ORIGINAL ARTICLE

Smart Medical Journal

Smart Medical Journal (SMedJour) April 2026, Vol. 9, No.1, pp : 18 - 32
DOI: https://doi.org/10.13057/smj.v9i1.115685
E-ISSN: 2621-0916 | P-ISSN: 2621-1408

The Role of Umbilical Cord–Derived Mesenchymal Stem Cell Secretome in Regulating Oxidative Stress and Inflammation in Skin Cells

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Recived: 12/02/2026
Accepted: 27/04/2026
Published: 05/05/2026

ABSTRACT

Introduction: Oxidative stress and inflammation are tightly interconnected processes that drive skin aging, impaired wound healing, and inflammatory skin disorders. Excessive reactive oxygen species (ROS) disrupt skin cell homeostasis, promote cellular senescence, and sustain inflammatory signaling, ultimately compromising skin regeneration. Umbilical cord–derived mesenchymal stem cell (UC-MSC) secretome has recently emerged as a promising cell-free therapeutic approach to modulate these pathological mechanisms.
Methods: A narrative literature review was conducted using PubMed, Scopus, ScienceDirect, and Google Scholar to identify studies investigating the role of UC-MSC secretome in regulating oxidative stress and inflammation in skin cells. Search terms included combinations of "UC-MSC secretome," "extracellular vesicles," "exosomes," "oxidative stress," "inflammation," "keratinocytes," "fibroblasts," and "wound healing." studies relevant to skin biology were included based on biological relevance and mechanistic insight rather than strict methodological filtering.
Results: The UC-MSC secretome, composed of soluble factors and extracellular vesicles enriched with bioactive proteins, cytokines, antioxidant enzymes, and regulatory microRNAs, consistently demonstrates antioxidant and anti-inflammatory effects in keratinocytes, fibroblasts, and melanocytes. Mechanistically, it reduces intracellular and mitochondrial ROS, activates endogenous antioxidant pathways such as Nrf2 and FOXO, preserves mitochondrial function, and NF-κB and MAPK. In vitro and in vivo studies show attenuation of UV-induced photoaging, enhanced wound healing, and protection of melanocytes from oxidative and immune-mediated damage.
Conclusion: Current evidence supports UC-MSC secretome as a potent regulator of oxidative stress and inflammation in skin cells. Its cell-free nature offers advantages in safety, scalability, and therapeutic flexibility, highlighting strong translational potential for dermatology and regenerative skin medicine.

Keywords: extracellular vesicles; inflammation; oxidative stress; secretome; UC-MSC

INTRODUCTION

The skin is a highly dynamic organ that serves as the primary barrier between the body and the external environment. Its homeostasis depends on tightly regulated interactions between cellular renewal, immune surveillance, redox signaling, and extracellular matrix maintenance. Disruption of these processes, particularly through excessive oxidative stress and persistent inflammation, is a central mechanism underlying skin aging, impaired wound healing, and a wide spectrum of inflammatory and degenerative skin disorders[1,2].

Reactive oxygen species (ROS) are continuously generated in skin cells as part of normal metabolic activity and play essential roles in physiological signaling. However, exposure to ultraviolet (UV) radiation, environmental pollutants, and chemical or microbial insults markedly increases ROS production, overwhelming endogenous antioxidant defenses[3,4]. Excessive ROS accumulation leads to oxidative damage to DNA, proteins, and lipids, ultimately triggering cellular dysfunction, senescence, or apoptosis [5]. In keratinocytes, oxidative stress compromises epidermal barrier integrity and promotes pro-inflammatory cytokine release; in dermal fibroblasts, it accelerates extracellular matrix degradation and cellular aging; and in melanocytes, oxidative injury contributes to pigmentary disorders such as vitiligo[6].

Excessive ROS accumulation activates multiple redox-sensitive signaling pathways, including nuclear factor κB (NF-κB), mitogen-activated protein kinases (MAPKs), and Janus kinase/signal transducer and activator of transcription (JAK/STAT). Activation of these pathways leads to increased production of inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6)[7]. These cytokines, in turn, further amplify ROS generation, establishing a self-perpetuating oxidative–inflammatory loop that drives chronic skin damage and disease progression[8].

In recent years, mesenchymal stem cells (MSCs) have emerged as a promising tool for skin regeneration due to their regenerative, immunomodulatory, and cytoprotective properties. Mesenchymal stem cells can be isolated from various tissues, including bone marrow, adipose tissue, and perinatal sources[9]. Among these sources, umbilical cord–derived mesenchymal stem cells (UC-MSCs) have gained increasing attention in dermatological applications. UC-MSCs are obtained through non-invasive procedures, exhibit higher proliferative capacity, and demonstrate lower immunogenicity compared with MSCs derived from adult tissues [9,10]. In addition, UC-MSCs possess strong immunomodulatory and anti-inflammatory properties, making them particularly suitable for the treatment of skin conditions driven by oxidative stress and inflammation. Growing evidence suggests that the therapeutic benefits of MSCs in skin repair are primarily mediated through paracrine mechanisms rather than direct differentiation into skin cell lineages [9].

