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Review

Exosomes derived from mesenchymal stem cells: A novel agent for skin aging treatment

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ABSTRACT

Skin aging, influenced by both intrinsic and extrinsic factors, leads to structural and functional deterioration characterized by wrinkles, reduced elasticity, and impaired wound healing. Mesenchymal stem cell-derived exosomes (MSC-exos) have emerged as a promising therapeutic option, offering multifaceted benefits for skin rejuvenation. These nano-sized extracellular vesicles exhibit exceptional bioavailability, biocompatibility, and immunomodulatory properties, addressing challenges associated with conventional treatments. MSC-exos enhance collagen synthesis, modulate inflammation, and promote angiogenesis through molecular pathways such as PI3K/Akt and Notch signaling. Furthermore, their ability to deliver bioactive molecules precisely to target cells underscores their therapeutic potential in skin repair and anti-aging applications. However, challenges remain regarding large-scale production, targeting efficiency, and regulatory frameworks, warranting further research to translate these innovative therapies into clinical practice.

Key words: Mesenchymal stem cell-derived exosomes (MSC-exos), Skin aging, Collagen remodeling, Immunomodulation, Angiogenesis

INTRODUCTION

Aging of the skin is a dynamic and multifactorial process influenced by genetic predispositions, hormonal shifts, and external stressors such as UV exposure, environmental pollutants, and lifestyle behaviors. This progression manifests as structural degradation, including wrinkles, pigmentation changes, and reduced elasticity, alongside diminished regenerative capacities, such as impaired wound healing. While existing anti-aging therapies—ranging from topical formulations to minimally invasive interventions—have achieved varying degrees of success, their effects are often transient and target isolated symptoms rather than the underlying biological mechanisms.

Emerging advancements in regenerative medicine, particularly the application of MSC-exos, offer a groundbreaking avenue for skin rejuvenation. These nanoscale vesicles, derived from stem cells, demonstrate remarkable potential to rejuvenate aged skin by orchestrating collagen remodeling, mitigating chronic inflammation, and stimulating angiogenesis. Unlike traditional approaches, MSC-exos provide a holistic solution, addressing both the causes and manifestations of skin aging.

This review delves into the transformative potential of MSC-derived exosomes in combating skin aging. By examining their unique bioavailability, immunomodulatory properties, and effects on collagen and vascular networks, we aim to highlight their promise as a next-generation therapy. Additionally, the challenges surrounding large-scale production, delivery precision, and regulatory barriers are discussed, offering insights into the future of this innovative field.

OVERVIEW OF SKIN AGING

The skin, the largest organ of the human body, covers an area of 2 m^2 and represents approximately 15% of the total body weight in adults. Its thickness ranges from 0.1 mm at its thinnest to 1.5 mm at its thickest[1,2]. Premature photoaged skin is characterized by various features, including a thickened epidermis, mottled discoloration, deep wrinkles, laxity, dullness, and a rough texture[3,4]. A prominent manifestation of aging is skin sagging, which occurs due to the gradual loss of elasticity[5,6]. In older adults, the rate of epidermal turnover and cell desquamation slows down, influencing the timing of aesthetic treatments. Accelerating the cell cycle has been shown to improve skin appearance and enhance wound healing, making these effects important targets for various products and procedures. The weakening of the dermal-epidermal junction in extrinsically aged skin may also contribute to wrinkle formation due to the loss of fibrillin-positive structures and a decrease in collagen type VII content[7–9]. Solar elastosis, commonly seen in the sun-exposed skin of the elderly, results from collagen breakdown by matrix metalloproteinases, serine proteases, and other proteases, which

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increase collagen degradation in photoaged skin [10,11]. As skin ages, the ratio of type III to type I collagen increases due to a decline in collagen levels [12,13]. Collagen content decreases by approximately 1% per year per unit area of skin [14]. Numerous studies available on PubMed have explored the impact of factors such as oxidative stress, ultraviolet (UV) radiation, and inflammation on skin aging [15]. These studies indicate that these factors contribute to the degeneration of collagen and other extracellular matrix (ECM) components, leading to wrinkles and loss of skin elasticity. The skin has a natural ability to heal itself, involving a cascade of processes such as hemostasis, inflammation, proliferation, and tissue remodeling. However, when this healing process is interrupted, altered, or prolonged, wound healing may be delayed, or chronic wounds may develop.

