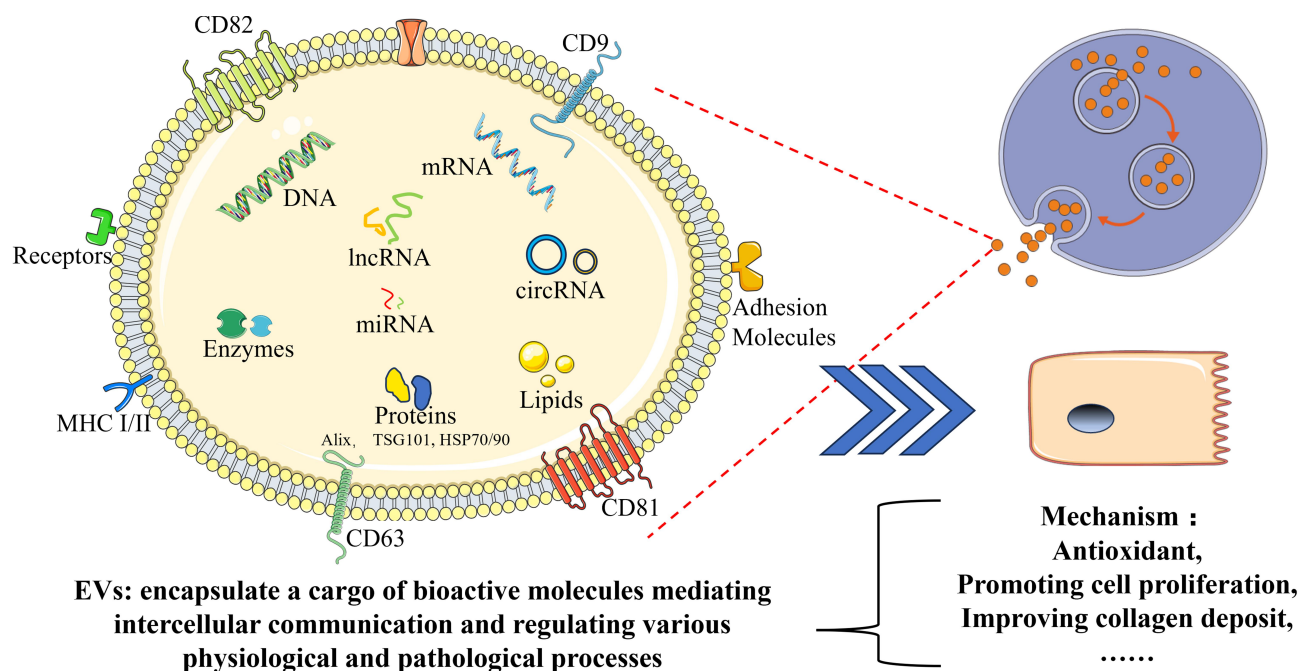
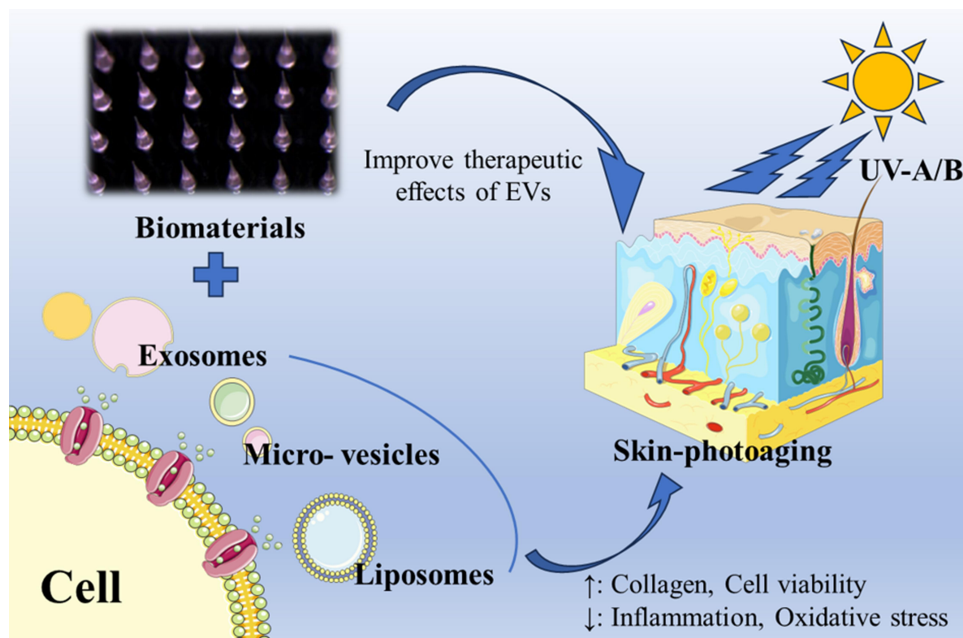


Figure 1 The structure and bioactive components of EVs were demonstrated and the mechanism of anti-photoaging.

