Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2025.390093.3975 Volume 31, Issue 8 August. 2025
Manuscript ID: ZUMJ-2505-3975
DOI: 10.21608/zumj.2025.390093.3975
REVIEW ARTICLE

Exosomes in Dermatology: Biological Functions and Clinical Applications.

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Conflict of Interest: The authors declare no competing interests.

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Submit Date:02-06-2025
RevisedDate:05-07-2025
Accept Date:13-07-2025

ABSTRACT:

Background: Exosomes (EXOs), a small extracellular vesicles, are released from many cells and are recognized as significant players in the intercellular communication via transporting molecular cargo, such as lipids, proteins, and nucleic acids thus influencing many types of biological processes. Their discovery have shifted from being cellular debris to their important role in cellular signaling and disease modulation. The role of EXOs in dermatology has obtained important consideration owing to their capability to mediate cellular processes that are pivotal for skin health. Our review aimed to present an overview of exosomes' biological functions, biogenesis, isolation techniques, mechanisms of action and classification along with highlighting EXOs potential role in regenerative medicine, therapeutic delivery, and diagnostic tools and their significant implications in various dermatological conditions, including inflammatory skin diseases, skin aging, wound healing, and hair restoration.

Conclusions: EXOs have significant clinical applications as diagnostic markers, therapeutic tools and targets for personalized medicine in dermatology and aesthetics.

Key words: Exosomes, skin, Regenerative Medicine, diagnostic biomarkers, inflammatory diseases.

INTRODUCTION:

Exosomes (EXOs) are tiny extracellular vesicles (30-150 nm) of endosomal origin, released by various cells and present in all body fluids. They carry biomolecules such as RNA, DNA, proteins, lipids, amino acids, and metabolites from their parent cells **[1]**. EXOs play a key role in intercellular communication by conveying their cargos to recipient cells, influencing biological responses and potentially modulating disease pathogenesis **[2]**. EXOs were considered apoptotic bodies for the expulsion of cellular debris and excretion of undesirable cellular waste. But, additional research has revealed that exos are essential molecular mediators for cellular communication and underscored their involvement in significant biological functions and disease mechanisms **[3]**. This review will explore the isolation, characterization, therapeutic potential, and challenges of exosomes, focusing on their significance in the field of dermatology.

Exosome biogenesis, release, and uptake

EXOs are formed from cells via the endosomal pathway. Formation of early endosomes is the first stage in exos generation via the internal budding of the plasma membrane, the bioactive substances then begin to accumulate in the early endosomes, which develop into active subcellular structures called MVBs (Multivesicular Bodies) followed by fusion with the plasma membrane releasing exos into the extracellular space **[4].**

The EXOs deliver their cargo and communicate with target cells through three diverse mechanisms: (a) receptor-ligand contact, (b) direct membrane fusion, and (c) endocytosis. Through these pathways, exosomes deliver their cargo, modulating cellular responses in various contexts **[5]** ***Figure 1***.

