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Mesenchymal Stem Cells and their Derivatives in Normal and Diabetic Wound Healing: Mechanisms, Therapeutic Advances, and Clinical Translation; A Systematic Review

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Abstract: Chronic wounds such as DFUs present an important problem in modern medicine because of chronic inflammation, poor angiogenesis, oxidative stress, and abnormal extracellular matrix remodelling, which interfere with wound healing. Stem cells, especially mesenchymal stem cells (MSCs), have attracted considerable attention due to their capability to regulate inflammation, stimulate angiogenesis, increase collagen production, support re-epithelialization, and manage immune response mainly through paracrine action. This systematic review was undertaken to assess the biological mechanisms, therapeutic potential, and translational value of MSCs and MSC-derived products (extracellular vesicles, exosomes, secretome, conditioned medium) in the process of normal and diabetic wound healing. The search strategy and inclusion criteria for the review were designed in accordance with PRISMA 2020 guidelines and were performed on PubMed/MEDLINE, Scopus, Web of Science, Embase, and ClinicalTrials.gov databases. Altogether, eleven eligible preclinical and clinical studies were included in a qualitative analysis. Because of the high level of heterogeneity in design, cell source, mode of administration, and outcomes, the meta-analysis could not be performed. All included studies revealed positive effects of MSC-based treatment on wound closure, angiogenesis, granulation tissue formation, collagen production, oxidative stress decrease, and pro-inflammatory macrophage polarisation modulation. MSC-derived cell-free therapy, especially exosomes and secretome, replicated the reparative effects of their parent cells and provided additional benefits like decreased immunogenicity, enhanced biosafety and ease of manufacturing. In addition, cell retention and sustained effect of therapeutic delivery were achieved through biomaterial-based systems such as hydrogels, nanofibers, injectable systems, and smart dressings. Even though the initial results from the clinical trials suggest promising safety and efficacy in chronic wound healing, there are several hurdles to be overcome, such as standardisation, manufacturing, regulatory approval, and clinical validation. Nevertheless, MSC and cell-free therapies seem to hold great potential in wound repair, especially in diabetic foot ulcers, and require further testing in RCTs before clinical use.

Keywords: *Mesenchymal Stem Cells, Wound Healing, Diabetic Foot Ulcer, Exosomes, Extracellular Vesicles, Regenerative Medicine, Cell-Free Therapy.*

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I. INTRODUCTION

Wound healing is a highly regulated and coordinated biological process that consists of four overlapping stages: hemostasis, inflammation, proliferation, and remodelling. These stages involve complex interactions among keratinocytes, fibroblasts, endothelial cells, inflammatory cells, cytokines, growth factors, and extracellular matrix

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molecules. Under physiological conditions, these coordinated processes restore tissue integrity, but disruption of any phase can impair healing, resulting in delayed wound repair and the development of chronic wounds [1,2]. Chronic wounds represent a major global public health challenge, causing substantial morbidity, mortality, and healthcare expenditures. Chronic wounds include various complications such as diabetic foot ulcers (DFUs), which are one of the worst complications of diabetes mellitus and affect approximately 19–34% of patients with diabetes during their lifetime [3]. In diabetic ulcers, persistent inflammation, poor angiogenesis, oxidative stress, defective extracellular matrix remodelling, neuropathy, and microvascular abnormalities lead to delayed wound closure, recurrent infections, and an increased risk of lower-limb amputation [4,5]. However, conventional methods of chronic wound treatment, which include debridement, infection management, pressure relief, negative-pressure wound therapy, skin substitutes, and growth factor therapy, often fail to achieve satisfactory outcomes because they do not adequately address the complex pathophysiological mechanisms underlying impaired wound healing [6]. Regenerative medicine strategies have therefore become increasingly popular in wound repair and regeneration.

Mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells, are multipotent adult progenitor cells that are able to self-renew and differentiate into various mesodermal derivatives such as osteoblasts, adipocytes, and chondrocytes [7]. MSCs can be obtained from different sources such as bone marrow, adipose tissue, umbilical cord, placenta, dental pulp, and amniotic membrane. According to the International Society for Cell & Gene Therapy (ISCT), MSCs are characterised by plastic adherence, expression of CD73, CD90, and CD105, and the absence of hematopoietic markers CD34, CD45, CD14, CD11b, CD79a, CD19, and HLA-DR [8]. Initially, the curative properties of MSCs were thought to be due to their ability to differentiate into specific cell types. However, there is increasing evidence suggesting that the regenerative effects of MSCs are mediated predominantly through paracrine mechanisms rather than by directly replacing cells [9]. The secreted substances include VEGF, FGF, HGF, TGF-β, IGF-1, and cytokines with anti-inflammatory properties that act in the following ways: decrease inflammation, induce angiogenesis, promote fibroblast proliferation, increase collagen production, and remodel the extracellular matrix [10,11]. Furthermore, MSCs regulate both innate and adaptive immune responses by inhibiting pro-inflammatory cytokine activity and shifting the phenotype of macrophages to an anti-inflammatory one, creating favourable conditions for regeneration [12]. In recent years, increasing attention has been directed toward MSC-derived products such as extracellular vesicles (EVs), exosomes, and conditioned medium (secretome) that reproduce many of the regenerative properties of MSCs without causing the risk of being recognised as foreign bodies, developing tumours, and having insufficient grafting efficiency [13,14]. Exosomes consist of proteins, lipids, messenger RNAs (mRNAs), and microRNAs (miRNAs), which regulate angiogenesis, cell proliferation, apoptosis, and inflammation. [15]. Although there are encouraging pre-clinical studies and an increase in the number of clinical trials, several challenges remain related to the selection of MSC sources, dosage, routes of administration, manufacturing process standardisation, quality assurance, and regulatory approval. Additionally, variations between physiological and diabetic wound environments might affect the therapeutic efficacy of MSCs and MSC-derived products [16].

II. MATERIALS AND METHODS

➢ *Protocol Registration and Reporting Standards*

This systematic review has been carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement and its updates for systematic reviews and meta-analyses [17]. The methodology has been created in order to be transparent, replicable, and complete in relation to the identification of relevant studies about mesenchymal stem cells (MSCs) and MSC-derived products in normal and diabetic wound healing.

➢ *Review Question and PICO Framework*

This review question was formulated based on the Population, Intervention, Comparison, and Outcome (PICO) criteria to make sure that a systematic approach was taken in selecting studies and synthesising the information gathered. This review set out to answer the following question:

In animal and human models with either normal or diabetic wounds of the skin (Population), does intervention using mesenchymal stem cells or their derivatives (Intervention), compared with conventional wound management, placebo, or no treatment (Comparison), lead to better wound healing outcomes and safety (Outcomes)? The PICO model for this review is shown in Table 1.

Table 1 PICO Framework of the Present Systematic Review

PICO Component	Description	Supporting References
Population (P)	Animal models and human patients with **normal (acute) cutaneous wounds** and **diabetic wounds**, including diabetic foot ulcers (DFUs) and chronic non-healing wounds.	[1–6], [69], [74], [80–83]
Intervention (I)	Mesenchymal stem cells (MSCs) from any source (bone marrow, adipose tissue, umbilical cord, placenta, dental pulp) and MSC-derived products, including extracellular vesicles (EVs), exosomes, secretome, and conditioned medium, delivered alone or with biomaterial-based systems.	[7–16], [23], [25], [30–41], [46–68]

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Comparison (C)	Standard wound care, placebo, untreated/control groups, vehicle-treated groups, or conventional therapies, depending on the design of the included preclinical and clinical studies.	[6], [23], [25], [69], [74], [80–86]
Outcomes (O)	**Primary outcomes:** wound healing rate, wound closure, healing time, re-epithelialization, angiogenesis, and collagen deposition. **Secondary outcomes:** inflammatory cytokines, macrophage polarization, granulation tissue formation, extracellular matrix remodelling, histological findings, limb salvage, adverse events, and treatment safety.	[10–16], [23–40], [69–90]

➢ *Study Selection*

Two reviewers independently screened titles and abstracts retrieved from electronic databases. Potentially eligible articles were further reviewed based on inclusion and exclusion criteria. In case of any disagreement between the reviewers, an agreement was reached either by discussion or with the assistance of a third reviewer. Study selection was done according to the PRISMA 2020 flow diagram [17].

