



## Innovative Approaches to Prolonged Wound Healing: Mesenchymal Stem Cells Derived Exosomes



### Review History:

Received: 2025-06-23  
Revised: 2025-09-06  
Accepted: 2025-09-14

### Article Type:

Original Research

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### ABSTRACT

Skin wound healing is a complex process involving multiple stages and interactions between growth factors, cytokines, chemokines, and various cell types. Impaired wound healing can lead to chronic wounds, causing pain, disfigurement, and a heavy burden on patients and healthcare. Traditional wound care involves removing damaged or infected tissue, then applying dressings and topical agents to protect and promote healing. Conventional methods also include nonsurgical treatments and pharmacological therapies. Regenerative medicine aims to restore function by repairing or replacing cells, tissues, and organs. Stem cells have remarkable regenerative potential, but their clinical use faces challenges due to the survival of transplanted cells. Additionally, factors such as determining the proper cell source, route of administration, and preparation of stem cells under accurate clinical conditions have led to the application of cell therapies for wound healing. It is important to note that the challenges posed by host immunological responses in cell therapy, which have attracted significant attention in recent years, are being effectively addressed through cell-free therapy, paving the way for more successful treatment. Exosomes, as the most significant cell-free therapy, which, based on their endogenous, biocompatible, and multifunctional properties, have become a new tool for drug delivery systems, immunotherapy, and regenerative medicine.

**Keywords:** Exosome, Regenerative medicine, Mesenchymal Stem Cells, Wound healing

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### Introduction

Skin generally constitutes one-tenth of the human body mass and covers an average space of 1.85 square meters. The skin is the largest organ in the human body. It acts as a physical obstacle to the surrounding environment, providing the skin with physical strength that makes it resistant to many mechanical and chemical factors(1). Skin injuries frequently occur, and human skin is naturally equipped to facilitate self-repair and regeneration. Wounds are classified based on the damaged skin layers as superficial, partial-thickness, and deep. They also fall into acute (healing within twelve weeks with minimal scarring) and chronic (requiring more time and prone to recurrence) categories.(2) While it can heal minor wounds, severe conditions such as

extensive skin loss, deep burns, chronic wounds, diabetes, and non-healing wounds may develop and require medical intervention(3). It is estimated that nearly one billion people suffer from acute and chronic wounds worldwide. The costs associated with wound treatment account for about 2-4% of the total healthcare costs in Europe(4). The application of various therapeutic methods for healing strategies in skin injuries, along with advancements in pharmaceutical research for wound healing, requires an understanding of the physiology of natural healing and changes in skin wound repair, which consist of interrelated and interdependent mechanisms of re-epithelialization, inflammation, angiogenesis, wound contraction, Extracellular Matrix (ECM) remodeling, and imbalances.

Incorporating factors that influence the regulation of these mechanisms can lead to delays in the healing process(5). This review explores the therapeutic applications of mesenchymal stem cell-derived exosomes in wound healing, highlighting the contribution of inflammation to the healing process and summarizing relevant findings from recent scientific studies.

## Wound healing

The process of wound healing is complex and relies on various interconnected biological mechanisms consisting of four overlapping stages: hemostasis, inflammation, hyperplasia, and tissue remodeling(6). Wound repair is a complex and dynamic sequence of events involving multiple interconnected mechanisms. These include (i) regulation of inflammatory mediators and growth factors; (ii) interactions between cells and the ECM that modulate cell proliferation, migration, and differentiation; (iii) processes governing epithelialization, fibroplasia, and angiogenesis; (iv) closure of wound edges; and (v) tissue remodeling. Notably, many of these events overlap temporally and functionally, ensuring a coordinated and efficient healing response, as shown in the Figure 1(7).

## Main cells and their effects on wound healing

The first process is stage hemostatic first seconds after injury, Cytokines and growth factors are released by platelets and injured cells, including IL-1 $\beta$  (interleukin-1 $\beta$ ), TNF- $\alpha$  (tumor necrosis factor- $\alpha$ ), FGF (fibroblast growth factor), and PDGF (platelet-derived growth factor), That

stimulate leukocyte migration to the area of inflammation(8). During the first 24 h, neutrophils are recruited to the injured area and begin to remove necrotic tissue and phagocytose pathogenic antigens. In addition, neutrophils release proinflammatory cytokines, such as VEGF, TGF- $\beta$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and IL-8, which are secreted from injured cells at the wound site and induce local proliferation of fibroblasts, keratinocytes, and endothelial cells, as shown in the figure 2(9). Within several days, monocytes migrate to damaged tissue and subsequently transform into macrophages that promote wound regeneration and are linked to the ECM via integrin receptors(10). At once, they are stimulated neutrophil-released TNF- $\alpha$  and IL-1. Macrophages begin to migrate to the wound area and recruit other inflammatory cells to the wound area. After a few days, macrophages begin to migrate to the wound site, recruit other inflammatory cells, and secrete pathogen antigens, growth factors, and cytokines that regulate the subsequent processes for debridement of necrotic tissue and phagocytosis. The proliferative stage is first involved in scar tissue formation based on the temporary wound matrix, and angiogenesis occurs, which allows the transport of fluid, oxygen, nutrients, and immune cells to the site. The final stage is remodeling, which is characterized by changes in ECM composition. Four days after injury, granulation tissue develops within the wound as part of the healing process, where fibroblasts are crucial for ECM formation and the adhesion of other healing cells.