LIMITATIONS OF CURRENT THERAPEUTIC STRATEGIES FOR SKIN AGING

Skin aging is a complex process influenced by both intrinsic and extrinsic factors, characterized by wrinkles, fine lines, irregular pigmentation, and a progressive loss of skin elasticity, firmness, and moisture. Given the increasing demand for effective anti-aging treatments, recent years have seen significant advancements in therapeutic approaches to address skin aging.

One widely adopted strategy involves the use of topical medicines that target specific aging pathways. These include antioxidants, retinoids, and alpha-hydroxy acids. Retinoids, derivatives of vitamin A, enhance collagen synthesis and reduce the appearance of wrinkles and fine lines. Alpha-hydroxy acids, such as glycolic acid and lactic acid, exfoliate the skin while promoting collagen production [16–18]. Antioxidants like vitamins C and E protect the skin from oxidative damage caused by UV rays and environmental toxins [19–21].

Minimally invasive approaches, such as injectable fillers and botulinum toxin (Botox) injections, are also commonly employed. Injectable fillers, including hyaluronic acid and calcium hydroxyapatite, restore skin volume and reduce the visibility of wrinkles [22–24]. Botox injections relax the facial muscles responsible for dynamic wrinkles, particularly around the eyes and forehead [25–27].

More invasive procedures, such as chemical peels and laser resurfacing, target deeper layers of the skin to stimulate collagen synthesis. Chemical peels are effective for treating acne scars and sun damage [28], while laser resurfacing is particularly useful for addressing uneven pigmentation and deeper wrinkles [29].

Emerging regenerative medicine approaches have garnered attention for their potential to repair and regenerate aged skin tissues. Stem cells and growth factors are central to these strategies. Stem cells possess the capacity to differentiate into a myriad of cellular phenotypes, encompassing dermal cells, and thereby facilitating the replacement of compromised or senescent cells. Growth factors, such as platelet-rich plasma, stimulate collagen production and ECM remodeling, facilitating tissue repair [30,31].

Among alternative treatments, exosome-based therapies are gaining traction due to their unique advantages. Exosomes, tiny vesicles released by cells, including stem cells, contain bioactive compounds like growth factors, cytokines, and microRNAs that aid in tissue repair and regeneration [32–34]. A key advantage of exosomes is their non-immunogenic nature, minimizing the risk of adverse immune reactions, unlike injectable fillers or other invasive procedures [35,36].

Exosomes also address multiple aspects of skin aging simultaneously. They enhance cell proliferation and differentiation [37], boost collagen synthesis [38,39], and reduce inflammation [40,41], all of which are critical for skin regeneration. Furthermore, exosomes can be efficiently isolated from various cell types, making them a promising therapeutic option. Preclinical research has shown that exosomes can enhance wound healing and stimulate tissue regeneration, as evidenced by studies on animal models and in vitro experiments using human skin cells [42–45].

EXOSOMES AND THEIR POTENTIAL IN DERMATOLOGY

Exosomes are nano-sized biovesicles released into surrounding body fluids when multivesicular bodies fuse with the plasma membrane [39]. These vesicles originate from the internal folding of endosomal membranes, resulting in the formation of intraluminal vesicles, which are then secreted as exosomes. Acting as mediators of intercellular communication, exosomes transfer their cargo to target cells or activate signaling pathways on the cell surface. They play essential roles in physiological and pathological processes, including immune responses, cell proliferation, tissue homeostasis, cancer, and neurodegenerative diseases [39].

Exosomes contain a wide variety of biomolecules sourced from their parent cells, such as proteins, lipids, nucleic acids, and carbohydrates [46]. Their protein cargo comprises functional categories such as

tetraspanins, heat shock proteins, and cytoskeletal proteins. Lipids, like sphingomyelin and cholesterol, are enriched in exosomes, contributing to their structural integrity and biological functions. Nucleic acids in exosomes, including messenger RNAs, long noncoding RNAs, and microRNAs, have the ability to modulate gene expression in recipient cells[47,48].