This paracrine activity is collectively referred to as the MSC secretome, which comprises a complex mixture of soluble factors and extracellular vesicles (EVs). The UC-MSC secretome contains growth factors, cytokines, chemokines, antioxidant enzymes, lipids, and nucleic acids, including microRNAs packaged within EVs such as exosomes. These bioactive components act synergistically to regulate cellular redox homeostasis. Consequently, research interest has increasingly shifted toward cell-free, secretome-based therapeutic strategies[11–13]. Compared with cell-based approaches, UC-MSC secretome therapy offers several advantages, including improved safety, reduced risk of immune rejection or tumorigenicity, ease of storage and handling, and greater potential for standardization and clinical translation [9].

In the context of skin biology, accumulating experimental and translational evidence indicates that the UC-MSC secretome and UC-MSC derived EVs exert potent antioxidant and anti-inflammatory effects across a range of models, including UV-induced aging, chronic and diabetic wounds, inflammatory dermatitis, and pigmentary disorders [9,11,13,14]. These effects are mediated through coordinated regulation of redox-sensitive signaling pathways, inflammatory cascades, and immune cell behavior within the cutaneous microenvironment [9].

This review provides a comprehensive narrative overview of the role of umbilical cord–derived mesenchymal stem cell secretome in regulating oxidative stress and inflammation in skin cells. By integrating mechanistic insights and evidence from in vitro studies, animal models, and emerging translational research, we aim to highlight the therapeutic potential of UC-MSC secretome based strategies, identify current limitations, and outline future research directions for their application in dermatology and cutaneous regenerative medicine.

METHOD

A narrative literature search was conducted to summarize current knowledge on the role of umbilical cord–derived mesenchymal stem cell (UC-MSC) secretome in regulating oxidative stress and inflammation in skin cells. Relevant articles were identified through PubMed, Scopus, ScienceDirect, and Google Scholar.

The search included studies published from 2016 to 2025 to capture recent advances in UC-MSC secretome research. Key search terms were used in various combinations, including “umbilical cord mesenchymal stem cells,” “UC-MSC secretome,” “conditioned medium,” “extracellular vesicles,” “exosomes,” “oxidative stress,” “reactive oxygen species,” “inflammation,” “keratinocytes,” “fibroblasts,” and “wound healing.”

A total of 7,018 records were initially identified across all databases. After removal of duplicates and screening of titles and abstracts, 46 articles were selected for full-text review. Of these, 12 studies were included in the final analysis based on their relevance to skin biology and their contribution to mechanistic understanding of oxidative stress and inflammation.

Exclusion criteria included: studies not related to skin cells or dermatological models, articles lacking mechanistic insight into oxidative stress or inflammation, review articles without primary experimental data, non-English publications, and conference abstracts without full-text availability.

Given the narrative nature of this review, study selection was based on biological relevance and mechanistic insight rather than strict methodological filtering.

RESULT

Umbilical Cord–Derived Mesenchymal Stem Cells and Their Secretome

Umbilical cord–derived mesenchymal stem cells (UC-MSCs) are one of the most extensively developed perinatal stem cell sources for regenerative applications, including dermatology[15,16]. UC-MSCs are obtained from abundantly available umbilical cord tissue and can be collected through non-invasive procedures, thereby posing no ethical concerns or risk to donors[15]. Compared with mesenchymal stem cells derived from adult tissues, UC-MSCs exhibit higher proliferative capacity, lower immunogenicity, and robust immunomodulatory activity, making them an attractive source for skin-directed therapies[17,18].

In the context of skin regeneration, the therapeutic benefits of UC-MSCs do not primarily rely on their ability to differentiate into skin cell types, but rather on the paracrine effects they mediate[15]. Substantial evidence indicates that UC-MSCs secrete a wide array of bioactive molecules capable of influencing the behavior of surrounding target cells. This collective set of bioactive factors, known as the UC-MSC secretome, includes soluble factors and extracellular vesicles that act synergistically to regulate cellular responses[11,18].

The UC-MSC secretome consists of soluble components such as cytokines, chemokines, and growth factors, as well as extracellular vesicles carrying proteins, lipids, and regulatory microRNAs[19]. These components play critical roles in maintaining cellular homeostasis, regulating redox balance, suppressing inflammatory responses, and supporting tissue repair processes[8,17]. In skin cells, the UC-MSC secretome has been shown to modulate the proliferation, migration, and survival of keratinocytes and fibroblasts, while also protecting melanocytes from damage induced by oxidative stress and inflammation[15,20].

Secretome-based therapeutic approaches using UC-MSCs offer several advantages over cell-based therapies. As a cell-free modality, the UC-MSC secretome demonstrates an improved safety profile, with minimal risk of immune rejection and ectopic tissue formation[19,21]. In addition, the secretome is more amenable to standardization, storage, and formulation for various routes of administration, including topical application or local injection into the skin[22.] These characteristics

position the UC-MSC secretome as a promising candidate for the development of dermatological therapies that simultaneously target oxidative stress and inflammation.