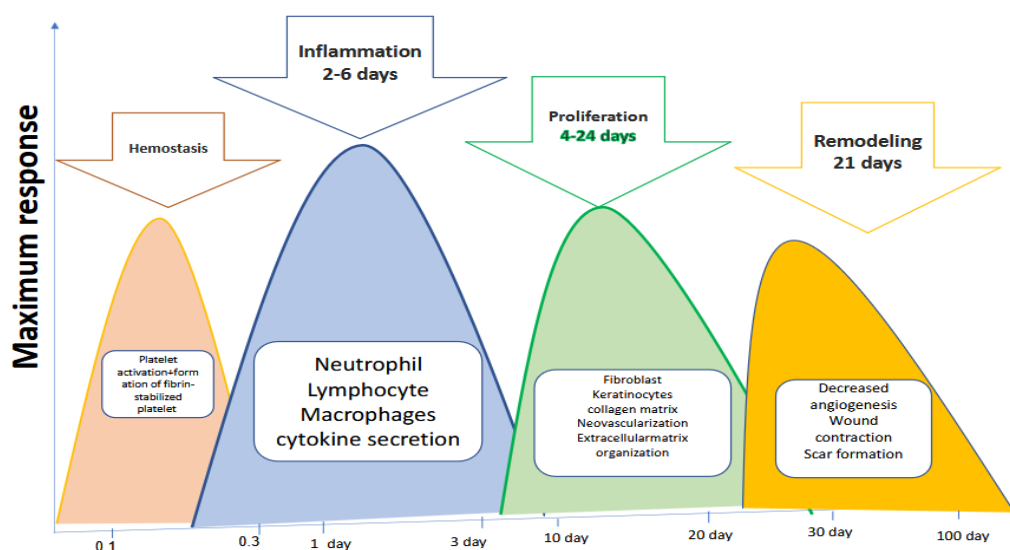
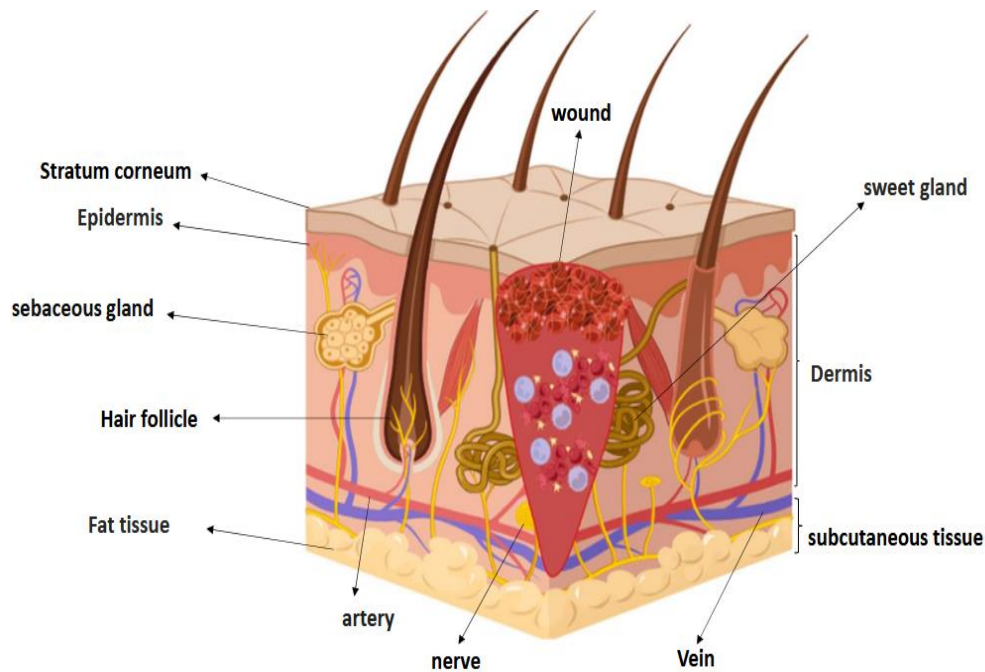


Figure 1: Schematic representation of cell-mediated wound healing.



**Figure 2: Wound-healing: An overview of the stages of healing also shows the contribution of key cell populations involved in different stages.**

The ECM plays a crucial role in tissue remodeling during the wound healing process by providing structural support and regulating cellular interactions essential for regeneration(11). The ECM plays a central role in the wound healing process, particularly during the tissue remodeling phase, and is dependent on the formation of the ECM, which is secreted by fibroblasts and epidermal cells throughout various stages of the healing process. The ECM is composed of collagen, glycosaminoglycans (GAGs), and proteoglycans. In particular, type I collagen not only enhances the strength of the wound, but In addition to its primary function, it facilitates the migration of endothelial cells and macrophages to the site of injury, promoting wound healing. Additionally, wound re-epithelialization is a key indicator of the complete wound-healing process is complete(12). A sign of wound healing is re-epithelialization of the wound (13). Skin wound healing relies on intricate interactions between cellular and tissue components of the surrounding damaged skin. These include dermal and epidermal cells, such as fibroblasts and keratinocytes, along with the ECM, neural elements, and vascular components, all of which contribute to effective tissue repair and regeneration.(14).

### **Emerging Therapeutics in Wound Care and Healing**

Treatment of difficult-to-heal or chronic

wounds follows the "TIME" guidelines, where this stands for tissue assessment (T) and debridement of dead tissues, infection/inflammation control (I) and etiological assessment, moisture balance (M) and epithelial edge cell progression (E) because the wound takes a long time to heal and suffer a high cost of treatment(15). Innovative therapeutic approaches for the treatment of chronic wounds, such as localized delivery of growth factors, cellular extracellular matrix, and bioengineered cellular skin substitutes, have shown varying degrees of effectiveness in a restricted set of clinical trials(16). This variability may be attributed to the inherent complexity of wound healing, which involves multifactorial etiology. Consequently, single-factor therapies might not yield satisfactory results compared with combinatorial approaches that address multiple processes to achieve the desired therapeutic benefit.

