

The Role of UCMSC Derived Secretome in Collagen Remodeling During Skin Photoaging Molecular Mechanisms and Therapeutic Potential

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Received: 14/07/2026

Accepted: 12/08/2026

Published: 19/10/2026

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ABSTRACT

Introduction: Skin photoaging is characterized by progressive disruption of the dermal extracellular matrix, particularly an imbalance between collagen synthesis and degradation. Umbilical cord mesenchymal stem cell-derived secretome has emerged as a promising cell-free regenerative approach because it contains soluble factors and extracellular vesicles capable of influencing skin repair and collagen homeostasis.

Methods: A structured literature search was conducted in PubMed, Scopus, and ScienceDirect for studies published from January 2016 to June 2026. Studies evaluating conditioned medium, whole secretome, extracellular vesicles, or exosomes derived from umbilical cord or Wharton's jelly mesenchymal stem cells in skin aging, photoaging, ultraviolet-induced skin damage, or collagen remodeling were included. The study-selection process followed the PRISMA 2020 framework. Of 166 identified records, 14 studies were included in the narrative synthesis.

Results: Most evidence was derived from in vitro, ex vivo, and animal studies, while human evidence was limited to small, short-term investigations. UCMSC-derived products were associated with increased collagen expression, procollagen production, collagen deposition, and improved dermal organization. They also reduced collagen-degrading matrix metalloproteinases and supported fibroblast survival. The proposed mechanisms involved antioxidant, anti-inflammatory, antisenescence, and extracellular-matrix-regulatory pathways. Comparative findings suggested that UCMSC-derived secretome may have particular antioxidant and antisenescence advantages, although it was not consistently superior to secretomes from other MSC sources.

Conclusion: UCMSC-derived secretome shows potential for supporting collagen remodeling in photoaged skin. However, methodological heterogeneity, inconsistent product characterization, and limited controlled clinical evidence prevent definitive conclusions. Standardized manufacturing and well-designed clinical trials are required to establish its efficacy, safety, and clinical applicability.

Keywords: collagen; remodeling; secretome; photoaging; skin; UCMSC

INTRODUCTION

Skin aging is a progressive biological process influenced by intrinsic and extrinsic factors. Intrinsic aging occurs naturally over time, whereas extrinsic aging is associated with environmental exposure and lifestyle-related factors. Among these external factors, chronic exposure to ultraviolet

radiation is considered a major contributor to premature skin aging, commonly referred to as photoaging. Photoaged skin is clinically characterized by wrinkles, roughness, uneven pigmentation, dryness, reduced elasticity, and loss of firmness^{1,2}. The visible manifestations of photoaging are closely associated with structural changes in the dermal extracellular matrix. Collagen is the main structural protein of the dermis and plays an essential role in maintaining skin strength, thickness, and elasticity. Repeated ultraviolet exposure disturbs the balance between collagen synthesis and degradation, leading to collagen fragmentation, reduced collagen renewal, and progressive deterioration of dermal structure. These changes are associated with increased matrix metalloproteinase activity, oxidative stress, and impaired signaling involved in procollagen production¹⁻³.

Several approaches have been developed to prevent or improve skin photoaging, including photoprotection, topical antioxidants, retinoids, energy-based procedures, microneedling, and injectable treatments. These interventions may improve selected clinical and structural features of aging skin. However, treatment responses vary, and some approaches require prolonged use or repeated procedures. These limitations have encouraged the investigation of regenerative strategies that may support cellular repair and restore extracellular-matrix homeostasis².

Mesenchymal stem cell-derived secretome has emerged as a promising cell-free approach in regenerative medicine. The secretome comprises biologically active substances released by mesenchymal stem cells, including growth factors, cytokines, chemokines, proteins, nucleic acids, and extracellular vesicles. These components may contribute to intercellular communication and regulate cellular survival, proliferation, migration, angiogenesis, inflammation, and tissue repair. Secretome-based therapy may also offer practical advantages over direct stem-cell transplantation because it does not require the administration of living cells⁴⁻⁶.

The regenerative properties of mesenchymal stem cell secretome have also been investigated in skin repair. Secreted soluble factors and extracellular vesicles may support fibroblast and keratinocyte activity, regulate inflammatory responses, promote angiogenesis, and facilitate extracellular-matrix remodeling. These biological properties provide a rationale for investigating MSC-derived secretome as a potential approach for restoring photodamaged skin⁷.

Among the available MSC sources, umbilical cord mesenchymal stem cells have received increasing attention because of their regenerative and immunomodulatory properties. UCMSC-derived secretome contains various bioactive components associated with fibroblast function, collagen synthesis, extracellular-matrix organization, and cellular protection. These components include growth factors, extracellular-matrix proteins, regulatory proteins, cytokines, and extracellular-vesicle cargo. However, the contribution of individual components remains difficult to determine because many studies evaluate the complete secretome rather than isolated factors⁸⁻¹².

Available studies indicate that UCMSC-derived conditioned medium, whole secretome, extracellular vesicles, and exosomes may improve collagen-related outcomes in aging and photoaging models. Reported effects include increased collagen expression or deposition, improved dermal structure, reduced activity of collagen-degrading enzymes, and protection against oxidative and inflammatory damage. These findings have been demonstrated primarily in cultured skin cells, reconstructed or ex vivo skin models, and experimental animals, while clinical evidence remains limited⁸⁻¹³.

Despite these promising findings, substantial differences exist among studies in terms of cell source, donor characteristics, culture conditions, secretome preparation, concentration, treatment duration, delivery method, and outcome measurement. Whole conditioned medium, concentrated secretome, extracellular-vesicle fractions, and purified exosomes are also different biological preparations and should not be considered interchangeable. Standardization of production, characterization, dosage, storage, and quality control is therefore important for improving reproducibility and supporting clinical translation^{4,14}.

Based on the preceding discussion, a review is needed to summarize the evidence regarding the potential of UCMSC-derived secretome in collagen remodeling in photoaged skin. This review is important for determining the extent to which UCMSC secretome can promote collagen synthesis, suppress collagen degradation, improve dermal matrix organization, and identify limitations in the existing evidence that require further investigation.