Role of the UC-MSC Secretome in Regulating Oxidative Stress in Skin Cells

Oxidative stress is a major factor contributing to dysfunction in skin cells, including keratinocytes, fibroblasts, and melanocytes. Excessive production of reactive oxygen species (ROS), whether induced by ultraviolet radiation exposure, environmental pollutants, or metabolic disturbances, disrupts cellular redox homeostasis and leads to biomolecular damage[16,20]. Reactive nitrogen species (RNS) also play a role in exacerbating oxidative stress. ROS and RNS are generated through mitochondrial activity, NADPH oxidases (NOXs), nitric oxide synthases (NOS), as well as chemical reactions such as the Fenton and Haber–Weiss reactions.

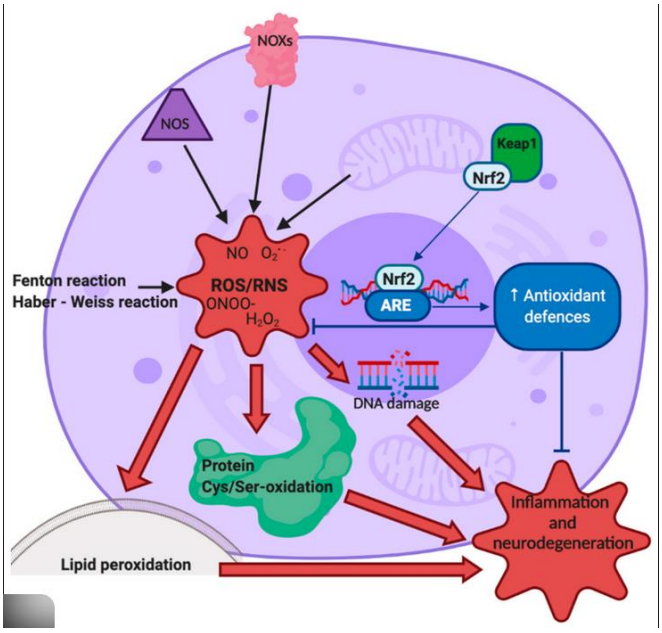

Figure 1. Schematic representation of the sources and effects of oxidative stress[23].

Accumulation of these reactive species triggers lipid peroxidation of cellular membranes, protein oxidation, and DNA damage, ultimately leading to cellular dysfunction and cell death[23]. Oxidative damage also contributes to the activation of redox-sensitive inflammatory pathways, thereby exacerbating tissue injury and impairing skin regenerative processes. As a major protective mechanism, activation of the nuclear factor erythroid 2–related factor 2 (Nrf2), antioxidant response element (ARE) pathway enhances the expression of endogenous antioxidant enzymes to suppress ROS/RNS accumulation and limit cellular damage. However, when antioxidant defense capacity is insufficient, oxidative stress persists and contributes to chronic inflammation and the progression of skin tissue degeneration[16,19].

Numerous studies have demonstrated that the umbilical cord–derived mesenchymal stem cell (UC-MSC) secretome possesses significant capacity to regulate oxidative stress in skin cells[15,16]. Treatment with UC-MSC–derived conditioned medium or extracellular vesicles has been reported to reduce intracellular and mitochondrial ROS accumulation in keratinocytes and fibroblasts exposed to oxidative stress[16,20]. This reduction in ROS is associated with enhanced cell viability, protection against DNA damage, and restoration of cellular proliferative and migratory capacities. Similar protective effects have also been observed in melanocytes, in which the UC-MSC secretome helps maintain cell

survival under conditions of excessive oxidative stress[15,20.] A summary of the principal bioactive components and involved signaling pathways is presented in Table 1.

Table 1. The main bioactive components of UC-MSC secretions involved in regulation oxidative stress and inflammation of skin cells

