

Mesenchymal Stem Cell-Derived Paracrine Products as Senotherapeutic Interventions for Skin Photoageing: A Systematic Review of the Senescence-SASP Axis

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ABSTRACT

Chronic ultraviolet (UV) exposure induces oxidative stress, mitochondrial dysfunction, DNA damage and cell-cycle arrest through p53/p21^{CIP1} and p16^{INK4a} pathways, leading to cellular senescence and the senescence-associated secretory phenotype (SASP). SASP-mediated inflammation and matrix degradation contribute to progressive photoageing. MSC-derived secretome represents a potential cell-free senotherapeutic strategy targeting this axis. To synthesise evidence on how MSC-derived secretome, conditioned medium and extracellular vesicles (EVs) modulate the senescence-SASP axis in UV-induced skin photoageing and assess its translational potential. Following PRISMA 2020, PubMed, Scopus and Web of Science were used to search original studies published between January 2021-July 2026 using terms related to skin photoageing, MSC secretome, conditioned medium, EVs/exosomes, cellular senescence, SASP and senotherapeutics. Eligible studies used MSC-derived secretome, conditioned medium, or EVs in UVA-, UVB-, or combined UVA/UVB-induced cutaneous photoageing models and reported senescence biomarkers, SASP mediators, or mechanistically implicated pathways. Of 211 records identified, 149 were screened after duplicate removal and 15 underwent full-text assessment, yielding eight studies for qualitative synthesis. All eight studies were preclinical, using in vitro and/or in vivo UVA/UVB models. MSC sources included umbilical cord, adipose tissue and hair follicle, with two studies using hypoxia- or three-dimensionally preconditioned adipose MSCs; two studies used engineered cargo (miR-125b-5p; circ_0011129). Secretome/EV treatment consistently attenuated senescence markers, oxidative stress and DNA damage while preserving collagen and elastin. Mechanisms involved PINK1/Parkin-mediated mitophagy, GATA2/PZP/GRP75, TIMP1-ADAM10-Notch1-HES1 and TGF- β 1/Smad signalling. Canonical SASP mediators were assessed in only four studies. Delivery route influenced efficacy, with subcutaneous and microneedle-assisted delivery showing dermal effects. Preclinical evidence supports MSC secretome/EV-mediated attenuation of UV-induced cellular senescence and upstream oxidative, mitochondrial and DNA damage pathways, converging on p16/p21/p53 signalling. Direct evidence for SASP suppression remains limited, and no included study examined paracrine senescence transmission. Effects are best characterised as senomorphic and predominantly senopreventive rather than senolytic. Clinical studies of MSC-derived products for photoageing exist



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outside the eligible mechanistic evidence base; however, no eligible interventional clinical study assessed senescence- or SASP-specific endpoints. Standardised senescence/SASP endpoints, human and immunocompetent models and long-term safety assessment are needed for translation.

INTRODUCTION

Skin photoageing is a complex process with continuous ultraviolet (UV) radiation as the primary cause, clinically characterised by wrinkles, loss of suppleness, dyspigmentation, and reduced skin integrity. Oxidative stress, inflammation and extracellular matrix (ECM) disintegration have long been known as hallmarks of photoageing. However, there is increasing evidence that they converge into a similar biological mechanism, namely cellular senescence. Chronic UV exposure results in overproduction of reactive oxygen species (ROS) that cause oxidative DNA damage, mitochondrial malfunction and persistent activation of DNA damage response (DDR). These events trigger irreversible cell-cycle arrest through p53/p21 and p16INK4a pathways, resulting in the accumulation of senescent dermal fibroblasts and keratinocytes (Lohakul, J et al, 2022; Guo, K et al, 2022; Miwa S et al, 2022).

Rather than being biologically dormant, senescent cells have a senescence-associated secretory phenotype (SASP), which is typified by the constant release of pro-inflammatory cytokines, chemokines, growth factors and matrix metalloproteinases (MMPs). Although MMPs are frequently included within the broader SASP repertoire, this review operationally analysed them separately as matrix-degrading outcome. The SASP establishes a chronic inflammatory microenvironment to strengthen oxidative stress, spread secondary senescence in neighbouring cells and promote extracellular matrix degradation, generating a self-perpetuating feed-forward cycle that drives progressive skin photoageing (Chin, T et al, 2023; Konstantinou, E et al, 2024.; Nan, L et al, 2025). Consequently, the senescence-SASP axis has emerged as a central therapeutic target because interrupting this pathological cascade may simultaneously attenuate multiple downstream mechanisms of photoageing rather than addressing individual manifestations independently.

Recent breakthroughs in regenerative medicine have turned treatment methods from traditional cell-based transplantation to cell-free techniques particularly those with mesenchymal stem cell (MSC)-derived paracrine products. These products are composed of a heterogeneous repertoire of bioactive mediators released by MSCs, including soluble substances found in conditioned medium (CM), extracellular vesicles (EVs) and exosomes that account for the paracrine effects typically attributed to transplanted MSCs. MSCs-derived paracrine products can deliver bioactive proteins, lipids, nucleic acids and other signalling molecules without the administration of viable cells, and may therefore have advantages over whole-cell therapy in terms of decreased concerns over cell survival, immune compatibility, uncontrolled differentiation and tumorigenicity (Kumar MA et al, 2024). Emerging research further reveals that biological impacts of these MSC-derived products extend beyond tissue repair and regeneration to modulate fundamental pathways driving cellular ageing.

The paracrine products obtained from MSCs may realise senotherapeutic effects via influencing numerous factors of senescence-senescence-associated secretory phenotype (SASP) axis instead of the traditional regenerative techniques focusing on the elimination or repair of injured tissue. MSC-derived conditioned media, EVs and exosomes have been reported to reduce senescence-associated markers and attenuate SASP-related signalling pathways thru the coordinated regulation of oxidative stress, mitochondrial dysfunction, intracellular senescence signalling, inflammatory mediators and extracellular matrix homeostasis. These effects may interfere with the molecular mechanisms that regulate cellular senescence and the associated chronic inflammatory and tissue remodelling responses

seen in photoaged skin (Konstantinou, E et al, 2024; Zhang T et al., 2025; Nan, Let al., 2025).

Thus, the present systematic review aims to mechanistically analyse the existing information regarding the methods by which MSC-derived paracrine products, such as conditioned media, extracellular vesicles, and exosomes, affect the senescence-SASP axis in UV-induced skin photoageing. This review particularly emphasises their effects on cellular senescence, SASP-related signalling, oxidative and mitochondrial dysfunction, inflammatory pathways, and extracellular matrix remodelling. It also evaluates the translational potential of these cell-free approaches in the development of future therapeutic approaches to treat skin photoageing.

