International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Exosome-Mediated Rewiring of Oxidative Stress–Inflammation–ECM Remodeling Axis Mitigates UVB-Triggered Skin Photoaging

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Abstract: Photoaging is a chronic and multifactorial form of skin aging primarily induced by ultraviolet (UV) radiation. It is characterized by oxidative stress, DNA damage, chronic inflammation, pigmentary alterations, and extracellular matrix (ECM) degradation, which ultimately lead to wrinkle formation, loss of elasticity, and uneven pigmentation. Exosomes, nanosized extracellular vesicles that mediate intercellular communication, have attracted growing attention in photoaging research. Emerging evidence suggests that exosomes may both contribute to photoaging and promote tissue repair by modulating cellular responses. However, despite the growing body of evidence, the field still lacks an integrated review that links exosome biogenesis and functional properties to the mechanisms of photoaging, their therapeutic potential, and the major translational barriers to clinical application. Therefore, this review aims to systematically summarize the biogenesis and biological properties of exosomes, clarify their mechanistic roles in photoaging, particularly in the regulation of oxidative stress, and evaluate their potential as therapeutic agents and delivery platforms for anti-photoaging and regenerative medicine. It further examines the effects of native exosomes derived from multiple cell sources, with a focus on stem cells, keratinocytes, and melanocytes. Finally, it outlines translational opportunities for exosome-based interventions in anti-photoaging and regenerative medicine, including engineered exosome mimetics and other nanomedicine-based strategies. It also highlights the key knowledge gaps and technical challenges that must be addressed to facilitate clinical translation. In conclusion, exosomes represent a promising yet still evolving strategy for the prevention and treatment of photoaging because of their dual roles in intercellular signaling and tissue regeneration. Nevertheless, further standardization of isolation, characterization, engineering, safety assessment, and regulatory evaluation is essential before their full clinical potential can be realized.

Keywords: exosomes, photoaging, UVB, oxidative stress, regenerative medicine, nanomedicine

Introduction

Skin aging is a complex biological process that encompasses both intrinsic (chronological) aging and extrinsic photoaging.[1] In contrast to intrinsic aging, photoaging results predominantly from chronic exposure to environmental stressors, particularly ultraviolet (UV) radiation. Its clinical manifestations include loss of skin elasticity, wrinkle formation, and irregular pigmentation.[2] Meanwhile, recent public health data further highlight the broad disease burden

https://doi.org/10.2147/IJN.S600909
Received: 3 February 2026
Accepted: 20 March 2026
Published: 8 April 2026

associated with chronic UV exposure. According to the World Health Organization, skin cancer accounts for approximately one in every three cancers diagnosed globally, and ultraviolet radiation is the principal environmental risk factor. Moreover, the International Agency for Research on Cancer reported that more than 80% of cutaneous melanoma cases worldwide in 2022 were attributable to ultraviolet radiation exposure. Although photoaging itself is not a malignant disease, these statistics underscore the widespread and clinically significant consequences of cumulative UV damage and reinforce the importance of mechanistic and preventive research on photoaging.[3,4] Accordingly, preventive measures that reduce environmental exposure may mitigate some of these effects.[5,6] However, ultraviolet radiation and other environmental stressors not only cause direct DNA damage in skin cells but also accelerate aging by inducing oxidative stress through free radical generation. Therefore, interventions targeting the cellular and molecular mechanisms underlying photoaging are needed to support more fundamental therapeutic strategies.[7] Recent studies further indicate that photoaging is not merely a cosmetic concern but a cumulative biological process involving oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, extracellular matrix (ECM) remodeling, pigmentary dysregulation, and impaired tissue repair. Contemporary reviews have also emphasized that UV-induced skin damage remains a central focus in dermatologic research because solar radiation continues to be the major modifiable external driver of premature skin aging and related cutaneous disorders.[8,9]

Research on exosomes has recently emerged as a promising avenue for elucidating the mechanisms underlying skin aging. Exosomes are nanoscale extracellular vesicles (30–150 nm in diameter) released by cells that carry diverse biomolecules, including proteins, lipids, and nucleic acids.[10] They play a crucial role in intercellular communication by transferring bioactive molecules between cells and thereby modulating the functions and responses of recipient cells.[11,12] Consequently, exosomes are increasingly recognized as important contributors to the pathophysiology of photoaging.[7] Studies indicate that exosomes mediate intercellular signaling in the skin and actively influence cellular behavior during photoaging. For instance, exosomes can deliver specific proteins and nucleic acids that regulate cellular damage responses and repair processes following UV exposure.[13] These findings underscore the pivotal role of exosomes at the interface between intercellular communication and skin aging and provide novel insights into the mechanisms of photoaging. Accordingly, exosomes represent valuable tools for investigating the mechanisms of photoaging and for elucidating complex intercellular communication networks.[14,15] Notably, recent studies have expanded this view by showing that exosomes are involved not only in oxidative stress responses but also in the regulation of inflammation, matrix homeostasis, melanogenesis, and regenerative signaling in aged or photodamaged skin. At the same time, exosome-based strategies, including native extracellular vesicles, engineered exosome mimetics, and nanovesicle-based delivery systems, are being increasingly explored as potential anti-photoaging interventions.[16–18]

Research on exosomes not only helps elucidate the cellular mechanisms underlying photoaging but also paves the way for novel therapeutic strategies. Photoaging, driven primarily by chronic UV exposure, involves pathological alterations in multiple cutaneous cell types and biomolecular pathways.[7,19] Research on exosomes provides a useful framework for understanding these complex processes, particularly the intercellular transmission of aging-related signals. Notably, exosomes themselves show considerable promise as therapeutic agents for non-invasive interventions and regenerative medicine.[20–22] Engineering exosomal cargo may offer opportunities to attenuate or even reverse features of skin aging, thereby providing new avenues for the treatment of photoaging. Such approaches may also provide new strategies for the management of aging-related skin conditions and promote the repair and regeneration of photodamaged skin through regenerative medicine. However, despite the rapid growth of this field, the current literature remains fragmented. Existing reviews have typically focused either on the general role of exosomes in skin aging or on the molecular mechanisms of photoaging. However, few have systematically integrated exosome biogenesis and biological properties with UV-induced pathological mechanisms, cell-specific functions, therapeutic applications, and the major barriers to translation, including standardization, safety evaluation, bioengineering, and regulatory considerations. This fragmentation represents an important knowledge gap in the field. Accordingly, this review aims to provide an integrated overview of the mechanistic links between exosomes and photoaging, with particular emphasis on oxidative stress regulation, intercellular communication, and ECM remodeling. It also summarizes the roles of exosomes derived from different cellular sources and evaluates the translational potential of exosome-based interventions, including engineered exosome mimetics and related nanomedicine strategies. The novelty of this review lies in its integration of basic exosome

biology with the pathogenesis of photoaging and its clinical translation, thereby providing a more comprehensive framework for the development of exosome-based preventive and therapeutic strategies. Overall, this review highlights the mechanistic links between exosomes and photoaging and discusses the potential of exosome-based approaches for the prevention and treatment of photoaging.

Molecular Mechanisms of Photoaging

Before discussing the role of exosomes in photoaging, it is necessary to first summarize the underlying pathophysiology, including amplification of signaling cascades and remodeling of tissue architecture. Photoaging is not limited to superficial epidermal injury. Rather, it reflects a broader disruption of cutaneous homeostasis initiated when ultraviolet (UV) radiation penetrates the dermis. UVradiation, particularly UVA and UVB, induces substantial intracellular production of reactive oxygen species (ROS),[23] which in turn activates key signaling pathways, including the mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) pathways. Sustained activation of these pathways promotes nuclear translocation and increases the transcriptional activity of key factors, including activator protein 1 (AP-1) and NF-κB.[1,24] A major downstream consequence is the marked upregulation of matrix metalloproteinase (MMP) expression and activity, such as MMP-1 and MMP-3, along with suppression of collagen synthesis through the transforming growth factor-β (TGF-β)/Smad pathway.[25] Consequently, collagen fibers, predominantly types I and III, in the dermal extracellular matrix undergo irreversible enzymatic degradation and net loss. This process ultimately drives a pathological cycle linking molecular dysregulation to structural breakdown of the tissue.

Types of Ultraviolet Radiation and Skin Damage

Solar ultraviolet (UV) radiation is categorized by wavelength into short-wave UVC (100–290 nm), medium-wave UVB (290–320 nm), and long-wave UVA (320–400 nm).[25] Most UVC is absorbed by the ozone layer, with negligible amounts reaching the Earth's surface. In contrast, both UVB and UVA penetrate the atmosphere to reach human skin. At ground level, UVB and UVA constitute approximately 5% and 95% of total UV radiation, respectively (Figure 1).[26]

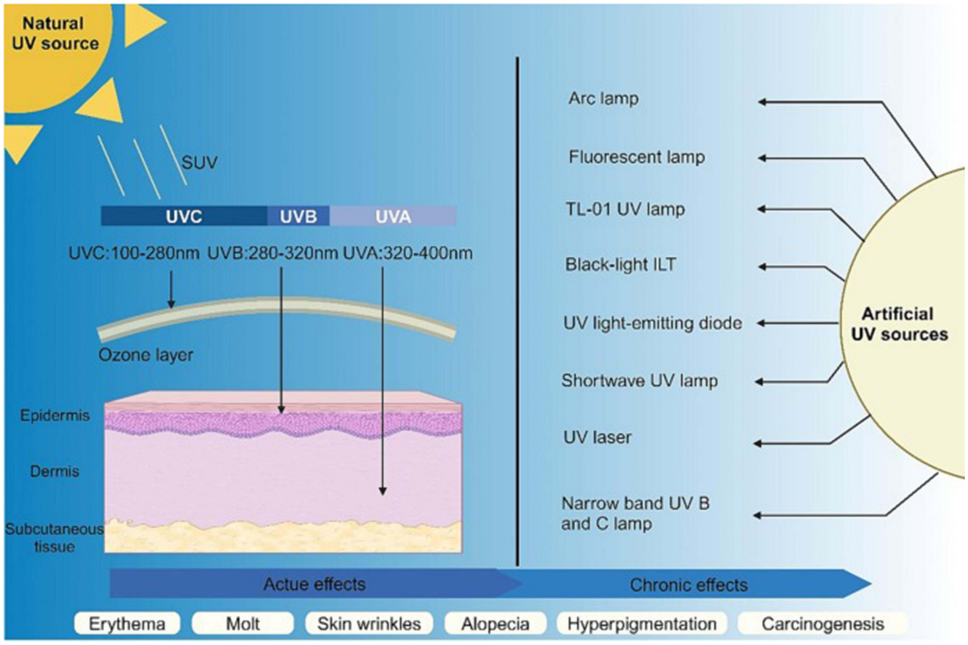

Figure 1 Types of ultraviolet (UV) radiation and their effects on human skinUV radiation is categorized by wavelength into UVC (100–290 nm), UVB (290–320 nm), and UVA (320–400 nm). Most UVC is absorbed by the ozone layer, with minimal amounts reaching Earth's surface, while UVB and UVA penetrate the atmosphere. At ground level, UVB accounts for approximately 5% and UVA for 95% of total UV radiation. Both UVB and UVA contribute to acute and chronic skin effects, such as erythema, skin wrinkling, alopecia, hyperpigmentation, and carcinogenesis. The figure also compares natural UV sources, including sunlight, and artificial UV sources, such as arc lamps and UV lasers. Reproduced from,[9] Copyright © 2024 by authors.

https://doi.org/10.2147/IJN.S600909

Ultraviolet A (UVA; 320–400 nm) has the longest wavelength among ultraviolet subtypes, allowing it to penetrate deeply into the dermis. Through type II photodynamic reactions, UVA generates substantial amounts of ROS. This process induces marked oxidative stress, which can indirectly damage DNA and may also affect deeper subcutaneous tissues. Within the dermis, UVA also damages critical structures, including fibroblasts and blood vessels. It also activates enzymes such as matrix metalloproteinases (MMPs), which degrade collagen and elastic fibers. These changes directly contribute to structural skin damage and photoaging.[27,28] Ultraviolet B (UVB; 280–320 nm) has higher photon energy than UVA but more limited tissue penetration, primarily affecting the epidermis. Approximately 50% of incident UVB and UVA radiation is attenuated by the stratum corneum and the epidermis, respectively. Consequently, only a small proportion of UVB reaches the basal layer of the epidermis. Notably, UVB is well established as a direct cause of DNA damage and mutation and remains a central mechanistic focus in photobiology research.[28,29] The primary mechanism of UVB-induced damage is direct photochemical injury. Its photon energy is directly absorbed by cellular macromolecules, particularly DNA, thereby initiating photochemical reactions that generate characteristic DNA photoproducts. These include cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6–4) pyrimidone photoproducts (6–4PPs). These lesions are highly mutagenic and provide the genetic basis for skin carcinogenesis.[30,31] UVB also induces oxidative DNA damage through ROS generation, as exemplified by the formation of 8-oxodeoxyguanosine.[32,33] Ultraviolet C (UVC; 100–290 nm) is largely absorbed by the atmospheric ozone layer and therefore rarely reaches the Earth's surface. Any residual UVC that reaches the skin is almost entirely absorbed by the stratum corneum, penetrating only 0.1–0.5 mm into the superficial skin layers and exerting minimal effects on the dermis. Studies using three-dimensional human skin models have shown that conventional UVC wavelengths (240–255 nm) can cause significant DNA damage in the skin[34] At equivalent doses, these longer UVC wavelengths induce a significant increase in CPDs across all layers of the skin model, including the entire epidermis, the basal layer, and the stratum corneum. In contrast, far-UVC radiation (215–235 nm) generated no detectable CPDs in the critical basal and stratum corneum layers. Instead, CPDs were confined to the superficial granular layer, resulting in negligible overall DNA damage. These findings demonstrate that high photon energy alone is insufficient to trigger photodamage cascades; the radiation must also physically reach its target, namely DNA within living cells.[1] Therefore, both research and prevention strategies should prioritize UVA and UVB radiation. Importantly, these wavebands often act synergistically: UVB induces initial genetic damage and acute inflammation, whereas UVA imposes sustained oxidative stress and chronic inflammatory stimulation. This synergistic interaction accelerates skin aging and significantly increases the risk of skin cancer. Consequently, effective prevention of photoaging requires further research and multifaceted strategies.