➢ *Data Extraction*

Data extraction was conducted independently by two reviewers utilising standardised data extraction forms. The following information was extracted from each selected study: first author name and year of publication; study design; characteristics of the animal model/patients; source of mesenchymal stem cells (MSCs); form of MSCs products (exosomes, secretome, conditioned medium); route of administration and dose; biomaterial carriers if present; duration of follow-up period; measured outcomes; main findings; adverse events.

➢ *Outcome Measures*

The main outcomes were wound healing rate, healing time, re-epithelialization, angiogenesis, and collagen production. The secondary outcomes were inflammatory cytokines, macrophage polarisation, granulation tissue formation, adverse events, limb salvage, and histological findings.

➢ *Risk-of-Bias Assessment*

The methodological quality of the included studies was assessed with the help of the Cochrane Risk of Bias 2 (RoB 2) tool for clinical randomised trials and the SYRCLE Risk of Bias tool for preclinical animal studies [18,19]. A total of five clinical studies and six preclinical studies were assessed. In general, the clinical studies were characterised by low to moderate risk of bias; however, the most problematic aspects include insufficient information about allocation concealment, blinding of participants and incomplete sample size [69,80-83]. The preclinical studies had an unclear risk of bias since the information about randomisation, allocation concealment, and outcome assessor blinding was lacking [23,25,27,36,37,74]. Despite that, all of the included studies showed beneficial effects of using MSC-based therapies in wound healing outcomes, which confirms the qualitative synthesis provided in this paper [23,25,27,36,37,69,74,80-83].

Table 2 Summary of Risk-of-Bias Assessment of Included Studies

Study	Study Type	Assessment Tool	Overall Risk
Wu et al., 2007	Preclinical	SYRCLE	Unclear
Chen et al., 2008	Preclinical	SYRCLE	Unclear
Sasaki et al., 2008	Preclinical	SYRCLE	Unclear
Kim et al., 2007	Preclinical	SYRCLE	Unclear
Zhang et al., 2015	Preclinical	SYRCLE	Low
Shabbir et al., 2015	Preclinical	SYRCLE	Low
Dash et al., 2009	Clinical	RoB 2	Some concerns
Procházka et al., 2010	Clinical	RoB 2	Some concerns
Lu et al., 2011	Clinical	RoB 2	Some concerns
Moon et al., 2019	Clinical	RoB 2	Low
Lee et al., 2019*	Clinical	RoB 2	Some concerns

➢ *Data Synthesis*

Due to significant heterogeneity amongst the studies included in this systematic review in terms of sources of MSCs, mode of administration, dose, animal models used, and outcome measures, a meta-analysis could not be carried out. Hence, a qualitative synthesis was conducted, where the literature was grouped based on the mechanism of action of MSCs/MSC-derived products, normal/wound healing in diabetes, biomaterial-based delivery, preclinical and clinical studies, and safety/translation challenges.

III. RESULTS

➢ *Search Results*

Literature search revealed 1,685 citations from PubMed/MEDLINE, Scopus, Web of Science, Embase, and ClinicalTrials.gov databases. In addition, 18 citations were generated by manual screening of references of relevant papers. After the removal of 512 duplicates and 45 citations that were automatically screened, 1,128 citations were left for title and abstract screening. After screening of titles and abstracts, 984 citations were excluded. Retrieval of 162 reports was attempted, but 11 could not be retrieved. Thus,

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151 full-text articles underwent further eligibility assessment. At the stage of full-text review, 140 articles were excluded for not meeting the set criteria for inclusion in the review. A total of 11 studies met the inclusion criteria and were included in the qualitative synthesis. Due to high heterogeneity between studies included in the review, a meta-analysis could not be done.