METHOD

Identification of relevant literature

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The review protocol was not prospectively registered. The literature search was conducted on PubMed, Scopus, and Web of Science. We used these three databases to systematically search for eligible studies published between January 2021 and July 2026. The search was run on 30 July 2026, and the search strategy combined three concept blocks using database-specific boolean operators and truncation: skin photoageing and ultraviolet exposure; mesenchymal stem cells; and secretome, conditioned medium, or extracellular vesicles/exosomes. This broad retrieval strategy was designed to maximise sensitivity; eligibility criteria relating to cellular senescence and the senescence-associated secretory phenotype (SASP) were applied at the title, abstract, and full-text screening stages rather than embedded in the search string, consistent with a broad-search, narrow-screening approach. The strings used on PubMed were (photoageing OR "skin photoageing" OR UVB OR ultraviolet) AND ("mesenchymal stem cell" OR MSC) AND (secretome OR "conditioned medium" OR exosome* OR "extracellular vesicle*" OR EV*) with filters English; 2021–2026; applied via interface. The strings used on Scopus were ((photoageing OR "skin photoageing" OR "skin ageing" OR rejuvenation OR "facial skin ageing") AND ("mesenchymal stem cell" OR MSC OR ADSC OR "adipose-derived stem cell" OR hUC-MSC OR "umbilical cord mesenchymal stem cell") AND (secretome OR "conditioned medium" OR exosome* OR "extracellular vesicle*")) AND (LIMIT-TO(DOCTYPE,"ar")) AND (LIMIT-TO (LANGUAGE,"English")) AND PUBYEAR > 2020 AND PUBYEAR < 2027 with filters Articles only; English; 2021–2026 (in-string). The strings used on Web of Science were TS=(photoageing OR "skin photoageing" OR UVB OR ultraviolet) AND TS=("mesenchymal stem cell" OR MSC) AND TS=(secretome OR "conditioned medium" OR exosome* OR "extracellular vesicle*" OR EV*) with filters english; 2021–2026; applied via interface.

Eligible study designs included in vitro, ex vivo, animal, and human interventional or observational studies meeting the predefined mechanistic eligibility criteria. Titles, abstracts, and subsequently full-text articles were independently screened according to the predefined eligibility criteria. Any disagreement regarding study selection was resolved through discussion until consensus was reached among the reviewers.

Eligibility Criteria

Inclusion criteria were original research articles published in English between January 2021 and July 2026. We included studies that evaluated mesenchymal stem cell (MSC)-derived secretome, conditioned medium (CM), extracellular vesicles (EVs), or exosomes

from any MSC source in experimental models of UVA-, UVB-, or combined UVA/UVB-induced skin photoageing, which reported senescence biomarkers, SASP mediators, or mechanistically implicated pathways. Eligible studies were required to assess cellular senescence, canonical senescence-associated secretory phenotype (SASP), or mechanistic pathways directly involved in senescence regulation in skin photoageing. Senescence-related outcomes included established senescence biomarkers (e.g., SA- β -gal, p16^{INK4a}, p21, and p53), canonical SASP mediators, or signalling pathways mechanistically linked to senescence.

For the purposes of this review, canonical SASP was operationally defined as secreted pro-inflammatory cytokines and chemokines quantified at the protein or transcript level, including, where reported, IL-6, IL-8, IL-1 β , and TNF- α . Matrix metalloproteinases (MMPs) were classified separately as the matrix-degrading arm of the photoageing response and were not counted as canonical SASP outcomes, although their regulation was considered in relation to extracellular matrix remodelling and senescence-associated tissue damage. Relevant senescence-associated signalling pathways included NF- κ B, TGF- β /Smad, SIRT1, Nrf2, PINK1/Parkin, and TIMP1/Notch1. Studies reporting SASP mediators without senescence markers were eligible under the SASP arm.

Studies were excluded if they were reviews, editorials, conference abstracts, preprints, letters, case reports, or duplicates. Studies assessing whole-cell MSC transplantation without a secretome or EV component, non-MSC-derived conditioned media or extracellular vesicles, or non-cutaneous models were also excluded. Additionally, studies focused solely on cosmetic or regenerative outcomes, such as wrinkle reduction, collagen synthesis, antioxidant effects, or delivery technologies, without assessment of cellular senescence, canonical SASP, or mechanistically relevant senescence pathways were excluded. Studies that were not available as full text after reasonable attempts to retrieve the article were excluded from the qualitative synthesis.

Assessment of Risk of Bias

Risk of bias in the six studies incorporating an *in vivo* component (Cui H et al., 2025; Zhang H et al., 2024; Huynh CB et al., 2025; Wang Y et al., 2025; Sun Z et al., 2024; Sun Z et al., 2025) was assessed using SYRCLE's risk of bias tool for animal intervention studies (Hooijmans et al., 2014). The tool comprises ten domains (D1–D10): D1 sequence generation (selection); D2 baseline characteristics (selection); D3 allocation concealment (selection); D4 random housing (performance); D5 blinding of caregivers/investigators (performance); D6 random outcome assessment (detection); D7 blinding of outcome assessor (detection); D8 incomplete outcome data (attrition); D9 selective outcome reporting (reporting); and D10 other sources of bias.

A 10-item bespoke checklist was used to assess the methodological quality of the *in vitro* components, adapted from established reliability assessment approaches. The checklist focused on key domains such as cell model, characterisation of MSC products, experimental controls, blinding, and outcome reporting. ToxRTool (Schneider et al., 2009) was not used directly because it was developed primarily for toxicological studies and does not comprehensively address several study-specific features relevant to this review, including MSC product characterisation and UV-induced photoageing models. Each item was scored as 0 (not addressed), 0.5 (partially addressed), or 1 (fully addressed), with a maximum score of 10. Predefined descriptive categories were ≥ 8 , high; 6.5–7.9, moderate-high; 5–6.4, moderate; and < 5 , low methodological quality. These categories were used for descriptive comparison and were not considered validated thresholds of study quality. Risk of bias was assessed independently by two reviewers, with disagreements resolved by discussion until consensus was reached.

Data Extraction and Synthesis

Data were extracted independently by two reviewers using a standardised extraction form capturing study identification, MSC source and product type (secretome, conditioned medium, extracellular vesicles or engineered cargo), model system and UV induction protocol, delivery route and dose, senescence biomarkers, canonical SASP mediators, matrix and phenotypic endpoints, and reported mechanistic pathways. Discrepancies were resolved by discussion until consensus was reached. Given substantial heterogeneity in cell and animal models, irradiation spectra and dosing, product characterisation and outcome reporting units, quantitative meta-analysis was not appropriate. Findings were therefore synthesised narratively and organised according to the tier of the senescence–SASP axis at which the intervention acted: upstream oxidative and mitochondrial homeostasis, cell-cycle arrest, secretory output, and matrix and phenotypic outcomes. Endpoint coverage across included studies was tabulated to identify systematic gaps in the evidence base (Table 4).

RESULTS AND DISCUSSION

Study Selection

A systematic search of PubMed ($n = 79$), Scopus ($n = 88$), and Web of Science ($n = 44$) identified a total of 211 records published between 2021 and 2026. After removal of 62 duplicate records, 149 records underwent title and abstract screening, of which 127 were excluded for not meeting the predefined eligibility criteria. Twenty-two reports were sought for retrieval, of which seven could not be obtained, leaving 15 full-text articles for eligibility assessment. Following full-text evaluation, seven studies were excluded: five for the absence of senescence-SASP-related outcomes and two for ineligible interventions. Ultimately, eight preclinical studies met the eligibility criteria and were included in the qualitative synthesis. No additional records were identified through websites, organisations, or citation searching. The study selection process is summarised in the PRISMA flow diagram (Figure 1).