Exosomes impact a range of cellular processes, including cell growth, differentiation, and apoptosis[39,46]. They also play a dual role in immune regulation, either stimulating or inhibiting immune responses depending on the context[49,50]. In addition, exosomes are involved in the progression of various diseases, such as cancer, cardiovascular diseases, and neurodegenerative disorders, underscoring their potential for diagnostic and therapeutic applications[51].

In regenerative medicine, exosomes derived from MSC-exos offer significant advantages over traditional live stem cell therapies. While adipose-derived stem cells (ADSCs) have shown limited efficacy due to apoptosis shortly after transplantation[52,53] and challenges related to circulation and thrombus formation[54,55], MSC-exos mitigate these issues. Intravenous injection of MSCs may cause aggregation in microcirculation and pose risks of mutagenicity or oncogenicity, risks that are absent with MSC-exos. Additionally, MSC-exos remain stable during long-term storage, facilitating safe transport and delayed therapeutic application.

The potential of exosomes in treating skin abnormalities has been extensively explored in recent years. Their primary advantages include stability, resistance to immunological rejection, and the capacity to directly stimulate target cells. Unlike conventional treatments, exosomes can exert multiple therapeutic effects through a single component, making them a versatile and promising option for clinical applications.

MSC-DERIVED EXOSOMES IN SKIN AGING TREATMENT

Bioavailability and Delivery Mechanisms

Exosomes, derived from the late endocytic compartment, diffuse easily into intracellular fluids and rapidly fuse with target cells, enhancing their potential for therapeutic delivery. They exhibit exceptional interaction with cellular membranes, which is crucial for efficient drug delivery. Recent in vivo studies have shown that exosomes exhibit specific cell tropism, guiding them to disease-affected tissues and organs[56]. This targeting ability is a result of both their intrinsic properties and engineered modifications. Exosomes express unique surface proteins that enhance their natural ability to bind to specific cell types, facilitating efficient targeting and drug delivery[57].

The lipid bilayer structure of exosomes contributes to their low immunogenicity, allowing prolonged circulation and reducing the risk of immune rejection. Their natural structure also helps maintain integrity, ensuring that they protect their cargo until reaching the target site[58–60]. Furthermore, exosomes are biodegradable, reducing long-term toxicity risks compared to synthetic carriers that may persist in the body and cause chronic inflammation[61,62].

Genetic modifications can enhance the targeting capabilities of exosomes. Incorporating homing peptides and ligands allows exosomes to be directed to specific organs or tissues, improving therapeutic efficacy[59]. These modifications can also facilitate on-demand drug release in response to specific stimuli, enhancing precision in drug delivery[58]. Additionally, surface proteins such as tetraspanins and integrins improve exosomes' natural targeting ability, ensuring efficient delivery to the intended tissues[57]. Engineered exosomes can also express chemokine receptors to enhance their tropism toward inflamed tissues, which has been demonstrated in treatments for conditions like atherosclerosis[63]. This ability is further supported by transcytosis, a process enhanced by factors such as inflammation[64].

Despite their promise, exosomes' targeting efficiency can be inconsistent, and their production remains challenging. Synthetic alternatives may offer more controlled delivery mechanisms, highlighting the need for further optimization of exosome engineering[60]. Exosome production involves extensive cell culture and purification processes, which are resource-intensive and time-consuming. Variability in exosome composition requires rigorous quality assessment to ensure therapeutic efficacy[65,66]. Additionally, the lack of standardized manufacturing guidelines is a significant barrier[67]. The regulatory landscape for exosome-based therapies is complex, varying by jurisdiction, and requires comprehensive pharmacokinetic and therapeutic efficacy data, along with toxicology studies and potency assays to ensure safety and efficacy in clinical settings[68]. Low yield and batch reproducibility further limit their scalability, posing another challenge for widespread clinical application. While the potential of exosomes as therapeutic agents is significant, these challenges must be addressed through ongoing research. Optimization of production methods, improvements in targeting precision, and regulatory advancements are crucial to unlocking the full therapeutic potential of exosomes.