Signaling Pathways in Photoaging

Skin photoaging is a multifactorial process primarily driven by UV radiation. At the molecular level, photoaging is mediated by a complex and interconnected signaling network. After penetrating the skin, UV radiation, particularly UVA, disrupts mitochondrial function and activates endogenous photosensitizers. These events increase intracellular production of ROS and induce oxidative stress.[35] As key signaling molecules, ROS activate members of the MAPK family, including p38, JNK, and ERK. This process leads to phosphorylation and activation of the transcription factor AP-1, thereby driving the upregulation of MMP expression. Concurrently, ROS impair TGF-β/Smad-mediated collagen synthesis. Collectively, these events disrupt the balance between extracellular matrix degradation and synthesis.[36,37] In parallel, ROS, together with DNA damage products, activate IκB kinase (IKK). This promotes the nuclear translocation of NF-κB and induces the expression of pro-inflammatory mediators, such as TNF-α and IL-1β, thereby establishing a chronic low-grade inflammatory state. Furthermore, direct DNA damage induced by UVB, such as CPDs, activates the p53 pathway, which mediates cellular responses including cell cycle arrest, DNA repair, and apoptosis. Recent studies have shown that this classical signaling network also intersects with additional pathways. These include dysregulation of the Nrf2/Keap1 antioxidant defense system[35,38] and activation of the type I interferon response initiated when the cGAS–STING pathway senses cytoplasmic DNA.[24] These pathways interact dynamically to form an integrated network that orchestrates processes ranging from oxidative damage and inflammatory amplification to metabolic imbalance, cellular senescence, and cell death. This cascade ultimately manifests as the hallmark phenotypes of photoaging, including dermal collagen loss, elastic fiber degeneration, impaired skin barrier function, and increased carcinogenic risk (Figure 2).

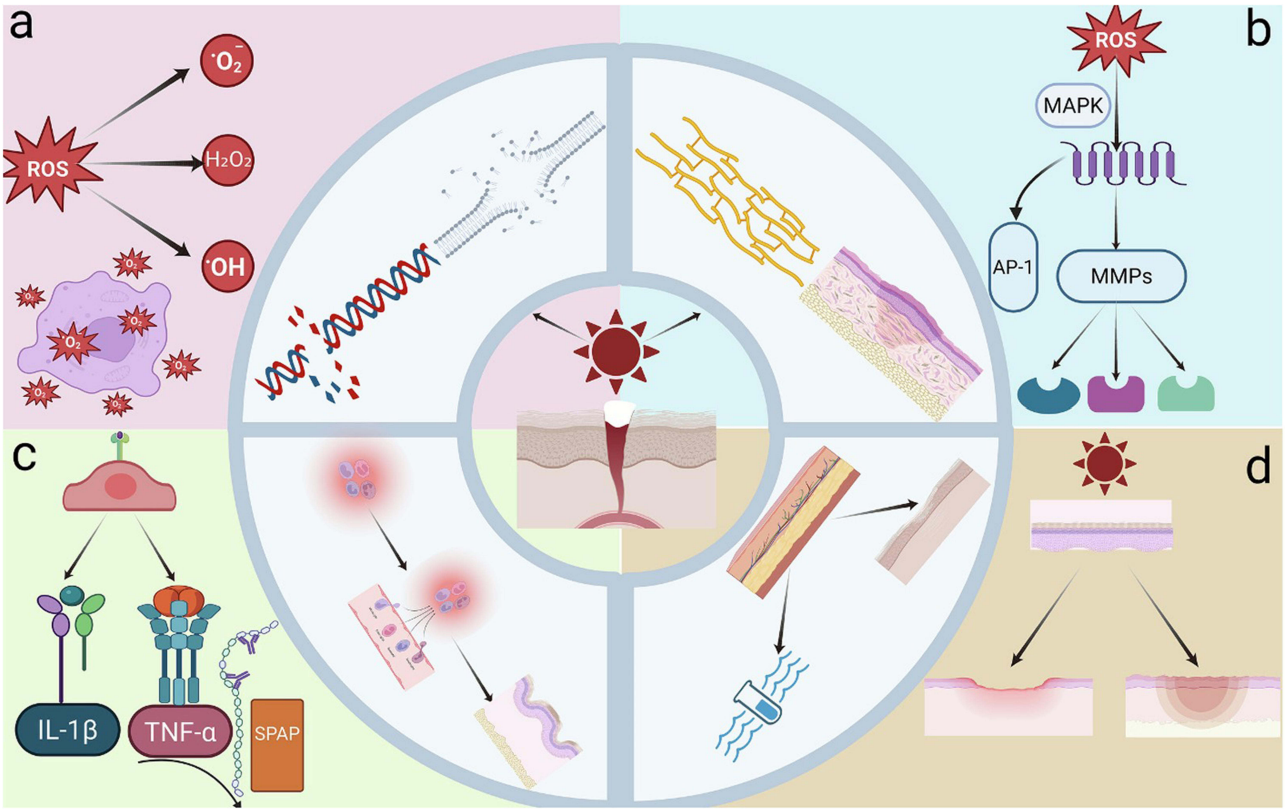

Figure 2 Mechanisms of photoaging in the skin. UV radiation induces skin photoaging through multiple interconnected molecular and cellular pathways. (**a**) UV exposure promotes excessive generation of reactive oxygen species (ROS), including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($^{\cdot}OH$), leading to oxidative stress and biomolecular damage. ROS accumulation contributes to cellular dysfunction and direct damage to nucleic acids, proteins, and membrane lipids. (**b**) ROS-mediated activation of MAPK signaling enhances activator protein-1 (AP-1) activity and upregulates MMPs, resulting in degradation of collagen and other extracellular matrix (ECM) components. (**c**) UV irradiation also triggers inflammatory responses by stimulating the production of pro-inflammatory mediators, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and other components of the senescence-associated secretory phenotype (SASP), thereby aggravating tissue injury and accelerating skin aging. (**d**) Collectively, these events lead to structural and functional alterations in the skin, including epidermal and dermal thinning, loss of elasticity, wrinkle formation, and disorganization of the dermal matrix. Together, these mechanisms contribute to the progressive development of photoaged skin. Adapted from,[39]

Oxidative Stress and Inflammatory Initiation

The initial and pivotal event in UV-induced skin photoaging is the rapid generation of ROS.[40] UV exposure induces robust production of ROS, including superoxide anion (O_2•−), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH). These ROS also act as key secondary messengers that amplify photoaging-associated signaling. In addition to directly damaging DNA and cellular membranes, ROS reshape cellular programs by modulating redox-sensitive signaling pathways.[41,42] Critically, ROS directly modify and activate upstream signaling proteins via redox-based regulatory mechanisms. For instance, ROS oxidize and inhibit protein tyrosine phosphatases, resulting in aberrant, sustained kinase phosphorylation signaling.[43] Concurrently, ROS-mediated oxidation of key proteins such as IκBα initiates downstream signaling cascades. These molecular events converge on two core signaling axes. The first is the MAPK pathway, in which ROS activate MKK3/6 and MKK4/7, leading to phosphorylation of p38 MAPK and JNK, respectively. Activated p38 and JNK subsequently phosphorylate c-Jun and c-Fos, thereby promoting assembly and activation of the AP-1 transcription factor complex. The second axis is the IKK/NF-κB pathway, which is activated through both ROS-dependent and DNA damage-dependent mechanisms. ROS promote ubiquitination and activation of the IKK complex. Alternatively, UVB-induced DNA double-strand breaks activate IKK through the ATM kinase pathway. Both mechanisms culminate in phosphorylation and degradation of the inhibitor IκBα, thereby allowing nuclear translocation of NF-κB, predominantly in the form of the p50/p65 heterodime.[44,45] Activated NF-κB acts as a master transcriptional regulator of inflammation, driving expression of a broad pro-inflammatory gene network (eg., TNF-α, IL-1β, IL-6, COX-2, iNOS). In contrast, AP-1—a central mediator of the early stress response—primarily induces expression of matrix-degrading enzymes like MMP-1, MMP-3, and MMP-9.[46] Crucially, these transcription factor networks operate synergistically, establishing a self-

https://doi.org/10.2147/IJN.S600909

reinforcing ROS–inflammation positive feedback loop. For example, NF-κB-induced iNOS and COX-2 generate nitric oxide (NO) and prostaglandins, respectively, which can further stimulate ROS production. This sustained ROS-rich environment perpetuates activation of both the MAPK and IKK pathways, thereby maintaining a state of chronic low-grade inflammation and oxidative stress. This vicious cycle constitutes a fundamental driver of disrupted tissue homeostasis and progressive extracellular matrix degradation, both of which are characteristic features of skin photoaging.[44,45]

Imbalance in Matrix Metabolism: Degradation and Synthesis

Within the photoaging signaling network, a critical biological outcome is the imbalance between matrix degradation and synthesis. This process translates molecular damage into the hallmark structural collapse of the dermis, characterized by collagen fragmentation, dermal thinning, and wrinkle formation. Therefore, understanding this imbalance not only explains the progressive nature of clinical photoaging but also identifies a key target for potential exosome-based interventions.[47,48] Photo-oxidative stress, primarily mediated by UVA and UVB, induces ROS generation, which drives the MAPK cascade (including ERK, JNK, and p38). This leads to activation of the AP-1 transcription complex, resulting in the upregulation of matrix-degrading enzymes such as MMP-1, MMP-3, and MMP-9, alongside inhibition of their endogenous inhibitors (TIMPs). Collectively, this cascade directly promotes collagen fiber degradation and fragmentation.[47,49] In human dermal fibroblast models, pharmacological inhibition of the MAPK/AP-1 axis significantly attenuates UVA-induced upregulation of MMP-1, −3, and −9 and reduces matrix degradation, underscoring its role as a core driver of the catabolic phase.[47] Simultaneously, ROS-related signaling activates the NF-κB pathway, which synergizes with MAPK signaling to further amplify MMP expression and pro-inflammatory cytokine production. This synergy shifts the dermal microenvironment toward a persistent catabolic and pro-inflammatory state.[48,50] Beyond acute signaling, UV-induced cellular senescence contributes to chronic matrix degradation via the senescence-associated secretory phenotype (SASP). SASP factors (eg., IL-6, CXCL12) induce MMP-1 expression in neighboring fibroblasts, thereby transforming transient photodamage into a self-sustaining degradation loop. Consistently, selective removal of senescent dermal fibroblasts reduces MMP expression and improves collagen density in photoaging models.[51] On the anabolic side, photoaging involves not only increased MMP activity but also suppression of the classic TGF-β/Smad signaling axis. This axis is crucial as it governs the transcription of type I procollagen genes (eg., COL1A1) and subsequent collagen deposition.[48,52] Furthermore, studies in dermal fibroblasts demonstrate that interventions restoring TGF-β/Smad signaling often concomitantly downregulate MMP-1/3 and upregulate type I collagen, thereby shifting the dermal matrix balance toward net synthesis.[53,54] Chronic UVA exposure activates stress-responsive metabolic signaling pathways, including the PI3K/AKT/mTOR axis, which have been implicated in aging-related phenotypes and collagen loss. Pharmacological or genetic inhibition of this axis attenuates UVA-induced collagen loss and photoaging features, supporting a role for PI3K/AKT/mTOR as an upstream regulator linking oxidative stress, cellular stress responses, and extracellular matrix homeostasis. Collectively, dermal remodeling in photoaging can be conceptualized as a synergistic dual-engine process: increased MMP expression and activity driven by ROS–MAPK/AP-1 and NF-κB signaling and further amplified by SASP-mediated paracrine cues, together with reduced collagen synthesis caused by inhibition of TGF-β/Smad signaling. This integrated network may explain why single-target interventions often yield limited and transient benefits and fail to restore durable dermal architecture.[49,51,55] In this context, exosome-based therapies may be advantageous because they enable multitarget modulation: they can attenuate catabolic signaling while reactivating procollagen synthesis, thereby addressing the principal pathological drivers of photoaging.[56,57]

Cell Fate Decision Pathways

During photoaging, UV-induced DNA damage and oxidative stress not only trigger inflammation and matrix remodeling but also drive keratinocytes and dermal fibroblasts toward a critical fate decision among repair, senescence, and programmed cell death. This fate decision determines whether the initial damage escalates into a persistent senescence-associated secretory phenotype (SASP) burden and consequent tissue functional decline. Consequently, it represents a key biological process that exosome-based therapies aim to precisely modulate.[56,58] In UVA-induced dermal photoaging, activation of cell cycle checkpoint signaling (eg., p53/p21/p16) commonly drives proliferative arrest and senescence. The mTOR-mediated nutrient-sensing network reinforces this senescent fate by modulating cellular stress

adaptation and cell cycle progression.[52,59] For instance, in UVA-irradiated human dermal fibroblasts, rapamycin inhibits p53 and HSP27 phosphorylation and alleviates photoaging phenotypes. This suggests that the interplay between the p53 axis and stress-response networks constitutes a druggable switch governing cell fate decisions toward survival or senescence.[52] Similarly, metformin reduces PI3K/AKT/mTOR pathway activation in models of chronic UVA damage. It concurrently alleviates mitochondrial oxidative stress and impaired mitophagy, thereby reducing the senescent burden. These findings indicate tight coupling among energy/nutrient sensing, mitochondrial quality control, and senescence arrest.[56] Furthermore, the NRF2/ARE antioxidant program and mitochondrial quality control (including dynamics and mitophagy) jointly determine the cellular trajectory toward reversible repair or irreversible senescence. Urolithin A ameliorates UVA-induced damage and senescence by activating NRF2 and enhancing mitophagy, underscoring the central role of redox homeostasis and mitochondrial renewal in determining fate plasticity.[60] The prolonged persistence of senescent cells allows their SASP to act as a potent signal source that amplifies chronic inflammation and tissue degeneration. Accordingly, selective clearance of senescent dermal fibroblasts reduces MMP expression and mitigates UVA-induced photoaging, indicating that senescent cell burden is itself an upstream regulatory node within the photoaging fate network.[51] In UVB-induced epidermal damage, cell fate frequently involves the parallel or sequential activation of multiple regulated cell death (RCD) pathways. For example, GSDME-mediated pyroptosis can be primed and amplified by inflammatory factors. Oncostatin M sensitizes keratinocytes to GSDME-dependent pyroptosis, thereby exacerbating UVB-induced inflammation.[61] Moreover, ROS-driven NF-κB activation and NLRP3 inflammasome assembly promote GSDMD cleavage, thereby amplifying a pyroptotic inflammatory loop. In UVB injury models, baicalin inhibits this axis by blocking NF-κB nuclear translocation, NLRP3 activation, and GSDMD maturation, thereby reducing pyroptosis-associated damage. This finding identifies the ROS–NF-κB–NLRP3–GSDMD axis as a critical driver that steers epidermal fate toward inflammatory cell deat.[62] In contrast to pyroptosis, a protective fate is mediated by mitochondrial quality control. In human keratinocytes, ATG5/ATG7-independent alternative autophagy clears UVB-damaged mitochondria and suppresses NLRP3 inflammasome activation. This indicates that autophagy functions not merely as a survival mechanism but as an active fate regulator that sets the threshold for inflammatory death.[63] Notably, ferroptosis is also activated by UVB and triggers a necroinflammatory response through HMGB1 release. Inhibition of ferroptosis blocks this inflammatory initiation, implicating the lipid peroxidation–DAMP release–inflammation amplification cascade as a critical link between specific modes of cell death and photodamage phenotypes.[64] Meanwhile, necroptosis constitutes another inflammatory death pathway, executed via UVB-activated RIPK3-MLKL. This process can occur independently of RIPK1 kinase activity under certain conditions, further underscoring that UVB-related cell fate is governed by a dynamic network of multiple, sometimes interconnected, RCD pathways.[65] From a therapeutic perspective, exosomes can recalibrate cell death thresholds by delivering cargoes that modulate antioxidant defenses, iron homeostasis, and mitochondrial integrity. For instance, donkey milk-derived exosomes reverse UVB-induced ferroptotic changes, including GPX4 depletion, GSH reduction, and lipid peroxidation, and ameliorate skin damage in experimental models, thereby providing direct mechanistic support for the use of exosomes to reprogram cell fate in photoaging.[66]