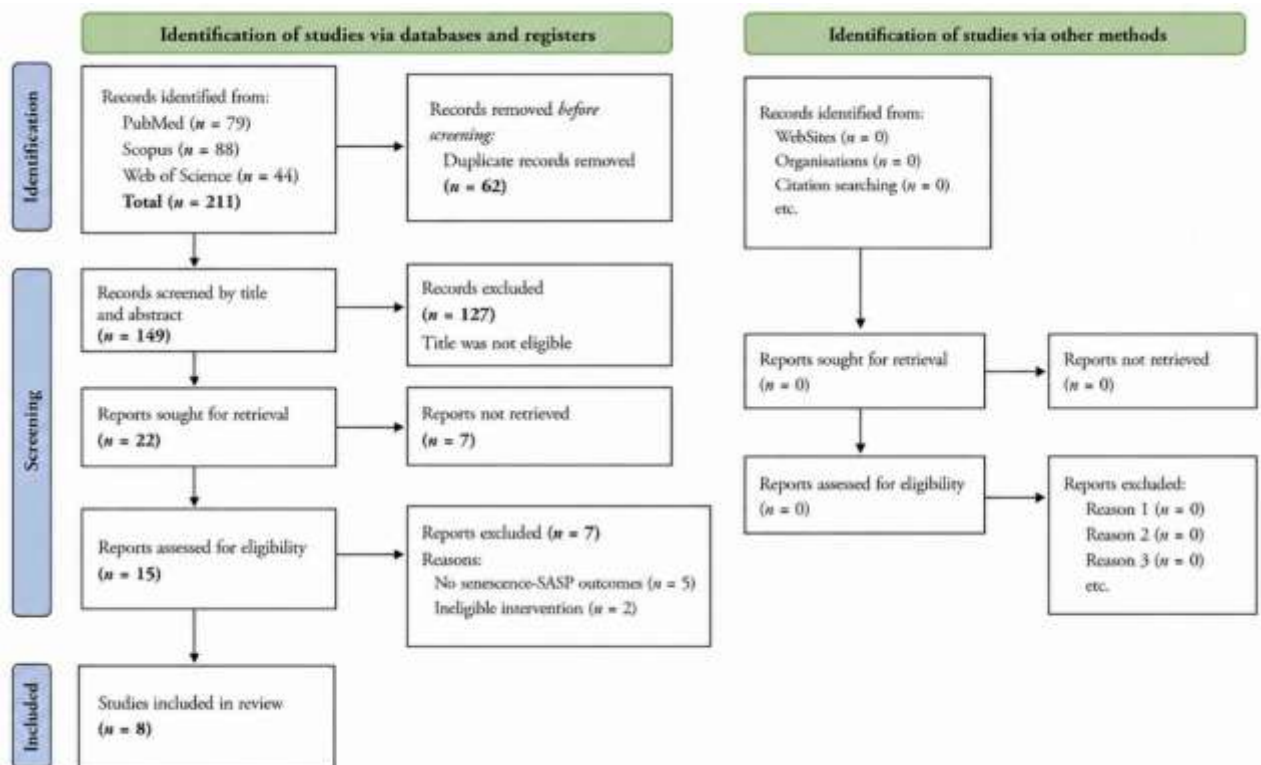


Figure 1 PRISMA flowchart

Study Characteristics

All eight included investigations were preclinical. Six incorporated both in vitro and in vivo components; two (Zou X et al., 2022; Zhang Y et al., 2025) employed exclusively in vitro designs. In vitro models included human dermal fibroblasts (HDF), HaCaT keratinocytes, primary human keratinocytes or reconstructed full-thickness skin equivalents (T-Skin) and were exposed to UVA, UVB or combination UVA/UVB irradiation at doses ranging from 20 mJ/cm² to 1170 mJ/cm² depending on the methodology and cell type. Six studies included an in vivo component using nude mice (Cui H et al., 2025; Zhang H et al., 2024; Wang Y et al., 2025; Sun Z et al., 2024), BALB/c mice (Huynh CB et al., 2025), or immunocompetent ICR mice (Sun Z et al., 2025). UV protocols ranged from fixed-dose alternate-day exposure to minimal erythema dose (MED)-escalating regimens over 4–12 weeks. Another study (Sun Z et al., 2024) also mechanistically analysed human tissue comparing PZP expression in specimens of actinic keratosis and squamous cell cancer.

MSC-derived material was obtained from umbilical cord (Sun Z et al., 2024, 2025; Zou X et al., 2022), adipose tissue (Zhang H et al., 2024; Huynh CB et al., 2025; Wang Y et al., 2025; Zhang Y et al., 2025), and hair follicle (Cui H et al., 2025) and administered as extracellular vesicles/exosomes, conditioned medium, or engineered cargo-loaded exosomes (miR-125b-5p in Cui H et al., 2025; circ_0011129 in Zhang Y et al., 2025). The delivery route varied between studies and was tested in three studies as a within-study comparison: topical vs subcutaneous injection (Cui H et al., 2025); microneedle roller vs intradermal injection (Sun Z et al., 2024); and topical application with occlusion vs untreated control (Huynh CB et al., 2025). Other research utilised direct addition to culture medium (Zou X et al., 2022) or only subcutaneous injection (Zhang H et al., 2024; Wang Y et al., 2025). Outcome measures across the eight studies encompassed senescence markers (SA- β -gal, p16, p21, p53), DNA damage response markers (γ -H2AX, p-ATM, 53BP1), oxidative stress and mitochondrial indices (ROS, mtDNA deletion, PINK1/Parkin pathway components), SASP mediators (IL-6, IL-8/CXCL8, IL-1 β , TNF- α), matrix components (collagen I/III, elastin, MMP-1/2/3), and phenotypic endpoints (wrinkle severity, dermal thickness, transepidermal water loss, hydration). Only one study measured across all six domains (Zhang H et al., 2024).

Table 1. Comparative summary of preclinical studies of the MSC secretome/EVs/ CM in photoageing and skin senescence (2021–2026).

Study	Source	Model (Inducer)	Delivery Route	Key Molecular Effects	Phenotypic Outcome
Cui H et al., 2025	Hair follicle MSC exosome (miR-125b-5p)	HDF + female nude mice, UVB (in vitro: 20 mJ/cm ² ; in vivo: 150 mJ/cm ² every other day $\times$ 8 wk, followed by 2 wk treatment)	In vitro: 10/20 μ g/mL. In vivo: 20 μ g/100 μ L every other day $\times$ 2 wk; topical vs. S.C. injection	$\downarrow$ SA- β -gal (dose-dependent); $\uparrow$ proliferation and migration; $\downarrow$ ROS; $\uparrow$ Nrf2; $\uparrow$ COL-1/COL-3; $\downarrow$ MMP-1; $\uparrow$ TGF- β 1 and $\uparrow$ p-Smad2/3. Luciferase assay confirmed that miR-125b-5p represses the TGF- β 1 3'UTR, although the increased TGF- β 1 direction remains unresolved. Serum IL-4/IL-6/IL-10 normalised in the S.C. arm. No CDKI (p16/p21/p53) or in vivo senescence marker was measured.	$\downarrow$ WSRs; $\uparrow$ dermal thickness; $\uparrow$ collagen volume fraction in the S.C. injection group only. Topical administration was ineffective. $\uparrow$ CD31.
Zhang H et al.	AD-MSC-EV & UC-	HaCaT/HKC/HDF/T-Skin +	In vitro: 200 ng/ μ L $\times$ 24	$\downarrow$ ROS; $\downarrow$ DNA damage; $\downarrow$ inflammation; $\downarrow$ Notch1 $\rightarrow$ $\downarrow$	$\uparrow$ hydration ($\downarrow$ TEWL); $\downarrow$