### **Challenges and Limitations of Common Wound Treatments**

Despite considerable advancements, the efficacy of current wound-healing techniques remains limited to approximately 50%, leaving the optimal treatment for chronic wounds an unresolved challenge. This gap underscores the growing demand for innovative medical approaches, particularly cell-based therapies that offer a dual-focused strategy by mitigating tissue

inflammation and promoting the repair of existing damage(17). Therapeutic strategies utilizing cellular-based approaches have been used for several decades of advancements in regenerative medicine and tissue repair have been dedicated to addressing various pathological conditions(18). Cell-based skin substitutes, including bioengineered skin grafts that utilize cellular components, represent a distinct model for cell-based therapy(19). These advanced treatments have demonstrated positive outcomes, including accelerated wound tissue closure, enhanced re-epithelialization, and improved vascularization(19). However, these therapies are expensive, need specific storage conditions, and increase the risk of infection and rejection for the patient(20). Recently, stem cell therapy has gained considerable recognition as a promising and effective approach to tissue repair(21). This method harnesses the unique properties of stem cells, such as their self-renewal potential, interact with the wound microenvironment, and secrete growth factors to promote wound healing(22). Although transplantation of internal stem cells and progenitor cells naturally aids the wound repair process, several challenges impede their clinical application(23). Key barriers include the danger of immunogenicity, tumorigenicity, and difficulty in selecting an appropriate stem cell source. Furthermore, chronic wound environments are often characterized by excessive inflammation, oxidative stress, and the presence of hostile wound fluid, which can hinder the survival and engraftment of transplanted cells (7). MSCs have been widely investigated in cell therapy and tissue regeneration for their potential in to treat a range of diseases and disorders(24). Increasing interest in MSCs is driven by their relatively simple and minimally invasive isolation process, along with their wide-ranging therapeutic potential. MSCs exhibit anti-inflammatory, angiogenic, immunomodulatory, antioxidative, and anti-apoptotic properties, making them promising tools for regenerative applications (25).

### **Mesenchymal stem/stromal cell (MSCs)**

MSCs are multipotent stromal cells capable of differentiating into various mesenchymal tissue lineages, including myocytes, osteoblasts, chondrocytes, and adipocytes.(26) MSCs are found in various tissues, including the bone

marrow (0.001–0.01%), placenta, umbilical cord (approximately one-third of its total volume), adipose tissue (only 0.05%), and dental pulp. (27). Consequently, they have been identified as a potential universal source for advancing allogeneic biotherapeutic development(28). To advance the use of MSCs as approved therapeutic factors, the International Society for Cell and Gene Therapy (ISCT) has established a standardized framework of essential criteria for defining the essential characteristics of human MSCs. These criteria include adherence to plastic surfaces, expression of CD105, CD73, CD90, and differentiation into adipocytes, osteoblasts, and chondroblasts in vitro. (12)

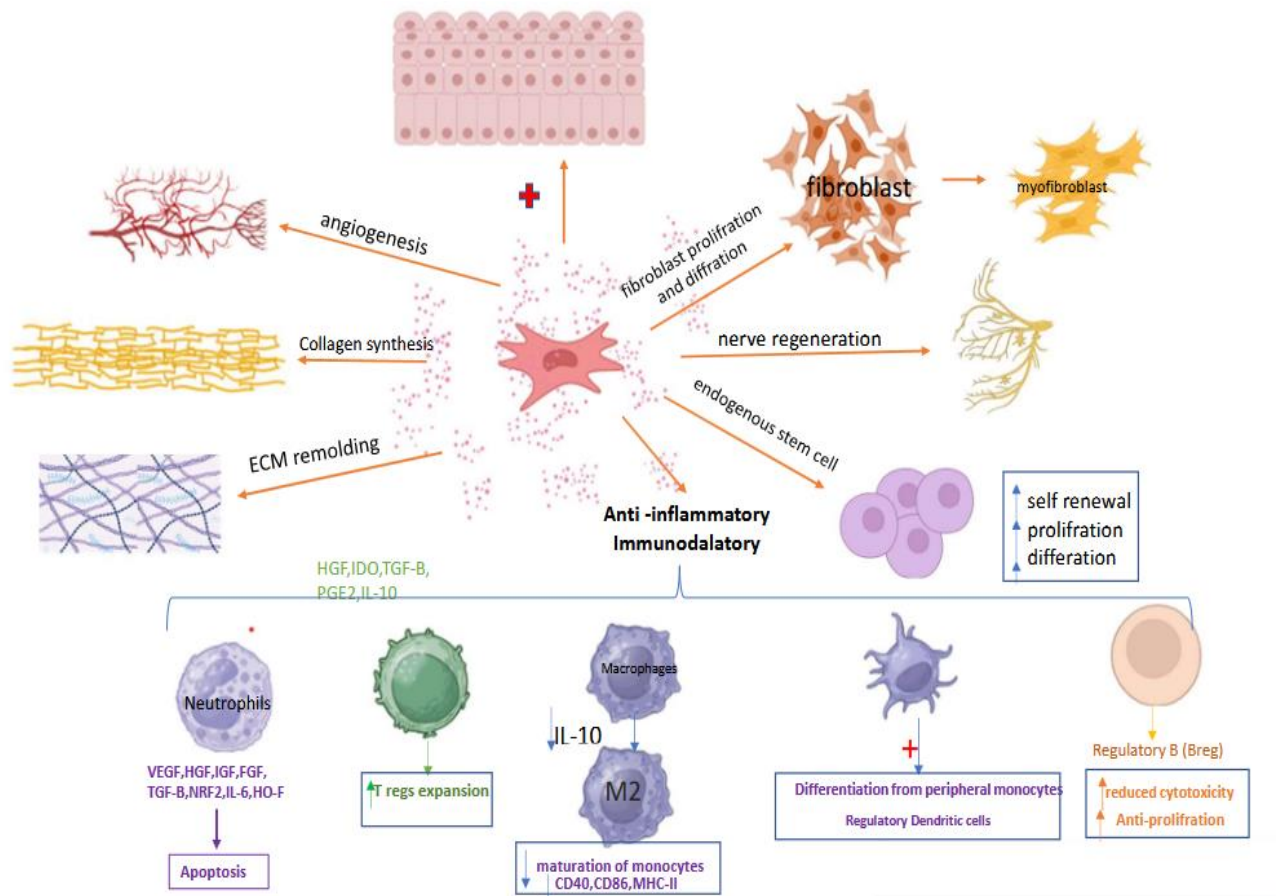
### **MSCs in wound healing and cutaneous regeneration**