Emerging Regulatory Axes

Beyond the classic MAPK/AP-1 and TGF-β/Smad frameworks, recent research has unveiled a set of emerging, more upstream regulatory axes in photoaging. These axes integrate UV-induced DNA damage, oxidative lipid peroxidation, inflammatory amplification, and cellular aging/matrix remodeling into a modifiable network. Elucidating these pathways not only helps explain the systemic origin of photoaging phenotypes but also identifies targetable nodes and suggests molecular logic for effector loading in exosome-based therapies.[7,24] Among these mechanisms, the cGAS–STING axis, a cytosolic DNA-sensing pathway, acts as a central hub linking genotoxic stress, innate immunity, and the pro-aging microenvironment. UV radiation, particularly UVB, promotes the release of nuclear and mitochondrial DNA into the cytosol, thereby activating cGAS–STING signaling. Activation of cGAS–STING triggers inflammatory gene programs and the senescence-associated secretory phenotype (SASP) through NF-κB and IRF3. It also remodels the cutaneous immune milieu, enabling the coexistence of chronic inflammation and immunosuppression, which promotes the stabilization and progression of photoaging at the tissue level.[24] Notably, this axis is tightly coupled with inflammatory programmed cell death. UVB-induced ROS and NF-κB not only prime the inflammasome but also promote NLRP3-

GSDMD-mediated pyroptosis, amplifying local inflammation. This process translates acute damage into sustained inflammatory and barrier-disruption signals within keratinocytes.[24,62] Parallel to inflammatory amplification, the ferroptosis axis represents another emerging pathway. UV radiation induces lipid peroxidation accumulation and disrupts iron homeostasis, with the GPX4/GSH system acting as a critical determinant of the ferroptotic threshold. For example, NMN alleviates UV-induced skin damage by bolstering GSH levels and enhancing GPX4-mediated defense, suggesting that modulating the energy metabolism/redox balance interface with ferroptosis presents a novel intervention point for photoaging.[67] At the level of redox homeostasis, the Nrf2/ARE axis is recognized as a core node coupling antioxidant, anti-inflammatory, and anti-MMP responses. In UVB-exposed HaCaT cells, atractylodin maintains Nrf2 levels, preserves antioxidant reserves such as SOD and GSH, and concurrently inhibits ERK, JNK, and p38 phosphorylation, AP-1 activity, and MMP-1 and MMP-9 expression. This indicates that reinforcing the Nrf2-mediated antioxidant program can indirectly attenuate the cascade leading to matrix degradation and wrinkle formation.[68] In parallel with protein-level signaling, epitranscriptomic regulation of miRNA biogenesis has emerged as another key mechanism in photoaging. In human dermal fibroblasts, UVB reduces global RNA m^6A levels and downregulates METTL14 expression. METTL14, in turn, promotes DGCR8-mediated processing of pri-miR-100 to generate miR-100-3p through an m^6A-dependent pathway. miR-100-3p inhibits ERRFI1 translation, thereby influencing p53/p21 signaling and collagen-related phenotypes and forming a novel METTL14–miR-100-3p–ERRFI1 regulatory axis.[69] Tissue-scale repair and remodeling are also governed by mechanical and growth factor signaling reprogramming. After UVB injury, FGF10 promotes keratinocyte proliferation and normalizes epidermal thickness via the ERK/YAP axis. Pharmacological or genetic inhibition of YAP or the MEK/ERK pathway abolishes this protective effect, thereby establishing the Hippo/YAP pathway as a key component in UVB damage repair and photoaging structural restoration.[70] The intersection of these emerging pathways with exosome-based therapy lies in the ability of exosomes to achieve multitarget modulation. By delivering defined molecular cargo, exosomes can coordinately regulate multiple signaling pathways and reprogram cellular states from pro-inflammatory and pro-aging phenotypes toward homeostasis, marked by enhanced autophagy, strengthened antioxidant defenses, and restored matrix synthesis. For example, adipose-derived stem cell (ADSC) exosomes engineered to overexpress miR-1246 inhibit GSK3β and increase autophagic flux, thereby reducing UVB-induced ROS accumulation, MMP-1 expression, and DNA damage while restoring type I procollagen. The loss of these protective effects upon autophagy inhibition supports an "exosome–autophagy axis" and highlights autophagy as both a mechanistic validation readout and a rational engineering target for improving efficacy.[71] In vivo, ADSC-derived extracellular vesicles ameliorate wrinkles, promote epidermal proliferation, and reduce macrophage infiltration and ROS in a UVB-induced mouse photoaging model. In parallel, in vitro studies show they mitigate fibroblast senescence/cell-cycle arrest and modulate inflammation-related phenotypes. Together, these findings support their ability to synchronously counteract multiple hallmarks of photoaging: oxidative stress, inflammation, senescence, and matrix degradation.[72] Moreover, preconditioning donor cells used for exosome production may enhance therapeutic efficacy. For instance, hypoxia-preconditioned adipose-derived stem cell (ADSC) exosomes have shown promise in mitigating photoaging-related changes. These findings suggest that tuning exosomal cargo by modulating donor-cell stress responses, in a manner consistent with emerging regulatory pathways, could shift anti-photoaging applications from empirical use toward mechanism-driven design.[73] In summary, these emerging regulatory pathways define key processes in photoaging, including DNA damage and danger signaling; remodeling of inflammatory and immune networks; lipid peroxidation and cell-death thresholds; the balance between autophagy and senescence; and YAP-mediated reparative proliferation with tissue mechanical reprogramming. Extracellular vesicles (EVs), through programmable cargo delivery, may enable "systems-level correction" by concurrently modulating multiple nodes within this network. This framework provides a structured basis for guiding EV engineering, defining critical quality attributes (CQAs), and prioritizing mechanistic biomarkers.[7,24,73]

Cellular Alterations in Photoaging

In photoaging research, perturbations in signaling pathways ultimately manifest at the level of cell fate decisions and tissue remodeling. Specifically, UV-induced oxidative stress, DNA damage, and inflammatory cascades drive phenotypic changes, including wrinkle formation, barrier impairment, and uneven pigmentation. These phenotypes result from the

accumulation and propagation of cellular senescence and functional reprogramming across various skin cell populations, including keratinocytes, fibroblasts, melanocytes, and immune cells. Exosomes and other extracellular vesicles are key mediators that can either amplify or reverse these cellular alterations within the tissue microenvironment.[74] For example, in the epidermis, environmentally relevant doses of UVA drive proteomic remodeling in primary keratinocytes, upregulate senescence markers, and enhance both pro-inflammatory and antioxidant responses. This altered secretion profile induces paracrine oxidative stress and immune activation in neighboring cells. Thus, epidermal cell senescence acts not only as a consequence but also as an amplifier of photoaging.[75] In UVB-exposed keratinocytes, senescence is tightly coupled with SASP release and matrix degradation. Marked increases in SA-β-gal, p16/p21, IL-1β/IL-6, and MMP-1/3/9, alongside activation of NF-κB and mTOR pathways, indicate that the inflammation-metabolism interface solidifies DNA damage into a persistent senescence and catabolic phenotype.[46] Within the dermis, core cellular events include stress-induced fibroblast senescence and subpopulation drift. Single-cell analyses of UVB-exposed skin have identified specific biomarkers and transcriptional programs in senescent fibroblasts, providing cellular-level evidence for the histopathological observation of decreased collagen synthesis alongside increased MMP activity.[76] Mitochondrial dysfunction and impaired autophagy/mitophagy are considered fundamental drivers of photoaging-related cellular alterations. For instance, UVA exposure induces ROS accumulation, DNA damage, and senescence in fibroblasts. Activating NRF2 and promoting mitophagy can reverse these alterations, highlighting the decisive role of redox homeostasis and mitophagic quality control in setting the cellular senescence threshold.[77] Pigment-related phenotypes also reflect altered cell fate. In models mimicking real-world exposure, combined UV and urban particulate matter induce senescent morphological changes, DNA damage responses, and abnormalities in pigment production and organelle dynamics in human melanocytes. This suggests that senescent melanocytes may provide a cellular link between uneven pigmentation and skin aging. The immune system undergoes bidirectional changes that shape a tissue background of chronic inflammation, immunosuppression, and immunosenescence in photoaging. Evidence indicates that UV radiation (UVR) induces local inflammation and a secondary expansion of immunosuppressive networks, driving a homeostatic disruption resembling immunosenescence during chronic exposure.[78] Consistent with this, the aged skin microenvironment polarizes macrophages toward a pro-inflammatory phenotype. Single-cell analyses reveal an increased proportion of senescent macrophages and inflammatory features in aged skin, suggesting that shifts in immune cell subsets can reciprocally shape the extracellular matrix and tissue regenerative capacity.[79] Single-cell transcriptomic studies further indicate that the immune microenvironment of photoaged skin undergoes measurable shifts in cellular composition and intercellular communication networks, and that these changes can be partially reversed by therapeutic interventions. These findings highlight intercellular communication as a central driver of photoaging-associated cellular remodeling.[80,81] Within this framework, extracellular vesicles (EVs), including exosomes, can function not only as therapeutic delivery vehicles but also as vectors for pathological signal transmission. For example, EVs from UVB-treated fibroblasts are enriched in miR-22-5p and promote a photoaging phenotype by targeting GDF11. Conversely, inhibiting this miRNA in EVs ameliorates photoaging in vitro and in vivo, directly demonstrating that aging signals can be packaged into EVs and disseminated between cells.[82] Therefore, exosome-based therapeutic strategies should aim to correct senescent cellular programs, reestablish extracellular matrix (ECM) homeostasis, and alleviate inflammatory oxidative stress. For instance, in a UVB model, exosomes derived from human dermal fibroblasts reduce ROS, enhance Nrf2-mediated antioxidant defense, promote DNA repair, and regulate the TGF-β/Smad axis. Consequently, they down-regulate p16 and SA-β-gal, inhibit MMP-1, and restore collagen and elastin levels (Figure 3).[13] Separately, exosomes derived from mesenchymal stem cells can improve tissue-level functional outcomes by targeting a central metabolism-inflammation hub. For instance, exosomes from human adipose-derived stem cells (hADSC-Exos), when combined with vitamin E, inhibit the UVB-induced photoaging response via the SIRT1/NF-κB pathway. This combination enhances skin firmness and elasticity in cellular, 3D, and animal models, demonstrating how a combined therapeutic strategy can translate anti-inflammatory signaling into measurable tissue mechanical improvements.[83] Notably, engineering exosome cargo enables the precise targeting of key cellular nodes. For example, exosomes overexpressing miR-1246 inhibit UVB-induced collagen degradation and inflammatory signaling by modulating the TGF-β/Smad axis and reducing MAPK/AP-1 activity. This suggests that future exosome-based interventions could focus on disrupting the coupled aging-ECM-inflammation loop to achieve more controlled cellular fate reprogramming.[84]

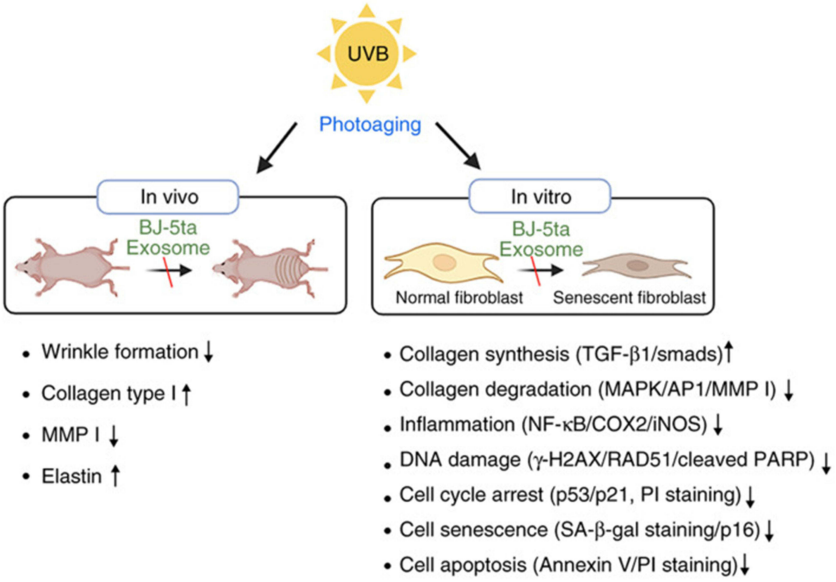

Figure 3 BJ-5ta Exo demonstrate a protective effect against photoaging induced by UVB. They help prevent wrinkle formation by blocking the MAPK/AP-1 signaling pathway, which reduces MMP-1 release and promotes collagen production. Additionally, BJ-5ta Exo mitigate UVB-induced inflammation, apoptosis, cell cycle arrest, and DNA damage. These results suggest that BJ-5ta Exo could serve as an effective anti-photoaging agent for use in cosmetic formulations. BJ-5ta Exo refers to exosomes derived from BJ-5ta cells; UVB stands for ultraviolet B; MMP denotes matrix metalloproteinase. Reproduced from,[13] Copyright © 2023 by authors.

Roles of Exosomes in Photoaging

Initially considered mere cellular waste products or passive messengers, exosomes are now recognized as highly regulated extracellular vesicles that carry specific biological information and play active, crucial roles in maintaining tissue homeostasis and mediating stress responses. The skin is a highly dynamic, continuously renewing organ system chronically exposed to the external environment. Within this context, exosomes are integral to the intricate communication network among keratinocytes, fibroblasts, immune cells, and vascular endothelial cells. They regulate key processes such as epidermal differentiation, dermal matrix renewal, inflammatory responses, and barrier function homeostasis. Under physiological conditions, exosome-mediated intercellular communication helps maintain the dynamic balance of skin structure and function. However, under chronic external stressors like UV radiation, the origin, composition, and signaling networks of exosomes undergo significant remodeling. This reprogramming allows exosomes to deeply participate in both adaptive stress responses and the pathological processes of photoaging. Therefore, elucidating the roles of exosomes in photoaging not only advances our understanding of the intrinsic regulatory mechanisms skin cells employ against UV damage but also provides a critical foundation for developing novel therapeutic strategies. This section systematically reviews the cellular origins, functional roles, and molecular mechanisms of exosomes in the context of photoaging.