Through their participation in intercellular communication, EVs play pivotal roles in regulating both physiological and pathological processes.

Among EVs, exosomes, micro-exosomes, apoptotic bodies, and liposomes represent distinct subtypes with unique characteristics and functions.³⁰ Exosomes are natural small extracellular vesicles, derived from the endosomal pathway and secreted by diverse cell types, including keratinocytes, fibroblasts, immune cells, and many kinds of plant cells, are

small vesicles ranging from 30 to 150 nm in diameter and carry a cargo of bioactive molecules, including proteins, nucleic acids, lipids, and signaling molecules.^{31,32} Micro-vesicles, larger in size with a diameter of 100 to 1000 nm, are directly shed from the plasma membrane and transfer a wide range of molecules.^{33,34} Apoptotic bodies, the largest vesicles ranging from 500 to 5000 nm, are released during programmed cell death and play a role in cellular clearance and immune regulation.^{35,36} In contrast, liposomes are artificial vesicles composed of lipid bilayers, engineered for drug delivery purposes.^{37–40} Understanding the distinct characteristics, functions, and origins of these EV subtypes is essential for harnessing their potential in intercellular communication and biomedical applications. Given the ability of EVs to mediate cellular communication and their potential cargo-based therapeutic applications, researchers have begun exploring their role in skin homeostasis and rejuvenation.

This review aims to provide a comprehensive overview of the current research progress in the application of EVs for the treatment of skin photoaging. It encompasses various types of extracellular vesicles, focusing on exosomes and liposomes, their biogenesis, cargo composition, and mechanisms of action. The review also covers methods for isolating and characterizing EVs from different sources, including skin cells and body fluids. Moreover, preclinical and clinical studies investigating the therapeutic potential of extracellular vesicles for skin rejuvenation and anti-aging effects will be examined. Finally, we will discuss the challenges and future directions in the development of EVs-based therapies for the treatment of skin photoaging.

Features of Skin Photoaging

Skin photoaging is a complex biological process characterized by premature aging and damage caused by chronic exposure to ultraviolet (UV) radiation from the sun.⁴¹ It is a major concern globally, given its significant impact on the appearance, health, and well-being of individuals. This section provides a comprehensive overview of the mechanisms underlying skin photoaging, including UV-induced molecular and cellular alterations. It explores the clinical manifestations of photoaged skin, such as wrinkles, pigmentation irregularities, and loss of elasticity.

UV radiation induces a cascade of molecular and cellular events that contribute to the accelerated aging of the skin. It triggers the generation of reactive oxygen species (ROS), leading to oxidative stress and DNA damage.^{42,43} Activation of inflammatory pathways, upregulation of matrix metalloproteinases (MMPs), and disruption of collagen and elastin synthesis further contribute to skin degradation and loss of elasticity.⁴⁴ Additionally, UV radiation promotes the formation of abnormal pigmentation, such as solar lentigines and uneven skin tone.⁴⁵

Multiple therapeutic strategies are employed to prevent and treat skin photoaging. Broad-spectrum sunscreens and photoprotective measures, such as avoiding excessive sun exposure and using protective clothing, form the cornerstone of prevention.⁴⁶ Topical antioxidants, including vitamins C and E, have shown promise in reducing oxidative stress and protecting against UV-induced damage.⁴⁷ Retinoids, derived from vitamin A, have demonstrated efficacy in improving skin texture, promoting collagen synthesis, and reducing pigmentation.⁴⁸ Advanced technologies, including laser therapy, intense pulsed light (IPL),⁴⁹ and photodynamic therapy (PDT),⁵⁰ offer targeted approaches to address specific manifestations of photoaging. Furthermore, emerging interventions, such as regenerative medicine approaches involving stem cells, growth factors, and tissue engineering, hold potential for skin rejuvenation and repair.⁵¹

Extraction, Synthesis and Characterization of EVs

EVs have emerged as key players in intercellular communication and have garnered significant attention in various fields of research.⁵² To harness their potential in diagnostics, therapeutics, and biomarker discovery, it is crucial to establish reliable methods for the extraction, synthesis, and characterization of EVs. This section provides an overview of the current techniques used for the extraction of EVs from biological samples, the synthesis of liposomes, and the identification and characterization of different types of EVs.