Source of Secretom	Secretomic Components	Categories	Molecular Targets/Pathways	Antioxidant Effects	Anti-inflammatory effect	Skin Cell Proof/Model
UC-MSC (standard culture, EV)	TIMP1	EV protein cargo	ADAM10–Notch1 Signaling	Reduces ROS accumulation and DNA damage	Suppresses age-related inflammatory cytokines	Keratinocytes, fibroblasts; UVB-induced photoaging model[16]
UC-MSC (exosome)	miR-200a-3p	Exosome miRNA	Keap1/Nrf2 Lines	Enable Nrf2, set HO-1, NQO1, SOD2, CAT	Indirect inhibition of NF-κB-induced inflammation	Keratinocytes (UVB in vitro and in vivo)[8]
UC-MSC (3D culture exosomes)	miR-125b-5p	Exosome miRNA	Bak1-mediated apoptosis	Reduces oxidative stress-induced apoptosis	Limits immune-mediated melanocyte damage	melanocytes vitiligo; Vitiligo mouse model[12]
UC-MSC (3D culture exosomes)	miR-132-3p	Exosome miRNA	SIRT1 Signaling	Indirect antioxidant effects through metabolic regulation	Promotes Treg expansion and immunosuppression	Vitiligo skin inflammation model[12]
UC-MSC (secret/EV)	SOD2	Antioxidant enzymes	Mitochondrial ROS detoxification	Direct ROS scavenger, protecting mtDNA	Reduces the amplification of ROS-induced inflammation	Keratinocytes exposed to UVB[20]
UC-MSC induced hypoxia	HIF-1α–regulated factors ,HIF-1α	Hypoxia-induced EV cargo	HIF-1α/VEGFA Axis	Reduces oxidative stress in hypoxia conditions	Promotes the polarization of M2 macrophages	Fibroblasts of diabetic and macrophage wounds[25]
UC-MSC (dissolved secretome)	IL-10	Cytokines	IL-10/STAT3 receptors	Indirect antioxidant effects through immune regulation	Suppresses TNF-α, IL-1β, IL-6	Wound healing model and inflammatory skin[11]
UC-MSC (dissolved secretome)	CCL2	Kemokine	CCR2 Signaling	Indirect (immune-mediated)	Improves macrophage recruitment and M2 polarization	Models of skin wounds with full thickness[14]
UC-MSC (inflammatory-	PDGF-BB	Growth factors	PI3K–AKT, MAPK LINE	Supports cell survival under	Promotes resolution of repair-related inflammation	Keratinocyte scratch

Source of Secretom	Secretomic Components	Categories	Molecular Targets/Pathways	Antioxidant Effects	Anti-inflammatory effect	Skin Cell Proof/Model
induced secretomery)				oxidative stress		wound model[17]
UC-MSC (inflammatory-induced secretomery)	VEGF	Growth factors	VEGFR2 Signaling	Improves tissue oxygenation, limiting ROS buildup	Anti-inflammatory through vascular normalization	Fibroblasts, endothelial cells, wound models[17]
UC-MSC + exogenous antioxidants	EGCG (shipped together)	Polyphenols (additional)	AMPK Line, Nrf2	Powerful ROS scavenger	Suppresses IL-1β, TNF-α, IL-6	Keratinocytes and skin of mice damaged by UVB [20]
apoptotic UC-MSC	ApoEV-related enzymes	Apoptotic EV cargo	Inflamasum NLRP3	Reduces oxidative stress in macrophages	Inhibits the release of IL-1β/IL-18 and pyroptosis	Macrophage model of diabetic wounds[13]

In addition to directly reducing ROS levels, the UC-MSC secretome also plays a role in strengthening endogenous antioxidant defense systems in skin cells[8,15]. Bioactive factors within the secretome are known to activate key antioxidant signaling pathways and upregulate the expression of cytoprotective enzymes, thereby enabling skin cells to adapt more effectively and sustainably to oxidative stress conditions[18,19]. This mechanism is particularly important in settings of chronic exposure, such as ultraviolet radiation induced skin aging or impaired wound healing[16].

Protection of mitochondrial function represents another critical aspect contributing to the antioxidant effects of the UC-MSC secretome. Mitochondria are both a primary source of ROS and a major target of oxidative damage[22]. Experimental evidence indicates that the UC-MSC secretome helps preserve mitochondrial integrity, stabilize mitochondrial membrane potential, and limit excessive ROS production. By maintaining mitochondrial function, the UC-MSC secretome supports energy homeostasis and promotes the survival of skin cells under stress conditions[15,18].

Collectively, the UC-MSC secretome regulates oxidative stress in skin cells through integrated mechanisms, including direct reduction of ROS, reinforcement of endogenous antioxidant systems, and protection of mitochondrial function[24].

Role of the UC-MSCSecretome in Regulating Inflammation in Skin Cell

Inflammation is an essential biological response of the skin to injury and environmental stress; however, excessive or prolonged inflammation can lead to tissue damage and impaired regeneration. At the cellular level, oxidative stress serves as a major trigger for the activation of inflammatory pathways through increased production of reactive oxygen species (ROS), which subsequently activate redox-sensitive transcription factors and kinases[25]. Persistent inflammatory activation in skin cells contributes to premature aging, disruption of epidermal barrier function, and delayed wound healing[26].

The umbilical cord–derived mesenchymal stem cell (UC-MSC) secretome exhibits potent anti-inflammatory effects across multiple skin cell types[16]. Treatment with the UC-MSC secretome has been reported to reduce the expression and release of key inflammatory mediators, including pro-inflammatory cytokines, in stressed keratinocytes and fibroblasts[15,16]. These effects are associated with inhibition of major inflammatory signaling pathways, particularly nuclear factor kappa B (NF-κB) and

mitogen-activated protein kinase (MAPK) pathways, which play central roles in regulating cutaneous inflammatory responses[19].