Exosome-Mediated DNA Damage Response

Within the "stress–damage–aging" continuum of photoaging, exosomes (small extracellular vesicles, sEVs) serve as intercellular messengers and as organizing hubs that link UV-induced DNA damage, oxidative stress, inflammatory amplification, cellular senescence, and extracellular matrix (ECM) remodeling. Accordingly, reframing these core processes through an exosome-centric lens may yield a more testable mechanistic framework and actionable targets for cell-free, exosome-based interventions against photoaging.[84] Chronic UVA/UVB exposure damages nuclear and mitochondrial DNA via direct formation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6–4) pyrimidinone photoproducts (6–4PPs), as well as indirect ROS attack. This activates the ATM/ATR–p53 axis, induces cell-cycle arrest, and promotes the accumulation of aging phenotypes, which manifest at the tissue level as collagen degradation, elastic fiber abnormalities, and wrinkle formation.[9,85] Exosomes, which carry miRNAs, proteins, and lipids and are efficiently taken up by keratinocytes and fibroblasts, can reprogram stress-response pathways—including MAPK, TGF-β/Smad,

Nrf2, and DNA damage response (DDR) networks—in recipient cells. Consequently, they can either propagate photodamage or mitigate it and promote repair. For example, extracellular vesicles (EVs) from UVB-irradiated human dermal fibroblasts are enriched in miR-22-5p and target growth differentiation factor 11 (GDF11), thereby modulating inflammatory responses and ECM-metabolism pathways. This suggests that exosome cargo can itself constitute a molecular axis that promotes photoaging. Conversely, EVs engineered to inhibit miR-22-5p ameliorate photoaging phenotypes in a UVB-irradiated nude mouse model, highlighting the therapeutic potential of targeting the exosome–miRNA–target gene axis.[82] In contrast, exosomes from healthy human dermal fibroblasts (BJ-5ta) regulate DNA damage markers—such as γ-H2AX, RAD51, and PARP-1 cleavage—in UVB-exposed cells and concurrently reduce apoptotic signaling. This suggests they may alleviate the UVB-induced genomic stress burden by influencing the initiation of the DDR and the recruitment of repair proteins. The same study also observed that exosomes restore antioxidant defenses (eg., SOD, GPX, CAT) and reverse hallmark downstream effects of photoaging—namely, MMP-1 upregulation and collagen synthesis inhibition. This indicates that exosome-mediated DDR regulation is not an isolated event but is coupled with the ROS–MMP–ECM cascade, jointly shaping the photoaging outcome.[13] Providing more direct evidence for DDR modulation, small extracellular vesicles derived from human umbilical cord mesenchymal stem cells (hucMSC-sEVs) reduce γ-H2AX levels and downregulate DDR-related markers (eg., phosphorylated ATM [p-ATM], 53BP1) in a UVA-induced fibroblast photoaging model. This effect is linked to the upregulation of perinuclear protein PZP and inhibition of MMP-1, thereby integrating the attenuation of ECM degradation with the alleviation of ATM-DDR signaling within a unified exosome-mediated regulatory framework.[86] Notably, exosome-mediated DDR regulation can also indirectly affect DNA damage through modulation of autophagy and mitochondrial homeostasis. For instance, exosomes from adipose-derived stem cells (ADSCs) overexpressing miR-1246 enhance autophagic flux by inhibiting GSK3β. This not only reverses UVB-induced abnormalities in ROS, MMP-1, and type I procollagen but also significantly improves DNA damage markers. These benefits are diminished upon autophagy blockade, suggesting that the exosome–autophagy axis serves as a DDR-buffering mechanism that limits damage accumulation.[71] Furthermore, exosomes from human adipose-derived stem cells (hADSC-Exos) reduce mitochondrial DNA common deletion and alleviate oxidative stress by promoting PINK1/Parkin-mediated mitophagy. They also downregulate the expression of p53 and p21, which are key to the DNA damage response and stress-induced senescence. These findings support the concept that exosomes can reshape the inter-organelle crosstalk linking mitochondrial damage, ROS overproduction, nuclear DDR, and cellular senescence.[87] In summary, recent evidence suggests that exosomes play a dual role in photoaging: acting as transcellular amplifiers of damage signals (eg., via the miR-22-5p–GDF11 axis) and as therapeutic delivery platforms. By modulating key DDR nodes, including the ATM/γH2AX axis, autophagy, mitochondrial homeostasis, and the ROS–MMP–ECM cascade, exosomes can reduce genomic instability and attenuate the aging process. This delineates a coherent mechanistic framework and identifies translatable targets for exosome-based interventions in photoaging[7,86,87]

Exosome-Mediated Regulation of Inflammation

In photoaging driven by chronic ultraviolet (UV) exposure, inflammation is not merely an accompanying phenomenon but rather a central amplifier that serially links oxidative stress, cellular senescence, and matrix degradation. Therefore, elucidating how exosomes reshape the inflammatory network in photodamaged skin is a crucial step in advancing their application from empirical skincare ingredients to mechanism-driven therapeutics.[7,87] Mechanistically, UVB radiation upregulates cytokines (eg., IL-1α, IL-1β, IL-6) and promotes cyclooxygenase-2 (COX-2) production via Toll-like receptor (TLR) signaling and inflammatory mediators. This establishes a persistent inflammation–MMP–ECM destruction positive-feedback loop that accelerates phenotypes like wrinkle formation and loss of elasticity.[7] Exosomes and other extracellular vesicles (EVs) serve as intercellular communication carriers, delivering miRNAs, proteins, and lipids to target cells like keratinocytes and fibroblasts. This cargo delivery can reset the threshold and duration of inflammatory responses at both transcriptional and signaling levels. For instance, in a UVB-induced model, exosomes derived from human dermal fibroblasts inhibit the expression of pro-inflammatory molecules and attenuate nuclear factor-kappa B (NF-κB) activation while ameliorating photoaging-associated damage. This suggests that downregulation of the COX-2/iNOS-NF-κB axis is a crucial mechanistic node in their anti-photoaging action.[13] In a combined intervention strategy, exosomes from human adipose-derived stem cells (hADSC-Exos) and vitamin E act synergistically to inhibit the

SIRT1/NF-κB pathway and ameliorate UVB-induced photoaging phenotypes. This indicates that enhancing anti-inflammatory deacetylation pathways to suppress NF-κB-driven transcription represents a therapeutic logic amenable to amplification by exosomes.[88] To address delivery challenges, a microneedle-based co-delivery system for human umbilical cord mesenchymal stem cell-derived exosomes (hUMSC-Exos) and epigallocatechin gallate (EGCG) significantly alleviates UV-induced inflammation and promotes tissue repair in vivo. This system downregulates key inflammatory and chemotactic factors, including IL-1β, CXCL10, and TGF-β1, demonstrating the ability of exosome-based strategies to concurrently reduce pro-inflammatory chemotaxis and promote regenerative repair (Figure 4).[89] Notably, plant-derived exosome-like nanoparticles also demonstrate specific anti-inflammatory effects. For example, those derived from ginseng root downregulate pro-inflammatory genes (eg., COX-2, IL-6) in UVB-irradiated HaCaT cells by inhibiting activator protein-1 (AP-1) signaling and reducing ROS. This suggests they attenuate photodamage-induced inflammatory amplification via a ROS–AP-1–inflammatory gene transcription axis.[90] Similarly, lavender-derived exosome-like nanoparticles attenuate UVB-induced photoaging via miR-166-mediated regulation. Their administration reduces inflammatory markers (eg., IL-1β, IL-6, TNF-α) and improves collagen homeostasis, indicating that a cross-kingdom miRNA–inflammation–collagen metabolism axis constitutes a novel regulatory mechanism underpinning their anti-inflammatory and anti-photoaging effects.[91] However, the functions of exosomes are context-dependent and not inherently beneficial. For example, extracellular vesicles (EVs) derived from UVB-stimulated fibroblasts become enriched in miR-22-5p and undergo pro-inflammatory cargo alterations. This modified cargo profile can itself serve as a vector that propagates photoaging and inflammatory expansion, underscoring the necessity for rigorous quality control and functional stratification based on both source-cell status and vesicle cargo.[82] Therefore, the therapeutic application of exosomes against photoaging should be conceptualized as a systematic engineering endeavor to recalibrate the inflammatory network. This entails, on one hand, targeting quantifiable anti-inflammatory endpoints such as NF-κB, COX-2, IL-6, and specific chemokines. On the other hand, it requires preventing the incorporation of pro-inflammatory EV cargo from senescent or UVB-damaged cells into therapeutic formulations. This dual-pronged approach provides a mechanistically verifiable pathway for the engineering and standardization of exosome-based therapies.[7,82]

Roles of Exosomes in Collagen Metabolism and ECM Remodeling

The integrity of the dermal extracellular matrix (ECM), particularly type I and III collagen and elastic fibers, underlies the visible clinical phenotypes of photoaging, including wrinkles, sagging, and skin roughness. This section therefore

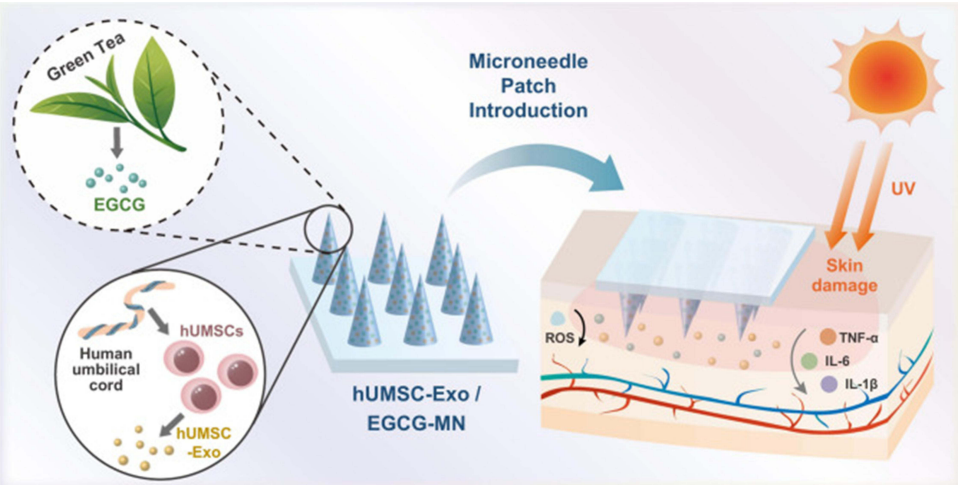

Figure 4 Schematic diagram of hUMSC-Exo/EGCG-MN to mitigate UV-induced skin damage. Epigallocatechin gallate (EGCG), a bioactive polyphenol derived from green tea, is incorporated into a microneedle (MN) platform combined with human umbilical cord mesenchymal stem cell-derived exosomes (hUMSC-Exo) to construct an hUMSC-Exo /EGCG-loaded microneedle system. Upon microneedle insertion, the therapeutic cargos are delivered across the skin barrier into UV-damaged skin tissue. This localized delivery system is proposed to alleviate photoaging-associated skin injury by reducing intracellular reactive oxygen species (ROS) levels and suppressing inflammatory mediators, including TNF-α, IL-6, and IL-1β. Collectively, these effects contribute to the attenuation of cutaneous inflammation and oxidative stress following UV exposure, supporting the therapeutic potential of microneedle-mediated exosome-based interventions for skin photoaging. Reproduced from,[89] Copyright © 2025 by authors.

focuses on how exosomes coordinately regulate collagen degradation and ECM remodeling following photodamage, providing mechanistic evidence to inform target selection and identify therapeutic markers for exosome-based therapy.[7,18] Ultraviolet (UV) exposure promotes matrix metalloproteinase (MMP) family expression via ROS amplification and inflammatory factor upregulation. For example, MMP-1 cleaves intact collagen fibers, while MMP-2, MMP −3, and MMP −9 further degrade the fragments. Concurrently, UV inhibits the TGF-β/Smad synthesis axis. These combined effects create an ECM imbalance characterized by decreased synthesis and increased degradation.[13,92] As representative evidence, exosomes derived from BJ-5ta fibroblasts inhibit UVB-induced phosphorylation of p38, JNK, ERK, and the AP-1 components c-Fos and c-Jun. They also alleviate suppression of the TGF-β1/Smad2/3 pathway and downregulate Smad7. Consequently, these exosomes reduce MMP-1 expression while restoring levels of type I procollagen, collagen I, and elastin. These effects correlate with reduced collagen fiber loss and improved wrinkles in both mouse and reconstructed human skin models.[13] Furthermore, small extracellular vesicles derived from human umbilical cord mesenchymal stem cells (hucMSC-sEVs) confer photoprotection by reversing UVA-induced downregulation of perinuclear protein PZP. A key outcome is the inhibition of MMP-1 and increased expression of the COL1A1 gene, suggesting that a "PZP–MMP-1–COL1A1" axis constitutes a novel mechanism for exosome-mediated inhibition of collagen degradation. Mechanistic studies confirm a detectable interaction and colocalization between PZP and MMP-1. Overexpression of PZP further reduces MMP-1 and upregulates COL1A1, whereas silencing PZP attenuates the ability of hucMSC-sEVs to inhibit MMP-1 and protect collagen. These findings support the role of PZP as a targetable hub molecule in ECM remodeling (Figure 5).[86] At the level of exosome engineering, exosomes from adipose-derived stem cells (ADSCs) overexpressing miR-1246 reduce MMP-1 by inhibiting the MAPK/AP-1 pathway while concurrently activating the TGF-β/Smad axis to promote type I procollagen secretion. In animal models, this alleviates UVB-induced collagen fiber loss and abnormal epidermal thickening. These findings indicate that simultaneous suppression of degradation and enhancement of synthesis constitutes an efficient paradigm for exosome-mediated ECM remodeling.[93] Subsequent studies further indicate that miR-1246-overexpressing exosomes downregulate GSK3β and enhance autophagic flux. This indirectly inhibits collagen degradation and ameliorates stress-induced, photoaging-related structural damage, supporting the existence of a verifiable exosome–autophagy–ECM mechanistic loop.[71] Co-delivery strategies further enhance ECM-level benefits. For example, human adipose-derived stem cell exosomes (hADSC-Exos) combined with vitamin E synergistically inhibit the UVB photoaging response and improve skin firmness and elasticity via the SIRT1/NF-κB axis. This suggests that by reducing inflammatory transcriptional stress, ECM homeostasis can be shifted toward a net anabolic state.[88] It is important to emphasize that exosomes do not inherently provide unidirectional protection for the ECM. Modulating EV cargo, for instance, downregulating miR-22-5p in EVs to relieve its inhibition of the GDF11-related protective network, can ameliorate photoaging both in vitro and in vivo under UVB stress. This suggests that EVs released by senescent or damaged cells may carry cargo that promotes ECM imbalance. Consequently, rigorous quality control of both the cellular source and vesicle cargo is essential for the therapeutic development of exosomes targeting photoaging.[82] From a more fundamental level, hADSC-Exos alleviate UVB-induced mitochondrial DNA (mtDNA) loss and oxidative stress by promoting PINK1/Parkin-mediated mitophagy. Given that oxidative stress is a key upstream driver of MMP upregulation and collagen degradation, mitochondrial quality control via exosomes represents an indirect yet crucial pathway for maintaining ECM homeostasis.[87] Notably, nanovesicles with exosome-like properties from cross-kingdom sources (eg., plants) are supplementing the mechanistic evidence. For instance, ginseng root-derived exosome-like nanoparticles inhibit AP-1 signaling and downregulate ECM-degradation genes like MMP2 and MMP3. Reviews summarize that such plant-derived nanovesicles protect collagen through integrated antioxidant, anti-inflammatory, and anti-MMP effects. This suggests they may serve as both a comparative model system and a potential complementary strategy to mammalian exosome mechanisms.[7,94,95]