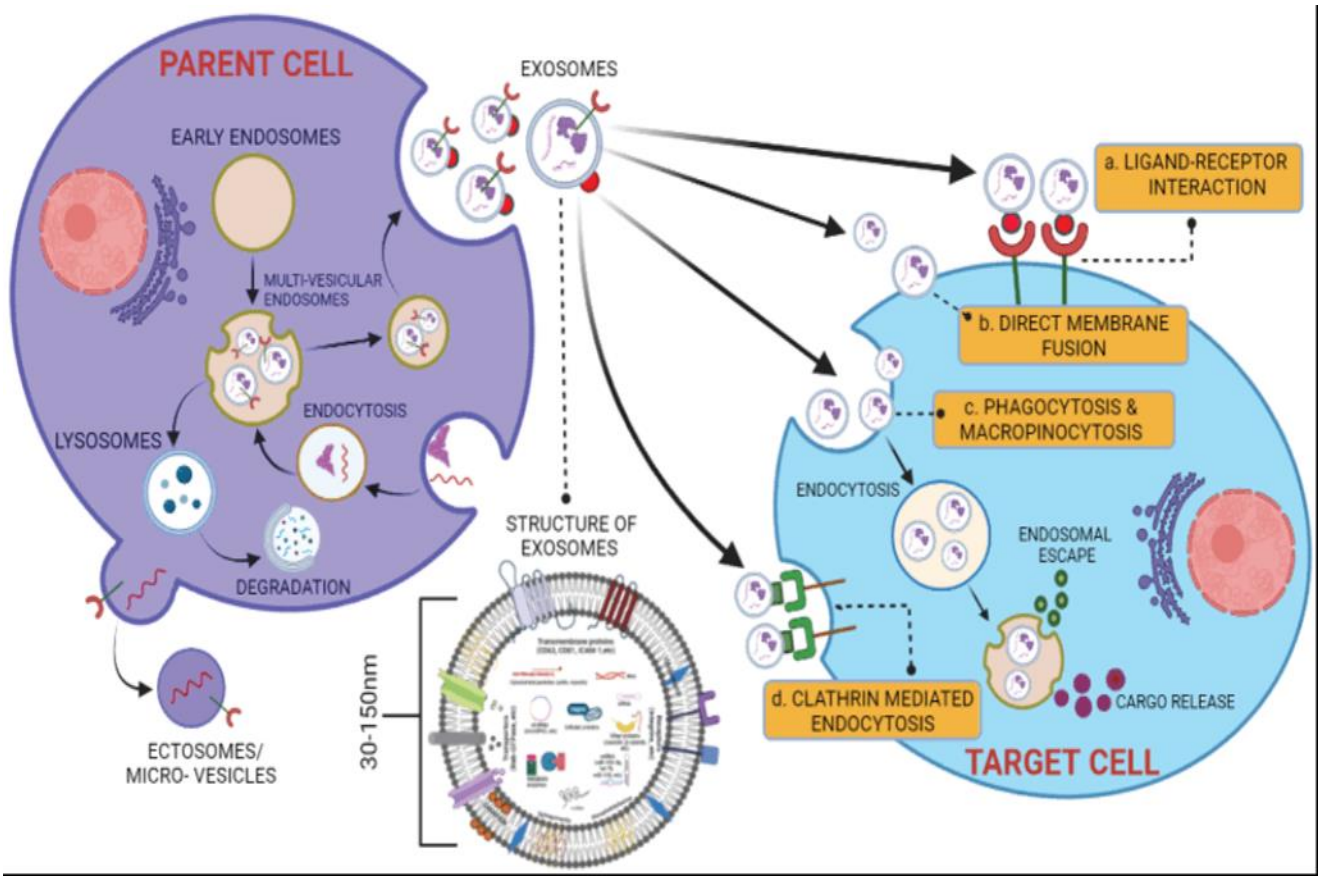

***Figure 1**. Exosome biogenesis, release, and uptake **[5]**.*

Origin and Classification of EXOs

The source of exos is generally classified into two classes; natural and engineered (artificially modified). Natural exos are further divided into human (also known as conventional) sources and the nonconventional sources including animal, plant and microbial (bacterial, fungal and parasitic) sources **[6]**.

Most normal cells can yield exosomes, as human umbilical vein endothelial cells, mesenchymal stem cells (MSC), T cells, B cells, macrophages, dendritic cells (DCs) and natural killer (NK) cells**.** MSCs are the principal sources from which exos are isolated and mainly are responsible for the paracrine effects of MSC therapy and are a hopeful next-generation cell-free therapeutic alternative **[8].**

Most research on exos focuses on conventional sources emphasizing their physiological roles and potential therapeutic uses. However, EXOs of nonconventional origin like animal or plant-derived exos are remarkable due to their role in interspecies communication, offering new avenues for developing therapeutic agents **[6, 7]**.