In addition to its direct effects on skin cells, the UC-MSC secretome also modulates immune responses within the cutaneous microenvironment. Bioactive components of the secretome are known to influence immune cell behavior, especially macrophages, by promoting polarization toward a more anti-inflammatory, tissue-repair–supportive phenotype. This immunomodulatory effect contributes to shortening the inflammatory phase and facilitating the transition to the regenerative phase during skin wound healing[14,17].

The reciprocal interaction between oxidative stress and inflammation represents another key aspect regulated by the UC-MSC secretome. By reducing ROS production, the UC-MSC secretome indirectly limits activation of redox-dependent inflammatory pathways[16,19]. Conversely, suppression of inflammation also decreases secondary ROS generation by skin cells and immune cells. This bidirectional regulation disrupts the pathological feedback loop between oxidative stress and inflammation, thereby creating a microenvironment more conducive to the restoration of homeostasis and skin regeneration[13,19,20].

Overall, the UC-MSC secretome inhibits inflammation in skin cells through a combination of suppressing pro-inflammatory signaling pathways, modulating immune responses, and controlling oxidative stress. These integrated anti-inflammatory effects form a critical basis for the potential application of UC-MSC secretome–based therapies in the management of various skin conditions characterized by chronic inflammation and tissue damage[15,16,20].

Evidence from In Vitro and In Vivo Studies

In vitro studies using skin-derived cells have provided important mechanistic insights into how the UC-MSC secretome regulates oxidative stress and inflammation at the cellular level. Across multiple experimental models, extracellular vesicles and conditioned media derived from UC-MSCs consistently reduce intracellular ROS accumulation, suppress the production of inflammatory cytokines, and restore essential cellular functions disrupted by stress. Keratinocyte based studies currently dominate the literature and clearly demonstrate the antioxidant capacity of the UC-MSC secretome. These protective effects are accompanied by significant reductions in pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, underscoring the close interplay between redox regulation and inflammatory suppression. Further mechanistic analyses have identified EV cargo, such as TIMP1 and microRNAs targeting redox-sensitive pathways, as key mediators of these effects[8,16].

In chemically induced inflammatory models, UC-MSC–derived extracellular vesicles also enhance keratinocyte viability and migratory capacity while suppressing intracellular and mitochondrial ROS accumulation. These effects are associated with inhibition of NF-κB activation and upregulation of antioxidant transcriptional regulators such as SIRT1, p53, and FOXO3. These findings indicate that the UC-MSC secretome restores redox balance through coordinated transcriptional regulation rather than solely through direct ROS scavenging[18].

Studies in dermal fibroblasts further reinforce the cytoprotective and anti-senescent effects of the UC-MSC secretome. In hydrogen peroxide–induced oxidative stress models, UC-MSC–derived exosomes restore fibroblast viability, reduce lactate dehydrogenase release, and significantly decrease the proportion of senescence associated β-galactosidase–positive cells. These effects are linked to suppression of ROS-activated NF-κB and MAPK signaling pathways, along with normalization of senescence markers such as lamin B1 and p21. These findings demonstrate that secretome-based treatment directly counteracts oxidative stress–induced inflammatory senescence in dermal cells[19].

Conditioned medium–based studies further reveal that the UC-MSC secretome supports extracellular matrix homeostasis under oxidative stress conditions. Fibroblasts treated with UC-MSC–conditioned medium exhibit increased production of procollagen and hyaluronic acid, reduced

expression of matrix metalloproteinases, and enhanced expression of antioxidant genes following UV exposure. Notably, secretomes generated under optimized culture conditions such as bioreactor based expansion or inflammatory priming demonstrate superior efficacy. These observations highlight the critical importance of secretome composition and production strategies in determining functional outcomes[15,17].

Although fewer in number, in vitro studies involving melanocytes provide compelling evidence for the relevance of the UC-MSC secretome in pigmentary disorders. In melanocytes exposed to oxidative stress, UC-MSC derived extracellular vesicles significantly reduce ROS accumulation and apoptosis while preserving melanocyte survival. These effects are mediated by EV-contained microRNAs that regulate oxidative stress and apoptosis-related pathways and are accompanied by suppression of inflammatory immune signaling. These findings underscore the dual role of the UC-MSC secretome as both an antioxidant and an immunomodulatory agent[13]. Collectively, in vitro studies consistently demonstrate that the UC-MSC secretome exerts broad antioxidant and anti-inflammatory effects across multiple skin cell types. By restoring redox homeostasis, suppressing inflammatory signaling, and preserving cellular function, these findings provide a strong mechanistic foundation for the beneficial therapeutic outcomes observed in in vivo models of skin injury and disease.

In vivo studies using animal models of skin damage and disease provide critical validation of the antioxidant and anti-inflammatory effects of the UC-MSC secretome observed in vitro. Across a range of pathological contexts including UV-induced photoaging, diabetic wounds, inflammatory skin injury, and autoimmune pigmentary disorders UC-MSC–derived extracellular vesicles and conditioned media consistently enhance tissue repair, suppress oxidative damage, and modulate inflammatory responses.

