Application and Prospect of Mesenchymal Stem Cells in the Field of Skin

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Abstract. Mesenchymal stem cells (MSCs) are non-hematopoietic multipotent cells with fibroblast like morphology and self-renewal abilities. MSCs exhibit both immunomodulatory and paracrine signaling properties which are beneficial for the fields of skin regeneration and rejuvenation. Specifically, in the process of wound healing, MSCs inhibit excess immune activities and secrete growth factors and cytokines that aid all four stages of injury recovery. Its abundance in bone marrow, adipose tissue and umbilical cord tissue allow harmless extractions, and its immunomodulatory property also made allogeneic sources of MSCs practical in clinical settings. In skin aging, there are two main ways that the skin ages, intrinsically and extrinsically. Both routes result in an ECM that breaks down faster that it is regenerated, which induces in the formation of wrinkles, roughness, enlarged pores, and reduced elastic recoil. MSCs can be applied through the various growth factors that synthesize collagen I/III and elastin which strengthens the ECM and anti-inflammatory mediators that reduce activator proteins that breaks down ECM. The extracellular vesicles derived from MSCs further support cell regeneration. The application of MSCs in the field of skin rejuvenation holds many potentials for growth in the new future, especially in standardizing MSC products and protocols, promoting personalized MSC-based skin care, and ensuring ethical sourcing and safety assurance of MSCs.

Keywords: Mesenchymal stem cells, skin regeneration, immunomodulation, wound healing, antiaging. cosmetic dermatology.

1. Introduction

Mesenchymal stem cells (MSCs) are non-hematopoietic multipotent cells with fibroblast like morphology and self-renewal abilities. Although it can be found in various part of the body, including the umbilical cord blood, adipose, pericytes, brain, liver, lungs and bone marrow, most utilized source of MSCs is extracted from the bone marrow and adipose [1, 2]. To distinguish definitions of MSCs and non-MSCs, the international society of cellular therapy proposed 3 minimum criteria: adherence to plastic, expression of the surface markers CD73, CD90 and CD105, lacking the expression of hematopoietic and endothelial markers (CD11b, CD14, CD19, et al.) and the capacity to differentiate into adipocyte, chondrocyte and osteoblast lineages under in-vitro conditions [3]. Despite the multipotency of MSCs under in vitro conditions, the cell in situ exercise its function mainly through its paracrine effects. The MSCs found in pericytes, cells that covers 90% of the surfaces of capillaries [4], are found to secrete a variety of bioactive molecules in large quantities for immunomodulatory purposes when nearby tissues are damaged. As shown in Fig. 1, the secretions serve two purposes: first to prevent autoimmune activities from occurring by inhibit the surveying of nearby immune cells, and second to create a regenerative microenvironment to assist the regeneration of the damaged tissue [5]. MSCs located in other part of the body, such as the bone marrow and placenta, showcases similar, but not identical functionalities [5].

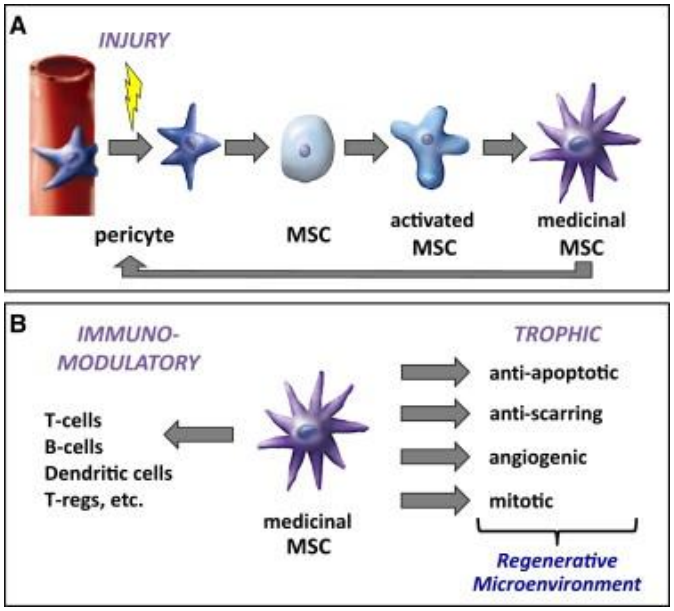


Figure 1. Diagram showcasing how MSCs activate during an injury [5]