Protective and Antioxidant Roles of Exosomes in Epidermal Cells

In the early stages of photoaging, epidermal keratinocytes act as the primary targets for ultraviolet (UV)-induced oxidative stress. The ensuing burst of ROS in these cells drives damage to DNA, lipids, and proteins, promotes cellular senescence, and additionally impairs barrier homeostasis while amplifying the inflammatory cascade. Therefore, elucidating how exosomes and exosome-like nanovesicles reshape the epidermal antioxidant network is crucial for

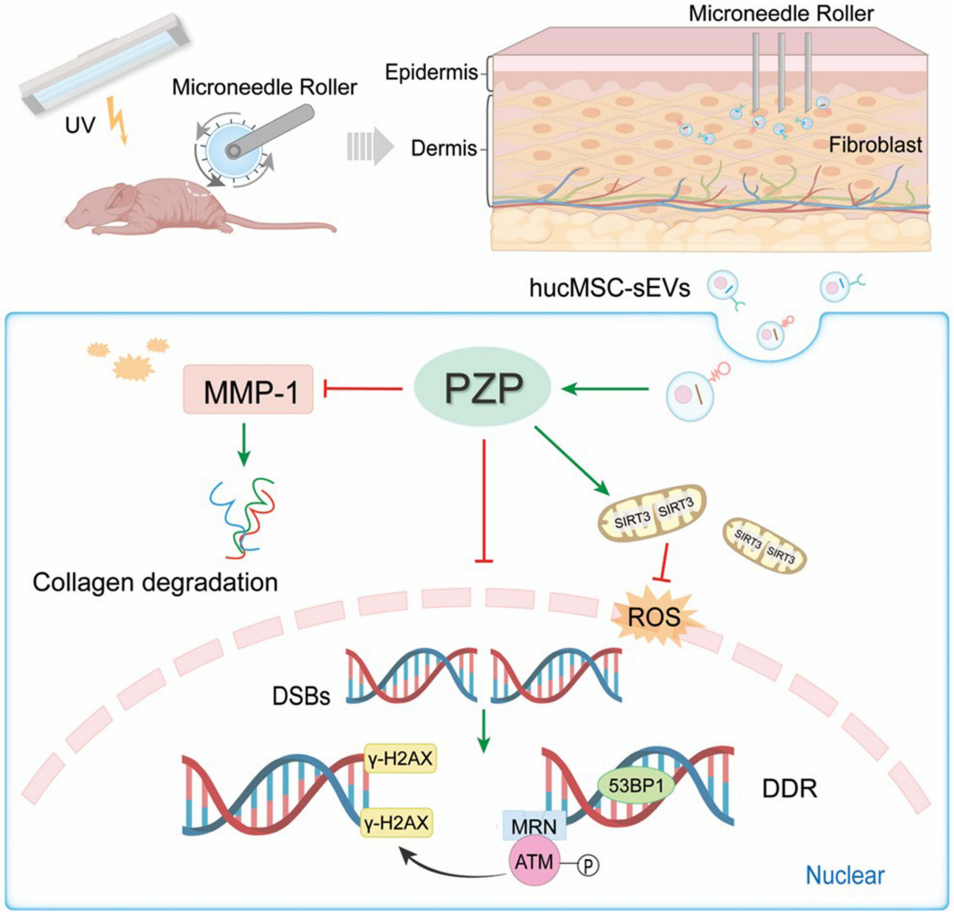

Figure 5 Schematic illustration of the therapeutic mechanism of hucMSC-sEVs delivered by microneedle roller in UV-induced skin photoaging. After UV irradiation, a microneedle roller is used to enhance the transdermal delivery of human umbilical cord mesenchymal stem cell-derived small extracellular vesicles (hucMSC-sEVs) into the dermis, where they are taken up by fibroblasts. Mechanistically, hucMSC-sEVs upregulate pregnancy zone protein (PZP), which suppresses matrix metalloproteinase-1 (MMP-1)-mediated collagen degradation and reduces intracellular ROS levels, at least in part through SIRT3-associated mitochondrial regulation. The reduction in oxidative stress alleviates DNA double-strand breaks (DSBs) and promotes DNA damage response (DDR) signaling, as indicated by the activation of the MRN–ATM pathway and the recruitment of γ-H2AX and 53BP1. Collectively, these effects contribute to extracellular matrix preservation and the attenuation of UV-induced photoaging. Adapted from,[86]

constructing a mechanistic framework for exosome-based photoaging therapies.[7] Research indicates that UVB upregulates oxidative stress-related genes in keratinocytes and engages pathways involving activator protein-1 (AP-1), inflammatory factors, and senescence markers like p21. This interaction forms a self-sustaining "ROS–transcription factor–inflammation/aging" loop. In this context, plant-derived exosome-like nanoparticles demonstrate direct epidermal protective effects. For example, ginseng root-derived exosome-like nanoparticles (GrDENs) reduce ROS levels and cell death in UVB- or H_2O_2-stimulated HaCaT cells, inhibit AP-1 signaling, and consequently downregulate transcriptional responses linked to apoptosis, inflammation (eg., COX-2, IL-6), and senescence (p21). This indicates they achieve synergistic antioxidant and anti-inflammatory effects by limiting ROS generation and suppressing the AP-1 transcriptional axis.[90] Similarly, exosomes derived from *Iris germanica* rhizomes reverse H_2O_2-induced ROS accumulation and cell viability decline in primary human epidermal keratinocytes (nHEKs). They also upregulate transcription of antioxidant enzymes (eg., HO-1, CAT, SOD) and improve wound-healing capacity and differentiation-related phenotypes. These findings suggest that such exosomes restore epidermal repair and homeostasis by enhancing the endogenous antioxidant enzyme repertoire.[96] Beyond the intrinsic antioxidant regulation conferred by vesicles alone, combining exosomes with classical antioxidant molecules represents a promising strategy for clinical translation. For instance, human adipose-derived stem cell exosomes (hADSC-Exos) combined with vitamin E exhibit synergistic inhibitory effects in a UVB-induced photoaging model, an effect correlated with downregulation of the SIRT1/NF-κB axis. This

indicates that a dual-pathway intervention—leveraging exosome-mediated signaling modulation alongside direct antioxidant ROS scavenging—can simultaneously suppress the coupled oxidative-inflammatory loop.[88] At the delivery level, microneedle systems help overcome the stratum corneum barrier. For example, a microneedle-based co-delivery of exosomes from human umbilical cord mesenchymal stem cells (hUMSC-Exos) and epigallocatechin gallate (EGCG) alleviates UV-induced skin damage. This provides a feasible engineering approach for achieving epidermal-targeted delivery and local remodeling of the antioxidant and anti-inflammatory microenvironment.[89] Notably, epidermal oxidative damage extends beyond traditional ROS metrics to include mechanisms such as lipid peroxidation and ferroptosis, which are now recognized as contributors to photo-damage amplification. Recent studies show that donkey milk-derived exosomes inhibit UVB-induced ferroptosis in skin cells in both in vitro and in vivo models. This suggests that exosomes may broaden the scope of antioxidant defense by inhibiting the lipid peroxidation chain reaction.[66] Conversely, exosomes are not invariably protective. Keratinocyte-derived extracellular vesicles (EVs) can also act as carriers of danger signals in photodamage. Following UVB irradiation, keratinocytes release increased numbers of EVs enriched with DNA and proteins, which trigger stimulator of interferon genes (STING)- and inflammasome-related pro-inflammatory responses in immune cells. Melatonin can attenuate this EV-mediated inflammatory effect, highlighting the need for a dual-pronged strategy: inhibiting the propagation of harmful EV-associated damage-associated molecular patterns (DAMPs) while supplementing therapeutic exosomes.[97] In summary, from the perspective of core biological processes, exosomes protect epidermal cells and exert antioxidant effects through multiple mechanisms, including upregulation of the Nrf2-centered antioxidant transcriptional network, inhibition of stress- and inflammation-associated nodes such as AP-1 and NF-κB, and, when necessary, suppression of damage-sensing pathways such as cGAS–STING to interrupt the ROS–inflammation–aging amplification loop. The importance of the Nrf2 pathway is further supported by pharmacological evidence from models of keratinocyte photodamage. Additionally, studies showing that mesenchymal stem cell (MSC)-derived exosomes reduce oxidative stress markers in UVB models provide further evidence of their antioxidant efficacy at the system level.[68,98]

Exosomes from Different Cellular Sources in Photoaging

In the context of photoaging, exosomes derived from diverse cellular sources have emerged as promising modulators of ultraviolet radiation-induced skin damage. These nanoscale vesicles, which carry bioactive cargos such as microRNAs, proteins, and lipids, exert protective effects by attenuating oxidative stress, suppressing inflammation, and promoting extracellular matrix remodeling in dermal and epidermal cells. Derived from sources such as mesenchymal stem cells, adipose-derived stem cells, and skin-resident fibroblasts, exosomes may provide distinct therapeutic mechanisms that promote skin rejuvenation. Their potential clinical applications, including topical formulations and regenerative therapies, highlight a promising strategy for mitigating photoaging manifestations and improving skin health outcomes (Figure 6 and Table 1).

Stem Cell-Derived Exosomes

Stem cell–derived exosomes, particularly those from mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), have attracted substantial interest because they carry diverse bioactive cargo.[110,111] Their cargo, which includes growth factors, anti-inflammatory molecules, and nucleic acids, can mitigate photoaging phenotypes by suppressing UV-induced inflammation and promoting cell proliferation and differentiation.[100] Notably, MSC-derived exosomes effectively stimulate fibroblast proliferation and migration, thereby promoting tissue regeneration, repairing the skin barrier, and reducing wrinkle formation and pigmentation.[112] For example, Gao et al investigated the effects of exosomes from human adipose-derived MSCs (haMSCs) on UV-induced damage in skin fibroblasts.[95] They found that haMSC-derived exosomes significantly reduced UV-induced fibroblast apoptosis and concurrently enhanced fibroblast proliferation and migration. Specific miRNAs and proteins within MSC-derived exosomes reduce MMP expression by inhibiting inflammatory responses and oxidative stress, thereby helping preserve skin structural integrity.[113,114] Furthermore, studies indicate that MSC-derived exosomes can enhance anti-aging effects by modulating gene expression and signaling pathways in fibroblasts.[115,116] In another study, Huang et al applied bone marrow MSC (BMSC)-derived exosomes to a UVB-induced skin photoaging model. They found that these exosomes significantly improved the survival and

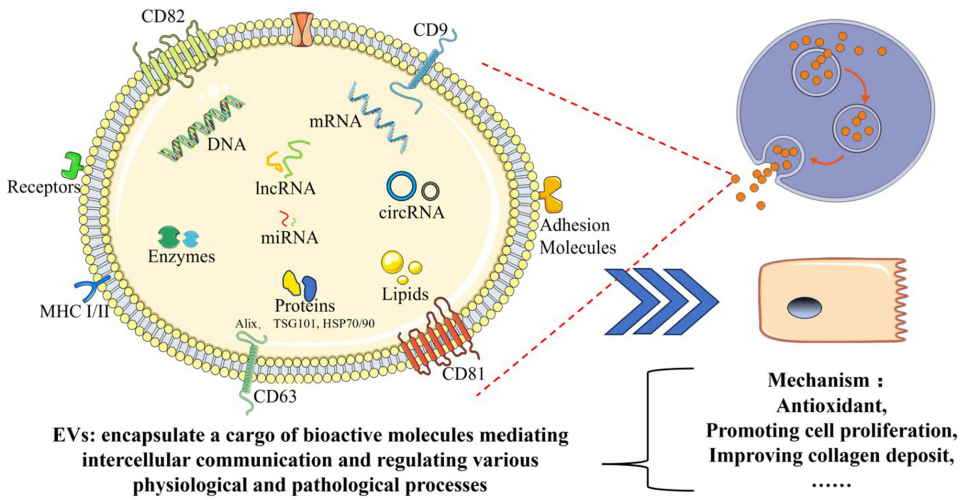

Figure 6 Overview of exosomes and extracellular vesicle (EV) composition with their anti-photoaging effects. EVs contain diverse bioactive cargos, including nucleic acids, proteins, lipids, and enzymes, and express characteristic membrane markers such as CD9, CD63, CD81, and CD82. By delivering these cargos to recipient cells, EVs regulate intercellular communication and modulate multiple biological processes. In skin photoaging, EVs may exert therapeutic effects by scavenging oxidative stress, promoting cell proliferation, enhancing collagen deposition, suppressing extracellular matrix degradation, and facilitating skin repair, thereby contributing to the attenuation of UV-induced photoaging. Adapted from,[99] Copyright © 2023 by authors.

migration of skin fibroblasts. These exosomes also reduced UVB-induced oxidative stress and apoptosis and lowered MMP-1 and MMP-3 expression, further supporting their therapeutic potential for photoaging. Notably, miR-29b-3p within these exosomes plays a crucial role, as inhibition of this miRNA significantly diminishes their anti-photoaging effects, identifying it as a key functional component.[117] Similarly, Lee et al investigated the application of exosomes from human induced pluripotent stem cells (hiPSCs) in skin repair. They found that hiPSC-derived exosomes promote fibroblast proliferation and migration and enhance skin elasticity and strength by reducing MMP expression and inhibiting collagen degradation.[118] By delivering antioxidant enzymes and growth factors, these exosomes significantly enhance skin repair capacity, demonstrating potent anti-photoaging effects. In summary, stem cell-derived exosomes,

Table 1 Mechanisms and Applications of Exosomes from Different Cellular Sources in Photoaging

Cellular Source	Mechanism of Action	Applications in Photoaging	References
Mesenchymal Stem Cells (MSCs)	MSC-derived exosomes alleviate oxidative stress by delivering antioxidants and modulating inflammatory pathways, including downregulation of TNF-α and IL-6 via NF-κB inhibition. They enhance collagen production through miRNA-mediated activation of fibroblast signaling, suppress MMP-1 and MMP-3 to prevent extracellular matrix breakdown, and promote autophagy while reducing senescence in UV-exposed keratinocytes and fibroblasts.	Integrated into topical creams or injectable therapies to enhance skin elasticity, diminish wrinkles, and support wound repair in photoaged skin, with preclinical evidence supporting adjunctive use with photoprotective agents for comprehensive anti-aging strategies.	[100–102]
Adipose-Derived Stem Cells (ADSCs)	ADSC exosomes inhibit NF-κB signaling with miRNAs like miR-146a to reduce inflammation and reactive oxygen species. They boost hyaluronic acid and collagen I synthesis in dermal fibroblasts, counteract UV-induced apoptosis and senescence, and stimulate angiogenesis via vascular endothelial growth factor upregulation.	Employed in regenerative cosmetics, such as anti-aging serums or microneedling enhancers, to hydrate and revitalize photoaged skin, with animal studies showing reduced pigmentation and strengthened skin barrier function.	[73, 103, 104]

(*Continued*)

Table 1 (Continued).