al., 2024	MSC-EV (TIMP1)	nude mice; UVB (in vitro: 60 mJ/cm ² /day × 3 d; T-Skin: 180 mJ/cm ² /day × 3 d; in vivo: 1→4 MED escalation, ~80 MED total over 8 wk)	h. T-Skin: topical to medium × 72 h. In vivo: subcutaneous injection at 10 dorsal sites, 200 µg/mouse, for 4 wk	p16/p21/p53; ↑ ECM	wrinkles; ↓ epidermal thickening; ↑ dermal thickness. HUMSC-EV > AMSC-EV in vivo.
Zhang Y et al., 2025	3D-cultured hADSC- derived exosomes loaded with circ_001112 9 (3D-circ- Exo)	Human dermal fibroblasts; chronic UVA irradiation (5 J/cm ² /day × 7 d)	Direct in vitro exosome treatment, 50 µg/mL, 24 h pre- treatment	↓ SA-β-gal, p53, p21, p16; ↑ collagen I and elastin; enhanced circ_0011129 delivery	Superior to unmodified exosomes; reduced cellular senescence and ECM degradation/phot oageing.
Huynh CB et al., 2025	HypADSC- Exo 1% O ₂ × 24 h; ultracentrifugation; 102.3 ± 35.4 nm; CD9/CD63/ CD81 ⁺ ; TEM cup- shaped, NTA + Bradford	UV-senescent HDF (UVB 1170 + UVA 720 mJ/cm ²) + photoaged BALB/c mice (UVA 51.8 J/cm ² + UVB 5.53 J/cm ² , 12 wk)	In vitro: 10 µg/mL. In vivo: topical 50 and 100 µg/mL, 2×/wk × 6 wk, with occlusion + massage	↓ SA-β-gal; ↓ p16; ↓ p21 (qPCR); ↑ proliferation (Alamar Blue); ↓ cell size; slight ↑ collagen I/III; ↓ MMP-1/-2/-3	↓ wrinkles; ↓ epidermal and dermal thickness; ↑ hydration; ↑ elasticity; ↑ collagen density; comparable to tretinoin without irritation.
Zou X et al., 2022	hUC-MSC- conditioned medium (crude CM)	Serum-starved HaCaT cells + UVB (20 mJ/cm ²)	Direct addition to culture medium	↓ SASP/IL-8, ROS, and p53; modulation of C-FOS/C- JUN, TGF-β, FGF-1, and cyclin A2. CDKN1A (p21) was downregulated after UVB	↓ apoptosis/G1 arrest; ↑ proliferation and motility; recovery of cell morphology.
Wang Y et al., 2025	Human adipose- derived stem cell exosomes (hADSC- Exos)	HDF (UVB 120 mJ/cm ² , 302 nm) + nude mice (n=4/group), UVB 100 mJ/cm ² , 3×/wk × 4 wk	In vitro: 100 µg/mL. In vivo: S.C. injection, 2 doses only (day 0 and day 14)	↑ PINK1/Parkin; ↑ LC3B- II/I; ↓ p62; ↓ TOM20; ↓ ROS; ↓ mtDNA 4,977-bp common deletion; ↓ SA-β- gal; ↓ p21 and p53	↓ epidermal thickening; ↑ collagen density; ↑ HDF motility.
Sun Z et al., 2024	hucMSC- sEVs (104.8 nm)	Neonatal SD rat dermal fibroblasts (xenogeneic pairing), UVA 5 J/cm ² × 5; BALB/c nude mice (n=6/group), UVA+UVB, 1 MED escalating, 7 or 10 rounds	In vitro: 1×10 ¹⁰ /mL, 24 h pre- treatment. In vivo: microneedle roller, 5×10 ¹⁰ particles; superior to intradermal injection based on imaging + IF	↑ PZP → ↓ MMP-1 (direct binding, CoIP + colocalisation); ↑ COL1A1; ↑ SIRT3; ↓ ROS; ↓ SA-β- gal; ↓ p-ATM/γ- H2AX/53BP1. PZP OE/si rescue. Comparators: 0.05% retinoic acid (positive control) and NMN ± sEVs	↓ desquamation/wri nkling; ↑ collagen volume fraction; preserved dermal thickness; outperformed retinoic acid.

			distribution		
Sun Z et al., 2025	Human umbilical cord MSC-derived small extracellular vesicles (hucMSC-sEVs)	Rat dermal fibroblasts (UVA 365 nm / UVB 311 nm) + ICR immunocompetent mice, UVA+UVB, 1 MED + 0.5 MED/cycle × 4 cycles	In vitro: 1×10 ¹⁰ particles/mL . In vivo: microneedle roller	GATA2 → binds PZP promoter (ChIP + dual-luciferase) → ↑ PZP → ↓ GRP75 → ↓ mitochondrial Ca ²⁺ overload and ↓ mtROS; ↓ SA-β-gal, ↓ p53, ↓ γ-H2AX; ↑ COL1A1; ↓ IL-6 mRNA. si-GATA2/oc-GATA2 sEVs + MKT-077 (GRP75 inhibitor) phenocopied the effects	↓ wrinkles; ↓ stratum corneum thickening; ↑ collagen density.

Risk of Bias Assessment Results

Risk of bias across the six in vivo studies was predominantly unclear rather than demonstrably low, driven by under-reporting rather than by documented methodological failure. All six declared randomised allocation, but only one: (Wang Y et al, 2025) specified the sequence-generation method or described any concealment procedure. No study reported randomised housing, blinding of animal caregivers, randomised outcome assessment, or blinded outcome assessment; all four of these domains were therefore rated unclear in every study. The principal identifiable high-risk domains were baseline comparability, where (Huynh CB et al, 2025) compared UV-exposed 6-8-week-old mice against an 18-20-week-old control cohort, and incomplete outcome data, where three studies (Sun Z et al, 2024; Huynh CB et al, 2025; Cui H et al, 2025) analysed substantially fewer animals than were allocated without explanation, or did not fix group size a priori. (Wang Y et al, 2025) was the only study to satisfy the selection-bias domains and to state explicitly that no animals or experimental units were excluded. The results of the risk-of-bias assessment are presented in Table 2, where L indicates low risk, H high risk, and U unclear risk due to insufficient reporting. (Huynh CB et al, 2025) compared UV-exposed 6-8 week-old mice against an 18-20-week-old control cohort, with the ten-week age differential introducing baseline physiological variation independent of UV exposure. (Cui H et al, 2025) did not measure senescence markers in the in vivo photoageing model, restricting senescence assessment to in vitro fibroblasts and inferring in vivo senescence suppression from serum cytokine normalisation alone.

Table 2. SYRCLE Risk of Bias Assessment Results across six In-vivo Studies

Study (year)	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Sun Z, 2024	U	L	U	U	U	U	U	H	U	H
Sun Z, 2025	U	U	U	U	U	U	U	U	U	L
Huynh CB, 2025	U	H	U	U	U	U	U	H	U	H
Wang Y, 2025	L	L	L	U	U	U	U	L	U	L
Zhang H, 2024	U	U	U	U	U	U	U	U	U	U
Cui H, 2025	U	L	U	U	U	U	U	H	U	H

The methodological quality of the in-vitro experiments was evaluated using a predefined 10-item checklist. Each item was scored as 1 (adequately addressed), 0.5 (partially addressed) or 0 (not addressed). The study comprised selection of the cell model, characterisation of the UV model, treatment concentration, control design, reference comparators, breadth of senescence markers, mechanistic investigation, characterisation of the MSC-derived product, biological replication and statistical technique. Higher scores denoted more complete reporting and design. (Zou X et al, 2022) received a score of 6.5/10, suggesting that cell selection, UV exposure, controls, mechanistic analyses, replication and

statistical methods were adequately reported, but dose-response assessment, reference controls, breadth of senescence markers and MSC-derived product characterisation were not. (Zhang Y et al, 2025) 7.0/10 with its strengths being in cell/model characterisation, control design, senescence-marker evaluation, replication, statistical reporting, but with certain limitations, such as limited concentration testing, weak mechanistic characterisation, and insufficient EV characterisation.