These cells not only stimulate fibroblast proliferation and differentiation in injured tissues , but also regulate excessive proliferation and migration of hypertrophic scar fibroblasts, contributing to controlled wound healing(29). In addition, MSCs secrete various growth factors, cytokines, and chemokines that regulate immune responses and angiogenesis via paracrine mechanisms, ultimately facilitating the repair of damaged tissues(30). It is well known that mesenchymal cells secrete a variety of angiogenesis-related cytokines, such as SDF-1, PDGF, b-FGF, GM-CSF, VEGF, HGF, IL-6, MMP, and TGF- $\alpha$ . Research has shown that it possess angiogenic and arteriogenic (the development of collateral blood vessels) properties, which significantly contribute to the treatment of hind organ ischemia, coronary artery disease, and the healing of skin wounds.(31) MSCs regulate the redox environment by secretion of glial cell line-derived neurotrophic factor (GDNF), heme oxygenase-1 (HO-1) stanniocalcin-1 (STC1).(31). It can promote the recruitment, mobilization, and migration of endothelial progenitor cells, thereby enhancing angiogenesis(32). MSCs function in each phase of the wound-healing process

#### *MSCs regulate the hemostasis phase*

MSC-induced coagulation is attributed to the high surface expression of phosphatidylserine and tissue factor (TF), triggering a thrombotic response and increased clot formation, which poses a significant challenge in MSC-based therapies.





**Figure 3: Effects of MSCs on wounds**

#### *MSCs regulate the inflammatory phase*

MSCs release various growth factors and cytokines that modulate the activity of neutrophils, macrophages (shifting them from an inflammatory M1 phenotype to an M2 phenotype), and lymphocytes (Th1-Th2).

#### *MSCs to improve the proliferative phase*

Treatment with MSCs increases the migration and survival of fibroblasts and enhances ECM deposition by fibroblasts, further supporting tissue regeneration and wound healing, thereby enhancing therapeutic effects.

#### *MSCs during the healing phase of maturation*

Migrating stem cells within the wound secrete hepatocyte growth factor (HGF) and prostaglandin E2 (PGE2), which suppress myofibroblast differentiation and inhibit epithelial-to-mesenchymal transition, ultimately contributing to regulated tissue regeneration(33).

MSC signaling also stimulates neighboring cells to produce the correct ECM. In addition to reducing inflammation, Enhancing TGF-β1 production, and promoting the proliferation of M2 macrophages, they accelerate collagen deposition, cellular infiltration,

neovascularization, and healing of skin injuries(34). Various priming strategies have been proposed to optimize the beneficial properties of MSCs; for example, studies have demonstrated that hypoxic preconditioning significantly improves the survival of MSCs in harsh environments. Additionally, this approach enhances the angiogenic capacity, collectively boosting the regenerative and immunomodulatory abilities of MSCs, as shown in the Figure 3. These effects contribute to the regulation of excessive fibrosis and cell death caused by uncontrolled inflammation, further highlighting the therapeutic potential of hypoxia-preconditioned MSCs.(25) The specific effects of preconditioning depend on the factors used in MSC culture ,that activate distinct signaling pathways, thereby tailoring the therapeutic potential of cells for targeted applications.Studies indicate that the anti-inflammatory properties of MSCs can be further enhanced, offering a promising strategy to improve the efficacy of immunomodulation. This approach has significant potential for advancing therapeutic applications in regenerative medicine, particularly in conditions characterized by excessive

inflammation or immune dysregulation(35).Despite the potential of these approaches, Limited clinical trials have investigated the application of primed MSCs to enhance therapeutic efficacy(36). Extensive evidence supports the advantages of preconditioning MSCs to enhance their regenerative and reparative capacity in a wide range of tissues and pathological conditions. Notably, inflammatory priming, a promising strategy, is yet to be investigated in clinical settings (25).

### Challenges in Utilizing MSCs for Wound Healing

Various obstacles have emerged in the clinical application of MSCs, including inconsistencies in the delivery protocols, wound models. This variability complicates the evaluation of critical factors such as timing, dosage, and delivery site, ultimately influencing engraftment success (37). Owing to the poor engraftment of MSCs, comprehensive studies are required to enhance the likelihood of successful integration into damaged skin. There are two primary methods for delivering MSCs to the body. The first method involves localized delivery into tissues using various scaffolds embedded with MSCs. Several scaffold techniques have been developed to support MSC transplantation in tissue-engineering clinical therapies. These scaffolds are composed of materials, such as biodegradable substances, ceramics, matrices, synthetics, and alternatives. The second method involves injecting MSCs through intracardiac, intramuscular, or intraperitoneal routes. Additionally, intravascular injection is an option either through the arterial (IA) or venous (IV) pathways. Notably, studies have demonstrated that MSC injection via IA results in more effective distribution than IV injections(27). Key concerns in the clinical application of MSCs include the risk of xenogeneic contamination (e.g., from animal serum) during ex vivo cell expansion, along with the poor survival rates of MSCs post-transplantation. Additionally, the potential transmission of infectious agents, induction of xenogeneic immune responses, and ethical considerations surrounding animal welfare pose significant challenges(38).These factors highlight the need for alternative approaches to minimize reliance on animal-based materials in