Cellular Source	Mechanism of Action	Applications in Photoaging	References
Fibroblasts	Fibroblast exosomes deliver growth factors like TGF-β and miRNAs such as miR-29 to regulate matrix remodeling, inhibit MMP expression, and promote elastin synthesis. They activate DNA repair mechanisms like nucleotide excision repair to counter UV-induced damage and mitigate fibrosis associated with photoaging.	Utilized in dermal fillers or targeted serums to restore firmness in sun-damaged areas, with in vitro data indicating benefits in wrinkle prevention and texture improvement.	[86, 94, 105]
Keratinocytes	Keratinocyte exosomes regulate epidermal differentiation via miRNAs like miR-203, which inhibit p63 to prevent hyperproliferation in UV-damaged skin. They upregulate anti-inflammatory cytokines such as IL-10 and inhibit apoptosis through caspase suppression, thereby protecting the epidermal barrier from UVB effects.	Incorporated into barrier-repair moisturizers to address epidermal dryness and impaired healing in photoaged skin, with research suggesting utility in preventive photoprotection protocols.	[7, 106]
Endothelial Cells	Endothelial cell exosomes enhance vascular repair by transporting angiogenic factors like VEGF and miR-126, reducing oxidative stress-induced endothelial dysfunction and suppressing the senescence-associated secretory phenotype in adjacent cells.	Applied in treatments for vascular manifestations of photoaging, such as telangiectasia, via injectable or transdermal systems, with preclinical findings showing improved circulation and reduced erythema.	[19, 107, 108]
Epidermal Stem Cells	Epidermal stem cell exosomes convey stemness regulators like Sox2 and Nanog to rejuvenate keratinocytes, maintain telomeres to combat UV-induced depletion, and activate Nrf2 for enhanced antioxidant responses against oxidative damage.	Investigated for advanced anti-aging regimens to preserve epidermal integrity in chronically exposed skin, with potential in customized regenerative therapies.	[7, 109]

particularly those from MSCs and iPSCs, hold considerable promise for anti-photoaging therapy.[119] They act not only by directly repairing UV-induced cellular damage,[120] but also by enhancing the antioxidant and anti-inflammatory capacity of skin cells through modulation of gene expression and signaling pathways,[93] thereby retarding the skin aging process. For example, overexpression of miR-1246 in adipose-derived stem cell (ADSC) exosomes (OE-EXs) inhibits GSK3β-induced autophagy and improves UVB-induced photoaging.[71] Future research should focus on optimizing the isolation and application of these exosomes to maximize their clinical efficacy.

Fibroblast-Derived Exosomes

Dermal fibroblasts are the primary supportive cells in skin, responsible for synthesizing and secreting ECM components that maintain skin elasticity and tensile strength. However, environmental stressors like UV radiation generate (ROS and other free radicals that damage fibroblasts, promoting their senescence. Senescent fibroblasts activate MMPs via multiple signaling pathways, thereby enhancing ECM degradation,[121,122] and ultimately reducing skin elasticity and strength. Exosomes from various sources, including human induced pluripotent stem cells (iPSCs), can mitigate fibroblast senescence through multiple mechanisms. For instance, they promote fibroblast proliferation and migration, facilitating the repair of damaged skin tissue. Additionally, they protect fibroblasts from stressors like UV radiation and reduce the expression of collagen-degrading enzymes (eg., MMP-1, MMP-3), thereby helping to preserve skin elasticity and structural integrity.[118] Similarly, exosomes from human umbilical vein endothelial cells (HUVEC-Exos) significantly increased the proliferation and type I collagen synthesis of UV-B-exposed skin fibroblasts while reducing matrix metalloproteinase levels.[107] In recent years, exosomes secreted by fibroblasts themselves have garnered increasing

attention in skin photoaging research. These fibroblast-derived exosomes play crucial roles not only in intercellular communication but also in regulating skin repair and counteracting aging processes. For example, Hu et al compared the effects of exosomes secreted by human dermal fibroblasts (HDFs) cultured in three-dimensional (3D) versus two-dimensional (2D) systems on skin aging. They found that, compared to exosomes from 2D cultures, those from 3D-cultured HDFs more effectively promoted HDF proliferation and migration, increased type I collagen expression, and inhibited MMP-1 expression—effects partially mediated by downregulating tumor necrosis factor-α (TNF-α).[21] In a related study, Xue et al explored the role of dermal fibroblast exosomes in skin repair. They demonstrated that these exosomes promote fibroblast migration and proliferation and activate skin growth factor signaling pathways, thereby enhancing tissue repair capacity. Furthermore, animal model studies confirmed that dermal fibroblast exosomes effectively reduce photoaging-induced skin damage, accelerate wound healing, and improve skin appearance and function. Regarding the protection of dermal fibroblasts themselves from damage, UVA radiation is a key external stressor that induces cellular damage and senescence. For example, the compound resveratrol cinnamate (RSV) has been shown to significantly increase the survival of UVA-irradiated human skin fibroblasts (HSFs), improve cell morphology, and reduce UVA-induced DNA damage, ROS generation, cell cycle arrest, and apoptosis. These findings suggest that RSV supplementation can protect HSFs from UVA-induced damage (Figure 7).[54] Mechanistically, resveratrol stimulates autophagy via AMPK pathway activation. This reduces UVA-induced oxidative stress and DNA damage, decreases fibroblast apoptosis, improves cell survival, and thereby delays skin aging. Thus, AMPK pathway-mediated autophagy activation represents an effective strategy for protecting fibroblasts and skin from UVA-induced photoaging.[123]

Keratinocyte-Derived Exosomes

Keratinocytes constitute the primary cell type in the epidermal layer and are the first line of defense against UV radiation, making them primary cellular targets in the initial stages of photoaging.[124] Beyond their crucial role in maintaining the skin barrier, keratinocytes secrete exosomes that exert significant regulatory and protective functions.[125,126] For example, Wang et al analyzed the effects of UVB radiation on keratinocyte-derived exosomes.[127] They demonstrated that UVB radiation induces keratinocytes to secrete increased numbers of exosomes. These exosomes contain specific microRNAs

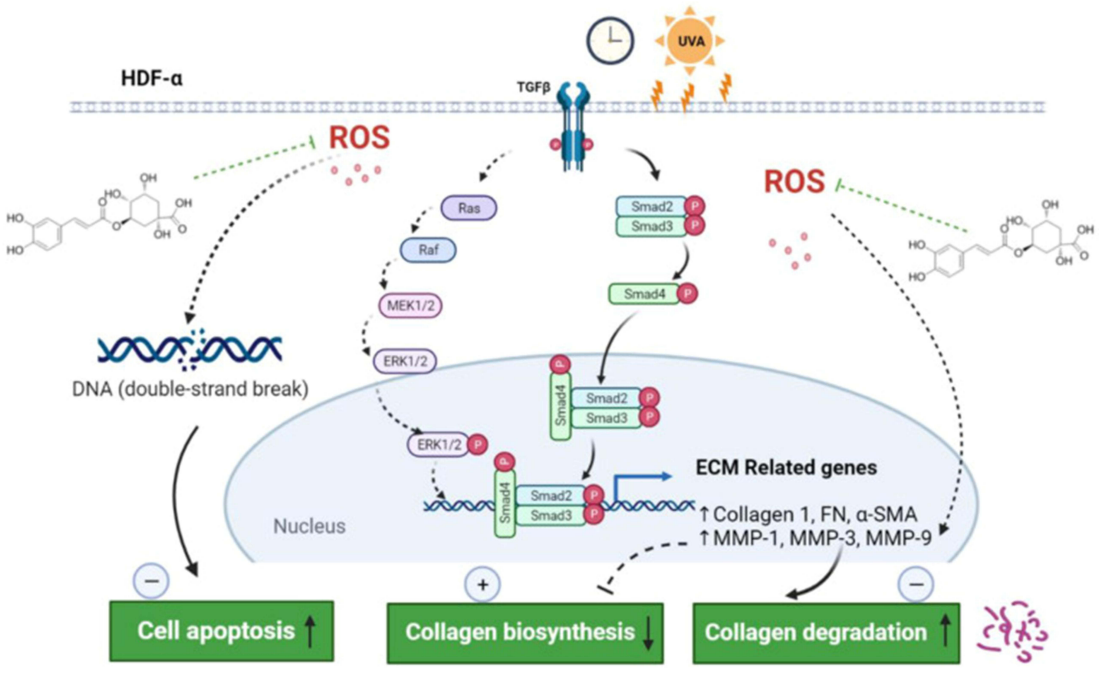

Figure 7 Schematic representation of the photoprotection of CGA on HDF-α cells. CGA promoted the collagen I synthesis through TGF-β-Smad2/3 signaling and inhibited the collagen degradation by downregulating the MMP-1 and MMP-3. In addition, CGA reduced the accumulation of UVA-induced ROS, attenuated DNA damage and promoted cell repair, resulting in inhibition the cell apoptosis. Green dotted T bars, potential inhibition; straight arrows, activation; dotted arrows, potential activation. ECM, extracellular matrix; MMP, matrix metalloproteinase; ROS, reactive oxygen species. Reproduced from,[54] Copyright © 2022 by authors.

(eg., miR-21) and proteins. These molecules can inhibit apoptosis and reduce DNA damage by modulating downstream signaling pathways.[64,128] Further research indicates that miR-21 can mitigate damage to skin elasticity and structure by inhibiting UV-induced inflammation and oxidative stress, thereby reducing MMP expression in fibroblasts.[129–131] In a related study, Tan et al found that irradiated HaCaT keratinocytes release exosomes enriched with miR-27a.[132] These exosomes can be internalized by non-irradiated WS1 fibroblasts, inducing oxidative stress and inhibiting their migration. Thus, miR-27a-enriched exosomes may act as key mediators of radiation-induced bystander effects. This study highlights the significant role of miR-27a and implicates exosomes as key mediators in radiation-induced bystander effects.[132] Whether such exosomes can be harnessed in UV damage models to combat photoaging warrants further investigation. Additionally, keratinocyte-derived exosomes contain antioxidant components and growth factors that protect skin cell DNA integrity and promote skin barrier repair by mitigating UV-induced free radical generation.[133,134] Furthermore, these exosomes alleviate UV-induced skin inflammation by modulating immune responses, thereby enhancing the skin's overall defensive capacity.[135] In summary, keratinocyte-derived exosomes hold broad application prospects in anti-photoaging strategies. Their potential applications include serving as natural anti-aging components in skincare products to enhance UV resistance and delay photoaging. Additionally, specific miRNAs and proteins abundant in these exosomes could be developed into therapeutic agents for directly repairing damaged skin cells and ameliorating photoaging-related skin conditions. Although current research has revealed their therapeutic potential, further studies are required to validate the efficacy of keratinocyte-derived exosomes in clinical settings.[136] Future research should prioritize optimizing exosome isolation and stability to ensure their bioactivity across different application contexts.[137,138] Concurrently, the potential for applying these exosomes in personalized treatment regimens should be explored to achieve more precise photoaging prevention and therapy.[99] In conclusion, keratinocyte-derived exosomes not only offer unique advantages for combating photoaging but also provide novel insights for skin repair and protection. With continued investigation, they are poised to become a key component of next-generation anti-aging products and therapeutic strategies.

Melanocyte-Derived Exosomes

Melanocytes protect the skin from UV damage primarily through melanin secretion.[125] Emerging evidence indicates that melanocyte-derived exosomes also contain diverse components that regulate pigmentation and skin immune responses.[139,140] For example, Shen et al demonstrated that melanocyte-derived exosomes confer significant protection against UV irradiation.[141] Their analysis revealed that UVB radiation alters the composition of these exosomes, enriching them with proteins involved in DNA damage repair and antioxidant responses. These protein cargos can reduce UV-induced oxidative stress by activating cutaneous antioxidant enzyme systems, thereby mitigating UV damage to skin cells. Furthermore, these exosomes may alleviate UV-induced inflammation by modulating immune cell activity.[142] Moreover, in a related study, Sha et al explored the role of melanocyte-derived exosomes in modulating skin immune responses. Their work showed that these exosomes modulate UV-induced inflammatory responses and decelerate photoaging through interactions with cutaneous immune cells.[139] Specifically, microRNAs and cytokines within these exosomes downregulate inflammatory mediators, reducing skin erythema and sensitivity.[128] These findings suggest that melanocyte-derived exosomes contribute not only to pigmentation but also to a broader photoprotective mechanism via immune regulation.