Table 3. Bespoke methodological quality checklist for the in vitro components of included studies

#	Item	Zuo X 2022	Zhang Y 2025	San Z 2024	San Z 2025	Heynck CB 2025	Wang Y 2025	Zhang H 2024	Cui H 2025
1	Cell source/line stated & appropriate	1 = HsCat + hUC-MSC (Procell), characterised lines	1 = primary HDF + hADSC; flow (CD90 CD105+) + vi-lineage	1 = rat DFs + hucMSC; flow (CD19 CD44 CD166+) lineage	1 = rat DFs + hucMSC; flow + vi-lineage	1 = HDF (CD90+ Viacount S100A4+) + hADSC	1 = HDF + hADSC (Immunocell); CD9+ CD63+	1 = HDF (ATCC), HsCat, HKSC; marker+verified	1 = HDF/HUVEC (STR) + hFATSC (flow, vi-lineage)
2	UV dose/metry fully reported	1 = UVB, 500 mW/cm ² , 20 mJ/cm ²	1 = 365 nm UV-A, 2.78 mW/cm ² , 5 J/cm ² * 7	1 = 365 nm UV-A, 5 cm, 5 J/cm ² * 5, radiometer	0.5 = UV-A UVB, radiometer, but dose not quantified	1 = UVB 1170 + UV-A 720 mJ/cm ² , two meters	1 = UVB 120 mJ/cm ² @302 nm, 330 s	1 = UVB 60 mJ/cm ² /day * 3, sublethal defined	0.5 = UVB 20 mJ/cm ² ; device wavelength unclear
3	Concentration range (dose-response)	0 = single CNF volume, no titration	0 = single 30 µg/mL, no titration	0.5 = SEV single dose; NNEN titrated	0.5 = SEV single 1.10 ⁻⁶ mL	0 = single 10 µg/mL	0.5 = single 100 µg/mL (BCA-based)	1 = TNFα gradient (2.5-10 ng/mL)	1 = two doses (10 & 20 µg/mL)
4	Negative vehicle control	1 = Cui (UVB-)	1 = light-shielded NC	1 = untreated Cui DFs	1 = CTR group	1 = Normal + UV+PBS	1 = hENC + UVB+hENC	1 = Control + UVB	1 = Control + UVB
5	Positive/reference comparator	0 = none	0.5 = internal 3D-Exo only; no external agent	1 = NNEN comparator	1 = NECT-077 (GPR15 inhibitor)	0 = none in vitro	0 = none (hPINK1 is mechanistic)	1 = TNFα, G134033X, VPA	0 = none (intrinsic OE mechanistic)
6	Multiple si/knockout markers	0.5 = p53, p21 only	1 = SA-β-gal, p53, p21, p16	1 = SA-β-gal, p53, p21, p16	0.5 = SA-β-gal, p53 (γ-H2AX)	1 = SA-β-gal, p16, p21	0.5 = SA-β-gal, p21, p53; no p16	1 = SA-β-gal, p16, LAMBL, γ-H2AX, p21, p53	0 = SA-β-gal only (COLA/NADP+ ECN)
7	Mechanistic readout beyond phenotype	1 = transgenic-proteomic; QO/KEO, qPCR-VB	0.5 = circRNA validated; splicing checked, not re-based	1 = RNA-seq, WB, psp, siOE, CoIP	1 = CoIP, luciferase, CoIP, docking, siOE	0.5 = qPCR, p16 p21 only	1 = WB, PINK1, parkin, LC3B, TEM, apoptosis rescue	1 = pro-mitotic-RNA-seq, luciferase, siRNA, rescue	1 = luciferase, miR-1, TOF-p1 OE, WB Smad3
8	EV/CNF characterisation	0 = crude CNF; none reported	0 = LC only; no NTA/TEM marker	1 = NTA, TEM, WB 5 markers, neg Calcein	1 = TEM, NTA, zeta, WB 4 markers, neg Calcein	1 = TEM, NTA, flow CD9+CD63+CD81	0.5 = TEM, NTA, WB CD9+CD63 only; no neg marker	1 = TEM, NTA, WB 4 markers, ExoView, neg Calcein	1 = TEM, Nanosight, WB CD9+CD63+CD81, neg Calcein
9	Replicate number (n) stated	1 = n = 3 throughout	1 = n = 3	1 = n = 3	1 = n = 3	0.5 = n = 2-3, inconsistent	1 = n = 3	1 = n = 3	1 = n ≥ 3

Scoring: each item scored 0 (not addressed), 0.5 (partially addressed), or 1 (fully addressed); maximum 10. Ratings: ≥8 high, 6.5-7.9 moderate-high, 5-6.4 moderate, <5 low methodological quality. These cut-points were predefined for descriptive comparison within this review and should not be interpreted as validated thresholds of study quality.

Abbreviations: CNF, conditioned medium; GSK, animal growth medium; DF, dermal fibroblast; EV, extracellular vesicle; hDF, human dermal fibroblast; HUVEC, human umbilical vein endothelial cell; hFATSC, human fat adipose mesenchymal stem cell; hADSC, human adipose-derived stem cell; hUC-MSC/huMSC, human umbilical cord mesenchymal stem cell; NTA, nanoparticle tracking analysis; TEM, transmission electron microscopy; UV, ultraviolet; vehicle, OE, overexpression.

Table 4. Endpoint coverage matrix across the eight included studies

Study	SA- β -gal	p16	p21	p53	γ H2AX/DDR	Lamin B1	IL-6	IL-8/CXCL8	IL-1 β	TNF- α	MMPs	Collagen I/III	Elastin	Group (n)
Cui H., 2025	✓	-	-	-	-	-	✓	-	-	-	✓ (MMP 1 only)	✓	-	≥5/group
Zhang H., 2024	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	5-6/group
Zhang Y., 2025	✓	✓	✓	✓	-	-	-	-	-	-	-	✓	✓	N/A
Huynh CB., 2025	✓	✓	✓	-	-	-	-	-	-	-	✓	✓	-	10/group
Zou X., 2022	-	-	transcriptomic	✓	-	✓	✓	✓	✓ (IL-1 α)	✓	✓	-	-	N/A
Wang Y., 2025	✓	-	✓	✓	-	-	-	-	-	-	-	✓	-	4/group
Sun Z., 2024	✓	✓	✓	✓	✓	-	-	-	-	-	✓ (MMP 1 only)	✓ (COL1A 1 only)	-	6/group
Sun Z., 2025	✓	-	-	✓	✓	-	✓	-	-	-	-	✓ (COL1A 1 only)	-	6/group
Total (/8)	7	4	5	6	3	2	4	2	1	2	5	7	2	-

✓ = reported; - = not reported; N/A = not available; Group (n) = number of animals/replicates per experimental group.

Photoageing can be understood as a linear cascade in which an initial photochemical injury is progressively converted into a self-sustaining tissue pathology (Figure 2). Ultraviolet radiation damages nuclear and mitochondrial DNA both directly and through the generation of reactive oxygen species (ROS), with UVB acting predominantly on the epidermis and UVA penetrating to the dermal fibroblast compartment (Fitsiou E et al, 2021; Franco AC et al, 2022). Mitochondrial DNA is particularly vulnerable, lying adjacent to the electron transport chain and possessing limited repair capacity; the resulting respiratory impairment generates further ROS, establishing a self-amplifying loop now regarded as a central driver of ageing rather than a consequence of it (Miwa S et al, 2022).