2. MSCs application in Skin Repair

2.1. Clinical Benefits of MSC

Since their discovery, MSCs have been investigated for cell therapy due to their diverse secretome and low-cost extraction. [6, 7]. The specifics of what the secretomes are and their exact function will be elaborated in the sections ahead, where it will be paired with examples to better showcase the potential of MSC. The derivation of MSCs made it a preferred candidate for cell therapy primarily because it allows for both autologous and allogeneic sources [2]. Since bone marrow are thought to be regenerative and adipose tissues unwanted, it isn't costly to collect the sample needed to then put them through in-vitro expansion [6]. For example, only 25ml of bone marrow are needed to produce 100–150 million human MSCs for clinical use [2]. Allogeneic sources of MSCs are also possible for clinical use due to MSC's immune-evasive property [6]. Surprisingly, there are more clinical trials that utilizes allogeneic MSCs compares to autologous sources in 2014 [6]. The capability to suppress T-cells and the expression of MHC class I allowed even allogeneic MSCs to enter a foreign body without immediate immune response and still perform its immunoregulatory role on the patient's immune system [8]. For example, in a treatment of a patient with severe burn, allogenic umbilical cord derived MSCs are applied to the patient's wounds with successful results: 3% of open wound after two months and discharged from the hospital with no open wounds three months after that [9].

2.2. Wound Healing

In a clinical setting, most MSCs are utilized for its paracrine signaling capability in suppressing auto-immune activities and enhancing regeneration. MSC do so by secreting an abundance of growth factors and cytokines that aid every stage of skin recovery which are: Hemostasis, Inflammation, Proliferation, and Maturation [7]. In the Hemostasis stage, the body coagulate the damaged area to prevent blood loss, and MSC will secrete VEGF, bFGF, CCL2, CD31, and α-SMA in the wound bed to promote angiogenesis. The inflammatory stage then gathers immune cells to clear up the injury of any pathogens. Here, MSC can turn Macrophages found in the dermis from its pro-inflammatory M1 phenotype into its anti-inflammatory M2 phenotype [10]. This M2 phenotype is important because excess immune activity will result in chronic inflammation which can delay skin healing [7]. Specifically, M2 phenotype macrophages can inhibit the proliferation of both T-reg and natural killer cells. MSC also suppresses interleukin-1 (IL-1) by releasing interleukin-1 receptor antagonist (IL1RA). Since IL-1 is responsible for the growth of T-helper 17 and therefore the expression of the

inflammatory marker IL-17, MSC released cytokine IL1RA reduces IL-17 [7]. During the proliferation stage, the wound undergoes epithelization so that the wound would be properly filled. MSC transformed M2 phenotype macrophage will release epidermal growth factor and transforming growth factor-α to excite the proliferation and migration of keratinocytes, which is the main component of the epidermis [11]. And lastly, in the Maturation stage, MSC aid the remodeling of the skin surface to form normal skin by supporting the growth of Extra Cellular Matrix (ECM) by releasing matrix metalloproteinases. ECM is crucial during the Maturation stage due to its ability to allow cells to group in a specific way to reconstruct what was lost from the damage. However, if there is an overproduction of ECM, then the result of maturation would be scarring, which is not as ideal as the complete regeneration of the skin. Through the release of VEGF and HGF and balancing the amounts of TGF1 and TGF3, MSC can limit the release of ECM to reduce scarring [12].

2.3. Msc Therapy for the Treatment of Clinical Burns

In the recent decade, many trials have been conducted utilizing MSCs for chronic skin wounds. In 2022, Carl I Schulman et al. enrolled ten adults with second degree burn wounds and conducted a dose-escalation clinical trial, where a group of five received doses of 2.5×10^3 BM-MSC/cm2 and the other group of 5 received doses of 5×10^3 allogeneic BM-MSC/cm2. In less than a month, most patients had 100% wound closure with zero or trivial scarring, and all achieved closure in less than two months, with an average wound closure rate of 3.64 cm2/day for the first dose concentration and 10.47 cm2/day for the second dose concentration. The researchers utilized allogeneic sources of MSC derived from bone marrow primarily because bone marrow suppression and dysfunction are likely to occur after severe burn injuries, which would inhibit extraction, and the expansion of autologous MSCs takes four weeks, which is past the window for therapeutic treatment. To ensure the safety of the cell transplantation, safety analysis was conducted through the evaluation of cytokine profiles before and after the cell transplant. Specifically, peripheral blood was taken from the patient and peripheral blood mononuclear cells (PBMC) were isolated. The patients PBMCs and the donor BM-MSC were mixed and levels of INF-γ, IL-10 and TNF-α were measured as INF-γ and TNF- α are presumed markers of rejection and IL-10 is a marker of immunosuppression. These cytokines levels were influenced minimally or without influence, and no rejections or adverse outcomes have been reported. Figure 1a showcases a flame burn of a 24-year-old Hispanic man in the left arm. A dose of 5×10^3 allogeneic BM-MSC/cm2 was treated once and the wound closed within 17 days. Figure 1b presents the same area on the left arm one year after the treatment. The dotted line marks the area of the original wound, and it has been observed that more hair developed at the site treated with BM-MSC and no scarring noted [13].