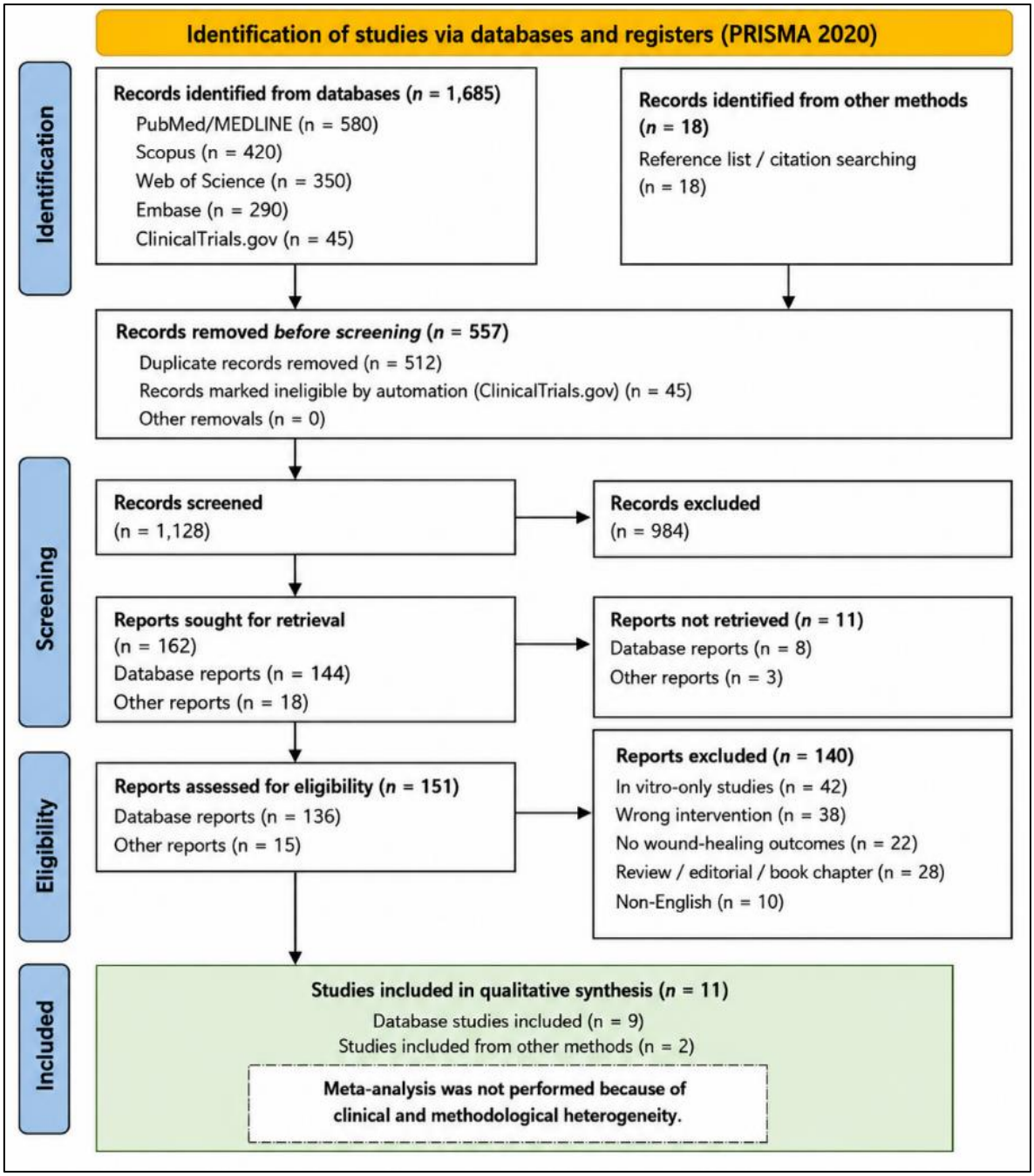

Fig 1 PRISMA 2020 Flow Diagram Illustrating the Study Selection Process.

➢ *Biology and Mechanisms of Action of MSCs in Wound Healing*

Mesenchymal stem cells (MSCs) are multipotent stromal cells capable of self-renewal and differentiation into multiple mesodermal lineages. ISCT defines MSCs as the cells with plastic adherence properties, positive staining for CD73, CD90, and CD105, and negative for hematopoietic cell surface molecules such as CD34, CD45, CD14, CD11b, CD79α, CD19, and HLA-DR [8].