The EXOs extracted from lyophilized snake venom have been analyzed through mass spectrometry, indicating their role in venom cytotoxicity and potential therapeutic applications for envenomation **[9]**. Additionally, exosomes derived from bee products, like honey and bee pollen, exhibit antibacterial and biofilm-inhibiting properties while promoting the migration of human

MSCs, highlighting their role in interspecies interactions **[10]**.

Plant-derived exosome-like nanoparticles (ELN) closely resemble mammalian exosomes and offer significant potential for research and therapeutic applications due to their ease of isolation in large quantities at a low cost and low toxicity from natural sources **[10]**. Exos isolated from Ginseng, has been recently studied and used in cosmetics in Asian countries owing to Ginseng anti-inflammatory, anti-cancer, immuneboosting, and osteogenic/anti-osteoporotic characteristics, leading to the rise of companies dedicated to this area of study **[11].**

The ELN extracted from grapes, carrots, broccoli, and ginger also exhibit anti-inflammatory properties and support intestinal homeostasis. Ginger derived exosomes showed superior chemotherapeutic action via boosted delivery of agents such as doxorubicin compared to the free drug. Additionally, ginger-derived particles have shown protective effects against alcohol-induced liver damage in mice **[1].**

However, the current classification of exos based on their sources does not address their characteristics and functional applications **[7]**.

Isolation and characterization of exosomes

Standardized methods for exosomes isolation and purification, along with optimizing their cargo loading and stability, are emerging aspect of research and remains a major challenge **[12]**. EXOs are isolated using various techniques such as ultracentrifugation, precipitation, immunoaffinity, and density gradient centrifugation. Ultracentrifugation is the gold standard for isolation depending on the idea that exos are smaller and denser than cells and can be isolated through centrifugation at various speeds. EXOs can be precipitated using the Exo Quick kit procedure, requiring a polymer addition to the sample **[13].** Nevertheless, each technique for isolating exosomes has its advantages and disadvantages, and selecting the appropriate method depends on the specific characteristics of the sample. Using a combination of isolation methods can enhance both the yield and purity of exosomes, and it is essential to verify their isolation through markers and electron microscopy **[14].** Accurate characterization of exosomes is vital for understanding their nature. Techniques such as Western blotting, mass spectrometry, and flow cytometry are employed to examine their size, surface markers, shape, and protein or lipid content. Moreover, transmission and scanning electron microscopy are utilized to visualize exosomes **[15]**. Exos from various cell types contain a diverse array of components, including about 4,400 proteins, 194 lipids, 1,639 mRNAs, and 764 miRNAs, underlining their complexity and potential functional variety **[16]**.

The emerging mechanisms of exosomes

EXOs encapsulate biomolecules within membranes that are studded with proteins and enriched with cholesterol, ceramide, sphingomyelin, and lipid rafts that enhance secretion, and signaling between cells. They deliver cargo to neighboring cells via receptor-mediated endocytosis **[17].** The bioactive particles within exos can supress inflammatory substances and modulate the immune response by regulating gene expression thus alleviating inflammation and autoimmune responses. MSC-derived exos have been reported to activate ERK signaling pathways, which can decrease melanin synthesis and help treat hyperpigmentation. They also inhibit pro-inflammatory mediators implicated in melasma pathogenesis like IL-6 and TNF-α, in addition to their regenerative properties [**18, 3].**

EXOs in skin biology

EXOs have significant clinical applications as therapeutic tools, diagnostic indicators, and goals for personalized medicine in dermatology and aesthetics **[19].** Their therapeutic benefits include their capability to convey therapeutic cargo, modulate immune responses, and enhance tissue repair, particularly in regenerative medicine which is promising areas of research **[12]**.