A major challenge in the clinical application of EVs in regenerative medicine is the lack of standardized methods for their isolation.⁵³ The isolation of EVs from complex biological samples is a critical step in their study. Common extraction methods include ultracentrifugation, filtration, precipitation, and size-exclusion chromatography.⁵⁴ Ultracentrifugation involves sequential centrifugation steps to pellet EVs based on their density.⁵⁵ Filtration methods employ filters with defined pore sizes to retain EVs while allowing other components to pass through.⁵⁶ Precipitation

methods, such as polyethylene glycol (PEG) precipitation, selectively precipitate EVs from the sample.⁵⁷ Consequently, combining two or more isolation methods has gained popularity to enhance EV purity. Size-exclusion chromatography separates EVs based on their size using columns with porous beads. To accurately identify and characterize EVs, multiple methods can be employed. Electron microscopy (EM) provides morphological information, allowing visualization of EVs' membrane-bound structures.⁵⁷ Techniques such as dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA) measure EVs' size distribution and concentration.⁵⁷ Immunological methods, including flow cytometry and Western blotting,⁵⁸ utilize specific markers for different types of EVs. For example, exosomes commonly express tetraspanins (CD9, CD63, CD81) and heat shock proteins (HSP70, HSP90), while micro-vesicles may express CD40, CD44, and tissue factor (TF).^{59,60} Apoptotic bodies are characterized by cell surface-exposed phosphatidylserine, cleaved caspase-3, and fragmented DNA, often detected using the TUNEL assay (Table 1).⁶¹ Mass spectrometry (MS) enables the identification and quantification of EVs' molecular components, such as proteins, nucleic acids, and lipids.⁶²

Liposomes, a type of artificial vesicle, have been widely used for drug delivery and research purposes. Common methods for liposome synthesis include thin-film hydration, reverse-phase evaporation, and extrusion.^{63,64} Thin-film hydration involves dissolving lipids in an organic solvent, followed by the removal of the solvent and hydration of the lipid film with an aqueous solution. Reverse-phase evaporation combines lipids, an aqueous solution, and an organic solvent, followed by evaporation to form multilamellar vesicles (MLVs).^{64,65} Extrusion involves passing a lipid suspension through membranes with defined pore sizes to obtain unilamellar vesicles (ULVs).⁶⁶

The extraction, synthesis, and characterization of EVs are crucial for advancing our understanding of their biology and exploring their potential applications. Various extraction methods facilitate the isolation of EVs from complex samples, while liposome synthesis techniques provide artificial vesicles for drug delivery and research purposes. Identification and characterization methods allow for the accurate classification and assessment of EVs based on their morphological, molecular, and functional features. Further advancements in these areas will contribute to the development of EV-based diagnostics, therapeutics, and biomarker discovery.

Properties of EVs for Skin Wound Therapy

In recent years, EVs have emerged as highly promising vehicles for delivering nucleic-acid-based therapeutics due to their inherent biocompatibility, ability to traverse physiological barriers, and minimal immunogenicity. EVs, including exosomes, are naturally generated by the body's cells, resulting in reduced inflammatory responses. Some cost-effective and streamlined methodologies in lab aimed to facilitate the future efficient and economical production of exosomes in large quantities.^{67–70} In the future, with the realization of commercialization and standardized production of EVs, it will become a cost-effective and efficient treatment.

Wound healing is a complex biological process that involves a series of coordinated events aimed at restoring tissue integrity and functionality.^{71–73} In recent years, EVs have emerged as promising candidates for enhancing wound healing due to their unique characteristics.^{70,74} The diverse composition of EVs enables them to regulate multiple cellular processes involved in wound healing, including inflammation, angiogenesis, cell proliferation, and extracellular matrix remodeling.^{68,75} Wang et al, in their study, developed a gelatin methacryloyl (GelMA) hydrogel loaded with VH298-loaded EVs (VH-EVs) derived from epidermal stem cells (ESCs). Their findings demonstrated that VH-EVs exhibited promotive effects on the function of human umbilical vein endothelial cells (HUVECs) in vitro by activating the HIF-1 α signaling pathway.⁷⁶ Moreover, in vivo experiments showed that GelMA hydrogel with sustained release of VH-EVs, possessing high biocompatibility and suitable mechanical properties, effectively promoted diabetic wound healing and angiogenesis in diabetic mice.⁷⁶ When it comes to the regulation of inflammation in wound healing, a study revealed that apoptotic bodies (Abs)