Current research indicates broad application prospects for melanocyte-derived exosomes in preventing and treating photoaging. They could serve as active ingredients in sunscreens and anti-photoaging products, leveraging their intrinsic antioxidant and anti-inflammatory properties to protect against UV damage. Furthermore, their immunomodulatory capacity suggests potential for development into therapeutics for photoaging-associated inflammatory skin conditions.[143] Engineering the composition or enhancing specific functions of these exosomes may open new avenues for comprehensive photoaging therapy.[144] However, the specific mechanisms of action of melanocyte-derived exosomes within different skin layers remain incompletely understood. Future research should elucidate how they mediate effective intercellular communication and confer protection within the skin tissue microenvironment.[145] Melanocyte-derived exosomes play a crucial dual role: regulating pigmentation and protecting against UV damage via multiple mechanisms. With continued research, melanocyte-derived exosomes are poised to play an expanded role in sun protection and anti-photoaging strategies, potentially becoming a key component of innovative skincare formulations.

Adipocyte-Derived Exosomes

Beyond their established roles in energy storage and metabolism, adipocytes secrete exosomes that are increasingly recognized for their relevance in skin aging.[146] Research indicates that specific microRNAs within adipocyte-derived exosomes can inhibit UV radiation-induced inflammation and collagen degradation.[147,148] Furthermore, these exosomes promote the proliferation of dermal fibroblasts and stimulate collagen synthesis, thereby helping to repair photoaging-induced structural damage to the skin.[95] Adipocyte-derived exosomes are now understood to mediate key functions beyond lipid metabolism, significantly influencing skin cell function and overall skin health. For example, Zhang et al demonstrated that adipocyte-derived exosomes are enriched with microRNAs, proteins, and lipids capable of regulating skin cell proliferation and differentiation.[149] Their work further showed that these exosomes mitigate UV-induced oxidative stress and inflammation, thereby protecting skin cells from damage. Additionally, they promote collagen synthesis in fibroblasts, which enhances skin elasticity and structural integrity.[150] Collectively, these functions position adipocyte-derived exosomes as a promising therapeutic tool against photoaging.In another study, Sun et al found that adipocyte-derived exosomes promote skin regeneration by modulating the Wnt/β-catenin signaling pathway.[151] Mechanistically, these exosomes inhibit MMP activity to reduce collagen degradation and activate fibroblast proliferation and migration to promote skin repair and regeneration. This suggests that adipocyte-derived exosomes can not only delay photoaging but also contribute significantly to the treatment of photodamage and skin repair. Consequently, several studies are exploring the therapeutic potential of adipocytes and their secretory products, particularly exosomes, for developing anti-photoaging treatments. The overarching aim is to mitigate UV-induced skin damage by bolstering the skin's intrinsic defense and repair mechanisms.

Exosomes from Other Cell Types

Beyond the cell types discussed above, exosomes secreted by other cells also play significant roles in preventing and treating photoaging.[74] For instance, exosomes derived from endothelial cells and immune cells (such as macrophages, dendritic cells) exhibit distinct functions relevant to anti-photoaging. Kim et al investigated the role of exosomes derived from human umbilical vein endothelial cells (HUVECs) in UVB-induced skin damage.[107] Their results demonstrated that HUVEC-derived exosomes effectively reduced UVB-induced wrinkles and sagging by promoting fibroblast proliferation and collagen synthesis. Furthermore, these exosomes protected skin structural integrity by reducing MMP expression.[152] This demonstrates the potential of endothelial cell-derived exosomes in promoting skin regeneration and combating photoaging. Macrophage-derived exosomes have also been shown to exert anti-photoaging effects. Using single-cell sequencing, Lin et al discovered that macrophage-derived exosomes carry anti-inflammatory factors that significantly inhibit UV-induced inflammation. These exosomes reduce levels of inflammatory mediators and protect skin cell viability by modulating the oxidative stress response, thereby delaying photoaging.[153] Research on dendritic cell-derived exosomes also reveals their protective role against photoaging. They can regulate cutaneous immune responses and enhance the skin's resistance to UV damage.[154] Specifically, microRNAs and proteins within these exosomes regulate the activity of cutaneous immune cells, reduce inflammation, and promote repair of damaged tissue.[155] This finding provides a rationale for developing novel immunotherapeutic strategies against photoaging. Exosomes from diverse cellular sources exhibit broad potential for preventing and treating photoaging. Research on exosomes from endothelial cells, macrophages, and dendritic cells has deepened our understanding of photoaging mechanisms. In the future, combining exosomes from multiple sources may enable the development of more comprehensive and effective therapies. These exosomes thus open new avenues for skincare and treatment research, providing diverse options for photoaging intervention.

Application Prospects of Exosomes in Photoaging

Nanoscale Exosome Mimetics

The development of nanoscale compounds that mimic exosomes, termed exosome mimetics, represents an important frontier at the intersection of nanotechnology and biomedicine.[156] This approach leverages principles of nanomaterial design and engineering to replicate key structural and functional features of natural exosomes for biomedical applications. Although exosome-based interventions represent a mechanistically attractive strategy for UV-driven photoaging,

their clinical translation is hampered by low yield, cargo heterogeneity, and limited control over cutaneous delivery. These limitations have spurred the development of nanoscale exosome mimetics, which are synthetic compounds designed to replicate key biological functions while offering advantages in manufacturability and formulation flexibility.[7,157] The following section summarizes the application prospects of nanoscale exosome mimetics, including their technical principles, current research progress, and future potential (Figure 8 and Table 2).

Nanoscale materials exhibit highly tunable physicochemical properties, including size, surface charge, and surface functionalization capacity, which enables their rational engineering to mimic EV functions. For example, nanocarriers loaded with antioxidants, anti-inflammatory agents, or gene-editing tools can reduce UV-induced oxidative stress, suppress inflammatory signaling, and promote DNA damage repair.[83] Furthermore, these nanoscale compounds can be modified to enhance targeting, facilitating more effective delivery to specific skin cell populations and thereby enabling more precise intervention against photoaging.[165,166] Among these, cell-derived nanocapsules (CDNs) generated via extrusion or shear stress represent a practical exosome-mimetic platform. CDNs retain the native membrane bilayer structure and can encapsulate much of the parental cell's protein and cargo repertoire at a higher yield than naturally secreted exosomes.[167,168] Mechanistically, these vesicle mimetics engage typical repair-related pathways, such as MAPK signaling in skin fibroblasts—promoting cell proliferation, migration, and ECM secretion. These processes align conceptually with reversing collagen loss and skin remodeling, which are central to photoaging biology.[7,167] Beyond simply replicating EVs, advanced nanotechnology enables programmable design—through surface-ligand modification, charge/size tuning, and reservoir-retention strategies—thereby addressing the short residence time and poor tissue targeting that often limit the efficacy of natural vesicles in vivo.[157] A particularly promising direction is extracellular vesicle (EV) membrane-coating technology. Here, synthetic nanoparticle cores are cloaked with EV-derived membranes, inheriting their immune-evasive and cell-interactive properties while retaining the high payload capacity and physicochemical stability of engineered nanomaterials.[157,169] Moreover, combining nano-formulations can harness synergistic effects at the pathway level. For example, co-delivering stem-cell exosomes with antioxidants can target signaling nodes like the sirtuin/NF-κB axis, which is critically involved in UVB-induced aging and inflammaging phenotypes.[83] Plant-derived extracellular vesicle-like nanoparticles (ELNs) further expand the mimetic concept by providing low-cost, scalable nanocapsules with unique compositions rich in bioactive phytochemicals. This positions ELNs both as intrinsic therapeutics and as natural nanocarriers.[92,170] Consistent with this, recent dermatology-guided approaches highlight the dual utility of plant ELNs: they can act either through their intrinsic bioactive cargo or serve as delivery vehicles for

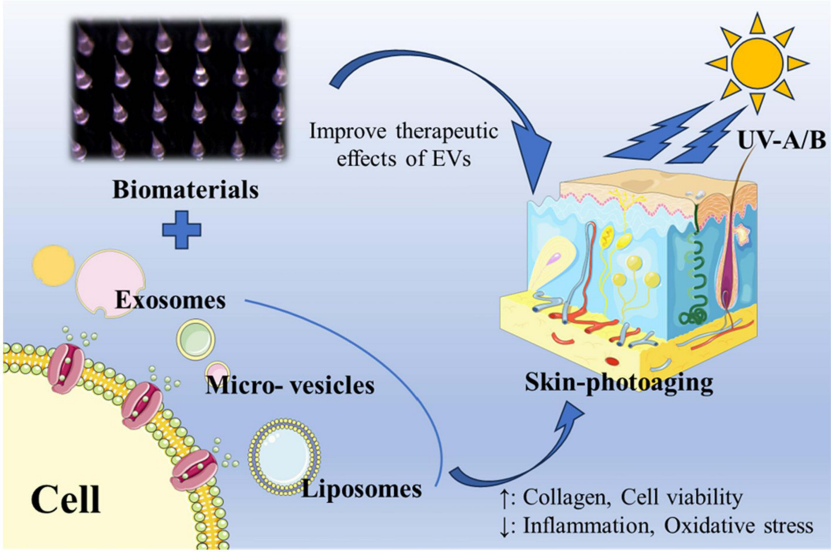

Figure 8 Schematic illustration of biomimetic nanomaterials mimicking exosomes (exosome-like nanoparticles or synthetic EVs) combined with biomaterials (eg., liposomes, micro-vesicles) to enhance therapeutic delivery and effects against UV-A/B-induced skin photoaging. Integration improves transdermal penetration, stability, and bioactivity, leading to increased collagen synthesis and cell viability while reducing inflammation and oxidative stress. Reproduced from,[99] Copyright © 2023 by authors.

https://doi.org/10.2147/IJN.S600909

Table 2 The Application of Nanoscale Compounds in Simulating Exosomes

Nanocomposite Type	Application Field	Function	Advantages	Application Examples	Reference
Nanoliposomes	Antioxidant	Simulated exosomes can carry antioxidants to reduce the damage of free radicals to the skin.	Improve skin antioxidant capacity and slow down the process of photoaging.	Nanoparticles containing antioxidants such as vitamin C and E.	[158]
Polymer nanoparticles	Repair the skin barrier	Exosome mimics can carry growth factors to promote skin cell repair and regeneration.	They improve skin elasticity and texture, enhancing self-repair capabilities.	They deliver nanocompounds such as epidermal growth factor (EGF).	[159, 160]
Inorganic nanoparticles	Anti-inflammatory	Simulated exosomes can carry anti-inflammatory factors, reduce inflammation caused by photoaging,	Lower inflammation levels and improve skin redness and irritation.	Nano-exosomes containing anti-inflammatory factors.	[161]
Nanoliposomes, magnetic nanoparticles	Targeted delivery	Simulated exosomes all possess the ability to deliver therapeutic components precisely to damaged areas,	Enhancing the efficiency and specificity of treatment while reducing side effects.	These nanocompounds are designed to target specific skin layers.	[162]
Colloidal gold, nano-gel	Skin moisturizing	Simulated exosomes can carry moisturizing factors to help maintain skin moisture balance.	Improve skin dryness and enhance skin moisturizing effect.	Nano-exosomes containing moisturizing factors such as hyaluronic acid.	[163, 164]

exogenous compounds, thereby expanding the pipeline for future photoaging cosmetics and pharmaceuticals.[92,171] Mechanistic evidence from UV-related models continues to accumulate. For instance, ginseng-root-derived ELNs protect keratinocytes by inhibiting activator protein-1 (AP-1) signaling and limiting ROS production, thereby directly intervening in the ROS–AP-1–MMP cascade that drives collagen degradation in photoaged skin.[90] Notably, ELNs derived from *Beta vulgaris* (beetroot) have been shown to alleviate photoaging phenotypes by coordinately mitigating oxidative stress and inflammation while promoting collagen biosynthesis. This underscores how plant vesicle-based nanoscale compounds target the core biological triad of photoaging: oxidative stress, inflammation, and ECM remodeling.[172] Future translation of exosome-mimicking nanoscale compounds from a promising concept to reproducible anti-photoaging therapies will hinge on rigorous standardization of source materials, purification/characterization metrics, mechanism-based efficacy determination, and comprehensive safety/immunogenicity evaluation.[157,171]

Anti-Photoaging Strategies

Extracellular vehicles (EVs) counteract photoaging through multiple mechanisms, primarily involving antioxidant, anti-inflammatory, and tissue-repair activities.[7,99] First, EVs exert antioxidant effects. UV radiation generates substantial ROS, causing oxidative stress and DNA damage in skin cells.[9] EVs derived from diverse cellular sources, including keratinocytes, fibroblasts, and melanocytes, carry antioxidant enzymes and other bioactive molecules that reduce ROS production and accumulation, thereby protecting skin cells from UV-induced oxidative damage.[103,120,173] Second, EVs are key regulators of inflammatory responses. UV radiation causes direct cellular damage and triggers skin inflammation. EVs can inhibit the release of inflammatory mediators and attenuate skin inflammation by delivering anti-inflammatory factors and miRNAs. This mechanism is particularly prominent in exosomes from macrophages and dendritic cells, which effectively alleviate UV-induced skin inflammation and promote tissue repair.[153] Third, EVs help maintain skin structural integrity by modulating MMP activity. UV radiation induces MMP overexpression, which degrades collagen and elastin, ultimately causing skin laxity and wrinkle formation. Various EVs, including those from fibroblasts and stem cells, inhibit MMP expression and promote collagen synthesis, thereby delaying photoaging.[13,107,117] Beyond these pathways, directly restoring proteostasis and autophagic flux via exosome cargo represents another important strategy.

For example, exosomes overexpressing miR-1246 enhance autophagic flux by inhibiting GSK3β and concurrently downregulate ROS, MMP-1, and DNA damage markers in UVB models. This suggests that an "exosome–miRNA–autophagy" axis can be a key module in anti-photoaging strategies, linking damage sensing to tissue repair.[71] An emerging "alternative" strategy involves using EVs to deliver nucleic acids for in situ regeneration of deficient structural proteins in the skin. For instance, COL1A1 mRNA-loaded EVs promote collagen restoration and wrinkle reduction in photoaged skin via intradermal or microneedle-array delivery. This reflects the potential of exosome-based interventions to achieve ECM structural reconstruction.[174] Because photoaging involves coupled oxidative and inflammatory stress, combination therapy represents a promising direction. For example, co-delivery of mesenchymal stem cell-derived exosomes (MSC-Exos) and the natural antioxidant epigallocatechin gallate (EGCG) via dissolvable microneedles can reduce oxidative injury, suppress inflammation, and promote tissue repair in models of UV-induced damage. These findings suggest that integrated exosome-small molecule-delivery device strategies may more effectively address the multidimensional pathology of photoaging.[89,175,176]

Future research should focus on several key directions. First, elucidating the specific mechanisms of action of EVs from different cellular sources will help determine their optimal application pathways in anti-photoaging therapy. Second, the interactions between EVs and skin cells require investigation, particularly how they vary across different skin types and stages of photoaging. Third, exploring synergies between exosomes and other anti-aging therapies will be crucial for optimizing their integration into comprehensive treatment strategies. In summary, EVs show considerable potential for preventing and treating photoaging, owing to their inherent biological advantages. With advancing technology and deeper research, EVs are poised to become a key component of next-generation anti-photoaging therapies, offering new avenues to delay skin aging and improve skin health.