METHOD

Review Design

This review used a structured literature search to identify studies evaluating umbilical cord mesenchymal stem cell-derived secretome in skin photoaging and collagen remodeling. Study identification, screening, eligibility assessment, and inclusion were reported using the PRISMA 2020 framework.

Information Sources and Search Strategy

The literature search was conducted in PubMed, Scopus, and ScienceDirect for studies published from January 2016 to June 2026. Search terms covered umbilical cord mesenchymal stem cells, Wharton's jelly, secretome, conditioned medium, extracellular vesicles, exosomes, skin aging, photoaging, and ultraviolet-induced skin damage. The search strategy was adapted to the indexing and search functions of each database.

The ScienceDirect search strategy was:

((("umbilical cord mesenchymal stem cell") OR ("Wharton's jelly"))) AND (secretome) AND ((("photoaging") OR ("skin aging") OR ("UVB-induced skin damage") OR (skin)))

The PubMed search strategy was:

((("Mesenchymal Stem Cells"[Mesh] OR "umbilical cord mesenchymal stem cell*" OR "Wharton's jelly mesenchymal stem cell*" OR "human umbilical cord mesenchymal stem cell*")) AND ("Secretome" OR "conditioned medium" OR "extracellular vesicles" OR "exosomes")) AND ("Skin Aging"[Mesh] OR photoaging OR "skin aging" OR "photoaged skin" OR "UV-induced skin damage" OR "UVB-induced skin damage")

The Scopus search strategy was:

((("umbilical cord mesenchymal stem cell") OR ("Wharton's jelly"))) AND ((("photoaging") OR ("skin aging") OR ("UVB-induced skin damage"))) AND (secretome)

Eligibility Criteria

Studies were included when they were published from 2016 onward and evaluated secretome, conditioned medium, extracellular vesicles, or exosomes derived from UCMSCs or Wharton's jelly MSCs. Eligible studies involved in vitro, ex vivo, animal, or human models and reported skin-related outcomes associated with photoaging, ultraviolet-induced damage, fibroblast function, collagen remodeling, extracellular-matrix regulation, oxidative stress, inflammation, or cellular senescence.

Studies were excluded when they were unrelated to skin photoaging or ultraviolet-induced skin damage, did not evaluate umbilical cord-derived MSC secretome or vesicular products, or focused exclusively on non-skin regenerative models.

RESULT

Study Selection

The database search identified 166 records, comprising 107 from Scopus, 54 from PubMed, and 5 from ScienceDirect. After 32 duplicate records were removed, 134 records underwent title and abstract screening. A total of 87 records were excluded, leaving 47 full-text reports for eligibility assessment.

Thirty-three full-text reports were excluded because 12 were unrelated to skin photoaging or ultraviolet-induced skin damage, 13 did not use UCMSC-derived secretome, exosomes, or extracellular vesicles, and 8 focused on non-skin regenerative models. 14 studies were included in the final review. The complete selection process is presented in the PRISMA 2020 flow diagram.

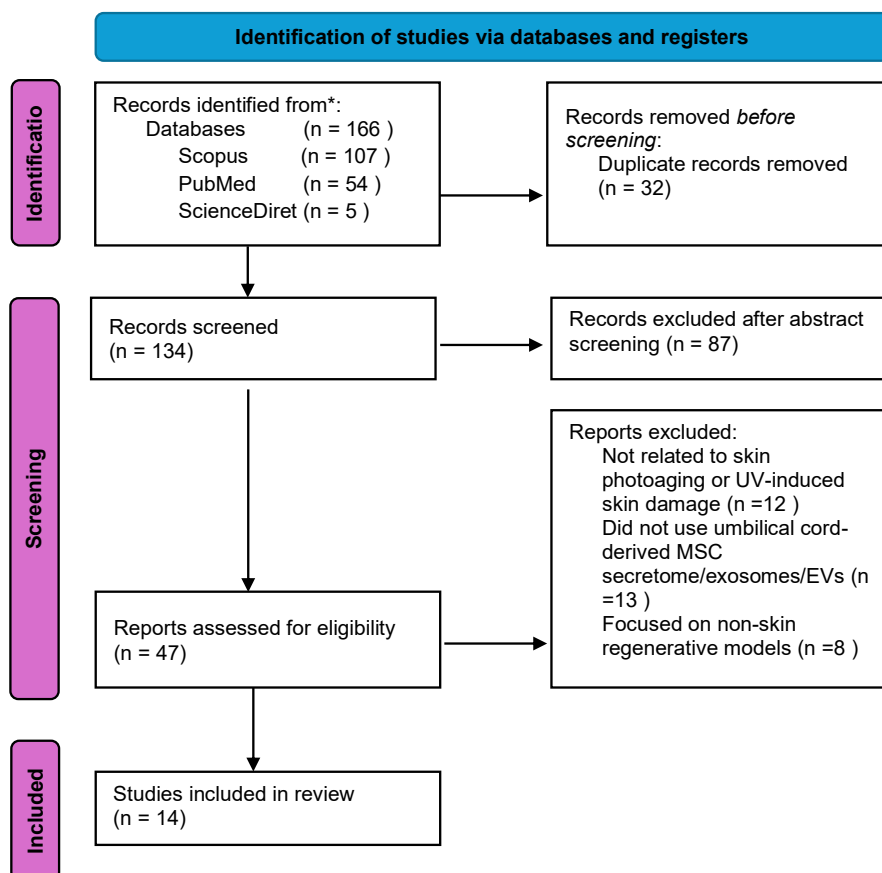


Figure 1. PRISMA 2020 flow diagram of the literature selection process

Study characteristics

The studies evaluated biologically different products, including whole conditioned medium, concentrated or freeze-dried secretome, EV preparations, and exosome-enriched fractions. Models included UVB-exposed keratinocytes and dermal fibroblasts, late-passage or replicatively senescent fibroblasts, reconstructed full-thickness skin, UVB-photoaged human skin explants, naturally aged mice, and chronic UVB-photoaging models. Delivery strategies ranged from direct addition to cell culture and topical application to subcutaneous injection, sponge-spicule-assisted penetration, and microneedle systems. Ten studies with direct or supportive collagen-remodeling outcomes are summarized in Table 1; the remaining included reports contributed primarily to the mechanistic synthesis