EXOs from blood, skin, and stem cells are involved in modulating the skin

microenvironment with anti-inflammatory and immunostimulant effects that benefit skin health, aid inflammatory skin condition treatment, and enhance rejuvenation **[7]**. EXOs act as essential messengers within the dermis facilitating skin cell and fibroblast connection, stimulating synthesis of elastin and collagen and enhancing dermal fat, thus augmenting skin regeneration and anti-aging property, leading to enhanced skin texture and reduced wrinkles and fine lines, thus conserving firm skin with a youthful look **[20]**. Their osteogenic properties enhance facial bone health, leading to a more youthful face. EXOs facilitate skin regeneration by delivering growth factors and cytokines, enhancing cell proliferation and angiogenesis. They promote repair via different pathways and growth factors, particularly TGF-β, influencing skin cell growth and differentiation. Also, exos modulate the extracellular matrix (ECM), aiding in remodeling for wound healing and scar prevention **[12, 13]**.

Clinical application of EXOs in dermatology

Dermatological Uses of exos varied from inflammatory skin conditions to cosmetic concerns **[8]** including psoriasis, atopic dermatitis (AD), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), wound healing, radiation dermatitis, acne vulgaris, allergic contact dermatitis, lichen simplex chronicus, vulvar lichen sclerosis, hypertrophic scar, keloid and skin aging, but research on treating autoimmune and inflammatory skin diseases is in the preclinical phase **[19, 21]**.

1. **Exosomes in Inflammatory Skin Diseases**

Inflammatory skin conditions, such as psoriasis, AD, and eczema, involve complex immune responses characterized by overactivation of immune cells like T-cells and DCs. Exos mediate these immune responses via transferring inflammatory mediators and antigens to other immune cells **[19]**. EXOs from DCs contribute to the pathogenesis of psoriasis by presenting autoantigens to T-cells, thereby exacerbating inflammation **[22]**. Conversely, exosomes from MSCs have anti-inflammatory effects, as they carry miRNAs that suppress pro-inflammatory cytokines and enhance the polarization of T-cells towards a regulatory phenotype, offering potential therapeutic benefits in inflammatory skin disorders **[23]**.

EXOs from different stem cells, such as epidermal stem cells (ESCs) and human umbilical cord MSCs (hucMSCs) have demonstrated effectiveness in alleviating psoriasis by modulating the immune response. When applied topically, ESC-derived exosomes helped relieve psoriasis symptoms in mice by decreasing levels of IL-17 and the terminal complement activation complex C5b-9 in skin tissue. Additionally, subcutaneous administration of exosomes from hucMSCs led to a marked reduction in IL-23, IL-17, and CCL20 levels in keratinocytes and suppressed DC activation by inhibiting STAT3 phosphorylation **[24]**. Most of the studies are still in the preclinical stage on cellular and animal levels **[25, 26]**. Lately, a clinical study by Mohseni Meybodi et al. **[27]** have reported the safety and efficacy of MSC-derived exosomes from adipose tissue of healthy donors for treating mild to moderate plaque psoriasis via reducing the inflammatory markers (IL-17, CD3, IL-23 and TNF-α) and increasing the anti-inflammatory markers (Foxp3 and IL-10) in patients with plaque psoriasis.

In addition to psoriasis, a number of preclinical studies have reported the use of exos in additional inflammatory and autoimmune skin diseases including, atopic dermatitis **[28-31]**, systemic lupus erythematosus **[23, 32-34]** and systemic sclerosis **[35, 36] (Table 1)**.