UV radiation induced skin injury models represent one of the most extensively studied systems. In murine models of UVB-induced photoaging, administration of UC-MSC–derived extracellular vesicles significantly reduces epidermal thickening, collagen degradation, and transepidermal water loss, while improving overall skin architecture. These structural improvements are accompanied by marked reductions in intracellular ROS accumulation, DNA damage markers such as γ-H2AX, and senescence-associated β-galactosidase positivity in epidermal and dermal cells. Importantly, treatment with UC-MSC extracellular vesicles suppresses UV-induced expression of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, indicating coordinated in vivo regulation of oxidative stress and inflammation[8,16]. Further mechanistic analyses have identified EV-associated factors, such as TIMP1 and regulatory microRNAs, as key mediators linking redox regulation to inhibition of pro-senescent signaling pathways.

Diabetic wound models provide additional insight into the therapeutic relevance of the UC-MSC secretome under conditions of chronic oxidative stress and inflammation. In streptozotocin-induced diabetic rodents, treatment with hypoxia-preconditioned UC-MSC–derived extracellular vesicles accelerates wound closure, enhances collagen deposition, and promotes angiogenesis within the wound bed. These effects are associated with reduced oxidative stress evidenced by lower ROS levels and diminished senescence markers as well as suppression of inflammatory mediators such as TNF-α. UC-MSC–derived extracellular vesicles also modulate immune responses by promoting macrophage polarization toward a reparative phenotype, thereby shortening the inflammatory phase and facilitating tissue regeneration[25].

Complementary studies using extracellular vesicles derived from apoptotic UC-MSCs have also demonstrated inhibition of inflammasome activation and oxidative stress–induced pyroptosis in macrophages, further confirming a direct link between redox regulation and suppression of inflammatory cell death pathways in diabetic wounds[13].

Models of inflammatory skin injury further substantiate the immunomodulatory capacity of the UC-MSC secretome in vivo. In full-thickness excisional wound models, secretomes derived from UC-

MSCs primed with inflammatory cytokines significantly improve wound-healing quality by enhancing granulation tissue formation, improving collagen organization, and reducing inflammatory cell infiltration. These benefits are mediated in part through enhanced recruitment and polarization of macrophages toward an anti-inflammatory phenotype via chemokines such as CCL2 and cytokines such as IL-6, illustrating how secretome conditioning influences immune–redox interactions during tissue repair[14].

In recent years, animal models of pigmentary and autoimmune skin disorders have expanded the scope of UC-MSC secretome research. In vitiligo models, UC-MSC exosomes cultured under three-dimensional conditions reduce oxidative stress–induced melanocyte apoptosis, restore pigmentation, and decrease infiltration of cytotoxic $CD8^+$ T cells in affected skin. These effects are mediated by EV-associated microRNAs that regulate oxidative stress pathways in melanocytes and promote regulatory T cell expansion, illustrating how the UC-MSC secretome simultaneously targets redox imbalance and immune dysregulation in complex inflammatory skin diseases[20].

Notably, several in vivo studies have also highlighted the importance of delivery strategies in maximizing therapeutic efficacy. For example, incorporation of UC-MSC exosomes into dissolvable microneedle systems enhances dermal penetration, retention, and antioxidant activity in UV-damaged skin, resulting in superior suppression of oxidative DNA damage and inflammatory cytokine production compared with free exosome administration [20]. These findings underscore the translational potential of combining UC-MSC secretome based therapies with advanced biomaterial-based delivery platforms Overall, in vivo studies provide strong and consistent evidence that the UC-MSC secretome effectively reduces oxidative stress and inflammation across diverse models of skin disease. By restoring redox homeostasis, suppressing inflammatory signaling, modulating immune cell behavior, and enhancing tissue regeneration, the UC-MSC secretome demonstrates broad therapeutic potential extending beyond simple wound repair to encompass chronic inflammatory and degenerative skin disorders.

DISCUSSION

Potential Applications of the UC-MSC Secretome in Dermatology

The antioxidant and anti-inflammatory properties of the umbilical cord–derived mesenchymal stem cell (UC-MSC) secretome make it a promising candidate for a wide range of dermatological applications [19]. Through its ability to regulate oxidative stress, suppress inflammation, and support tissue regeneration, the UC-MSC secretome holds potential for the management of skin conditions characterized by cellular damage and chronic inflammation[28]. One potential application of the UC-MSC secretome is in skin aging, particularly aging induced by ultraviolet radiation exposure. Oxidative stress and inflammation play critical roles in dermal matrix degradation and impairment of epidermal barrier function. Based on preclinical evidence, the UC-MSC secretome is capable of reducing oxidative damage, preserving collagen structure, and improving skin cell function, suggesting its potential use as a therapeutic or adjuvant approach for the prevention and treatment of skin aging[18].

In addition, the UC-MSC secretome demonstrates substantial potential in wound healing, including chronic wounds and wounds associated with metabolic conditions such as diabetes[11]. By regulating oxidative stress, modulating inflammation, and supporting angiogenesis and cell migration, the UC-MSC secretome can accelerate wound repair and improve the quality of tissue regeneration.