Table 1 The Special Markers of Each Type of EVs

EVs Types	Specific Markers
Exosomes	CD9, CD63, CD81, HSP70, HSP90
Micro-vesicles	CD40, CD44, Tissue Factor (TF)
Apoptotic bodies	Phosphatidylserine, Cleaved Caspase-3, Fragmented DNA

derived from MSCs play a crucial role in promoting cutaneous wound healing by inducing the polarization of macrophages towards the M2 phenotype.⁷⁷ Furthermore, these functionally converted macrophages enhanced the migration and proliferation abilities of fibroblasts, synergistically facilitating the wound healing process.⁷⁷ In another study, the researchers compared the functions of EVs derived from mesenchymal stem cells (MSCs) isolated from bone marrow (BMSCs) and adipose tissue (ADSCs) in the context of wound healing. Both types of EVs showed potential benefits for tissue regeneration, but they exhibited distinct biological properties. They found that ADSC-EVs contain molecules that are associated with angiogenesis, while BMSC-EVs were correlated with cellular proliferation.⁷⁸ And Kevin Las Heras found that EVs derived from hair follicle MSCs (HFMSC-EVs) exhibited the capability to enhance the proliferation and migration of human dermal fibroblasts (HDFs). Furthermore, HFMSC-EVs stimulated angiogenesis in HUVECs as well.⁷⁹

The utilization of EVs in wound healing holds great potential for improving the outcomes of wound repair and regeneration. Their ability to modulate immune responses, promote angiogenesis, stimulate tissue regeneration, and facilitate ECM remodeling makes them valuable tools in promoting efficient wound healing and reducing scar formation.

Skin Rejuvenation of EVs

Skin aging is another major concern and EVs promote wound healing through physiological regulation of cells and, in particular, stem cell-derived external vesicles, which can also alter cell states to achieve cell anti-aging, thereby delaying skin aging and improving skin aging caused by UV light (Table 2).^{80,81} Some exosomes of plant cells, organoid or probiotics also contribute to skin rejuvenation, and some researchers combine EVs with biological materials to make EVs have better transdermal delivery effect, and finally achieve better efficacy.

Stem Cell Derived EVs for Treatment of Photoaging

The potential of adipose-derived stem cells (ADSCs) for skin rejuvenation has been well-documented. However, a complete understanding of the effects of ADSC-derived exosomes on photoaged skin still requires further clarification. Jun-Xian Liang et al conducted a study to investigate the anti-aging effects of ADSC-derived exosomes on photoaged skin. They extracted exosomes from cultured ADSCs using ultracentrifugation. The exosomes were then subjected to verification through examination of cell morphology using transmission electron microscopy and identification of specific biomarkers.⁸² Subsequently, the researchers injected the exosomes at an optimal concentration and treatment time into the photoaged skin of Sprague-Dawley rats that had been exposed to ultraviolet B radiation. The results showed that the injected exosomes significantly reduced epidermal thickness and increased dermal thickness of the photoaged skin after 7 days of treatment.⁸² Additionally, the proportion of the stratum corneum in the epidermis was reduced. Furthermore, real-time RT-PCR analysis demonstrated an increase in the mRNA expression of type I collagen and a decrease in the expression of type III collagen, MMP-1, and MMP-3. Other researchers in Korea have also demonstrated the remarkable effects of ADSC-derived extracellular vesicles (ADSC-EVs) in mitigating the adverse effects of UVB irradiation on skin. Specifically, they observed that ADSC-EVs effectively suppressed the overexpression of MMP-1, MMP-2, MMP-3, and MMP-9 induced by UVB irradiation, thereby promoting the biosynthesis of collagen.⁸³ Notably, the researchers observed an upregulation of tissue inhibitor of metalloproteinase-1 (TIMP-1) and transforming growth factor beta-1 (TGFβ-1) in HDFs treated with ADSC-EVs after UVB irradiation.⁸³ These factors play pivotal roles in suppressing MMP activity and stimulating extracellular matrix (ECM) synthesis. Furthermore, the study revealed that ADSC-EVs also exhibited the remarkable ability to enhance the migration capacity of HDFs that had been subjected to UVB irradiation.⁸³ Peng Xu conducted a study demonstrating that ADSC-derived extracellular vesicles (ADSC-EVs) effectively reduced skin wrinkles in mice with UVB-induced photoaging.⁸⁴ This effect was attributed, in part, to the attenuation of Raw 264.7 cell differentiation from M0 to M1 macrophages, resulting in a decrease in intracellular reactive oxygen species (ROS) production. Additionally, ADSC-EVs promoted the expression of antioxidant enzymes and rescued fibroblasts (FBs) from cell cycle arrest.⁸⁴