Low Immunogenicity and Safety Profile

MSC-exos have attracted considerable interest due to their immunomodulatory and regenerative capabilities. They increase Treg production in vivo and in vitro through TGF-α and IFN-γ[69].

MSC-exos regulate pattern recognition receptors (PRRs), modulate B-cell activities, polarize macrophages toward anti-inflammatory phenotypes, and fine-tune T-cell activity. These processes orchestrate diverse immunological responses, making MSC-exos valuable for precision medicine and therapeutic interventions[70].

MSC-exos primarily induce M2-like macrophage polarization through CD73 activity, which converts AMP to adenosine. This adenosine activates A2A and A2B receptors, triggering AKT/ERK signaling pathways that alleviate inflammation and immune dysfunction[71]. Furthermore, MSC-exos pre-treated in a diabetic environment (Exo-pre) enhance M2 polarization via miR-486-5p, which targets PIK3R1 and modulates the PI3K/Akt pathway[72].

Additionally, miR-150-5p within MSC-exos downregulates the PI3K/Akt/mTOR pathway by targeting Irs1 in recipient macrophages, promoting M2 polarization and inhibiting M1 activation[73]. They also inhibit LPS-induced inflammatory responses, increase IL-10 and Arg-1 levels, enhance CD206 expression, reduce NF-κB signaling, and stimulate STAT3 activity, further supporting M2 macrophage polarization[74]. In vivo studies show MSC-derived extracellular vesicles enhance M2 macrophage polarization, providing a novel therapeutic strategy to mitigate inflammatory conditions[75].

MSC-exos modulate T-cell activity by decreasing T-cell proliferation and Th1 differentiation while promoting Treg differentiation and restoring the Th17/Treg balance. These effects are mediated through pathways involving TGF-β and autophagy, as demonstrated in studies on primary Sjögren's syndrome[76,77]. MSC-exos also promote the generation of IFN-γ^+/Foxp3$^+$ T cells with suppressive capacity and influence Th1 metabolism. Proteins such as p27kip1 and Cdk2 play significant roles in cell cycle arrest and T-cell suppression mediated by MSC-exos[78]. Moreover, exosomes enriched with CD73 can inhibit T-cell proliferation, modulate T-cell differentiation, and enhance immunosuppressive effects, making them potential therapeutic agents for autoimmune diseases[79].

MSC-exos reduce neutrophil infiltration, attenuate NLRP3 inflammasome activation, and suppress the formation of neutrophil extracellular traps (NETs). They achieve this by up-regulating miR-199 in neutrophils, thereby decreasing NETs expression after stimulation[80].

Effects on Collagen Synthesis and Remodeling

Managing wound healing is a complex process involving sequential, overlapping stages, where disruptions can lead to chronic, non-healing wounds. Collagen, a critical component of the ECM in the dermis, provides structural integrity and support to the skin[81]. In aging skin, collagen type I and elastic fibers become fragmented, causing dermal layer damage and impairing skin elasticity[82,83]. Reconstructing the dermal structure can potentially mitigate aging effects and improve wound healing.

Several treatment options have been explored to counteract collagen degradation. Topical agents such as retinoids, alpha-hydroxy acids, and antioxidants stimulate collagen synthesis and inhibit its breakdown, but their effects are often limited and require prolonged use[84–86]. Invasive procedures like laser resurfacing, micro-needling, and injectable fillers can improve skin texture and reduce wrinkles. However, these methods carry risks such as scarring and infection[84,87–91].

Exosomes, nano-sized extracellular vesicles, offer a promising alternative. They can be applied topically or injected into the skin, allowing precise delivery to the dermis while minimizing systemic side effects. Exosomes contain bioactive molecules, including growth factors and cytokines, which promote angiogenesis and tissue remodeling[91–93]. Derived from various cell types, exosomes can influence collagen metabolism by breaching the epidermal barrier and interacting with target cells to regulate ECM homeostasis[94,95].