Table 1. Characteristics and principal findings of studies with collagen-remodeling outcomes

Experimental model Study and model	Secretome preparation	Treatment	Main collagen-related findings	Other relevant findings
A. Photoaging and aging models				
Ahn et al., 2025 Human skin fibroblasts and naturally aged 96-week-old male BALB/c mice	Filtered whole UCMSC-conditioned medium (UCMSC-CM); compared with ADMSC-CM	In vitro: 10% CM (30 ppm protein). In vivo: 100 µL of 30 ppm CM daily for 2 weeks by topical, subcutaneous, or intravenous administration	Collagen deposition increased by 40.58% after topical treatment and 47.23% after subcutaneous injection. Topical UCMSC-CM and ADMSC-CM produced comparable collagen deposition.	Fibroblast number, epidermal/dermal thickness, and Ki-67 increased; epidermal β-galactosidase decreased. Intravenous treatment was ineffective; no detected skin toxicity or genotoxicity.
Gui et al., 2025 UVB-exposed HaCaT keratinocytes and C57BL/6 mice	UCMSC exosomes; differential centrifugation/ultracentrifugation; ~100 nm; CD9/CD63/TS G101/Alix-positive	In vitro: 25 µg/mL for 24 h before 100 mJ/cm ² UVB. In vivo: 2 µg SC after each UVB exposure for 5 days	Masson's trichrome staining showed preservation of collagen area and architecture versus UVB + PBS. COL1A1, procollagen, MMPs, and TIMPs were not measured.	Reduced ROS, NF-κB activation, IL-1β, TNF-α, IL-6, iNOS, COX-2, and epidermal thickening; improved viability and migration; activated Keap1/Nrf2 antioxidant signaling.
He et al., 2025 UVB-exposed HaCaT keratinocytes and female BALB/c mice	hUMSC exosomes; ultracentrifugation; 119.4 ± 4.3 nm; CD9/TS G101/Alix-positive	In vitro: exosomes 10 µg/mL, EGCG 5 µg/mL, or both. In vivo: HAMA/PVA microneedles containing 200 µg exosomes + 100 µg EGCG every other day	Combination microneedles increased total collagen and collagen I and reduced collagen III versus UVB and blank microneedles. The independent contribution of exosomes was not established.	Reduced erythema, desquamation, epidermal thickening, ROS, 8-OHdG, γ-H2AX, IL-1β, IL-6, and TNF-α; improved viability and tissue regeneration.
Lee et al., 2025 UVB-exposed HS68 fibroblasts; HaCaT cells; mouse penetration model; single-arm pilot in 21 women	Whole WJ-MSC-conditioned medium from three donors; serum-free conditioning for 48 h; abundant EV fraction	In vitro: 1.6–3.9 mg/mL after UVB. Delivery: ~200 µg secretome on sponge spicules. Clinical: topical essence twice daily for 2 weeks	Restored UVB-suppressed COL1A1 and COL3A1 protein expression and increased type I procollagen secretion, with the strongest response at 3.9 mg/mL.	Improved fibroblast/keratinocyte viability, migration, antioxidant capacity, and skin penetration. Short-term reductions in wrinkles, pores, and pigmentation were reported.
Ponnikorn et al., 2026 Late-passage human dermal fibroblasts and UVB-photoaged ex vivo human skin explants	UCMSC exosomes; ultrafiltration/ultracentrifugation; CD9/CD63/CD81-positive	Skin explants: 60 mJ/cm ² UVB followed by topical exosomes at 1 × 10 ⁹ particles/mL once daily for 7 days; ADMSC exosomes and retinoid comparators	Increased Masson's trichrome-positive collagen area and reduced MMP-1 versus UVB control; collagen improvement was smaller than with ADMSC exosomes.	Improved aged-fibroblast viability and reduced SA-β-gal, IL-6, MMP-1, and pigmentation; UCMSC exosomes produced the strongest IL-6 suppression.

Experimental model Study and model	Secretome preparation	Treatment	Main collagen-related findings	Other relevant findings
Widowati et al., 2024 Male DDY mice exposed to UVB twice daily for 14 days	Freeze-dried whole hWJ- MSC secretome formulated in CMC/carbopol gel	Topical secretome gel once or twice daily after UVB; vehicle gel and SPF50 sunblock comparators	Increased histological collagen density (highest: 74.75% with twice-daily treatment), increased COL4A1, and reduced MMP-2 and MMP-13.	Increased TGF- β 1 and IL-10 and reduced IL-18, p53, and inflammation scores; twice-daily application generally had the strongest effects.
Zhang et al., 2024 UVB-exposed keratinocytes/fibroblasts, reconstructed full-thickness skin, and nude mice with chronic photoaging	HUMSC-EVs; ultracentrifugation; ~150 nm; CD9/CD63/CD81/TSG101/Allyx-positive	Cells: EVs 200 ng/ μ L after repeated UVB. Mice: chronic UVB followed by 200 μ g EV per mouse SC across 10 sites for 4 weeks	Restored COL1/COL3, increased collagen area, increased TIMP1, and reduced MMP1 and MMP3/MMP9-related degradation; elastin also recovered.	Reduced wrinkles, transepidermal water loss, ROS, DNA damage, senescence, epidermal thickening, and inflammatory cytokines; improved dermal thickness, viability, and migration.
B. Supportive collagen-remodeling evidence				
Lee et al., 2026 fibroblasts, HaCaT cells, macrophages, HUVECs, and a single-arm pilot in 21 women	Whole WJ- MSC-conditioned medium pooled from three donors; compared with ADMSC and BMMSC secretomes	Cells treated with whole secretome or recombinant ApoA4/SERPIN H1. Participants applied topical WJ-MSC secretome twice daily for 7 days	Type I procollagen reached 3.34 ± 0.26 μ g/mL; COL1A1 increased ~2.4-fold and COL3A1 ~2.1-fold, exceeding ADMSC and BMMSC secretomes.	Improved fibroblast proliferation, wound closure, antioxidant capacity, and angiogenesis; reduced ROS and inflammatory mediators; short-term hydration and elasticity increased.
Quintero-Gil et al., 2025 Adult and replicatively senescent human dermal fibroblasts	WJ-MSC exosomes produced under 5% O ₂ ; tangential-flow filtration and size-exclusion chromatography; pooled from three lots	Exosome dilutions 1:90, 1:30, and 1:10 (~16.7, 50, and 150 million particles/mL)	COL1A2 mRNA increased significantly at 1:30 and 1:10, with the strongest response at 1:10; 1:90 was not different from control.	Fibroblast proliferation increased and senescence-associated β -galactosidase decreased dose-dependently.
Vu et al., 2022 Human dermal fibroblasts without UV exposure or aging induction	EV fractions from normal or TGF- β -primed UCMSCs: apoptotic bodies, microvesicles, and exosomes	Fibroblasts treated with 10 μ g/mL of each EV fraction for ~48 h	TGF- β -primed exosomes increased total collagen; all primed EV fractions increased elastin. COL I and COL III mRNA were lower than EV-free control.	Effects on proliferation and migration were inconsistent; findings support collagen remodeling but not photoaging specifically.