Persistent DNA damage activates the DNA damage response, with ATM phosphorylation, γ -H2AX foci formation and p53 stabilisation. Where damage exceeds repair capacity, the transient cell-cycle pause becomes permanent: p53 induces p21^{CIP1}, p16^{INK4a} is engaged independently, and the cell enters senescence, viable and metabolically active but irreversibly arrested, with morphological enlargement, elevated senescence-associated β -galactosidase activity and loss of Lamin B1 (Huang W et al, 2022). Current consensus holds that no single marker defines this state and that senescence must be identified by a combination of features (Gorgoulis V et al, 2019).

The pathological weight of the axis lies in what follows. Senescent cells initiate the senescence-associated secretory phenotype (SASP), secreting interleukin-1 β , IL-6, IL-8, TNF- α and matrix metalloproteinases (MMPs) (Fitsiou E et al, 2021; Cuollo L et al, 2020). This converts an arrested cell into an active source of tissue injury through two routes. First, secreted MMPs degrade collagen and elastin faster than the remaining functional fibroblasts can replace them. Second, SASP cytokines induce senescence in neighbouring healthy cells, paracrine or bystander senescence, allowing a limited number of primary senescent cells to

seed a substantially larger population (Admasu TD et al, 2021). The cumulative effect of chronic matrix catabolism is the clinical and histological phenotype of photoaged skin: wrinkling, laxity, xerosis and disorganised, fragmented dermal collagen (Franco AC et al, 2022).

This cascade identifies three distinct points of intervention: upstream protection of mitochondrial and redox homeostasis; interruption of entry into arrest; and suppression of secretory output from cells already arrested. Agents acting through the third mechanism are termed senomorphics, and are conceptually distinct from senolytics, which eliminate senescent cells (Takaya K et al, 2023). The mesenchymal stem cell (MSC) secretome is of interest in this context because extracellular vesicles (EVs) deliver proteins, microRNAs, circular RNAs and lipids simultaneously, and may therefore engage several tiers of the cascade concurrently (Kumar MA et al, 2024; Hajialiasgary Najafabadi A et al, 2024). This review examined the extent to which that expectation is supported by the available preclinical evidence.

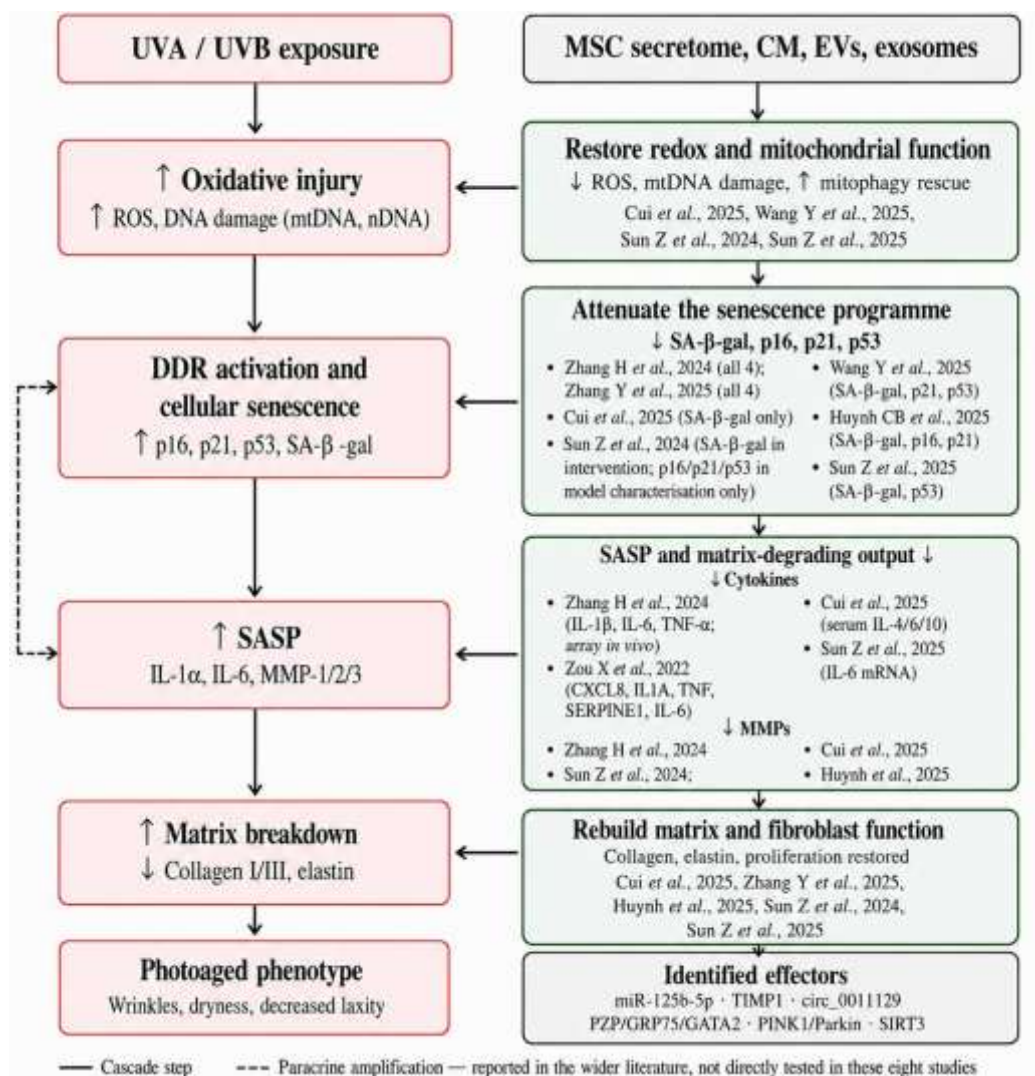


Figure 2 The Senescence-SASP Axis and Sites of Action of MSC Secretome/CM/EVs/exosomes

Evidence for intervention at the upstream tier

Four included studies addressed this tier, two establishing causality and two providing supporting observations. Together they position mitochondrial quality control as a mediator of secretome activity rather than a correlate. (Wang Y et al, 2025) demonstrated that adipose MSC-derived exosomes restore PINK1/Parkin-mediated mitophagy in UVB-exposed human dermal fibroblasts, raising PINK1, Parkin and the LC3B-II/I ratio while lowering p62 and TOM20, with a corresponding reduction in the 4,977-base-pair mitochondrial common deletion, an established index of accumulated mitochondrial damage. Silencing PINK1 by siRNA abolished the reduction in ROS, mtDNA deletion, SA- β -gal positivity, p21 and p53, establishing that the anti-senescence effect is mitophagy-dependent.

(Sun Z et al, 2025) identified an independent route to the same organelle. Human umbilical cord MSC-derived small EVs (hucMSC-sEVs) were shown to carry the transcription factor GATA2, which binds the promoter of pregnancy zone protein (PZP), confirmed by chromatin immunoprecipitation and dual-luciferase reporter assay. Elevated PZP restrained GRP75 at endoplasmic reticulum-mitochondria contact sites, relieving mitochondrial calcium overload, restoring membrane potential and reducing mitochondrial ROS. The pathway was tested bidirectionally: sEVs from GATA2-knockdown MSCs lost efficacy, sEVs from GATA2-overexpressing MSCs gained it, and the selective GRP75 inhibitor MKT-077 reproduced the effect independently. Notably, this mechanism was prospectively predicted: (Sun Z et al, 2024) concluded by proposing that hucMSC-sEVs must carry an unidentified transcription factor acting on the PZP promoter, and specified dual-luciferase validation as the intended next step. The PZP axis is therefore the only mechanism in this evidence base to have been hypothesised in one publication and confirmed in a subsequent one.