Table 1: Therapeutic role of exosomes in various inflammatory skin diseases

Disease	Type of the study with Reference	Conclusion
psoriasis	Animal experiment on mouse models (Zhang et al.,2022**) [24]** An in vitro study **Kim et al., 2023 [25]** In vitro and in vivo mouse model. **Wang et al., 2024 [26]** Clinical study Mohseni Meybodi et al., 2024 **[27]**	Injecting human umbilical cord MSC exosomes reduced psoriasis-like skin inflammation, including epidermal proliferation and psoriasis area and severity index scores, in imiquimod-induced mice by regulating IL-23 and IL-17 expression. ASC-exosomes suppressed the production of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) and expression of oxidative stress-related factors (Nox2 and Nox4) and induced autophagy in HaCaT cells. Patients' serum-derived exosomes containing miR-6785-5p could alleviate psoriasis-like skin lesions both in vitro and in vivo. keratinocytes actively took up the serum-exosomes containing miR-6785-5p, which then inhibited the abnormal proliferation and inflammatory state of keratinocytes by interfering with the MNK2/p-eIF4E axis. MSC-derived exosomes from adipose tissue of healthy donors are effective for treating mild to moderate plaque psoriasis via reducing the inflammatory markers (IL-17, CD3, IL-23 and TNF-α) and increasing the anti-inflammatory markers (Foxp3 and IL-10) in patients with plaque psoriasis.
Atopic Dermatitis	Mouse model Cho et al., 2018 **[28]** Mouse model Shin et al., 2020 **[29]** Mouse model Shi et al., 2023 **[30]** In-vitro test Yoo et al 2023 **[31]**	IV or SC injection of ADSC-Exos ameliorated AD symptoms in NC/Nga mice treated with house dust mite via decreasing serum IgE levels, immune cell infiltration, and the IL-4, IL-23, IL31, and TNF-α expression. SC injection of ADSC-exos promoted epidermal barrier repair in an oxazolone-induced AD mouse model via enhancing stratum corneum hydration decreasing the levels of inflammatory cytokines, such as IL-4, IL-5, IL-13, IL-17, IFN-γ, TNF-α, and TSLP, and stimulating the production of epidermal ceramide. miR-147a-overexpressing ADSC-exos inhibited inflammatory response, cell apoptosis, and angiogenesis in the DNCB-induced AD mouse model via targeting VEGF-A and MEF2A-TSLP axis and normalized the expression of genes altered during AD pathogenesis, which involved skin barrier, lipid metabolism, cell cycle, and inflammatory response Exosomes derived from dermal fibroblasts restored expression levels of skin permeability barrier maintenance biomarkers in DNCB-treated keratinocytes, such as FLG, LOR, IVL, and HAS1, thus increasing the recovery rate of skin damage in AD (42)
SLE	In-vitro test	Dou et al. suggested that tsRNA-21109 was down-regulated in SLE patients

Disease	Type of the study with Reference	Conclusion
	Dou et al., 2024 [32]	compared to healthy control, and Bone marrow MSC (BMSC) exosomal tsRNA-21109 alleviated SLE by inhibiting macrophage M1 polarization.
	Mouse model **Sun et al., 2022 [23]**	Intravenous injection of hucMSC-exos regulated the balance of the T cell subset and the activation of B cells in SLE.and alleviated nephritis, liver, and lung injuries of MRL/lpr mice via increasing the ratio of M2 macrophages and the expansion of Tregs.
	In-vitro test **Tu et al., 2022 [33]**	HucMSC-exos restored the balance of Th17/Treg and inhibited inflammatory cytokine secretion of peripheral blood mononuclear cells (PBMC) from SLE patients via delivering miR-19b and inhibiting KLF13 expression.
	In-vitro test **Zhao et al., 2023 [34]**	hucMSC-exos promoted B cell apoptosis, prevented B cell overactivation, and reduced IL-16, IL-10, and TNF-α expression of B cells in SLE patients via the miR-155/SHIP-1/ERK axis.
Systemic sclerosis	Mouse model **YU et al., 2022 [35]**	HucMSC-exos alleviated skin fibrosis, suppressed the epithelial-mesenchymal transition (EMT) process, and promoted M1 polarization of macrophages in BLM-treated mice.
	Mouse model **Xie et al., 2023 [36]**	BMSC-exos attenuated the fibrosis of BLM-treated mice via transferring miR-214 to inhibit the IL-33/ST2 axis.

2. *Role of EXOs in diagnosis*

EXOs have emerged as valuable tools for prognosis and diagnosis in various skin disorders, including skin cancers**.** Tumor cells release exosomes that contain distinct biomarkers representing their molecular and genetic characteristics. Tumor-derived exos carry specific molecular signatures detectable in blood or skin lesions, enabling non-invasive early diagnosis and treatment monitoring **[14, 3]**.