Note: Section A includes photoaging or aging models with collagen-related outcomes. Section B includes supportive collagen-remodeling studies without a direct UV-photoaging model. Combination treatment in He et al. (2025) does not isolate the independent effect of exosomes.

Abbreviations: ADMSC, adipose-derived mesenchymal stem cell; BMMSC, bone marrow-derived mesenchymal stem cell; CM, conditioned medium; ECM, extracellular matrix; EV, extracellular vesicle; MMP, matrix metalloproteinase; SC, subcutaneous; UCMSC, umbilical cord mesenchymal stem cell; UVB, ultraviolet B; WJ-MSC, Wharton's jelly mesenchymal stem cell.

Bioactive components relevant to collagen remodeling

The UCMSC secretome is a composite product rather than a single active agent. Whole conditioned medium may contain soluble proteins together with vesicular material, whereas EV or exosome-enriched preparations represent selected fractions. The term exosome should be used cautiously unless endosomal origin has been demonstrated; otherwise, the broader term extracellular vesicle is more appropriate under current MISEV recommendations^{15,16}. Wharton's jelly MSCs are treated in this review as a subtype of UCMSCs.

Growth factors identified in UCMSC-derived products include TGF-beta, FGF2, HGF, VEGF, PDGF, EGF, and KGF. These molecules may support fibroblast proliferation, migration, survival, angiogenesis, epithelial repair, and ECM production. Their individual contribution is

difficult to isolate because most studies tested the complete product rather than purified factors. Proteomic analyses also identified proteins with closer links to collagen homeostasis, including TIMP1, the collagen-specific chaperone SERPINH1/HSP47, fibrillar collagen proteins, fibronectin, decorin, lumican, and basement-membrane or matricellular proteins. Vesicular cargo such as miR-200a-3p, 14-3-3 zeta, ApoA4, and IL-10 may indirectly preserve the collagen matrix by reducing oxidative and inflammatory injury^{8-11,17-20}.

Table 1. Key Components of UCMSC Secretome Relevant to Collagen Remodeling

Component/ group	Category	Main pathway/ function	Main skin and collagen effect	Evidence	References
TGF-β1/2/3	Growth factors/cytokines	TGF-β receptor–Smad signaling	May regulate fibroblast ECM production, collagen synthesis and matrix organization; individual contributions were generally not isolated.	Detected; mechanistic relevance inferred or product-level	8,10,11 or
FGF2/bFGF	Growth factor	FGFR–ERK signaling	Supports fibroblast proliferation and migration and may indirectly enhance ECM production and dermal repair.	Detected; component isolated	not 8,10,11,17
HGF	Growth factor	HGF/c-Met signaling	May support fibroblast survival, migration, and tissue repair, thereby indirectly facilitating dermal regeneration.	Detected; component isolated	not 8,11,17
VEGF/VEGF-A	Growth factor	VEGFR signaling	Promotes angiogenic and regenerative support; its relationship with collagen remodeling is primarily indirect.	Detected; component isolated	not 8,10,11,17
PDGF-AA/PDGF-BB	Growth factor	PDGFR signaling	May stimulate fibroblast activity and ECM production, although factor-specific collagen effects were not demonstrated.	Detected; component isolated	not 8,11
EGF and KGF	Epithelial growth factors	EGFR/FGFR-related signaling	Support keratinocyte activity and epidermal regeneration, with secondary benefits for dermal repair rather than direct collagen regulation.	Detected; indirect evidence	8,10