MSC-exosomes exhibit remarkable capability in delivering functional molecules, including proteins, lipids, mRNAs, and miRNAs, to recipient cells. Their phospholipid bilayer enables efficient delivery, influencing cellular processes like gene regulation, immune modulation, and tissue repair[96–99]. MSC-exosomes can enhance collagen production and reduce breakdown, particularly in fibroblasts, leading to smoother, more elastic skin[95,100–103]. They also address oxidative stress and inflammation, major contributors to skin aging[104,105].

MSC-exosomes are a promising strategy for treating skin disorders characterized by collagen dysregulation. These exosomes regulate collagen synthesis and

degradation in fibroblasts by modulating the expression of key genes and pathways. For instance, they enhance the expression of collagen-related genes such as col1a1 while reducing the levels of matrix metalloproteinases (MMPs) and increasing the expression of tissue inhibitors of metalloproteinases (TIMPs), thereby preserving the balance of the ECM [100,106]. Furthermore, MSC-exosomes contain miRNAs, such as miR-34b-3p and miR-144-3p, which regulate fibroblast behavior and collagen metabolism through pathways like PI3K/Akt [107–109].

During the early stages of wound healing, MSC-exosomes enhance type I and III collagen formation, promoting effective tissue regeneration. In later stages, they limit excessive collagen deposition, reducing scar formation. For instance, ADSC-derived exosomes adjust the type III-to-type I collagen ratio, aiding in balanced tissue repair [110,111]. Exosomes rich in miR-21-5p and miR-125b-5p suppress TGF-β receptors, preventing myofibroblast differentiation and promoting better skin regeneration [112]. Additionally, UCB-MSC-exos inhibit collagen I production while encouraging skin cell proliferation and migration, further optimizing wound healing outcomes.

Promotion of Angiogenesis

Aging induces significant morphological and functional changes in cutaneous blood vessels, impacting overall skin health and vascular functionality. Structural remodeling includes vascular adventitia thickening and a decrease in the density of skin lymphatic vessels, impairing fluid transport and immune responses [113,114]. Functional decline manifests through reduced vasomotor function, increased blood viscosity, and heightened platelet aggregation, compromising vascular health. Furthermore, aging diminishes the ability of blood vessels to respond to stimuli, evidenced by reduced skin blood flow and impaired post-occlusive hyperemia [115].

Endothelial dysfunction in aging cutaneous blood vessels is marked by reduced nitric oxide (NO) production, increased oxidative stress, and impaired vasodilation. Aging reduces NO bioavailability due to heightened superoxide anion production, leading to vascular dysfunction [116,117]. This dysfunction affects nutrient delivery and waste removal in skin tissues, contributing to skin sagging, dryness, and wrinkle formation, all hallmarks of declining skin health [116,118]. Increased vascular stiffness further exacerbates these conditions, reflecting overall skin aging.

Exosomes, especially those originating from MSCs and endothelial cells, play a key role in angiogenesis. They transport pro-angiogenic factors, including VEGF and bFGF, to target cells, thereby stimulating endothelial cell proliferation, migration, and the formation of blood vessels [119,120]. Both *in vivo* and *in vitro* studies show that exosomes derived from MSCs promote wound healing and angiogenesis. This is evident in diabetic skin ulcer models, where they accelerate wound closure and the formation of new blood vessels [121–123].

MSC-derived exosomes promote angiogenesis and improve skin health through various molecular pathways. Exosomal miR-126 activates the PI3K/Akt signaling pathway, enhancing VEGF and angiopoietin-1 expression, thereby stimulating endothelial cell proliferation and migration [124,125]. Exosomal miR-17-92 further supports angiogenesis by inhibiting ferroptosis and enhancing endothelial cell functions [126]. MicroRNA-125a, found in adipose-derived MSC exosomes, suppresses the angiogenic inhibitor DLL4, promoting the formation of endothelial tip cells [120]. MSC-derived exosomes exhibit anti-aging effects on skin vasculature by regulating angiogenic factors and improving collagen production. These exosomes stimulate dermal fibroblast proliferation, migration, and collagen deposition, facilitating tissue regeneration and wound healing [127]. Additionally, exosomal Jagged1, derived from HIF-1α-overexpressing MSCs, enhances angiogenesis via Notch signaling activation in endothelial cells, further supporting vascular rejuvenation [128].