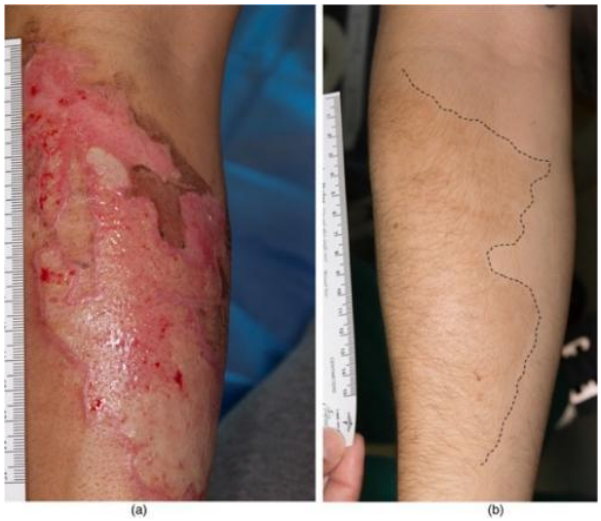


Figure 2. (a) Flame burn of a 24 years old Hispanic man while pouring an accelerant into a fire, wound area measured to be $29cm^2$ (b) 1 year after treatment with BM-MSC [13]

Another study conducted in this recent decade was a 2019-2020 study by TN Dung et al. in the Wound Healing Center of Vietnam National Burn Hospital. 30 patients with chronic wounds were treated with autologous AD-MSCs and observed weekly. As figure 3 illustrates, one week after the treatment, wound beds are filled with granulation tissue and re-epithelialization are appearing on the wound edge. In two weeks, keratinocytes proliferated and immigrated up to form a thin epidermis layer. In three weeks, fibroblast, neo-vascular and collagen grew at a higher rate in comparison to the previous weeks, with epithelial cells covering the majority of the wound surface. Normal chronic wounds lack an ECM that facilitates the recovery, as without a healthy ECM the skin could not properly undergo epithelialization. Almost all the wounds before applying AD-MSC had unhealthy granulation which prevents normal healing. A week follows the treatment, unhealthy granulation tissue decreased, and healthy granulation tissue arises followed with epithelialization. Overall, AD-MSC have been proven useful in its ability to aid the proliferation stage by supporting ECM growth.

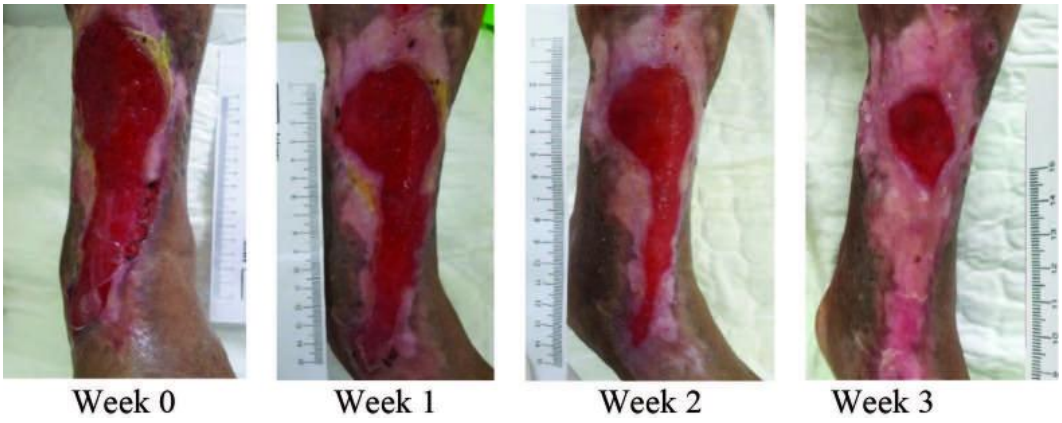


Figure 3. Chronic burns treated with autologous ADSC sheets, comparison pictures for week 0, 1, 2, and 3 [14]

3. Applications of MSCs in Anti-Aging Cosmetic Dermatology

Building on the understanding of the mechanics of MSCs, their relevance to facial skin aging will be examined through an overview of their applications, outlining their roles in aging processes and supporting experimental evidence.