Component/ group	Category	Main pathway/ function	Main skin and collagen effect	Evidence	References
TIMP1	Metalloproteinase inhibitor	MMP inhibition; ADAM10/Notch1/HES1	Reduces senescence, oxidative injury, and inflammatory responses while limiting collagen-degrading MMP activity and preserving ECM.	Direct mechanistic evidence	12
SERPINH1/HSP47	Collagen-specific chaperone	Collagen folding and secretion; TGF- β /Smad-associated signaling	Supports collagen processing and secretion and was associated with increased COL1A1 expression and ECM accumulation.	Direct functional evidence	10
Type I and III collagens (COL1A1, COL1A2, COL3A1)	Structural ECM proteins	Dermal collagen matrix	Provide the principal fibrillar framework of the dermis; cargo detection suggests structural relevance, but functional transfer was not established.	Cargo/proteomic detection	8–12
Other collagen proteins (COL5A1, COL6A1, COL28A1)	Structural ECM proteins	Fibrillogenesis and pericellular ECM organization	May support collagen-fibril organization, fibroblast–matrix interactions, and overall ECM architecture.	Cargo/proteomic detection	9,10,12,18
Fibronectin/FN1	ECM glycoprotein	Cell–ECM adhesion and matrix assembly	Supports cellular attachment, migration, ECM assembly, and organization of collagen-containing matrices.	Detected; functional contribution not isolated	8–10
Decorin/DCN and Lumican/LUM	Small leucine-rich proteoglycans	Collagen fibrillogenesis and TGF- β regulation	Regulate collagen-fibril formation, diameter, alignment, and matrix organization.	Cargo/proteomic detection	12,18
LAMC1, NID1, FBLN2, and MFAP4	Basement-membrane/structural ECM proteins	Basement-membrane, elastic-fiber, and ECM assembly	May maintain dermal–epidermal integrity and support structural organization and elasticity of the skin matrix.	Cargo/proteomic detection	9,12,18
TGFBI, THBS1, FSTL1, and MXRA5	Matricellular /ECM-regulatory proteins	Cell–matrix interactions and tissue-repair signaling	May coordinate fibroblast activity, matrix adhesion, organization, and controlled ECM remodeling.	Cargo/proteomic detection; indirect relevance	9,10,12,18
miR-200a-3p	Exosomal microRNA	Keap1 targeting and Nrf2 activation	Reduces ROS and inflammatory cytokines and improves keratinocyte viability and migration, potentially protecting collagen indirectly from UVB-related damage.	Direct mechanistic evidence; collagen directly measured	20
14-3-3 ζ	Exosomal regulatory protein	SIRT1-dependent antioxidant and autophagy pathways	Reduces ROS, DNA damage, inflammation, and apoptosis and may indirectly preserve dermal collagen by protecting skin cells.	Direct mechanistic evidence; collagen directly measured	19

Component/ group	Category	Main pathway/ function	Main skin and collagen effect	Evidence	References
ApoA4	Apolipoprotein/antioxidant mediator	Oxidative-stress and inflammatory regulation	Reduces oxidative and inflammatory injury and promotes keratinocyte migration, with a possible indirect collagen-preserving effect.	Direct functional evidence; collagen effect indirect	9,10
IL-10	Anti-inflammatory cytokine	Inflammatory and immune regulation	May preserve collagen indirectly by limiting inflammation-associated fibroblast dysfunction and matrix degradation.	Detected; indirect mechanistic relevance	11

Note: Components were consolidated across studies. “Detected” indicates identification in conditioned medium or extracellular-vesicle cargo without factor-specific functional testing. Direct evidence indicates that the component or its pathway was experimentally evaluated.

Abbreviations: ECM, extracellular matrix; EV, extracellular vesicle; MMP, matrix metalloproteinase; ROS, reactive oxygen species; UCMSC, umbilical cord mesenchymal stem cell.

Molecular mechanisms

UCMSC-derived products appear to influence collagen remodeling through convergent antioxidant, anti-inflammatory, antisenescence, prosurvival, and matrix-regulatory pathways. These processes are biologically connected: lowering ROS can suppress inflammatory signaling and MMP induction; preserving fibroblast viability maintains the cellular source of collagen; and restoring the MMP/TIMP balance reduces destruction of newly synthesized matrix.

Exosomal miR-200a-3p has been linked to Keap1 suppression and Nrf2 activation, increasing antioxidant defense and reducing ROS and inflammatory signaling in UVB-exposed models²⁰. The exosomal regulatory protein 14-3-3 zeta may activate SIRT1, Nrf2, and autophagy-related responses, thereby reducing oxidative stress, DNA injury, apoptosis, and defective autophagy¹⁹. ApoA4 in Wharton's jelly MSC secretome similarly contributed to cytoprotection, lower intracellular ROS, reduced inflammatory mediators, and improved keratinocyte migration⁹. In several of these experiments, collagen was not directly measured, so the collagen-preserving effect remains mechanistically plausible but indirect.

Inflammatory and senescence pathways provide a second major mechanism. UCMSC-derived secretome or EVs suppressed NF-kappa B activation and reduced IL-1 beta, IL-6, TNF-alpha, iNOS, COX-2, GM-CSF, and related mediators. EV treatment also decreased senescence-associated beta-galactosidase, p16, p21, p53, IL-6, and MMP-1 in aged fibroblast models^{11,12,19,20}. Limiting the senescence-associated secretory phenotype may reduce the persistent catabolic signaling that promotes collagen degradation.

Fibroblast survival is supported through PI3K/Akt signaling. UCMSC-conditioned medium increased Akt phosphorylation in UVB-exposed fibroblasts, whereas PI3K inhibition attenuated the protective response, indicating that this pathway contributes to resistance against ultraviolet-induced apoptosis²¹. More direct stimulation of matrix production may involve SERPINH1/HSP47 and TGF-beta/Smad signaling. SERPINH1 promotes collagen folding, processing, and secretion and was associated with increased TGF-beta signaling, COL1A1, COL3A1, fibronectin, and ECM accumulation in Wharton's jelly MSC-secretome experiments⁹.

The MMP/TIMP axis connects these protective effects to matrix turnover. UCMSC-derived EVs restored TIMP1 and reduced MMP-1 and MMP-3/MMP-9-related degradation, accompanied by recovery of type I and III collagen, greater collagen deposition, and improved dermal architecture^{11,12}. TIMP1 may also act beyond direct MMP inhibition by suppressing ADAM10-dependent Notch1/NICD1/HES1 signaling, thereby reducing fibroblast senescence and its associated catabolic phenotype¹².