Anti-inflammatory and Immunomodulatory Effects

Chronic inflammation significantly contributes to skin aging through mechanisms often referred to as "inflammaging." This persistent low-grade inflammation accelerates cellular senescence and disrupts skin homeostasis. The accumulation of senescent cells triggers the secretion of pro-inflammatory factors, known as the senescence-associated secretory phenotype, which perpetuates inflammation and induces further senescence in neighboring cells [129,130]. Aging is also associated with immunosenescence, a decline in the immune system's ability to manage inflammation, leading to increased senescent cells and inflammatory mediators [131]. External factors like UV radiation and pollutants exacerbate this process, with UVB-induced inflammation being mediated by molecules such as nitric oxide, prostaglandin E2, and cytokines like IL-1 and IL-6, predominantly regulated by NF-κB in keratinocytes [132].

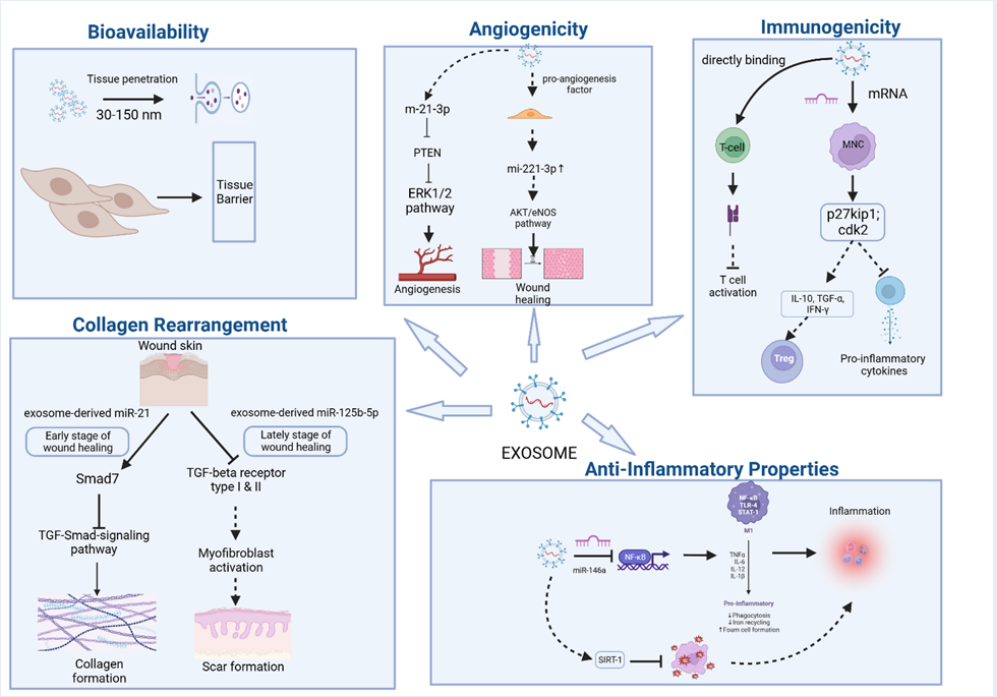

Figure 1: **The beneficial role of MSC-derived exosomes in skin rejuvenation**. MSC-derived exosomes are essential in skin treatment due to their superior bioavailability and low immunogenicity. They efficiently penetrate tissues and are safe for therapy. These exosomes also possess immunomodulatory properties, reducing inflammation and promoting immune balance. They stimulate collagen production and prevent its breakdown, thus improving skin texture. Additionally, they promote angiogenesis, addressing vascular changes in aging skin. Exosomes have anti-inflammatory properties, providing protection against inflammation-related damage.