Subsequently, Myeongsik Oh made an exciting discovery regarding exosomes derived from the conditioned medium of human induced pluripotent stem cells (iPSCs). These exosomes exhibited similar effects to ADSC-EVs when applied to HDFs cells irradiated with UVB. They stimulated the proliferation and migration of HDFs, leading to increased

Table 2 Exosomes Derived from Different Types of Cells and Their Effects

Cells Types	Markers	Functions	Concentration	Reference
Adipose-derived stem cells (ADSCs)	TSG101, CD9, CD63, CD81, GM130, Calnexin	↑: Col-I, TIMP-I, TGFβ-I ↓: Col-III, MMP-I/2/3/9, ROS	25 µg/mL; 150 µg/mL, 1.1 × 10 ¹⁰ particles/mL, 10 ⁸ particles/mL	[82–84]
Human umbilical cord mesenchymal stem cells (HUCMSCs)	CD9, CD63, CD81, CD105, Calnexin	↑: fibroblast proliferation GPX-I and Col-I ↓: MMP-I	250 µg/mL	[85]
Three-dimensional spheroids of human dermal fibroblasts	CD81, Alix,	↑: Col -I; TGF-β, TIMP-I/2 ↓: MMP-I, IL-1β, TNF-α	10 ⁸ /mL	[86]
Human induced pluripotent stem cells (iPSCs)	Mean diameter: 85.8 nm, zeta potential: −15.6 mV	↑:Col -I; ↓: β-galactosidase (SA-Gal), MMP-I/3	20×10 ⁸ particles/mL	[87]
Bone marrow mesenchymal stem cells (BMSCs)	CD9, HSP70 miR-29b-3p	↑:Col-I; proliferation and migration of HDFs ↓: oxidative stress, cell apoptosis, MMP-I/2/3	25 µg/mL	[88]
circ_0011129 overexpressing ADSCs	CD34, CD45, CD63, CD90, CD105, TSG101, Alix,	↑: Col-I/III, Elastin, ↓: oxidative stress, MMP-I/3, p53, p21, p16, Cathepsin K,	50 ug/mL	[89]
miR-1246 overexpressing ADSCs	CD9, CD63, CD81	↑: ProCol-I, proliferation of HSFs, IκB-α (anti-inflammation) ↓: MMP-I,		
Phellinus linteus	Diameters of FELNVs ranged from 100 to 260 nm	↑:Col-I; ↓: MMP-I	2% PL	[90]

expression levels of collagen type-I. Notably, the expression levels of senescence-associated β -galactosidase (SA-Gal) and MMP-1/3 were significantly reduced, indicating a potential anti-aging effect.⁸⁷

Human umbilical cord mesenchymal stem cells (HUCMSCs) have gained recognition as a versatile and efficacious therapeutic option in clinical settings.⁹¹ Deng's research group undertook a study in which they isolated and characterized EVs derived from both HUCMSCs and HDFs.⁸⁵ Subsequently, they assessed and compared the effects of HUCMSC-derived EVs and HDF-derived EVs on UVB-induced photoaging in dermal fibroblasts. Their findings revealed that pretreatment with HUCMSC-derived EVs or Fb-derived EVs effectively upregulated the expressions of GPX-1 and Col-1, while downregulating the expression of MMP-1. Importantly, both HUCMSC-derived EVs and Fb-derived EVs demonstrated a protective effect on dermal fibroblasts against UVB-induced photoaging, likely attributed to their antioxidant activity.⁸⁵ And Shi-Jie Liu et al demonstrated that HUCMSC-EVs had same ability to modulate the photo-aging of HaCaT keratinocytes.⁹²

In addition to exosomes derived from human stem cells, exosomes obtained from other types of human cells through specific treatments are also being explored for their potential in photoaging therapy, showing promising results. Shiqi Hu et al created three-dimensional spheroids of human dermal fibroblasts (HDFs), from which they isolated exosomes (referred to as 3D HDF-XOs). These exosomes demonstrated an ability to enhance the expression of procollagen type I, a crucial component of the extracellular matrix, while significantly reducing the expression of MMP-1, an enzyme associated with collagen degradation.⁸⁶ The effects were primarily attributed to the downregulation of tumor necrosis factor- α (TNF- α) and the upregulation of transforming growth factor beta (TGF- β) mediated by the 3D HDF-XOs.⁸⁶ This research suggests that exosomes derived from 3D spheroids of HDFs can modulate the expression of key molecules involved in skin rejuvenation, providing a potential therapeutic approach for addressing photoaging.