therapeutic settings. Orthobiology, which involves biological substances designed to enhance tissue healing, has gained attention in response to these challenges, with examples such as platelet lysate (PL), human AB serum (HABS), platelet-rich plasma (PRP), and chemically defined media (CDM) offering potential alternatives to MSC-based therapies. Despite the advancements in MSC-based therapies, several challenges must be addressed before MSCs can be effectively utilized for wound healing.

### Cellular Secretions in MSC Cell Therapy

Initially, it was thought that cells exert their therapeutic effects by engrafting into the target tissue, but it has recently been shown that only a limited proportion of these cells successfully reach the target tissue and that the immunomodulatory properties of these cells are due to cell-derived extracellular secretory factors, called extracellular vesicles. Therefore, instead of using the cell, their secretory factors or exosomes can be used. Exosomes are composed of various types, including oncosomes ,exosomes, ectosomes, microvesicles , and apoptotic bodies .Secretions refer to the used/wasted/consumed medium of cultured cells after defined incubation period, which contains proteins, including growth factors, cytokines, chemokines, and ECM secreted by the cultured cells(38). Exosome biogenesis involves three main steps: generation of endocytic vesicles through invagination of the plasma membrane, formation of multivesicular bodies (MVBs) through inward budding of the endosomal membrane and the final step of MVB communication with the plasma membrane, culminating in the release of vesicular composites known as exosomes.(39) Secretoms offer a promising approach for allogeneic applications because they contain proteins that promote cell proliferation, differentiation, migration, and tissue repair. Notably, the composition of secreted factors varies based on the age of the cells, influencing their therapeutic potential.(40). Cellular secretions contain a diverse array of cell-specific proteins that play crucial roles in various functions, including signal transduction (G proteins, beta-catenin, and protein kinases), cell adhesion (integrins, ICAM), and intracellular trafficking (RAB, GTPases, and annexins) (41).

### **Exosome biogenesis**

The lipid composition of Exosome comprises phosphatidylserine, sphingomyelins, ceramides, and cholesterol, which contribute to their structural integrity and functional properties(42). Exosomes are divided into two categories, classical and non-classical, based on the expression of markers CD63, CD81, and CD9. Because Alix and TSG101 Play vital roles in the formation of MVBs, the presence of these proteins is essential to confirm the endocytic origin of exosomes. These biomarkers serve as key indicators of the biogenesis pathway, ensuring that the isolated vesicles are exosomes derived from the endosomal compartment(43). The surfaces of various Exosome are surrounded by polysaccharides and glycans. The nucleic acid cargo carried by Exosome includes mitochondrial DNA, genomic DNA, messenger RNA (mRNA), microRNAs (miRNAs), and long non-coding RNAs (lncRNAs). (44). Exosomes are small and densities ranging from 1.11 to 1.19 g/ml. Under an electron microscope, they display a characteristic 'disk-like' morphology, appearing as flattened spherical structures.(45) The isolation techniques for high-quality exosomes should provide high yields with a high degree of purity(40). It is essential for purification to identify the physicochemical characteristics of exosomes, such as surface charge, shape, size and density(39). Various techniques have been developed to facilitate the isolation of exosomes, including ultracentrifugation, sequential centrifugation, ultrafiltration, immunoaffinity precipitation, and size-exclusion chromatography, which have been employed to separate different populations of Exosome. (46) Exosomes have gained significant attention in clinical research for their role in vaccine development, biomarker discovery, drug delivery, and therapies offer a rapid approach for managing acute conditions like military trauma, cerebral ischemia, and myocardial infarction (20).

### **Role of MSC-Derived EV(MSC-Exosome) in wound healing**

Exosomes are bioactive vesicles primarily responsible for the effects of cells on their surrounding microenvironment. Exosomes are essential regulators of physiological and pathological processes, influencing recipient cell survival, proliferation, migration, and gene

expression. Additionally, they contribute to reprogramming the target cell behavior, thereby influencing cellular functions and intercellular communication(47). Exosomes are considered one of the important models of intercellular communication that can be conferred by mediators expressed at their surface into target cells after internalization, such as keratinocytes, fibroblasts, endothelial cells, adipocytes, and immune cells, through fusion or endocytosis. Exosomes derived from various types of MSCs have been shown to mitigate inflammatory responses triggered by multiple stimuli. This anti-inflammatory effect is facilitated by the suppression of proinflammatory enzymes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and MCP-1(48). During regeneration, MSC exosome activity interacts with key ECM components, including collagen, non-collagen proteins (fibronectin, laminin), elastin, proteoglycans, and aminoglycans.(37). Fibroblasts, key therapeutic targets of exosomes in wound healing, play a crucial role in ECM remodeling. They serve as the main cells responsible for the synthesis, secretion, and deposition of collagen and elastic fibers, contributing significantly to tissue regeneration and repair(49). The proliferation, migration, and protein synthesis abilities of dermal fibroblasts are crucial for wound healing. Early activation of fibroblasts during wound healing enhances wound closure and promotes matrix protein synthesis, establishing a crucial role for tissue regeneration(50). In the context of wound healing and skin regeneration, the most frequently reported signaling pathways include Wnt/ $\beta$ -catenin, PI3K/AKT, ERK, and TGF- $\beta$ /Smad (51). Wnt signaling specifically induces the activation of  $\beta$ -catenin in endothelial cells via exosomes, thereby promoting skin repair and regeneration (52).