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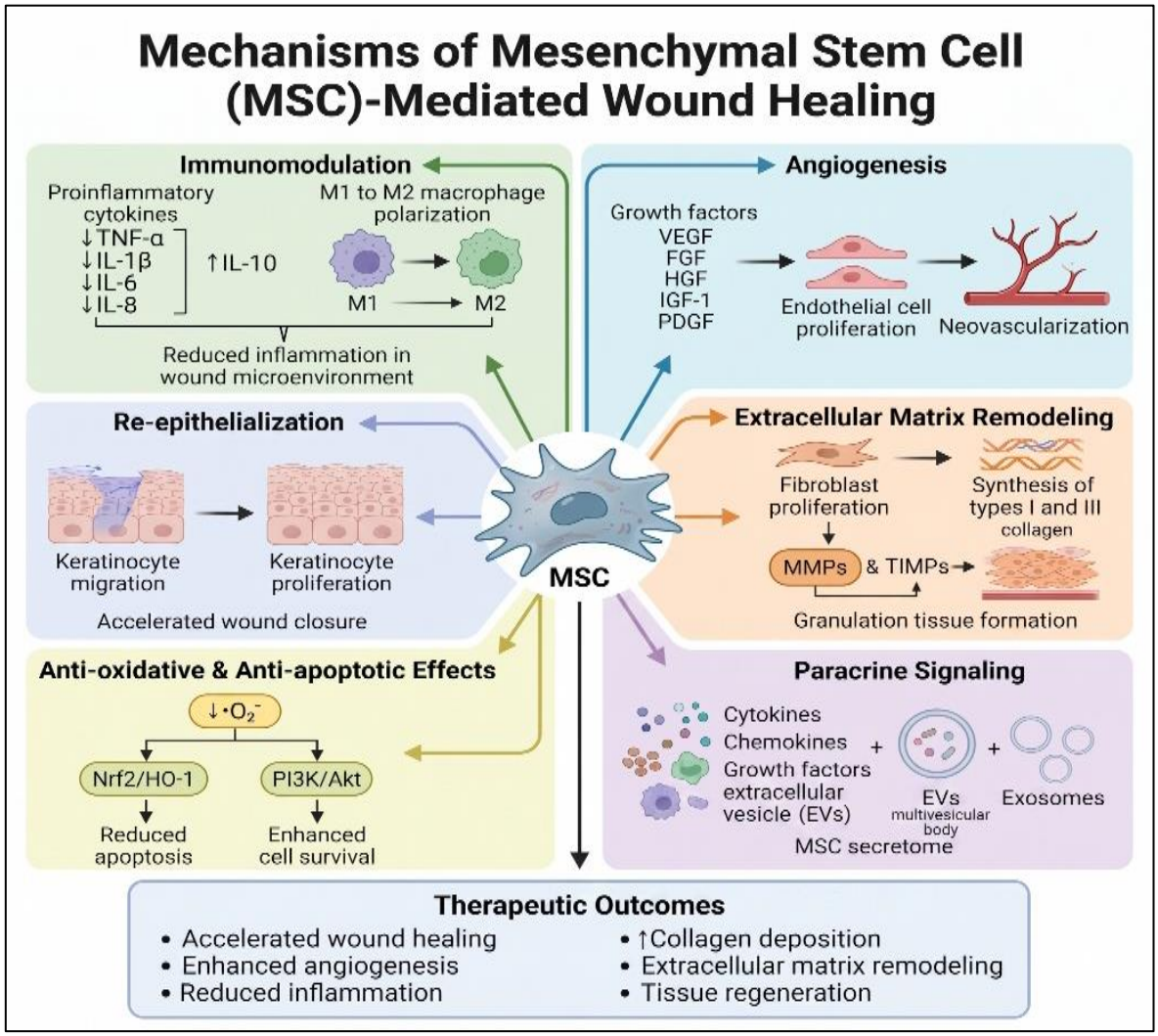

Fig 2 Mechanisms of MSC-Mediated Wound Healing

➢ *Immunomodulatory Effect of MSCs*

The process of inflammation is an important part of wound healing, and chronic inflammation is a leading cause of non-healing wounds in the case of diabetes mellitus. MSCs are involved in immunomodulation processes through interaction with macrophages, neutrophils, dendritic cells, T lymphocytes, and natural killer cells [12]. One of the critical processes that helps facilitate wound healing via MSCs is macrophage polarisation. In normal conditions, the macrophages undergo switching from the pro-inflammatory M1 state to the anti-inflammatory M2 state. However, in the case of diabetic wounds, the persistent presence of the M1 state leads to increased secretion of TNF-α, IL-1β, and IL-6, thus limiting tissue regeneration [4]. The M2 polarisation of macrophages occurs because of the secretion of IL-10, TGF-β, PGE2, and tumour necrosis factor-stimulated gene-6 (TSG-6), which results in reduced inflammation and tissue remodeling [12,21]. Moreover, MSCs influence the adaptive immunity through suppression of T helper cell proliferation and stimulation of regulatory T cell (Treg) expansion [3,22].