3.1. Types of Skin Aging

There are two main types of skin aging commonly described, chronological (intrinsic) and photoaging (extrinsic) [15]. First, photoaging is driven by often chronic ultraviolet (UV) exposure. Clinically, photoaging presents with coarse and fine wrinkles, surface roughness/laxity, enlarged-appearing pores, and mottled pigmentation; histologically this pattern reflects solar elastosis, characterized by defective elastin aggregates in the upper and mid dermis accompanied by fragmented collagen bundles [15]. Second, chronological aging, an unavoidable time-linked decline. Typically features finer lines, thinning and dryness, and slower elastic recoil. Microscopically, collagen I/III bundles become sparse and disorganized, hyaluronan declines (hydration loss), and the dermal-epidermal junction (DEJ) flattens, weakening mechanical anchoring and nutrient exchange [16, 17]. Finally, in the extrinsic manner beyond UV exposure, air pollution ($PM_{2.5}$/ozone), cigarette smoke, diet-related glycation and sleep/circadian disruption can all potentially further contribute to oxidative and inflammatory stress which biases remodeling toward breakdown and can amplify photoaging changes [16].

3.2. Mechanistic Basis of Aging

First, in intrinsically aged skin, dermal fibroblasts progressively enter senescence and develop a senescence-associated secretory phenotype (SASP), while mitochondrial/oxidative stress rises and

TGF-β/Smad anabolic signaling declines. As a result, matrix degradation exceeds synthesis, hence, affecting the dermis, dermal-epidermal junction and hydration via hyaluronan/glycosaminoglycans [16, 18]. By contrast, photoaged skin is driven by UV radiation as it increases reactive oxygen species (ROS) and activates AP-1 and NF-kB, up-regulating MMP-1/3/9 and cleaving collagen and elastin, while also suppressing TGF-β/Smad needed for new matrix synthesis [16, 19]. This repeated injury yields solar elastosis in the upper and mid dermis with surface roughness and enlarged-appearing pores. Overall, despite different triggers, the two routes both result in an ECM that breaks down faster than it is rebuilt, explaining the shared phenotype of wrinkles, roughness, enlarged pores, and reduced elastic recoil [16, 20].

3.3. The Mechanisms of MSC Action on Skin

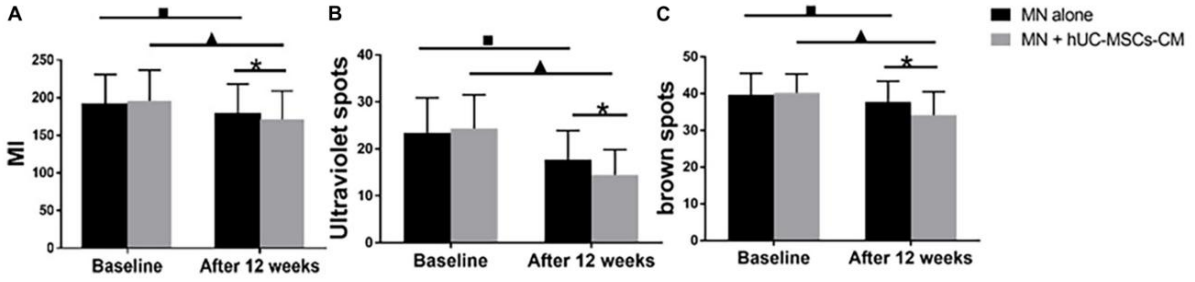
Given the convergence of intrinsic aging and photoaging on inflammation and protease dominant remodeling, MSC-derived secretomes and extracellular vesicles (EVs/exosomes) are shown to be well positioned to counteract these nodes [1, 20]. To be specific, MSC secretomes supply growth factors such as TGF-β, FGF-2, PDGF, IGF-1, and HGF which stimulate dermal fibroblasts to synthesize collagen I/III and elastin [21]; they also contain anti-inflammatory mediators (e.g., IL-10, PGE_2) and the MMP inhibitor TIMP-1, which together reduce AP-1/NF-kB activity and matrix cleavage caused by MMP-1/3/9 [7]. EV cargo (proteins, lipids, and miRNAs) further reprograms recipient fibroblasts toward an anabolic phenotype and may support microvasculature and hyaluronan homeostasis [1, 7]. Additionally, because secretome and EV cargos are large and hydrophilic, the stratum corneum strongly limits passive delivery. Clinical protocols therefore apply MSC-derived products immediately after microneedling, when transient microchannels permit diffusion into the viable epidermis and upper dermis [22]. This pairing is biologically coherent and has shown objective improvements in elasticity and texture when tested against microneedling alone (see Section 2.4) [22]. Alternative carriers (e.g., liposomes or hydrogels) are under study, however, at present, post-microneedling application remains the most practical approach for depositing MSC factors at fibroblast depth [22].