Table 3. Molecular mechanisms of UCMSC-derived secretome in photoaged skin

Photoaging process	Secretome mediator/pathway	Mechanistic action	Collagen/ECM outcome	References
UVB-induced oxidative stress	Exosomal 200a-3p–Keap1/Nrf2	miR-200a-3p suppresses Keap1 and activates Nrf2-dependent antioxidant enzymes, reducing ROS and inflammatory signaling.	Creates a less degradative environment and may preserve collagen; direct regulation of collagen genes was not demonstrated.	20
Oxidative stress, apoptosis, and impaired autophagy	Exosomal 14-3-3ζ–SIRT1/Nrf2 and autophagy	Increases SIRT1, Nrf2, and autophagic activity while reducing ROS, DNA damage, apoptosis, and inflammatory signaling.	Protects ECM-producing and barrier cells and may indirectly maintain dermal collagen; collagen was not directly measured.	19
Oxidative and inflammatory injury	ApoA4-associated cytoprotection	Reduces intracellular ROS and inflammatory mediators and improves keratinocyte migration; knockdown weakens these effects.	May indirectly limit inflammation- and oxidation-associated ECM degradation.	9
UVB-induced inflammation and SASP	NF-κB/IκBα and inflammatory cytokines	Suppresses NF-κB activation and reduces IL-1β, IL-6, TNF-α, iNOS, COX-2, GM-CSF, and related inflammatory responses.	May reduce inflammation-associated MMP activity and ECM degradation, supporting collagen preservation.	11,12,19,20
UVB-induced fibroblast apoptosis	PI3K/Akt survival signaling	UCMSC-conditioned medium increases Akt phosphorylation; PI3K inhibition attenuates this protective response.	Preserves viable fibroblasts responsible for collagen production, although no collagen endpoint was measured.	21
Reduced collagen synthesis and impaired ECM processing	SERPINH1/HSP47–TGF-β/TGFβR–Smad2/3	SERPINH1 supports collagen folding and secretion and is associated with increased TGF-β signaling, COL1A1, COL3A1, and fibronectin.	Promotes collagen processing, expression, and ECM accumulation.	9
UVB-induced collagen degradation	TIMP1/MMP balance	UCMSC extracellular vesicles restore TIMP1 and suppress collagen-degrading MMP-1 and MMP-3/MMP-9-related expression.	Reduces collagenolysis and restores COL1/COL3 expression, collagen deposition, and dermal matrix organization.	11,12
Fibroblast senescence and catabolic SASP	TIMP1–ADAM10–Notch1/NICD1–HES1	EV-delivered or recombinant TIMP1 suppresses Notch1/HES1 signaling and decreases SA-β-gal, p16, p21, p53, IL-6, and MMP-1.	Maintains fibroblast function and limits senescence-associated collagen degradation and ECM disorganization.	11,12

Note: Mechanisms were consolidated across studies. Statements marked as indirect indicate that collagen or ECM endpoints were not directly measured in the cited experiment.

Abbreviations: ECM, extracellular matrix; EV, extracellular vesicle; MMP, matrix metalloproteinase; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; UCMSC, umbilical cord mesenchymal stem cell; UVB, ultraviolet B.

Preclinical and preliminary clinical evidence

Across cell-based studies, UCMSC-derived products generally supported fibroblast function and matrix production. Wharton's jelly MSC-conditioned medium restored UVB-suppressed COL1A1

and COL3A1 expression and increased type I procollagen secretion in dermal fibroblasts (Lee et al., 2025). A related comparative study reported higher type I procollagen secretion and stronger COL1A1 and COL3A1 expression with Wharton's jelly MSC secretome than with adipose- or bone-marrow-derived products under the tested conditions⁹. Hypoxia-conditioned WJ-MSC exosomes increased COL1A2 expression and reduced senescence-associated beta-galactosidase in adult and replicatively senescent fibroblasts¹⁸. TGF-beta-primed UCMSC exosomes also increased total collagen in fibroblasts, although the gene-expression response for collagen I and III was not uniformly concordant¹⁷.

Ex vivo and reconstructed-skin models strengthened the evidence that the effects extend beyond monolayer culture. In UVB-photoaged human skin explants, topical UCMSC exosomes increased collagen-positive areas and reduced MMP-1. The collagen response was smaller than that produced by adipose-derived MSC exosomes, whereas UCMSC exosomes showed stronger suppression of IL-6 and several senescence-related outcomes¹¹. In reconstructed full-thickness skin, human umbilical MSC-derived EVs restored collagen I and III, increased TIMP1, and reduced MMP-related matrix degradation, with parallel improvements in oxidative stress, inflammation, and senescence¹².

Animal models consistently showed improvement in collagen density or organization. In naturally aged mice, topical and subcutaneous UCMSC-conditioned medium increased collagen deposition, fibroblast numbers, and skin thickness; intravenous administration was ineffective, demonstrating that delivery route influenced activity⁸. In UVB-photoaged mice, UCMSC exosomes preserved collagen architecture and reduced oxidative and inflammatory injury²⁰. A topical freeze-dried WJ-MSC-secretome gel increased collagen density and COL4A1 while reducing MMP-2 and MMP-13, with twice-daily administration producing the strongest histological response¹³. Chronic photoaging experiments with HUMSC-EVs similarly restored collagen and elastin, improved dermal thickness, and reduced wrinkles, transepidermal water loss, ROS, DNA damage, senescence, and inflammatory cytokines¹².

Human evidence remains preliminary. A small single-arm study involving 21 women reported short-term reductions in wrinkles, pores, and pigmentation after twice-daily application of a topical WJ-MSC-secretome essence for two weeks¹⁰. A related investigation reported improvements in hydration and elasticity after seven days of topical use⁹. These studies did not include placebo-controlled comparisons, had short follow-up periods, and provided limited direct measurement of dermal collagen remodeling.

Comparisons with other MSC-derived secretomes

Direct comparisons indicate that tissue source may influence the biological profile of an MSC-derived product, but the findings are endpoint-specific. UCMSC-conditioned medium showed a richer measured growth-factor profile and stronger fibroblast proliferation than ADMSC-conditioned medium, although topical collagen deposition was comparable⁸. WJ-MSC secretome produced stronger procollagen secretion and collagen-gene expression than ADMSC and BMMSC secretomes in one study⁹. In contrast, ADMSC exosomes produced greater collagen deposition and slightly stronger MMP-1 suppression in UVB-photoaged human skin explants, while UCMSC exosomes showed stronger anti-inflammatory and antisenescence activity¹¹. HUMSC-EVs contained more TIMP1 and demonstrated broader efficacy across several oxidative, inflammatory, senescence, and ECM outcomes than adipose MSC-derived EVs in another preclinical system¹².