Special Ingredients in EVs Promoting Skin Rejuvenation

EVs contains proteins, nucleic acids and other substances, which are involved in various cellular interactions. Many researchers have explored which EVs components have the therapeutic effect on skin photoaging, and some researchers also have specifically increased the expression of certain components in EVs, thereby improving its therapeutic effect on skin photoaging.

Tingting Yan, a Chinese researcher, conducted a study involving the extraction of exosomes derived from bone marrow mesenchymal stem cells (BMSCs). The research aimed to explore the effects of these exosomes on human dermal fibroblasts (HDFs) exposed to UVB irradiation. Notably, the study revealed that the presence of miR-29b-3p in BMSC-derived exosomes played a pivotal role in reversing the inhibitory effects of UVB irradiation on HDFs.⁸⁸ Specifically, miR-29b-3p counteracted the hindered migration of HDFs, alleviated oxidative stress, and mitigated the promotion of apoptosis induced by UVB irradiation.⁸⁸ These findings highlight the potential of BMSC-derived exosomes, particularly through the action of miR-29b-3p, in counteracting the detrimental effects of UVB irradiation on skin cells.

Yu Zhang et al conducted a previous study in which they discovered a non-coding circular RNA, circ_0011129, that acts as an adsorption sponge for miR-6732-5p.⁸⁹ This interaction was found to inhibit the reduction of type I collagen and prevent the denaturation and accumulation of elastin in a UVA-induced photoaging model using human dermal fibroblast (HDF) cells. To enhance the stability and delivery efficiency of circRNA, they loaded it into small extracellular vesicles (sEVs) derived from human adipose-derived stem cells (hADSCs) through overexpression of circ_0011129 in hADSCs.⁸⁹ Through miRNA sequencing (miRNA-seq) and GEO data analysis, they identified an enrichment of miRNAs in the 3D-circ-sEVs that were associated with apoptosis, cellular senescence, and inflammation-related cellular activities. They demonstrated that 3D-circ-sEVs can interfere with the process of cellular photoaging and protect cells from UVA radiation damage, as well as in an H₂O₂-induced oxidative stress model.⁸⁹

In another study by Wei Gao et al, they confirmed miR-1246 as a crucial therapeutic agent employed by ADSCs to protect against UVB-induced photoaging. They generated miR-1246-overexpressing ADSCs and exosomes (OE-EX) through lentivirus infection. Their findings revealed that OE-EX significantly reduced MMP-1 expression by inhibiting the MAPK/AP-1 signaling pathway.⁹³ Moreover, OE-EX markedly increased procollagen type I secretion by activating the TGF- β /Smad pathway. Additionally, OE-EX exhibited anti-inflammatory effects by preventing UVB-induced

degradation of I κ B- α and inhibiting NF- κ B overexpression.⁹³ Animal experiments demonstrated that OE-EX could reduce UVB-induced wrinkle formation, epidermis thickening, and the reduction of collagen fibers in Kunming mice.⁹³

Special Cells Derived EVs for Treatment of Photoaging

Plant-derived ingredients are frequently incorporated into skincare products due to their anti-aging properties. Notably, certain plant-derived cellular exosomes have been shown to possess regenerative, anti-inflammatory, and low immunogenicity characteristics.^{94,95} In this context, we will provide a brief overview of how specific exosomes secreted by specialized cells contribute to the rejuvenation of photoaged skin.

Phellinus linteus (PL), a medicinal fungus known for its antitumor and anti-inflammatory properties, has also been investigated for its potential anti-photoaging effects.⁹⁰ Dr. Han et al conducted a study to explore these effects by fungi isolating exosome-like nanovesicles (FELNVs) from PL. They further evaluated the anti-aging activity of PL-FELNVs through clinical volunteer testing, which demonstrated promising results.⁹⁰

Their research into the molecular mechanisms of PL-FELNVs revealed that a specific microRNA, miR-CM1, present in the FELNVs, played a crucial role. Through cross-kingdom regulation, miR-CM1 inhibited the expression of Mical2 in HaCaT cells, subsequently promoting the expression of COL1A2. Moreover, it was found that miR-CM1 also suppressed MMP1 expression in skin cells. Consequently, the levels of reactive oxygen species (ROS), malondialdehyde (MDA), and senescence-associated β -galactosidase (SA- β) were decreased, suggesting a decrease in oxidative stress and cellular aging processes. There is another research group that has clinical trials about investigating the effect of *Lactobacillus plantarum* (LP) EVs on skin aging, their results demonstrated that LP-EVs have a great effect on skin aging by inducing cell proliferation of fibroblasts and regulating ECM related genes (MMP-1 decreased, Type I procollagen, Filaggrin and HAS2 increased).