3.4. Human Evidence of Effectiveness

In 2022, a report published by Frontiers in Medicine captures the study done by a dermatology team at Beijing Friendship Hospital and Xuanwu Hospital, Capital Medical University, where they investigated whether adding human umbilical cord mesenchymal stem cell conditioned media to micro needling improves facial aging outcomes more than micro needling with saline.

The study used a randomized, controlled, split-face design and with a purpose to capture changes in structure, such as wrinkles, pores and elasticity, as well as changes in tone, such as melanin and spot indices. During the experiment, twenty-eight adults with clinical facial aging completed five treatment sessions spaced two weeks apart. At each visit both sides of the face underwent microneedling with a 0.5 mm device. The test side additionally received about 1 mL of human umbilical cord mesenchymal stem cell conditioned media before and after needling, while the control side received saline [22].

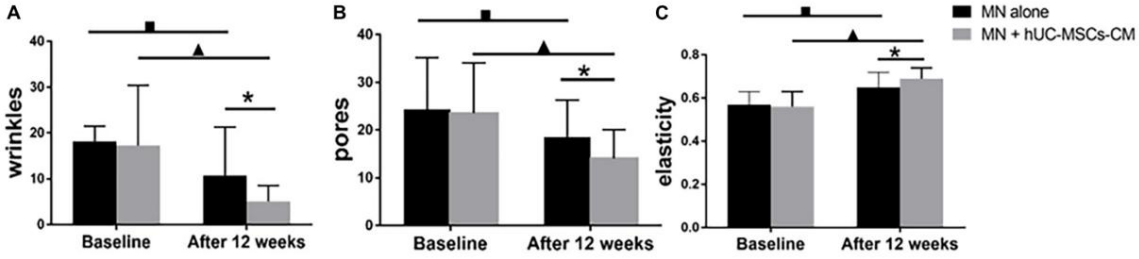
Outcomes were recorded two weeks after the final session using standardized digital photography to quantify wrinkle, pore and pigment metrics, and a Cutometer to measure biomechanical elasticity. The Cutometer reports R indices in which higher values indicate better elastic recoil. Overall, the results show significant improvements in both structural endpoints and in skin tone and brightness on the MSC-treated side, as illustrated in Fig.4 and 5.



Objective non-invasive skin pigmentation measurements. **(A)** Melanin index (MI); **(B)** Ultraviolet spots; **(C)** Brown spots. MN: microneedling; hUC-MSCs-CM: human umbilical cord-derived mesenchymal stem cells conditioned media. *$P < 0.05$, post-treatment comparison between MN alone and MN plus hUC-MSCs-CM; ▲$P < 0.05$, pre-treatment and post-treatment in MN plus hUC-MSCs-CM. ■$P < 0.05$, pre-treatment and post-treatment in MN alone.

Figure 4. Results for structural endpoints [22]

(1) The pore score fell from 23.55 to 14.05 on the test side compared with 24.40 to 18.59 on the control side. (2) Elasticity increased from 0.56 to 0.69 on the test side compared with 0.57 to 0.65 on the control side. (3) The endpoint wrinkle score was 5.06 on the test side compared with 10.73 on the control side.



Objective non-invasive skin texture measurements: **(A)** wrinkles; **(B)** pores; **(C)** elasticity. MN: microneedling; hUC-MSCs-CM: human umbilical cord-derived mesenchymal stem cells conditioned media. *$P < 0.05$, post-treatment comparison between MN alone and MN plus hUC-MSCs-CM; ▲$P < 0.05$, pre-treatment and post-treatment in MN plus hUC-MSCs-CM; ■$P < 0.05$, pre-treatment and post-treatment in MN alone.