Table 4. Head-to-Head Comparisons of MSC-Derived Secretomes in Skin Regeneration and Photoaging

Study	MSC products compared	Experimental model	Key comparative findings	Overall interpretation	Main limitations
Ahn et al., 2025	UCMSC-conditioned medium (UCMSC-CM) vs ADMSC-CM	Human skin fibroblasts and naturally aged 96-week-old BALB/c mice	UCMSC-CM contained higher concentrations of the eight measured factors and produced stronger fibroblast proliferation. Both preparations increased skin thickness and collagen deposition; topical collagen deposition did not differ significantly between groups.	UCMSC-CM showed a stronger growth-factor and proliferative profile, but collagen deposition was not established.	Natural-aging rather than UV-photoaging model; small animal groups; no human clinical evaluation.
Lee et al., 2026	WJ-MSC secretome vs ADMSC and BMMSC secretomes	Human fibroblasts, keratinocytes, macrophages and endothelial cells; short single-arm human pilot	WJ-MSC secretome contained SSmore ApoA4 and SERPINH1 and produced the greatest fibroblast proliferation, wound closure, type I procollagen secretion, COL1A1/COL3A1 expression, antioxidant activity and angiogenesis.	WJ-MSC secretome demonstrated the strongest regenerative and collagen-related activity under the tested conditions.	Pooled three-donor WJ-MSC preparation was compared with single-donor ADMSC and BMMSC preparations; limited clinical design.
Ponnikorn et al., 2026	UCMSC exosomes vs ADMSC exosomes; topical retinoid comparator	Late-passage human dermal fibroblasts and UVB-photoaged human skin explants	Both exosome products improved photoaged skin. UCMSC exosomes produced stronger IL-6 suppression and antisenesescence effects, whereas ADMSC exosomes produced greater collagen deposition, hyaluronic-acid-related effects and slightly greater MMP-1 suppression.	The sources showed different therapeutic strengths; neither exosome product was uniformly superior.	Ex-vivo model and short treatment period; active cargo responsible for the differences was not established.
Zhang et al., 2024	HUMSC-derived EVs vs AMSC-derived EVs	UVB-exposed skin cells, reconstructed human skin and chronic UVB-photoaged nude mice	Both EV preparations reduced photoaging and restored collagen-related outcomes. HUMSC-EVs contained more TIMP1 and showed stronger effects for several oxidative-stress, senescence, inflammatory and ECM-remodeling endpoints.	HUMSC-EVs showed broader efficacy in this experimental system, but the advantage was product- and endpoint-specific.	Preclinical evidence; limited donor and batch information; superiority was not consistent across every outcome.

Note: Comparative findings are study-specific and should not be interpreted as universal superiority of one MSC source. WJ-MSCs are a subtype of UCMSCs.

Abbreviations: ADMSC, adipose-derived mesenchymal stem cell; AMSC, adipose mesenchymal stem cell; BMMSC, bone marrow-derived mesenchymal stem cell; CM, conditioned medium; ECM, extracellular matrix; EV, extracellular vesicle; HUMSC, human umbilical mesenchymal stem cell; MMP, matrix metalloproteinase; UCMSC, umbilical cord mesenchymal stem cell; UVB, ultraviolet B; WJ-MSC, Wharton's jelly mesenchymal stem cell.

DISCUSSION

Overall Interpretation of the Evidence

The available evidence generally supports the potential of UCMSC-derived secretome to improve collagen remodeling in aging and photoaged skin. The most consistent findings include increased collagen expression or deposition, preservation of dermal architecture, reduced matrix metalloproteinase activity, improved fibroblast function, and attenuation of oxidative stress, inflammation, and cellular senescence. However, the strength of evidence differs among outcomes. Direct collagen-related effects have been demonstrated in several studies, whereas other proposed benefits are based on indirect indicators such as reduced reactive oxygen species, inflammatory mediators, or senescence^{8–13,18}.

Comparative findings indicate that UCMSC-derived products may have particular strengths in fibroblast proliferation, antioxidant activity, inflammatory regulation, and antisenesescence effects. Nevertheless, UCMSC secretome was not consistently superior to ADMSC- or BMMSC-derived products for every collagen-related outcome. The observed effects appear to depend on the MSC source, secretome preparation, experimental model, delivery method, and measured endpoint. The current findings should therefore be interpreted as product-specific rather than evidence that one MSC source is universally superior^{8–12}.

Therapeutic Delivery and Clinical Potential

The therapeutic activity of UCMSC-derived secretome depends not only on its biological composition but also on its delivery to the target skin layer. Topical application is attractive because it is non-invasive and suitable for repeated treatment. Whole secretome and conditioned medium have been incorporated into gels, essences, and other topical formulations. Topical UCMSC-conditioned medium increased collagen deposition in naturally aged mice, while Wharton's jelly MSC secretome gel improved collagen density and reduced collagen-degrading enzymes in UVB-exposed skin^{8,13}.

The skin barrier may limit the penetration of large proteins and extracellular vesicles. Physical and biomaterial-assisted approaches have therefore been investigated to improve delivery. Sponge spicules were used to enhance the penetration of topical WJ-MSC secretome, whereas dissolving microneedles were used to deliver UCMSC exosomes combined with epigallocatechin gallate into UVB-damaged skin^{10,22}. These approaches may improve local retention and penetration, although combination treatments make it difficult to determine the independent contribution of the secretome or extracellular vesicles.