This approach is particularly relevant given the limitations of conventional therapies in managing wounds accompanied by prolonged inflammation[13,14,29].

In inflammatory skin diseases and pigmentary disorders, the immunomodulatory properties of the UC-MSC secretome also offer promising therapeutic opportunities. By suppressing excessive inflammatory responses and protecting skin cells vulnerable to oxidative damage, the UC-MSC secretome may help restore cutaneous homeostasis[8,20]. Another key advantage of secretome-based

approaches is their cell-free nature, which confers an improved safety profile, reduced immunogenicity risk, and greater flexibility in formulation and routes of administration[17,19]. Nevertheless, challenges related to production standardization, dose determination, and long-term safety evaluation remain to be addressed through further research.

Table 2. Representative studies investigating the effects of umbilical cord–derived mesenchymal stem cell secretome on oxidative stress and inflammation in skin cells.

UC-MSC Secretome Type	Model / Cell Type	Stress / Inflammatory Stimulus	Key Findings	Mechanistic Insights	Study
HUMSC-EV (umbilical cord MSC–derived EVs), compared with AMSC-EV; isolated by ultracentrifugation; characterized by TEM, NTA, ExoView, and WB (CD63, CD9, TSG101, Alix)	*In vitro:* HaCaT keratinocytes, primary human keratinocytes (HKCs), human dermal fibroblasts (HDFs), reconstructed full-thickness T-Skin model. *In vivo:* UVB-induced photoaging in nude mice (subcutaneous EV injection).	UVB irradiation (cellular and murine photoaging); ROS/DNA damage induced by UVB; inflammatory readouts (IL-1β, IL-6, TNF-α).	EV treatment (HUMSC-EV and AMSC-EV) reduced intracellular ROS, decreased γ-H2AX foci and SA-β-gal positivity, restored proliferation and migration, reduced IL-1β/IL-6/TNF-α, restored TIMP1 and collagen (COL1/COL3), reduced MMP1/MMP3, improved skin histology, reduced wrinkles and transepidermal water loss; HUMSC-EV showed slightly stronger effects.	Proteomics identified TIMP1 enrichment in EV cargo; TIMP1 recapitulated multiple EV effects (↓ROS, ↓γ-H2AX, ↓SA-β-gal, ↓MMPs). RNA-seq showed EV-mediated suppression of UVB-induced Notch pathway genes (NOTCH1, HES1). Functional assays demonstrated TIMP1 inhibition of ADAM10 → reduced Notch activation. Notch activator (VPA) attenuated EV/TIMP1 efficacy, whereas ADAM10 inhibition mimicked EV effects. Luciferase reporter, WB, siRNA, and rescue experiments validated the TIMP1–ADAM10–Notch1 axis in ROS regulation and senescence.	Zhang H., Xiao X., Wang L., *et al.* Signal Transduction and Targeted Therapy, 2024
Hypoxia-induced HUCMSC-EVs (hy-EVs) vs normoxic EVs (n-EVs); ultracentrifugation; characterized by NTA, TEM, WB (CD63, CD9, TSG101)	*In vitro:* Human skin fibroblasts (HSFs), HUVECs, macrophages (polarization assays). *In vivo:* Streptozotocin-	High-glucose conditions (*in vitro*) and diabetic wound microenvironment (*in vivo*).	hy-EVs (more than n-EVs) enhanced proliferation, migration, and tube formation of HSFs and HUVECs; reduced intracellular	Hypoxia increased HIF-1α expression in parental HUCMSCs. hy-EVs activated HIF-1α/VEGFA/CD31 signaling in recipient cells (WB/IF). hy-EVs promoted	Su Y., Lu J., Liang F., Cheng J., *Biomolecules*, 2025