Figure 5. Result for tone and brightness [22]

(1) The melanin index declined by 24.25 units compared with 12.36 units on the control side. (2) The ultraviolet spot score dropped from 24.39 to 14.47 compared with 23.08 to 17.72. (3)Brown spot score decreased from 40.21 to 34.18 compared with 39.71 to 37.75.

Furthermore, safety outcomes were reassuring. No severe adverse events occurred, and barrier measures including hydration, trans epidermal water loss and erythema did not worsen, which indicates good tolerability of post microneedling application of human umbilical cord MSC conditioned media. Taken together, the results support a mechanism guided approach in which cell free MSC factors augment microneedling to address the shared biology of intrinsic aging and photoaging. The split-face design strengthens internal validity by controlling for subject level variables. At the same time the follow up was short and the enrolment was from a single center, so durability and generalizability will require multicenter studies with six-to-twelve-month outcomes and standardized product specifications [22].

3.5. Future Directions of MSCs in Cosmetic Dermatology

In the near term, developments in MSC-based cosmetic dermatology are expected to focus on cell-free, potency-defined formulations, that incorporate EVs, secretomes and growth factor rich conditioned media [1]. These formulations promote dermal repair by preserving the paracrine activity of MSCs, while also being easier to standardize, store, and administer than live cells, improving safety, stability, and shelf-life of MSC-based products for cosmetic use [23]. Furthermore, delivery methods for MSC-derived products are also expected to improve. A common current approach is to apply such products immediately after microneedling, which exploits transient microchannels created in the stratum corneum [23]. However, these microchannels close quickly, resulting in limited residence time and making microneedling less suitable for sustained cosmetic delivery. Newer systems such as

liposomes, niosomes, or in situ-gelling hydrogels aim to prolong residence time in the upper dermis. These carriers are designed to increase penetration and provide controlled release, thereby enhancing anti-aging effects and achieving overall rejuvenation [23].

Additionally, another development direction is personalized MSC-based skincare. Future MSC-derived cosmetics are likely to be tailored to each customer. According to their skin type, specific concerns and aging profile, with adjustments in dose and schedule to meet individual needs. The use of standardized imaging, biomechanical measures and simple exposome profiling can further guide customization and track response over time [24]. Moreover, regarding the specific concern of skin aging, formulation work is expected to be increasingly mechanism-driven. While many current MSC-based products already claim to act on underlying pathways such as fibroblast stimulation and antioxidant protection, their efficacy is often limited by variability and lack of standardization. Future formulations are expected to advance further by being precisely targeted to key biological checkpoints of aging. For instance, actives may be selected to counter oxidative stress, suppress pro-inflammatory signaling, prevent collagen degradation, or stimulate fibroblast activity [25].

Ultimately, ethical sourcing and safety assurance will remain as the central target for developments of MSC-based cosmetic products. Developers should ensure documented donor consent and strict source screening, with preference for ethically accessible sources such as adipose tissue rather than umbilical cord or fetal tissues. It is also essential to follow GMP-level manufacturing standards, alongside identity and purity testing of MSC-derived components, thus, ensuring consistency and product integrity [16]. Furthermore, with the cosmetic sector moving toward animal-free testing, safety validation of such products should rely more on in vitro assays and clinical studies. Finally, the long-term safety of such MSC-based products still requires confirmation through further research.

4. Conclusion

MSCs have emerged as one of the most multi-purposed and effective tools in the current medical field. In this case, their unique ability of immune modulation and paracrine signalling enables them to address acute tissue injury, chronic wounds, and combating against skin aging. With clinical evidence showing acceleration in wound closure and reducing scarring to improving elasticity, pigmentation, and texture in aged skin, further supporting their therapeutic benefits. Looking forward, the field is progressively moving towards more precise and personalized MSC-based skincare, with more mechanism-driven formulations designed to address specific aging pathways. These next-generation approaches are expected to be more effective and efficient. Nevertheless, safety, ethical sourcing, and long-term validation will remain to be the essential priorities, especially given the shift from therapeutic to cosmetic use in otherwise healthy populations. Overall, MSC-based technologies capture a unique "cross frontier" between medicine and aesthetics, combining regenerative science with consumer demand for effective, biologically based skin care solutions. With continued research and following of strict standards, MSCs are expected to redefine the landscape of skin repair and cosmetic dermatology in the coming decade.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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