In terms of diagnostic utility, exos from immune or skin cells have been found helpful in identifying autoimmune and inflammatory skin diseases. For instance, exos carrying autoantibodies, cytokines, or microRNAs have been identified in the bloodstream or skin lesions of individuals with conditions such as pemphigus vulgaris, AD, vitiligo and SLE. The concentrations of these exosomal contents correlate with disease activity, severity and treatment outcomes **[37].**

In psoriasis, patients exhibit significantly higher levels of exosomal TNF-α and IL-23 mRNA in the circulation compared to healthy individuals, with IL-23 levels positively correlating with disease severity **[38]**. Similarly, SLE patients show elevated levels of exosomal miR-21 and miR-155 in the blood stream, particularly in those with lupus nephritis (LN), compared to healthy controls **[3]**.

3. **EXOs for hair growth.**

Exos have shown promise in hair regeneration and hair loss treatment via enhancing growth of hair and hair follicle function **[39, 40]. Zhou et al. [41]** found that injecting dermal progenitor cell-derived exosomes (DPC-exos) into mouse hair follicles promoted hair growth by increasing levels of beta-catenin in the Sonic Hedgehog signaling pathway. For hair restoration, exos can be applied topically with microneedling or injected directly into the scalp, with injections being potentially more effective **[42]**

4. EXOs in combating skin aging

Skin aging largely results from prolonged exposure to ultraviolet (UV) radiation and the resulting generation of reactive oxygen species (ROS). These ROS cause DNA harm, increase the expression of matrix metalloproteinases (MMPs), promote cellular aging, degrade collagen, and trigger inflammation. Collectively, these molecular processes lead to evident marks of aging in the skin as wrinkles, pigmentary alterations, and structural modifications. Exos have demonstrated the ability to ameliorate these age-related alterations**,** primarily through the action of exosomal microRNAs and proteins **[13]**. Exosomes derived from bone marrow stem cells (BMSC-exos) have been found to enhance collagen synthesis and mitigate oxidative stress in UVB-damaged human dermal fibroblasts (HDFs) by delivering miR-29b-3p **[43].** Additionally, exosomal proteins contribute to anti-aging effects. For instance, exosomes from hucMSC-exos lowered the expression of aging-related markers in UV radiated skin via delivering natural protein 14-3-3ζ, which shields keratinocytes from oxidative stress through upregulating SIRT1 and promoting autophagy **[44]**. Similarly, exosomes from human induced pluripotent stem cells (hiPSC-exos) reduce cellular aging by decreasing levels of senescence-associated β-galactosidase. Additionally, exosomes from human umbilical cord blood help slow skin aging by regulating the synthesis of collagen and elastin **[19]**.

5. EXOs in Skin Rejuvenation and Wound Healing

Exosomes are increasingly recognized in dermatology for their regenerative and wound-healing properties, helping scar improvement, pigmentation correction, and skin rejuvenation **[45].** Exos, particularly from MSCs, aid wound healing through stimulating cell proliferation, angiogenesis, collagen synthesis, and immune regulation, offering an alternative to traditional growth factor therapies which are limited by instability or side effects **[2, 7]**.

In skin rejuvenation, EXOs help reverse skin aging, reduce oxidative stress, and inflammation and improve skin quality **[7]**, with adipose tissue-derived EXOs (ADSC-EXOs) showning potential in rejuvenating photodamaged skin and enhancing collagen via specific signaling pathways e.g. mitogen activated protein kinases (MAPK)/AP-1 and TGF-β/Smad signaling pathways and upregulating the SIRT1/Nrf2 pathway **[46]**. Similarly, exos derived from HDF and human iPSCs protect against UV damage, decreased MMP overexpression, and restored collagen type 1 expression. While embryonic stem cell-derived EXOs reverse fibroblast aging through the TGF-B receptor 2 pathway **[20, 4].**