PL-FELNVs possess several notable advantages, particularly in terms of biocompatibility, cellular uptake, and targeting capabilities. Unlike current synthetic drug delivery systems, such as inorganic and polymeric nanoparticles, which are foreign materials and may carry potential risks of toxicity and immunogenicity, PL-FELNVs are derived from natural and endogenous sources. As a result, they are regarded as highly biocompatible, exhibiting compatibility with various biological functions akin to their parent cells. This characteristic renders PL-FELNVs a safer and more reliable option for drug delivery systems.

Biomaterials Strengthen Anti Photoaging Effects of EVs

Microneedle (MN) is a widely utilized and minimally invasive tool for delivering drugs to the dermal layer. Its efficacy stems from its ability to create small injuries and initiate the wound healing process, which in turn leads to neocollagenesis.⁹⁶ In pursuit of enhancing the treatment efficacy of skin photoaging, Xiuli Wang's research team explored the use of roller microneedles for delivering adipose-derived stem cell-derived extracellular vesicles (ADSC-EVs) to the skin.⁹⁷ Their findings validated that microneedles are an effective means of delivering drugs to the skin, thereby improving treatment outcomes.⁹⁷

More recently, Van Dat Bui et al developed a dissolving microneedle patch (EV@MN) composed of hyaluronic acid and loaded it with human ADSC-derived EVs (hADSC-EVs) for skin photoaging treatment.⁹⁸ The EV@MN patch facilitated precise and convenient intradermal delivery, enabling sustained release of EVs in the dermis layer. Consequently, EV@MN significantly enhanced the biological functions of hADSC-EVs on dermal fibroblasts by promoting the synthesis of proteins crucial for the extracellular matrix, such as collagen and elastin, while also boosting fibroblast proliferation.⁹⁸ Comparatively, other administration methods did not yield the same level of improvement. A kind of natural biomaterial, sponge *Haliclona* sp. spicules (SHSs), were also used as a carrier of EVs to improve its delivery efficiency, SHSs increased the skin absorption of human umbilical cord-derived MSC-Exos (hucMSC-Exos), and improved anti-photoaging effects in mice.⁹⁹

Apart from naturally produced EVs derived from stem cells, researchers have begun exploring the use of artificial EVs, where specific substances are encapsulated within liposomes. For instance, a research team from Peking University successfully generated COL1A1 mRNA-containing EVs (COL1A1-EVs) from human dermal fibroblasts using their own cellular nanoporation (CNP) technique as shown in Figure 2A, which enhances the loading efficiency