### **Preclinical investigations into the therapeutic potential of MSC-derived exosomes in wound healing**

Numerous studies have explored the therapeutic potential of MSC-EV in promoting skin rejuvenation by reducing oxidative stress and counteracting photoaging effects(53).

Studies have shown that MSC-Exosome are the main source of miRNAs(54). Thirteen distinct

proteins and 14 microRNAs (miRNAs), derived from various sources, have been identified as key regulators of different wound healing stages and were observed to enhance tissue repair following exosome treatment, highlighting their crucial roles in regeneration and recovery(55). Kim et al. observed that inflammation was reduced through macrophage polarization. This study demonstrated that exosome administration triggered a transition from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, thereby modulating the healing cascade and enhancing therapeutic outcomes.(56). In parallel, a study by Su et al. observed that after administration of derived exosomes, T cell activation was suppressed during the inflammatory phase and the expression of programmed death ligand-1 (PD-L1) or interferon (IFN) was upregulated in the cells (57). Indeed, exosomes directly act on wound bed fibroblasts by stimulating Notch signaling or activating PTEN, thereby enhancing fibroblast migration(58). Recently, Zhang et al. conducted a study demonstrated that Human Amniotic Epithelial Cell-Derived Exosomes (hAEC-derived exosomes) significantly enhanced keratinocyte proliferation within the group by activating the AKT/HIF1 $\alpha$  signaling pathway, ultimately promoting faster wound closure. (59). In 2020, Zhang et al. conducted a study on exosomes derived from epidermal stem cells in the context of wound healing in mice. Their findings demonstrated that these exosomes contributed to wound healing by downregulating the expression of TGF- $\beta$ 1(60). A trial clinical study has suggested that a pharmaceutical composition utilizing exosomes may promote or enhance hair growth, resulting in thicker and longer hair. The exosomes used in this composition were derived from stem cells such as MSCs (61). A study by Ieyuan Zhang in 2019 on diabetic wounds using bone marrow-derived exosomes in combination with deferoxamine increased angiogenesis through the PI3K/AKT and miR-126 signaling pathways (62). A 2020 study by Lei Wang on Schwann cell-derived exosomes (SC-Exosome) in diabetic wounds in mice showed that these exosomes improved sciatic nerve conduction velocity, increased thermal and mechanical sensitivity, and significantly improved wound healing in diabetic mice (63). Zhang et al. conducted a study

demonstrated that exosomes derived from iPSC-MSCs (iPSC-MSC-exosomes) exerted significant regenerative effects following subcutaneous injection around wounds in rats. Their findings indicate that these exosomes enhance re-epithelialization, minimize scar expansion, and promote collagen maturation along with the formation of new blood vessels.(64). All these combined effects improved skin wound outcomes.

### **Pioneering Structural Innovations with Biomaterials for MSC-Exosome in Wound Healing**

Recent studies have indicated that intravenous injections enhance wound healing more effectively than topical applications. This effect occurs due to the loss of exosomes following local injection, primarily caused by syringe-induced disruption (49). However, when exosomes are injected intravascularly, they undergo rapid systemic clearance, compromising their healing properties. Injected exosomes cannot concentrate in defined locations because of the flow of body fluids; therefore, their time in the wound is short. Recent studies have integrated exosomes with novel materials, predominantly scaffold-based structures. Scaffolds play a crucial role in delivering complement proteins for sustained therapeutic effects, while also providing a native microenvironment, such as ECM, to aid tissue regeneration. Consequently, reinforced scaffolds can serve as acellular tissue substitutes, such as skin patches. (65). Scaffolds can be fabricated by using biological or synthetic biomaterials to regenerate various tissues and organs. Hydrogels can be used as scaffolds for exosome accumulation to synergistically promote wound healing. Researchers have developed a CTS SF/SA/Ag-Exo dressing with silver nanoparticles and exosomes, offering antibacterial activity and supporting water-electrolyte balance to treat diabetic wound infections (66). Collagen scaffolds are widely used in biomedical applications and can be obtained from various sources, including human, animal, marine, plant, and recombinant technologies (67). From the NIH Clinical Trials website (<https://clinicaltrials.gov>), a total of 265 clinical trials related to EV have been published. Among these, 17 clinical trials have specifically investigated the effects of Exosome on wound healing, as shown in the Table 1.



**Table 1: Application of MSC-Exosome in humans to enhance wound healing and promote skin regeneration.**

NCT Number	Conditions	Phases	Enrollment	Study Type	Locations
NCT02565264	Ulcer	EARLY_PHASE1	5	INTERVENTIONAL	Japan
NCT05475418	Wounds and Injuries	NA	5	INTERVENTIONAL	China
NCT06896747	Thin Endometrial Lining	PHASE1 PHASE2	90	INTERVENTIONAL	China
NCT05261360	Knee;	PHASE2	30	INTERVENTIONAL	Turkey
NCT05058768	Acute Lung Injury		180	OBSERVATIONAL	China
NCT06319287	Diabetic Foot Ulcer	PHASE2	40	INTERVENTIONAL	United States
NCT06391307	Pilonidal Sinus Pilonidal Disease	NA	120	INTERVENTIONAL	Turkey
NCT04664738	Skin Graft	PHASE1	8	INTERVENTIONAL	United States
NCT04798716	Covid19	PHASE1 PHASE2	55	INTERVENTIONAL	United States
NCT05243368	Foot, Diabetic	NA	30	INTERVENTIONAL	Spain
NCT04602104	Acute Respiratory Distress Syndrome	PHASE1 PHASE2	18	INTERVENTIONAL	China
NCT05354141	Acute Respiratory Distress Syndrome ARDS	PHASE3	970	INTERVENTIONAL	United States
NCT04384445	Corona Virus Infection	PHASE1 PHASE2	20	INTERVENTIONAL	United States
NCT04657406	Covid19	-		EXPANDED_ACCE SS	-
NCT05451342	COVID19	-	200	OBSERVATIONAL	China
NCT05387278	COVID19	PHASE1	20	INTERVENTIONAL	United States
NCT06599346	Mucositis	NA	120	INTERVENTIONAL	China