Chronic inflammation disrupts epidermal balance, leading to common aging features like skin thinning and a weakened barrier [3]. Pro-inflammatory cytokines, such as IL-1β and TNF-α, stimulate the production of matrix metalloproteinases (MMPs) and cathepsins, enzymes that break down the ECM, particularly collagen. This ECM breakdown results in reduced skin elasticity and wrinkle formation [133,134]. Advanced glycation end products (AGEs) further contribute to skin dysfunction by triggering oxidative stress, disrupting collagen and elastin, and amplifying inflammation through reactive oxygen species (ROS) [135–137].

Exosomes, which are small extracellular vesicles, are crucial in regulating inflammation by promoting communication between immune cells. Exosomes released from LPS-preconditioned MSCs can alter macrophage polarization, steering it towards an anti-inflammatory M2 phenotype through the NF-κB/NLRP3 signaling pathway [138]. Furthermore, engineered exosomes loaded with anti-inflammatory agents, such as curcumin, show potential in treating inflammation-related conditions, including rheumatoid arthritis and spinal cord injuries [139]. Modifications like hyaluronic acid or polyethylene glycol enhance exosome targeting and therapeutic efficacy [138]. MSC-Exos exhibit significant anti-inflammatory effects, outperforming exosomes from other cell types. These vesicles are enriched with microRNAs, proteins, and cytokines that modulate immune responses and reduce inflammation [140,141]. In skin aging, MSC-Exos downregulate pro-inflammatory cytokines like IL-1β and TNF-α and inhibit the NF-κB pathway, mitigating chronic inflammation and oxidative stress while promoting cell survival [19,20]. Additionally, MSC-Exos enhance protective proteins like SIRT1 and P53, improving skin cell viability under stress conditions [142].

The anti-inflammatory potential of adipose-derived stem cell exosomes (ADSC-Exos) has shown promise in treating atopic dermatitis. ADSC-Exos notably reduce the levels of pro-inflammatory cytokines, including IL-4, IL-13, and TNF-α, by 30-50%, in a dose-dependent fashion [143,144]. Clinical studies demonstrate their efficacy in reducing erythema, improving

skin hydration, and lowering clinical scores over 12 weeks[143]. MSC-Exos similarly reduce inflammatory cytokines like TNF-α and IL-17 in aged skin, inhibiting pathways such as STAT3 and suppressing dendritic cell activation, contributing to a balanced immune environment[145,146].

CONCLUSIONS

MSC-derived exosomes represent a revolutionary approach to combating skin aging, integrating regenerative and immunomodulatory capabilities into a single therapeutic platform. Their ability to modulate collagen remodeling, reduce inflammation, and enhance vascularization positions them as superior to traditional treatments in both efficacy and safety. Despite these advantages, significant obstacles, including manufacturing scalability, quality control, and regulatory hurdles, must be overcome to facilitate widespread clinical adoption. Future research should focus on optimizing exosome engineering, improving delivery mechanisms, and standardizing therapeutic protocols to unlock the full potential of this innovative treatment for skin aging.

ABBREVIATIONS

ADSCs: Adipose-Derived Stem Cells, **AKT/ERK**: Protein Kinase B / Extracellular Signal-Regulated Kinase, **AMP**: Adenosine Monophosphate, **DLL4**: Delta-like Ligand 4, **ECM**: Extracellular Matrix, **IFN-γ**: Interferon-gammam, **iRNAs**: MicroRNAs, **MMPs**: Matrix Metalloproteinases, **MSC-exos**: Mesenchymal Stem Cell-derived Exosomes, **NETs**: Neutrophil Extracellular Traps, **NF-κB**: Nuclear Factor Kappa B, **PI3K/Akt**: Phosphoinositide 3-Kinase / Protein Kinase B, **PRRs**: Pattern-Recognition Receptors, **ROS**: Reactive Oxygen Species, **SIRT1**: Silent Information Regulator T1, **STAT3**: Signal Transducer and Activator of Transcription 3, **TGF-α**: Transforming Growth Factor-alpha, **Th1/Th17/Treg**: T-helper cells type 1 / type 17 / Regulatory T-cells, **TIMPs**: Tissue Inhibitors of Metalloproteinases, **UCB-MSC**: Umbilical Cord Blood-Mesenchymal Stem Cells

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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