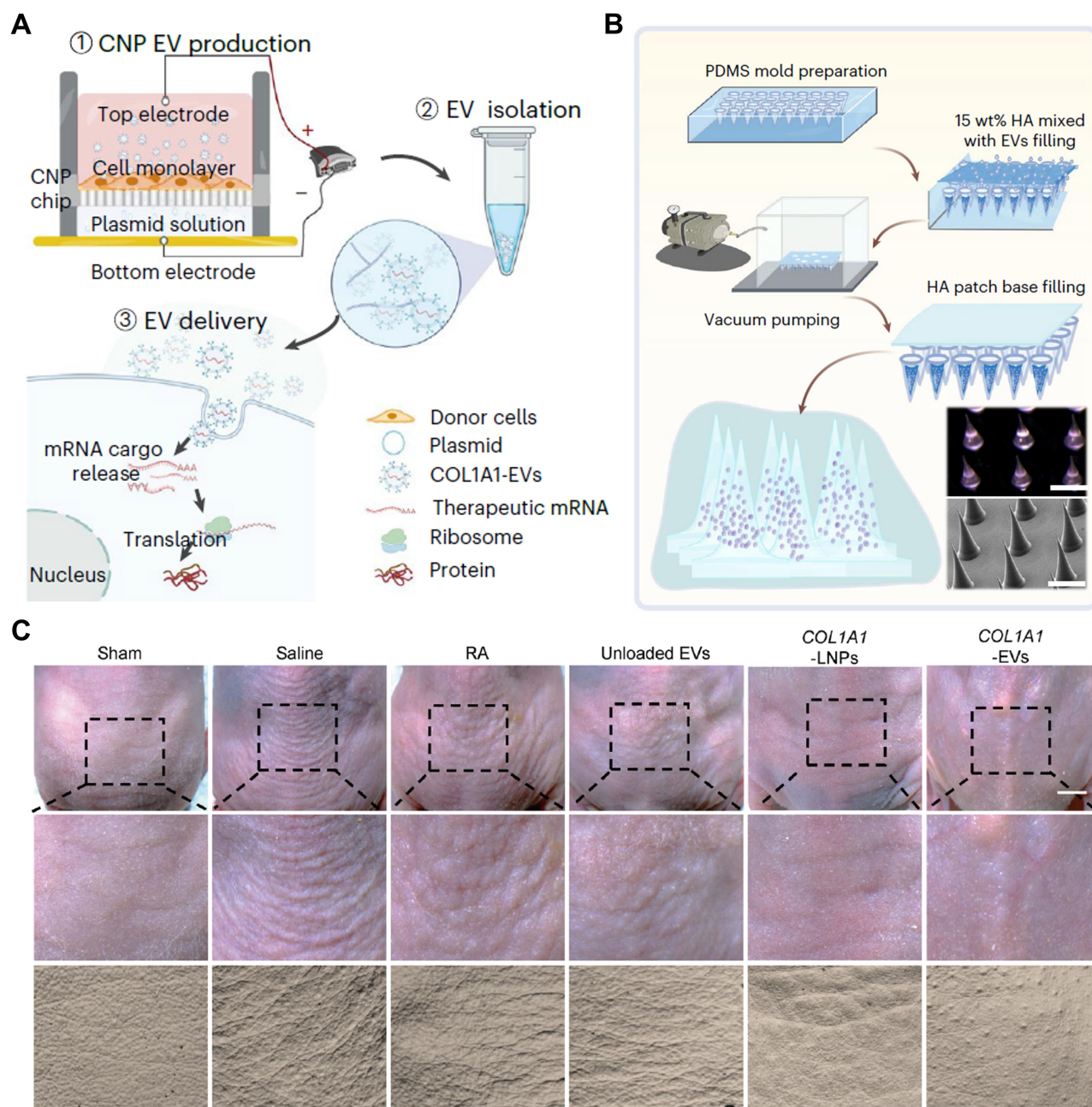


Figure 2 The EVs introduced by microneedle patch has a good therapeutic effect on photoaging. **(A)** Scheme of CNP EV production process. **(B)** Scheme of microneedle patch production process. **(C)** Skin plaster assessment of dorsal skin after COL1A1-EV treatment. Adapted from You Y, Yang Z, Shi J, et al. Intradermally delivered mRNA-encapsulating extracellular vesicles for collagen-replacement therapy. *Nat Biomed Eng.* 2023;7:887–900, Springer Nature.¹⁰⁰

of mRNA in EVs.¹⁰⁰ The team also demonstrated that intradermal delivery of the mRNA-loaded EVs via a microneedle array, as shown in Figure 2B, resulted in more prolonged and uniform synthesis and replacement of collagen in the dermis, surpassing the effects of traditional injection of COL1A1-EVs.¹⁰⁰ Intradermal delivery of EV-based COL1A1 mRNA holds promise as an effective protein-replacement therapy for treating photoaged skin (Figure 2C).

With the rapid development of biomaterials, the application of exosomes in skin rejuvenation is anticipated to make substantial advancements. The clinical utilization of exosomes is poised to become more diverse, with a focus on enhancing the treatment of skin photoaging.

The Future Perspectives

Skin photoaging is a common concern resulting from prolonged exposure to ultraviolet (UV) radiation. Researchers have explored various therapeutic approaches to combat the signs of photoaging and restore skin health. One promising avenue is the use of EVs, which are nanosized vesicles released by cells and carry bioactive molecules. EVs derived from adipose-derived stem cells (ADSCs) and human dermal fibroblasts have shown potential in rejuvenating photoaged skin. These EVs can suppress the overexpression of matrix metalloproteinases (MMPs), enhance collagen synthesis, and promote fibroblast proliferation.

However, the clinical application of EVs faces several challenges. The lack of standardized guidelines leads to variations in EV preparation, purification, quality control, and dosing, causing differences among EVs used in different studies. Establishing unified standards and guidelines is crucial to ensure consistency and quality. While EVs are generally considered safe, long-term safety and optimal dosing require further evaluation. Monitoring and assessing potential risks and side effects associated with EVs are essential. Large-scale production of EVs for clinical use remains challenging. Standardizing production processes and optimizing culture and purification methods are necessary to meet patient demands. Additionally, cost-effectiveness is a factor to consider.

In conclusion, EVs hold promise for skin photoaging treatment, but standardization, safety assessment, large-scale production, and cost considerations are important areas for further research and development. Addressing these challenges will advance the clinical application of EVs and enhance their potential in skin rejuvenation.

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Disclosure

The authors report no conflicts of interest in this work.

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