Supporting observations at this tier were reported by (Sun Z et al, 2024), in which sEV pretreatment restored SIRT3 and reduced the full DNA damage response panel (p-ATM, γ -H2AX, 53BP1), and by (Cui H et al, 2025), in which Nrf2 was upregulated alongside reduced ROS. Across four studies employing three MSC sources, the common endpoint was restoration of endogenous mitochondrial and antioxidant homeostasis rather than exogenous radical scavenging. Independence at this tier is partial: (Sun Z et al, 2024) and (Sun Z et al, 2025) originate from the same research group and the same hucMSC-sEV source, with the GATA2/PZP/GRP75 pathway characterised in the second study explicitly extending a mechanism proposed in the first. The upstream tier is therefore better described as two independent groups (Wang Y et al., 2025, via PINK1/Parkin; Sun

Evidence for intervention at the arrest tier

All eight investigations measured at least one senescence marker. They varied primarily in the thoroughness of route evidence. The most extensively characterised mechanism revealed in the review was by (Zhang H et al, 2024). TIMP1 was identified as the major common cargo of adipose- and umbilical cord-derived EVs by proteomic screening. TIMP1 was discovered to inhibit ADAM10, therefore blocking Notch1 S2 cleavage, reducing the Notch intracellular domain and its downstream effector HES1 and subsequently decreasing p16, p21 and p53 (Zhou B et al, 2022). The route was pharmacologically bracketed in both directions, with the Notch activator valproic acid abrogating EV efficacy and the ADAM10 inhibitor GI254023X recapitulating EV efficacy in the absence of EVs. Recombinant TIMP1 at 5 ng/mL did reduce ROS, γ -H2Ax and SA- β -gal, and siRNA reduction of TIMP1 promoted senescence markers. These findings were duplicated over four model tiers, HaCaT keratinocytes, primary human keratinocytes, dermal fibroblasts and a reconstructed full thickness human skin equivalent. The most clear graded effect at this tier was presented by (Zhang Y et al, 2025). SA- β -gal positivity was increased from 5% to 70% after 7 days of UVA exposure, decreased to 50% with unmodified three-dimensionally

cultivated exosomes and to 20% with circ_0011129-loaded exosomes, with concomitant decreases in p53, p21 and p16 and recovery of collagen I and elastin. The internal comparison shows that modified cargo can increase the baseline secretome activity.

(Huynh CB et al, 2025) reported decreased SA- β -gal, p16 and p21 with improved proliferation, and interpreted the accompanying decrease in mean cell size as expansion of the non-senescent population rather than reversal of established senescence - a distinction consistent with the senomorphic classification adopted here.

(Sun Z et al, 2024) turned PZP into a verified mediator by direct manipulation in fibroblasts, moving it from an associated marker: overexpression reduced SA- β -gal in the absence of vesicle treatment and knockdown attenuated the effect of sEVs on senescence, MMP-1 suppression, SIRT3 restoration and DNA damage markers.

(Cui H et al, 2025) demonstrated a dose-dependent decrease in SA- β -gal in UVB-exposed fibroblasts, the clearest dose-response for senescence in the review. However, SA- β -gal was the only senescence marker examined. No cyclin-dependent kinase inhibitor was measured in either compartment.

A design feature shared across most of the included studies bears on the senopreventive classification adopted in this review. In vitro, secretome or EV treatment was administered either before UV exposure (Sun Z et al., 2024, Sun Z et al, 2025; Zhang Y et al., 2025) or within 24 hours of a single exposure, prior to the establishment of a senescent phenotype (Zou X et al., 2022). In vivo, treatment was most commonly co-administered alongside an ongoing UV induction protocol rather than introduced after photoageing was established (Zhang H et al., 2024; Wang Y et al., 2025; Sun Z et al., 2024, Sun Z et al, 2025). Only two studies administered treatment after a completed induction period, once the photoaged phenotype was present (Cui H et al., 2025, subcutaneous arm; Huynh CB et al., 2025). This design pattern, intervention before or during senescence induction rather than after it is established, is a stronger basis for the senomorphic/senopreventive classification used throughout this review than the molecular data alone, and it correspondingly limits what the evidence base can say about reversal of already-established senescent phenotypes.

Evidence for intervention at the secretory tier

Assessment of the SASP was substantially less complete than assessment of arrest. (Zhang H et al, 2024) were the only investigators to characterise a canonical SASP panel alongside arrest markers within a single experimental system, in vitro and in vivo. IL-1 β , IL-6 and TNF- α were quantified by qRT-PCR and ELISA in keratinocytes, fibroblasts and the T-Skin model, and an inflammation antibody array applied to murine dorsal skin demonstrated UV-induced elevation of GCSF, IFN- γ , IL-6 and GM-CSF among others, each restrained by EV treatment. The matrix-degrading arm was captured in parallel, with reductions in MMP1, MMP3 and MMP9, restoration of TIMP1, and recovery of Lamin B1.

(Zou X et al, 2022) applied paired transcriptomic and proteomic profiling to hUC-MSC conditioned medium in serum-starved HaCaT keratinocytes, generating an unbiased rather than targeted characterisation. The UVB transcriptome carried a recognisable SASP signature (CXCL8, IL-6, IL1A, MMP-9, TNF and SERPINE1 upregulated; LMNB1 downregulated), and conditioned medium reversed CXCL8, MYC, FGF-1 and EREG. Interpretation is constrained by the model: a single 20 mJ/cm² UVB exposure assayed at 24 hours, without SA- β -gal or p16 assessment, and with CDKN1A (p21) downregulated (log₂FC -1.04), a pattern more consistent with acute DNA damage response and apoptosis than with an established senescence programme. This study is therefore best regarded as evidence for suppression of an inflammatory-secretory phenotype rather than of senescence as such. (Cui H et al, 2025) measured serum IL-4, IL-6 and IL-10 in photoaged mice, each normalised by subcutaneous exosome administration. Because senescence was assessed in cultured cells while cytokines were measured in blood, the two tiers of the axis were not linked within a

single compartment. Sun Z et al. (2025) measured a single canonical mediator, IL-6 at the transcript level, alongside SA- β -gal and p53 in the same fibroblast and murine systems; this links the two arms of the axis within one compartment but does not constitute characterisation of the secretory phenotype. The remaining four studies (Zhang Y et al., 2025; Huynh CB et al., 2025; Wang Y et al., 2025; Sun Z et al., 2024) measured senescence markers without any SASP mediator.

Evidence at the matrix and phenotypic tier

Two independent groups converged on delivery or induction of endogenous protease inhibitors as the proximate mechanism of collagen preservation. (Zhang H et al, 2024) identified TIMP1, a physiological inhibitor of MMPs and ADAMs, while Sun Z et al. (2024) identified PZP, an α 2-macroglobulin family endopeptidase inhibitor, and confirmed direct PZP-MMP-1 binding by co-immunoprecipitation and immunofluorescence colocalisation in both fibroblasts and skin tissue. This mechanism acts at the enzymatic rather than the transcriptional layer and is therefore independent of the synthetic capacity of the residual fibroblast population.