UC-MSC Secretome Type	Model / Cell Type	Stress / Inflammatory Stimulus	Key Findings	Mechanistic Insights	Study
	induced diabetic full-thickness dorsal wounds in rats (subcutaneous EV injection).		ROS (DCFH-DA), reduced SA-β-gal; decreased TNF-α and CD86, increased CD206; promoted angiogenesis (↑HIF-1α, VEGFA, CD31), increased collagen deposition, and accelerated wound closure in diabetic rats.	macrophage polarization from M1 to M2 (CD86↓, CD206↑). Effects were attributed to hypoxia-regulated EV cargo (miRNAs/proteins), although no causal knockdown or rescue of specific cargo was performed.	
HuMSC-derived exosomes (ultracentrifugation; CD9, CD63, TSG101, Alix positive)	*In vitro:* HaCaT keratinocytes. *In vivo:* UVB-irradiated C57BL/6 mouse skin.	UVB irradiation (100 mJ/cm² *in vitro*; cumulative UVB *in vivo*).	Exosomes reduced intracellular ROS, suppressed IL-1β, TNF-α, and IL-6, decreased iNOS and COX-2, inhibited NF-κB activation, restored keratinocyte migration, and reduced epidermal thickening and collagen damage *in vivo*.	Exosomal miR-200a-3p directly targeted Keap1, activating Nrf2 signaling; increased nuclear translocation of Nrf2 and expression of antioxidant genes (HO-1, NQO1, CAT, SOD2). Effects were reversed by miR-200a-3p inhibition or Nrf2 knockdown.	Gui Q. *et al.*, *International Journal of Stem Cells*, 2025
hUMSC-Exo (ultracentrifugation; TEM/NTA; CD9, TSG101, Alix positive) co-delivered with EGCG via dissolvable HAMA/PVA microneedles (hUMSC-Exo/EGCG-MN)	*In vitro:* UVB-exposed HaCaT keratinocytes. *In vivo:* BALB/c mouse UVB photodamage model (daily UVB × 7 days).	UVB irradiation (50–220 mJ·cm^{-2}, assay-dependent).	hUMSC-Exo and EGCG individually reduced ROS and inflammatory cytokines; microneedle-delivered Exo+EGCG produced the strongest effects: reduced intracellular ROS (DCFH-	RNA-seq with qPCR/WB identified IL-1β suppression and SOD2 regulation as central nodes. Functional validation showed that IL-1β activation or SOD2 inhibition attenuated Exo/EGCG protection (↑ROS, ↑γ-H2AX). Transcriptomics	He C., Wang Z., Jiang Z., *et al.*, *Journal of Nanobiotechnology*, 2025

UC-MSC Secretome Type	Model / Cell Type	Stress / Inflammatory Stimulus	Key Findings	Mechanistic Insights	Study
			DA), decreased γ-H2AX and 8-OHdG, reduced IL-1β/IL-6/TNF-α, reduced epidermal thickness, increased collagen I expression.	revealed modulation of endocytosis, AMPK, JAK-STAT, PI3K-AKT, MAPK, and VEGF pathways (GSEA). Microneedle delivery enhanced endocytic pathway activity.	
UCMSC-derived EVs (TFF isolation; TEM/NTA; CD9, CD63, CD81 positive)	*In vitro:* HaCaT keratinocytes.	Oxazolone-induced keratinocyte inflammation and oxidative stress.	UCMSC-EVs increased keratinocyte viability and migration, reduced intracellular and mitochondrial ROS, decreased IL-1β and TNF-α secretion, and inhibited NF-κB activation.	UCMSC-EVs regulated SIRT1 and p53, suppressed p65 (NF-κB), and enhanced p53 binding to the FOXO3 promoter (ChIP-qPCR), activating FOXO3-mediated antioxidant and anti-inflammatory responses.	Lin T.-Y. *et al.*, *International Journal of Molecular Sciences*, 2023

Clinical Translation and Current Evidence Gaps

Despite the strong preclinical evidence supporting the antioxidant and anti-inflammatory effects of the UC-MSC secretome, clinical evidence remains limited. To date, most studies are confined to in vitro systems and animal models, with very few early-phase clinical investigations exploring secretome-based therapies in dermatology.

Preliminary clinical approaches using mesenchymal stem cell–derived products, including conditioned media and extracellular vesicles, have shown promising safety profiles and potential efficacy in wound healing and inflammatory skin conditions. However, standardized clinical trials specifically evaluating UC-MSC secretome are still lacking.

Several challenges hinder clinical translation, including variability in secretome composition depending on cell source, culture conditions, and isolation methods, as well as the absence of standardized dosing protocols and potency assays. Furthermore, long-term safety, optimal delivery systems, and regulatory considerations remain unresolved.

Future research should focus on well-designed clinical trials, standardized manufacturing protocols, and integration of advanced delivery systems to bridge the gap between preclinical findings and clinical application.

CONCLUSION

The umbilical cord–derived mesenchymal stem cell secretome plays a crucial role in regulating oxidative stress and inflammation in skin cells by reducing reactive oxygen species production, strengthening endogenous antioxidant systems, suppressing major inflammatory pathways, and modulating immune responses, thereby supporting the restoration of homeostasis and skin tissue

regeneration. Although preclinical studies demonstrate promising therapeutic potential, the clinical application of the UC-MSC secretome remains limited by factors such as insufficient standardization of production processes, incomplete mechanistic understanding, and a lack of robust long-term safety and efficacy data. Therefore, optimization of UC-MSC culture and preconditioning strategies, integration of omics-based technologies, development of standardized potency assays, and implementation of well-controlled clinical studies are required to ensure the consistency, safety, and effectiveness of secretome-based therapies. With sustained interdisciplinary efforts, the UC-MSC secretome has the potential to evolve into a reliable and clinically applicable cell-free therapeutic modality in regenerative dermatology.

ACKNOWLEDGEMENT

The authors would like to acknowledge all researchers whose studies contributed to the understanding of umbilical cord–derived mesenchymal stem cell secretome and its role in regulating oxidative stress and inflammation in skin biology. We also thank colleagues and collaborators for their valuable discussions and scientific insights that supported the development of this review. No specific funding was received for the preparation of this manuscript

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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