### **Challenges to Reproducibility and Standardization in Clinical Exosome Applications**

Effective treatment of skin wounds and the development of novel wound-healing therapies necessitate a thorough understanding of the natural healing physiology and its dynamic processes. These interconnected mechanisms re-epithelialization, inflammation, angiogenesis, wound contraction, and ECM remodeling. However, imbalances in regulatory factors governing these processes can lead to delayed healing (68). Consequently, understanding the mechanisms involved in the healing process, factors that can influence healing, and various functions of wound healing can provide a strong foundation for the development of new drugs for the treatment of skin wounds. Despite various wound treatments, only a few effectively heal chronic wounds. Conventional care involves debridement, dressings, and topical agents, whereas emerging therapies focus on novel drugs, biocompatible dressings, and non-immunogenic skin substitutes(69). Researchers are looking for ways to speed up healing, speed wound closure,

prevent wound contraction and scar formation, and ideally regenerate skin using stem cells. Wound-healing materials with appropriate components and structural configurations create optimal microenvironments, such as moisture, that support skin cell functions and accelerate and enhance wound repair(70). Regenerative medicine has garnered significant interest because of the ability of stem cells to self-renew and differentiate into multiple cell types, thus playing a crucial role in tissue repair and regeneration following injury(71). Key factors influencing cell therapy include site selection, cell availability, patient demographics (age and sex), and potential risks, such as diminished stem cell efficacy from repeated culture or malignant transformation. Among the methods used are cell-based allogeneic skin substitutes and acellular tissue scaffolds, which may cause problems such as cell changes at the site of thick wounds, delayed healing time, and even disease transmission to the recipient. Despite the significant potential of cell therapies, several challenges remain that hinder their widespread application. These include concerns related to safety, standardization of processes, and practicality of delivering viable

cells to the often hostile microenvironments found within injured tissues. Addressing these obstacles is crucial for advancing the field and ensuring the effective translation of cell-based therapies into clinical practice(25). Initially, it was believed that the therapeutic effects of cells were primarily mediated through their engraftment into the target tissue. However, recent studies have revealed that only a small fraction of these cells reach the target site. Instead, the immunomodulatory and regenerative properties of these cells are largely attributed to their secreted factors. These findings suggest that the therapeutic benefits are not solely dependent on the cells themselves but are significantly driven by the paracrine effects of their secretory components, such as exosomes and other bioactive molecules. Consequently, researchers are now exploring the potential of using these cell-derived secretory factors or exosomes as an alternative to whole-cell therapy, offering a promising and potentially safer approach for regenerative medicine. Over the past decade, scientists have discovered exosome derived from stem cells exhibit therapeutic benefits similar to those of stem cells in some diseases. Stem cell-derived exosomes play a key role in cellular activation, inflammation regulation, angiogenesis, tissue fibrosis, and ECM remodeling by delivering various bioactive molecules. These functions pave the way for innovative, non-cellular approaches to wound repair(72). Exosome therapy has gained considerable attention as a promising approach to enhancing repair wound. Due to their endogenous, biocompatible, and multifunctional nature, exosomes are emerging as an innovative tool for drug delivery systems, immunotherapy, and precision medicine(73). Exosomes from various cellular sources may exhibit beneficial effects on disease. It is important to note exosomes have a complex composition, and their biosafety and efficacy can vary and are somewhat unpredictable(74). now, Exosomes challenges in origin, isolation, purification, and identification, requiring stringent quality control and standardization for clinical applications. Their abundance is influenced by stem cell tissue origin, differentiation, proliferation activity, and culture conditions(75). The efficiency of exosome production is enhanced by various culture factors, including basal medium composition, stable

glutamine and glucose concentrations, and protein regulators exosome biogenesis(76). Extensive research has confirmed the effectiveness of exosomes in Enhancing skin wound repair by regulating essential stages in the wound healing process. Throughout the proliferation phase, exosomes facilitate wound closure by stimulating endothelial cells and fibroblasts, promoting angiogenesis and triggering ECM formation. Throughout the regenerative phase, exosomes modulate the balance between matrix metalloproteinases and their tissue inhibitors, enhancing wound recovery(77). Exosomes have the potential to serve as an effective clinical tool for wound healing while reducing risks such as infections and painful wounds(78). The findings support the hypothesis that Exosome such as exosomes could be ideal therapeutic tools for wound healing and regenerative purposes. Despite efforts to harmonize research approaches, the revised position statement by the International Society for EV (2023) provides guidelines for researchers studying exosomes. However, significant variability remains in their definition, isolation, and characterization, particularly in strategies for wound healing .the most important challenge of exosomes is the insufficient number of exosomes to meet application standards. For clinical applications, obtaining large quantities of exosomes with controlled quality is a major challenge. It has been observed that exosomes have a remarkably short half-life in the bloodstream, lasting approximately two minutes. Moreover, following intravenous administration, exosomes predominantly accumulate in the liver, lungs, spleen, gastrointestinal tract, and bone marrow.(79). Different studies have used different cell types and secretome doses. It is crucial to produce clinical-grade Exosome using a GMP-compliant process and implement rigorous QC measures for the development of EV-based therapeutics(80). Pharmacokinetic studies of exosomes play a crucial role in advancing the clinical application of exosomal therapeutics, bridging the gap between laboratory research and clinical practice. Among these studies, biodistribution—defined as the relative pattern of tissue distribution—constitutes a fundamental step in understanding exosome behavior within the body.(79). This consequently leads to the absence of standardization for secretome