The Role of Extracellular Vesicles in Regenerative Medicine

The rapid advancement of regenerative medicine has introduced novel approaches for skin wound repair and anti-aging. Among these, EVs, key mediators of intercellular communication, have shown considerable potential for application.[15,177] EVs carry diverse bioactive molecules, including proteins, RNAs (eg., microRNAs), and lipids, which enable their direct participation in skin tissue repair and regeneration. These vesicles promote cell proliferation, migration, and differentiation. They also modulate the local microenvironment by attenuating inflammation and oxidative stress, thereby accelerating wound healing and restoring skin structure and function.[115] Moreover, exosomes deliver antioxidant and anti-inflammatory factors that mitigate UV-induced oxidative stress and inflammation, thereby protecting the skin from photoaging damage. Particularly, exosomes derived from stem cells have attracted significant research interest due to their potent regenerative capacity and multifunctionality. They are anticipated to play a pivotal role in regenerative medicine by repairing damaged tissues and enhancing skin quality.[178,179] Evidence from models that recapitulate photoaging more closely indicates that mesenchymal stem cell–derived extracellular vesicles (MSC-EVs) reduce UVB-induced ROS generation and DNA damage, suppress senescence-associated markers, and improve dermal ECM remodeling in both in vitro and in vivo settings. A key EV cargo, TIMP1, further attenuates photoaging-associated senescence and tissue degeneration by inhibiting Notch1 signaling and its downstream Hes1-p16-p21-p53 axis. These findings suggest that an EV cargo–mediated developmental/differentiation–aging program may be reprogrammed through regenerative strategies.[101] Another regenerative strategy is to engineer EVs from natural delivery vehicles into platforms for protein or gene replacement. For example, EVs can be produced at scale using cellular nanoporation and loaded with COL1A1 mRNA. Intradermal administration of these engineered EVs increases collagen deposition and reduces wrinkle formation in photoaged mice, reframing collagen depletion as a modifiable regenerative endpoint.[174] Delivery modality is also a critical determinant of the efficacy of EV-based regenerative interventions. Co-loading human umbilical cord mesenchymal stem cell–derived exosomes (hUMSC-Exo) and epigallocatechin gallate (EGCG) into a dissolvable microneedle system markedly improves transdermal co-delivery efficiency. In UV injury models, this approach reduces oxidative stress, inflammation, and DNA damage while enhancing tissue regeneration. These results suggest that combining materials-based delivery with multimodal cargo synergy may enable stable presentation of EV regenerative cues within the epidermal–dermal microenvironment.[89] In parallel, more scalable extracellular vesicle–like nanoparticles (EVLNs) are emerging as regenerative candidates. For example, lavender-derived EVLNs reduce

inflammatory mediators and improve epidermal thickness and collagen preservation in UVB-induced photoaging models, including cell-based systems and animals. The miR166 family carried by these vesicles is associated with enrichment of pathways related to DNA repair, oxidative stress responses, and collagen metabolism. Collectively, these findings suggest that plant-derived vesicles may help address translational barriers because of their natural origin, potentially low immunogenicity, and scalable production.[91]

Based on recent advances, future research should focus on several key areas. First, the specific mechanisms of action of EVs from different cellular sources require in-depth exploration to optimize their application in skin regeneration and anti-photoaging therapies. Second, it is necessary to study EV secretion profiles across different skin types and pathological conditions to develop more targeted therapeutic strategies. Finally, exploring synergistic effects between EVs and other regenerative medicine technologies could further enhance their efficacy in skin wound repair and photoaging prevention and treatment. In conclusion, EVs hold broad application prospects in skin regeneration and anti-aging. With in-depth research and technological optimization, EVs are poised to become a vital therapeutic tool in regenerative medicine, offering novel solutions for skin health and anti-aging.[180]

Challenges and Research Directions

Challenges and Limitations

Ultraviolet radiation, particularly UVB and UVA, drives photoaging through a core pathological network. This network integrates oxidative stress, the DNA damage response, chronic low-grade inflammation, and MMP-mediated degradation of collagen and elastin, ultimately leading to cellular senescence, imbalanced ECM remodeling, and compromised barrier function. EVs, key carriers of intercellular communication, are increasingly regarded as a multifunctional and potentially programmable platform for intervention. They can simultaneously act on multiple skin cell types, including fibroblasts, keratinocytes, immune cells, and endothelial cells.[21,91,181] Currently, a major research gap is the lack of mechanism-resolved study designs that extend beyond endpoint phenotyping.[7] Future studies could combine cargo perturbation, uptake inhibition, lineage-specific tracing, and pathway rescue experiments to establish causal links between specific EV components and photoaging-relevant cellular responses.[82,182] Rather than merely reporting reduced ROS or increased procollagen, next-generation studies should clarify which EV cargo, delivered to which recipient cell type, via which intracellular route, and under which UV-damage context, is responsible for the observed therapeutic effect.[183,184] We should shift from descriptive observation to causal analysis, which will provide a more informative roadmap for the field.

Recent studies indicate that EVs derived from mesenchymal stem cells (MSCs), skin cells, or 3D culture systems can mitigate UV-induced damage by reducing ROS, alleviating inflammation and aging phenotypes, and promoting ECM synthesis. Furthermore, specific miRNA-mediated axes, such as those involving EV cargo alterations in fibroblasts, provide a molecular leverage point for intervening in photoaging.[7,185] However, most current research remains descriptive, focusing on phenomena like antioxidant, anti-inflammatory, and procollagen-promoting effects. It lacks rigorous verification of the causal chain connecting EV cargo (miRNAs, proteins, lipids) to downstream effects. This chain encompasses recipient cell uptake pathways, subcellular localization, and the activation of UV-triggered signaling axes such as DDR-p53/p21, NF-κB, and AP-1/MMPs.[186–188] Moreover, single-vesicle heterogeneity, including distinct EV subpopulations and diverse cargo repertoires, remains incompletely characterized. This knowledge gap hampers the definition of robust potency markers and the establishment of release criteria for EV-based therapeutics. A major challenge in EV isolation and purification is not extraction per se, but the fact that different workflows, differential ultracentrifugation, density-gradient centrifugation, size-exclusion chromatography (SEC), tangential flow filtration (TFF), polymer-based precipitation, and immunocapture—can systematically shift EV subpopulation composition, co-isolated protein/lipoprotein impurity profiles, and particle-size distributions. Such process-dependent variations may materially affect EV potency in modulating photoaged skin.[189,190] To address this issue, emerging single-vesicle resolution technologies, such as high-sensitivity nano-flow cytometry, imaging flow cytometry, super-resolution microscopy, Raman-based approaches, and single-vesicle omics, should be incorporated more systematically into photoaging research. These tools can reveal the true complexity of EV populations by distinguishing vesicles based on size, surface markers, cargo composition, and functional state, thus overcoming the limitations of bulk-averaged measurements.[191–193]

Furthermore, a key delivery challenge arises from the skin's stratum corneum barrier, which hinders access to the target dermal site in photoaging. Topical application alone often suffers from insufficient penetration, short residence time, and uncontrollable dosing. Consequently, the field is shifting from direct application to engineered delivery systems—such as soluble microneedles, composite hydrogels, and core-shell structures for sustained release, sometimes combined with antioxidant molecules—to achieve quantifiable dermal exposure and controlled release kinetics.[175,185] From a translational perspective, however, delivery optimization alone is not sufficient. Real-world clinical application will also depend on whether EV-based products can be consistently manufactured at scale, stored stably, distributed cost-effectively, and regulated within a clear product classification framework.[194] Major barriers to clinical use include high production costs, batch-to-batch inconsistency, variability introduced by donor cell source and culture conditions, limited comparability across purification platforms, incomplete long-term safety data, and regulatory uncertainty over whether such products should be classified as biologics, advanced therapy medicinal products, drug-delivery systems, or combination products.[195,196] These issues should be addressed early in preclinical development rather than postponed until late-stage translation. In addition, the current evidence base for EVs in photoaging is limited by several practical and conceptual constraints.[7] Many studies rely on small-scale in vitro or short-term animal experiments, with inadequate standardization of UV protocols, EV dosing, administration frequency, and endpoint selection. Cross-study comparisons are therefore difficult, and clinical extrapolation remains premature.[86,99]

Future Research Direction

In the future, to achieve depth and translatability, research should focus on four main directions. First, integrating multi-omics with single-vesicle analysis to identify effective EV subpopulations, key cargo, and action circuits. These mechanistic insights must then be translated into quantifiable potency assays and release indicators, forming an integrated closed-loop from mechanism to chemistry, manufacturing, and controls (CMC).[187,197] Second, programmable exosomes can be advanced using synthetic biology approaches—such as controlled cargo loading, surface-ligand engineering for targeting, and stabilization against photo-oxidation—to enable selective modulation of specific cell types (eg., dermal fibroblasts, senescent keratinocytes, and inflammatory macrophages). These designs should minimize off-target effects and limit systemic exposure.[198,199] Third, integrative multi-omics approaches should be used to systematically map the photoaging microenvironment and EV-responsive networks. In parallel, artificial intelligence (AI) and machine learning (ML) can support high-dimensional feature selection, prediction of synergistic cargo combinations, optimization of targeted delivery, and refinement of manufacturing parameters. Together, these advances can shift the field from empirical formulation toward data-driven, mechanism-informed design.[200,201] Fourth, personalized approaches can leverage the dual role of EVs as liquid biopsy readouts and functional nanodelivery platforms. Stratifying individuals by UV sensitivity, inflammatory and oxidative stress status, and aging phenotype could enable matching to specific EV sources or engineered EV designs, together with optimized delivery routes. This framework supports precise, integrated prevention-to-repair interventions.[200,202,203] More importantly, future research should go beyond cataloging heterogeneity and define the functional roles of different EV subpopulations in photoaging models.[190] For example, distinct vesicle subsets may vary in their ability to suppress ROS accumulation, inhibit NF-κB-mediated inflammation, modulate melanogenesis, restore fibroblast collagen synthesis, or attenuate senescence-associated secretory phenotypes.[7] Comparative studies using fractionated or marker-enriched EV subpopulations in standardized UV-induced photoaging models would help clarify whether all vesicles contribute equally or whether only specific subsets drive therapeutic benefits.[204,205] This distinction is crucial for both mechanistic interpretation and translational development. These advances should, in turn, support more precise quality-control strategies. Instead of relying solely on total particle number, protein concentration, or a limited set of canonical markers, future quality control should integrate subpopulation-sensitive metrics, cargo-associated potency markers, functional release assays, and process-linked impurity profiles.[194,206,207] In the context of photoaging, such quality systems could include assay panels reflecting antioxidant capacity, anti-inflammatory activity, ECM-restorative potential, and the reproducibility of subtype composition across batches.[7,194] A quality-by-design framework built on these parameters would greatly improve batch consistency and translational reliability.

Overall, to advance the treatment of photoaging using extracellular vesicles, we believe future studies should ideally follow a staged pipeline: (1) identify bioactive EV subpopulations and causal cargo-pathway axes using single-vesicle and perturbation approaches; (2) establish standardized potency assays and subtype-sensitive quality benchmarks; (3) optimize delivery systems for dermal targeting, dosing control, and local retention; (4) validate safety, pharmacodynamics, and durability in clinically relevant animal models; and (5) advance to early-phase human studies with harmonized manufacturing processes and regulatory documentation. Such a roadmap would guide the field from exploratory proof-of-concept studies toward clinically meaningful translation.

Conclusion

This review systematically summarizes the multifaceted roles of exosomes in photoaging, covering their biogenesis, biological properties, and mechanistic involvement in ultraviolet (UV)-induced skin damage. The evidence indicates that exosomes play a significant role in key pathological processes of photoaging, such as oxidative stress, inflammatory signaling, DNA damage responses, extracellular matrix degradation, pigmentary dysregulation, and intercellular communication among cutaneous cell types. Depending on their cellular origin and molecular cargo, exosomes may either contribute to photoaging progression or promote tissue repair and regeneration, underscoring their dual and context-dependent roles in photodamaged skin. In recent years, significant research efforts have focused on enhancing the anti-photoaging efficacy of exosomes through various engineering strategies. For instance, exosomes engineered via gene editing or by preconditioning parent cells with specific drugs show enhanced anti-inflammatory and antioxidant properties. Additionally, integrating nanotechnology, particularly through engineered delivery systems, presents innovative solutions for improving exosome stability and enabling tissue-specific targeting. These advances reinforce the idea that exosomes are not only important mediators of photoaging-related cellular signaling but also promising therapeutic tools and delivery platforms for anti-photoaging interventions. However, as previously discussed, several important challenges remain that limit their clinical translation. These include the heterogeneity of exosome populations, lack of standardization in isolation and characterization methods, limited loading efficiency, targeting specificity, and variability in bioactivity due to donor cell source and culture conditions. Furthermore, unresolved issues regarding large-scale production, long-term safety, storage stability, and regulatory evaluation also hinder their clinical use. Despite these challenges, exosome-based strategies for photoaging hold considerable promise but remain in the developmental stage, requiring further optimization before they can be reliably translated into clinical and cosmetic applications.

As our understanding of the mechanisms of exosome action advances, exosomes are poised to become pivotal therapeutic agents for photoaging. Their application holds particular promise in the development of next-generation cosmeceuticals, pharmaceuticals, and skin-repair formulations. Overall, the findings of this review suggest that exosomes offer a valuable framework for understanding the pathogenesis of photoaging and represent a highly promising avenue for regenerative and anti-photoaging therapies. Future progress will depend on the integration of mechanistic discoveries with bioengineering innovations, translational validation, and regulatory standardization. Building on these achievements, exosomes have extensive potential in skin damage repair and photoaging interventions. Continued advancements in this field are expected to bridge biomedicine and cosmetology, leading to novel insights and platforms for treating a broader range of skin disorders.

Data Sharing Statement

No new data has been generated, all references are cited in the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, 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.

Funding

This study was sponsored by National Natural Science Foundation of China (No. 82504308), University-Level Natural Science Foundation General Project of Chengdu Medical College (2024CDYXY-01), Clinical Science Research Foundation of Chengdu Medical College & the First Affiliated Hospital of Chengdu Medical College (24LHLNYX1-08), Clinical Science Research Foundation of Chengdu Medical College & Nanbu People's Hospital (2024LHFBM1-04) and Clinical Science Research Foundation of Chengdu Medical College & Chengdu Pidu People's Hospital (2024LHFYSZ1-41).

Disclosure

The authors declare that there are no competing interests associated with this work.

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