➢ *Pro-Angiogenic Properties of MSCs*

Angiogenesis plays an important role in delivering oxygen and nutrients to regenerating tissue. Inadequate angiogenesis is one of the characteristic features of diabetic wound pathology and is responsible for the delayed wound healing process [5]. Pro-angiogenic growth factors such as VEGF, FGF, PDGF, HGF, angiopoietin-1, and IGF-1 secreted from MSCs cause increased proliferation and new vessel formation in endothelial cells [10,11]. Low oxygen concentration in wounds leads to the production of HIF-1α, which causes upregulation of VEGF secretion and angiogenic signal transduction. In several studies, it was shown that the effect of VEGF secreted from MSCs on endothelial cell migration and tubule formation takes place via PI3K/Akt and ERK1/2 pathways activation [23,24]. This process is especially important for diabetic wounds, where there is poor microcirculation.

➢ *Extracellular Matrix Remodelling and Fibroblast Activation*

Wound healing is associated with ECM remodelling. MSCs play an important role in the process of ECM regulation as a result of stimulation of fibroblast proliferation, collagen synthesis, and matrix deposition [10]. MSCs produce TGF-β1, CTGF, and PDGF, which enhance fibroblast migration and lead to the synthesis of collagen types I and III and granulation tissue formation [25].

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Regulation of ECM turnover is related to the activity of MMPs and their inhibitors (TIMPs). Chronic diabetic wounds are characterized by increased activity of MMPs, causing destruction of growth factors and extracellular matrix proteins. MSCs normalise the MMP/TIMP ratio, contributing to regulated tissue remodelling and reduction of scarring [26].

➢ *Stimulation of Re-Epithelialization*

Proliferation and migration of keratinocytes are required for the recovery of the epidermis. MSCs produce EGF, KGF, and HGF, which are responsible for the acceleration of re-epithelialization and regeneration of the epidermis [11]. Moreover, cytokines produced by MSCs promote the proliferation of epidermal stem cells and interaction between keratinocytes and fibroblasts [27].

➢ *Anti-Oxidative and Anti-Apoptotic Effects*

The other pathological factor that causes delayed healing of diabetic wounds is oxidative stress. The formation of reactive oxygen species (ROS) due to hyperglycemia leads to cellular senescence and cell death [4]. Moreover, the MSCs act as antioxidants by increasing the levels of Nrf2 and HO-1, which helps to alleviate oxidative stress [28]. The other mechanism used by the MSCs to improve the healing process is the anti-apoptotic effect through the stimulation of the PI3K/Akt and Wnt/β-catenin pathways. These two pathways increase the survival of the endothelial cells, fibroblasts, and keratinocytes, leading to improved tissue regeneration [29].

➢ *Paracrine Signalling as the Dominant Path of Action*

Although it has been documented that the MSCs can differentiate into skin cells, there is evidence suggesting that only a few MSCs graft into the wounded area. Therefore, their healing effects are achieved through the secretion of cytokines, growth factors, chemokines, extracellular vesicles, and exosomes [9,13]. This paracrine pathway plays an important role in angiogenesis, immunomodulation, fibroblast activation, remodelling of the extracellular matrix, and epithelial cell regeneration [10,15].