EXOs also accelerate healing from aesthetic procedures like fractional lasers and micro-needling, reducing inflammation and side effects and enhancing collagen production leading to better skin tone, texture, and reduced fine lines, pores, pigment, and oiliness **[45, 47].**

Research suggested that exos from adipose stem cells, probiotics, platelet-derived sources, and natural compounds like beetroot and bovine colostrum improve skin elasticity, hydration and pigmentation while reducing wrinkles and redness [**47, 48]**. Overall, exosomes hold significant potential in dermatology for anti-aging and regenerative therapies. Despite their potential, injectable EXO therapies lack FDA approval, and current use is limited to topical applications, often paired with micro-needling or laser treatments **[42]**.

Advantages of EXOs as targeted drug delivery

EXOs are promising cell-free therapeutic tools used in cancer and gene therapy for targeted drug delivery. They improve drug

bioavailability, reduce side effects, and enhance pharmacokinetics **[16]**. EXOs offer key advantages such as low toxicity, tissue repair, personalized treatment, and their small size allows them to evade immune clearance and cross biological barriers. Their surface proteins (CD55 and CD59) help them evade immune detection, making them stable in biofluids **[45].**

In comparison to liposomes and other synthetic nano-delivery systems, EXOs are naturally derived, providing superior biocompatibility and lower immunogenicity**.** These advantages make EXOs a promising approach for safer and more effective skin disease treatments **[16]**.

EXOs versus platelet-rich plasma

Platelet-rich plasma (PRP), a plasma concentrate extracted autologously from the blood, contains growth factors and proteins that support healing but shows inconsistent effectiveness due to individual variability in age, health, and environment. In contrast, exos are lab manufactured, ensuring standardized supply of growth factors, enzymes and proteins. EXOs trigger more powerful regenerative pathways than PRP due to their greater growth factor concentration and customizable cellular cargo **[42]**.

Studies suggest that concentrated PRP-exosomes have a superior results in osteoarthritis treatment than PRP alone, suggesting that the favorable results of PRP treatments are due to EXOs. While PRP promotes tissue repair and regeneration, EXOs not only facilitate these processes but also enhance immune responses and boost cellular proliferation and differentiation, making them a more potent and consistent regenerative therapy **[45]**.

Challenges

EXOs hold great promise in dermatology and regenerative medicine, but face several challenges. Firstly, Current isolation techniques, such as ultracentrifugation and size exclusion chromatography, are labor-intensive, time-consuming, and produce low amounts with potential contaminants, highlighting the need for better methods **[49]**. Secondly, their cargo and functions vary depending on cell type and condition, leading to inconsistent therapeutic outcomes and requiring further research to identify specific markers to distinguish subpopulations with distinct functions **[19].**

Thirdly, diagnostic approaches based on single biomarkers are insufficient, indicating a need for multi-biomarker signatures for improved diagnosis and assessment. Furthermore, most exosome-based therapies are still in pre-clinical stages, with more clinical trials and animal studies necessary to establish their safety and efficacy **[2]**.

CONCLUSIONS:

Exosomes have been shown as promising therapeutic agents in dermatology, providing benefits in regenerative medicine and tissue repair. Their capability to convey therapeutic cargo, modify immune responses, and stimulate tissue regeneration makes them promising candidates for treating various inflammatory skin conditions, skin aging, and wound healing, but several challenges must be addressed. These include inconsistent isolation methods, variability in sources, the need for standardized characterization, and the lack of long standing safety and efficacy data evolving the necessity for further research and clinical trials before exosomes can be widely adopted in the field to confirm their efficacy and safety.

Conflict of interest: None.

Financial Disclosures: None

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Citation

Nassar, A., KHATTAB, F., Sharobim, A., Abdelhamid, A., Samir, M. Exosomes in Dermatology: Biological Functions and Clinical Applications.. *Zagazig University Medical Journal*, 2025; (4057-4066): -. doi: 10.21608/zumj.2025.390093.3975