production, culture media, and secretome processing. Shortly, Soon, advances in scale-up technology for GMP-compliant exosomes production will increase the application of exosomes for wound healing. The standardization of secretions could facilitate large-scale production by pharmaceutical companies, enabling their utilization in therapeutic applications(81). This leads to increased production, workload, and labor costs, as well as the demand for additional space for culturing processes. It is crucial to produce clinical-grade exosomes using a GMP-compliant process and rigorous QC measures to ensure the safety, efficacy and consistency of exosomes-based therapeutics. (43). The main challenge in scaling up cell cultures and cell-based therapies is ensuring the consistent maintenance of their therapeutic potency

Currently, information regarding the biodistribution and retention time of stem cell-derived exosomes in skin wounds remains limited. However, since the retention time of exosome in various organs is generally brief and largely influenced by their origins, efforts to extend their half-life and enhance their resistance to biodegradability through diverse engineering techniques are actively underway(28). Scaffolds made from synthetic materials have also been studied, but these scaffolds do not create structures similar to the extracellular matrix, do not have mechanical properties similar to skin, and many of them are not biodegradable. However, the use of scaffolds made from acellular plant materials does not have any of the limitations mentioned above. MSCs have been widely investigated in cell therapy and tissue regeneration for their potential in to treat a range of diseases and disorders(24). Increasing interest in MSCs is driven by their relatively simple and minimally invasive isolation process, along with their wide-ranging therapeutic potential. The use of immortalized MSCs, which exhibit similar functionalities and safety profiles compared to naïve MSCs, could serve as an alternative strategy for the stable and scalable production of MSC-derived exosomes [29, 30]. The successful commercialization of MSC-exosomes has the potential to revolutionize therapeutic approaches, offering a novel paradigm in human healthcare(43).

The challenge of applying MSC-derived

Exosome focuses on three key points:

1. Manufacturing and Storage: Regulating the process to produce high-quality Exosome from non-autologous MSC sources and determining optimal storage conditions.
2. Ethical and Legal Challenges: The application of MSC-Exosome faces ethical and legal hurdles, including limitations imposed by patents and varying laws across different countries, which present significant obstacles.
3. Collaboration: Effective cooperation between scientists and clinicians is crucial to facilitate the translation of MSC-EV research from the laboratory to patient care(12)

The characteristics of exosomes can be influenced by a range of genetic, physiological, and environmental factors, leading to variations in exosomes heterogeneity and potential alterations that may affect analysis and reproducibility. For instance, parameters such as age, sex, body mass index (BMI), Pharmaceutical consumption, physical activity, and ethnicity play a significant role in determining exosomes levels(81). Therefore, large, well-characterized cohort studies are essential to evaluate exosomes heterogeneity. Moreover, several issues must be addressed before integrating Exosome into clinical practice. These factors include latent toxicity, the dose-toxicity relationship, appropriate therapeutic strategies, and the determination of optimal dosage and administration regimens. Transparent reporting of experimental methodologies is essential for data accuracy and reproducibility. To support exosomes research, a publicly accessible knowledge base has been developed, while researchers are advised to consult literature to determine the most suitable isolation method due to the lack of universally accepted protocols.(82).

## **Conclusion**

Recent evidence strongly supports the development of exosomes as an innovative therapeutic tool for treating impaired wound healing. The reviewed studies emphasize Exosome significant role in regulating physiological processes and intracellular pathways across wound healing phases, including hemostasis, inflammation, proliferation, and remodeling. The rising interest in exosomes has been a key driver of progress and innovation in this field. To date, thousands of studies have been

published, and exosomes are being explored for commercialization purposes. This review highlights exosomes as promising candidates for skin treatments. By utilizing exosomes as ingredients, the current limitations of skin therapies can be addressed(40).

### Compliance with ethical guidelines

This study is a narrative review without involving humans or experimental animals.

### Acknowledgment

There is nothing to say.

### Conflicts of interest

The authors report no conflicts of interest.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Abbreviations

FOXP3	fork head box P3
CTS	Chitosan-Silk Fibroin/Sodium
SF/SA/Ag-Exo	Alginate/Silver nanoparticles-adsorbed Exosomes.
IL-1 $\beta$	interleukin-1 $\beta$
TNF- $\alpha$	tumor necrosis factor- $\alpha$
FGF	fibroblast growth factor
PDGF	platelet-derived growth factor
VEGF	Vascular endothelial growth factor
ECM	Extracellular matrix
GAGs	glycosaminoglycans
GM-CSF	Granulocyte-macrophage colony-stimulating factor
SDF-1	Stromal cell-derived factor-1 $\alpha$
b-FGF	Basic fibroblast growth factor
HGF	Hepatocyte growth factor
TGF- $\alpha$	transforming growth factor
QC	quality control
MMP	Matrix metalloproteinases
STC1	stanniocalcin-1
HO-1	heme oxygenase-1
GDNF	glial cell line-derived neurotrophic factor
PGE2	Prostaglandin E2
GMP	Good Manufacturing Practice
iNOS	nitric oxide synthase
COX-2	cyclooxygenase-2
TNF- $\alpha$	tumor necrosis factor-alpha
IL-1 $\beta$	interleukin-1 $\beta$
MCP-1	monocyte chemoattractant protein-1

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