Transcriptional routes to matrix preservation were reported by (Cui H et al, 2025), who demonstrated upregulation of collagen I and III and downregulation of MMP-1 via TGF- β 1/Smad2/3 signalling, and by (Huynh CB et al, 2025), who observed the same directional pattern for collagen I/III and MMP-1, MMP-2 and MMP-3, without reaching statistical significance. Elastin, the principal component of the elastotic lesion characteristic of human photoaged skin, was assessed in only two studies, by Western blot (Zhang Y et al, 2025) and Verhoeff-Van Gieson staining (Zhang H et al, 2024).

At the phenotypic level, several studies incorporated clinically established comparators. (Sun Z et al, 2024) benchmarked hucMSC-sEVs against 0.05% retinoic acid and reported superior preservation of collagen volume fraction and dermal architecture. (Huynh CB et al, 2025) benchmarked topical hypoxia-preconditioned exosomes against 0.05% tretinoin, achieving comparable wrinkle reduction while the tretinoin arm developed erythema and scaling. (Cui H et al, 2025) applied the validated Wrinkle Severity Rating Scale, and (Zhang H et al, 2024) additionally quantified transepidermal water loss as a measure of barrier function.

Delivery route

Four investigations focused on cutaneous delivery. The results were consistent. In Cui H et al. (2025), both topical and subcutaneous delivery were used as parallel arms in the same animals, with subcutaneous injection improving wrinkle score, skin thickness and collagen volume fraction, and topical treatment having no discernible impact. (Sun Z et al, 2024) compared microneedle roller against intradermal injection using in vivo fluorescence imaging and histological distribution analysis, demonstrating a stronger and more uniform dermal signal with microneedle delivery, which was adopted for subsequent work by the same group (Sun Z et al., 2025). (Huynh CB et al, 2025) obtained effectiveness by topical method but under 1 h of occlusive dressing with 2 min of massage, with penetration in part owing to the murine stratum corneum thickness of $\sim$ 5 μ m.

To summarise, the evidence suggests that an intact stratum corneum acts as a functional barrier to EV transport and thus unassisted topical treatment should not be presumed to reach the dermal fibroblast compartment in human skin. Microneedle-assisted administration remains the most promising approach among routes evaluated in included studies (Lyu S et al, 2023).

Limitations of the evidence base

Seven of 22 reports sought for retrieval could not be obtained, introducing a potential risk of availability bias and limiting certainty that all eligible evidence was captured. Only (Zhang H et al, 2024) characterised a canonical SASP panel alongside arrest markers within a single system, with (Sun Z et al, 2025) reporting a single mediator (IL-6 mRNA) in the same compartment; as the SASP constitutes the mechanism by which senescent cells damage surrounding tissue, current claims of senotherapeutic activity therefore rest predominantly on the arrest arm of the axis. Bystander senescence was not examined in any included study, despite its proposed role in the accumulation of senescent cells (Admasu TD et al, 2021). The required experiment, transfer of conditioned medium from treated or untreated UV-senescent fibroblasts onto naive recipients, with quantification of secondary senescence, has not been performed. Preconditioning effects remain untested: (Zhang Y et al, 2025) compared three-dimensionally cultured exosomes against cargo-loaded exosomes of the same origin rather than against two-dimensionally cultured preparations, and (Huynh CB et al, 2025) included no normoxic comparator; neither study contains the arm required to support a preconditioning claim.

Dose-response synthesis is precluded by non-comparable units, with five studies reporting protein mass, two reporting particle number and one reporting conditioned medium volume. MISEV2023 recommends dual reporting of particle count and protein content (Welsh JA et al, 2024). Phenotypic endpoints are not uniformly interpretable. Dermal thickness decreased following UV exposure in the nude-mouse models of (Cui H et al, 2025; Zhang H et al, 2024; Sun Z et al, 2024), but increased in the haired BALB/c model of (Huynh CB et al, 2025), consistent with elastotic thickening described in human photoaged skin; this endpoint should not be pooled across strains. Spectral heterogeneity is a further constraint, with UVA-only, UVB-dominant and combined UVA/UVB protocols represented. The evidence base also has limited group-level independence: two of the eight included studies (Sun Z et al., 2024; Sun Z et al., 2025) derive from the same laboratory and the same hucMSC-sEV source, with the second study's mechanism prospectively predicted by the first. This does not weaken the individual findings, which were internally validated by bidirectional manipulation (knockdown/overexpression) in each case, but it means the upstream and PZP-related conclusions rest on independent confirmation from only one external group rather than two.

Immunodeficient models predominate, with four of six *in vivo* studies using nude mice, in which immune surveillance of senescent cells is absent by construction. (Sun Z et al, 2025) addressed this by adopting immunocompetent ICR mice. No eligible interventional clinical study assessed senescence- or SASP-specific endpoints; available clinical photoageing studies lie outside the eligible mechanistic evidence base; human tissue was examined only observationally, in the actinic keratosis and squamous cell carcinoma series reported by (Sun Z et al, 2024). No study included a post-treatment observation period or extended follow-up beyond twelve weeks, precluding assessment of durability of effect or delayed dysplastic change. Also, one detail that remains to be resolved comes from (Cui H et al, 2025), where luciferase reporter assays confirmed repression of the TGF- β 1 3'UTR by miR-125b-5p. However, exogenous miR-125b-5p mimic treatment in the same study increased TGF- β 1 protein expression rather than decreased it, leaving the direction of this regulatory arm unresolved. This does not detract from the main senescence findings of the study, as these were evaluated independently of the TGF- β 1 axis. However, the miR-125b-5p/TGF- β 1/Smad mechanism presented as the mechanism in the title of the paper is not totally internally consistent as reported.

Long-term safety was not assessed. All included studies report suppression of p16, p21 and/or p53 in chronically UV-exposed skin, the checkpoints that constrain actinic

carcinogenesis, without corresponding tumour-watch endpoints. Within their human tissue series, (Sun Z et al, 2024) observed reduced PZP in actinic keratosis and squamous cell carcinoma in situ with a rebound in invasive squamous cell carcinoma, an observation the authors identified as requiring further clinical data.

CONCLUSION

The evidence is strongest at the upstream and arrest tiers. Restoration of mitochondrial quality control was established causally through PINK1-dependent mitophagy (Wang Y et al., 2025) and through the GATA2/PZP/GRP75 axis (Sun Z et al, 2025), a mechanism prospectively proposed by the same group in an earlier publication (Sun Z et al, 2024) and confirmed in the later one. A complete pathway through the arrest node, TIMP1-ADAM10-Notch1-HES1-p16/p21/p53, was demonstrated with pharmacological bracketing, target knockdown and recombinant protein rescue across four model tiers including reconstructed human skin (Zhang H et al, 2024). Preservation of dermal extracellular matrix was consistent, converging in part on delivery or induction of endogenous protease inhibitors, and phenotypic improvement was benchmarked favourably against retinoic acid and tretinoin. Two limitations constrain the conclusions that can be drawn. First, the secretory arm of the axis was assessed in four studies, characterised as a panel alongside arrest suppression within a single system in only one, and reduced to a single mediator in a second; claims of senotherapeutic activity therefore rest predominantly on cell-cycle arrest markers rather than on the secretory phenotype through which senescent cells are proposed to damage tissue. Paracrine transmission of senescence was not examined in any included study. Second, an intact stratum corneum consistently blocked vesicle delivery, indicating that unassisted topical application should not be expected to reach the dermal fibroblast compartment in human skin; microneedle-assisted delivery emerged as the most promising approach among the delivery routes evaluated in the included studies. The observed effects are best characterised as senomorphic and predominantly senopreventive rather than senolytic: most included studies administered secretome before or during UV exposure rather than after senescence was established, and no study demonstrated clearance of already-senescent cells.

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