An additional consideration is whether the delivery process preserves the structural integrity and biological activity of secretome cargo. Proteins and extracellular vesicles may undergo additional processing during encapsulation, drying, incorporation into polymers, storage, and release from a delivery matrix; therefore, improved skin penetration should not automatically be interpreted as preserved biological potency. Importantly, He et al. evaluated exosomes after incorporation into and release from their HAMA/PVA microneedle matrix using transmission electron microscopy and nanoparticle-tracking analysis, providing an example of post-formulation structural assessment²². Nevertheless, comparable post-formulation characterization and functional potency testing are not consistently reported across dermatological secretome studies, including different spicule-, gel-, and microneedle-based systems. Future studies should therefore compare secretome or EV identity, particle characteristics, relevant protein or cargo markers, and biological activity before formulation and after release from the delivery system. Such testing would help distinguish improvements caused by enhanced penetration from changes in the intrinsic activity of the secretome product.

Subcutaneous administration has also produced collagen-related improvements in experimental models. Ahn et al. (2025) reported increased collagen deposition following subcutaneous UCMSC-

conditioned medium, while Zhang et al. (2024) demonstrated improvements in collagen, dermal structure, and photoaging indicators after subcutaneous administration of human umbilical MSC-derived extracellular vesicles. However, injection-based delivery is more invasive and requires further evaluation of dose, distribution, treatment frequency, and safety.

Biomaterial-based delivery systems may eventually improve the stability, sustained release, and local bioavailability of secretome products. Research on MSC secretome in skin repair has similarly emphasized the potential value of incorporating secreted factors into scaffolds, hydrogels, and other controlled-delivery platforms⁷.

Clinical Potential

UCMSC-derived secretome has potential applications in regenerative and aesthetic dermatology because it may simultaneously influence fibroblast function, collagen production, oxidative stress, inflammation, and cellular senescence. Preliminary human studies have reported short-term improvements in wrinkles, pigmentation, pores, hydration, and elasticity following topical WJ-MSC secretome application^{9,10}.

These findings remain preliminary because the available human investigations involved small samples, short treatment durations, and single-arm designs. Direct clinical measurements of dermal collagen remodeling were also limited. Well-designed randomized controlled trials are therefore required to determine whether improvements in clinical appearance are accompanied by measurable changes in collagen synthesis, collagen degradation, dermal thickness, and long-term skin quality.

The most appropriate clinical product has not yet been established. Whole conditioned medium provides a broad mixture of soluble and vesicular factors, while isolated extracellular vesicles may offer a more defined preparation. However, each preparation requires specific characterization, dose determination, formulation, stability testing, and potency assessment before reliable clinical use.

Challenges And Limitations

The translation of UCMSC-derived secretome into clinical treatment remains limited by variability in donor characteristics, cell passage, culture conditions, conditioning methods, secretome processing, storage, and dose reporting. Whole conditioned medium, concentrated secretome, extracellular-vesicle fractions, and purified exosomes are biologically different products, making direct comparison among studies difficult. Standardized manufacturing, characterization, potency testing, and batch-to-batch quality control are therefore required^{4,16}.

A standardized minimal-information framework is particularly needed for dermatological studies of MSC-derived secretome. MISEV2023 provides an important foundation for studies involving extracellular vesicles by emphasizing transparent reporting of EV production, separation, characterization, and functional assessment. However, dermatological secretome research also includes whole conditioned medium, concentrated secretome, and soluble-factor preparations that are not fully covered by EV-specific terminology. Future studies should therefore report, at minimum, the MSC source and donor characteristics, cell passage and culture conditions, conditioning duration and medium composition, secretome collection and concentration methods, storage conditions, and the exact basis used for dose normalization. For EV-containing preparations, particle concentration and size distribution, vesicle-associated and non-vesicular markers, morphology, isolation method, and assessment of contaminants should be reported in accordance with MISEV principles. Dermatology-specific reporting should additionally include formulation composition, delivered dose per skin area, delivery depth or route, treatment frequency, and stability and potency after incorporation into the final topical or transdermal formulation. Adoption of such a framework would allow more meaningful comparison between studies, improve batch-to-batch reproducibility, and facilitate translation of UCMSC-derived products toward standardized clinical use¹⁶.

The current evidence is also dominated by in vitro, ex vivo, and animal studies. Human investigations remain limited by small sample sizes, short treatment periods, and uncontrolled designs. Differences in experimental models, delivery routes, treatment doses, and collagen-related measurements further restrict comparison and prevent firm conclusions regarding clinical efficacy. Long-term safety is also uncertain, particularly for products that influence inflammation, angiogenesis, cellular proliferation, and tissue remodeling. Regulatory caution remains necessary because unapproved exosome products have been associated with reported adverse events, and the FDA states that no exosome products are currently approved in the United States²³.

Future research should prioritize standardized UCMSC-secretome production, direct identification of active components, dose-response evaluation, and consistent measurement of collagen synthesis and degradation. Studies should adopt a minimal reporting framework based on MISEV principles where extracellular vesicles are involved, while extending these requirements to whole-secretome manufacturing and dermatology-specific delivery parameters. Randomized controlled clinical trials with adequate sample sizes and longer follow-up periods are required to evaluate efficacy, safety, and durability. Improved topical formulations, hydrogels, spicule-assisted systems, and microneedles should also be evaluated not only for penetration and local bioavailability but also for their ability to preserve secretome cargo integrity and biological potency after formulation and delivery.

CONCLUSION

UCMSC-derived secretome represents a promising cell-free approach for collagen remodeling in photoaged skin. Available evidence suggests that conditioned medium, whole secretome, extracellular vesicles, and exosomes may support collagen synthesis, reduce collagen degradation, preserve fibroblast function, and improve dermal organization through interconnected antioxidant, anti-inflammatory, antisenescence, and extracellular-matrix-regulatory mechanisms.

The evidence is strongest in cellular, ex vivo, and animal models, while human findings remain limited and preliminary. Variability in product preparation, dose, delivery, and outcome assessment also prevents firm conclusions regarding clinical efficacy or superiority over other MSC sources. Standardized manufacturing, detailed product characterization, mechanistic validation, and controlled clinical trials are therefore essential before UCMSC-derived secretome can be established as a reliable therapy for skin photoaging.

ACKNOWLEDGEMENT

The authors gratefully acknowledge YARSI University, Jakarta, Indonesia, for the academic and institutional support provided during the preparation of this article.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this article.

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