➢ *MSC-Derived Exosomes, Secretome, and Conditioned Medium: Cell-Free Therapeutic Approaches*

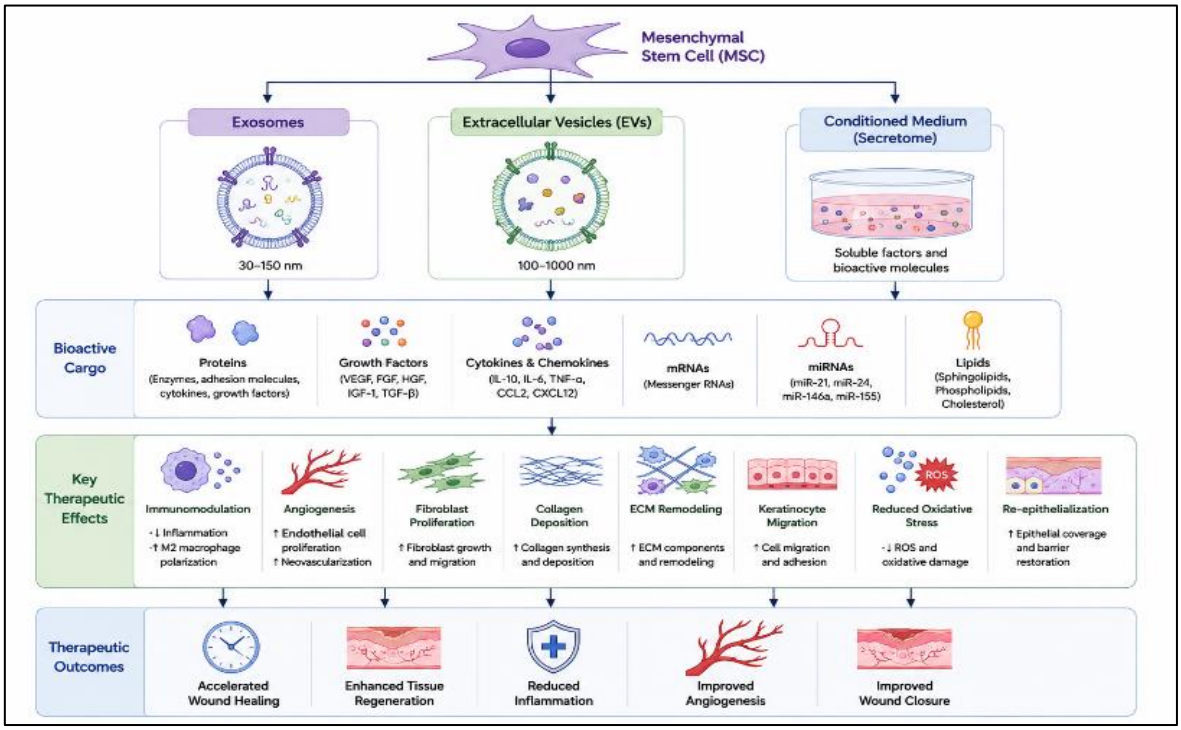

Fig 3 MSC-Derived Cell-Free Therapeutic Products in Wound Healing.

➢ *MSC-Derived Cell-Free Products*

Even though MSCs have proven to possess high regenerative capacity, the application of these cells in a clinic is limited due to low engraftment and survival rate, variability between donors, risk of tumor formation, and difficulties in large-scale production [9,13]. It was found that the effect of MSC therapy is caused primarily by bioactive molecules released by these cells rather than by their ability to differentiate into a certain type of tissue [9,13]. Thus, MSC-derived extracellular vesicles (EVs), exosomes, conditioned medium, and secretome became interesting cell-free options for regenerative medicine and wound healing [13,15].

➢ *Extracellular Vesicles and Exosomes*

Extracellular vesicles are membrane-associated nanoparticles derived from cells and are subdivided into apoptotic bodies, microvesicles, and exosomes based on size and mode of biogenesis. Exosomes are nanosized vesicles having a diameter between 30 to 150 nm, formed from multivesicular bodies and released into the extracellular space by the process of exocytosis [30]. These vesicles act as mediators of intercellular communication by transporting various proteins, lipids, messenger RNAs (mRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and microRNAs (miRNAs) to target cells [31]. MSC-Exosomes (MSC-Derived Exosomes) are receiving much

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attention since they mimic most biological activities of parent MSCs, and at the same time reduce the potential hazards related to cellular transplantation. Moreover, exosomes are known to have low immunogenicity, biocompatibility, and superior stability, which makes them ideal candidates for translational medicine [15].

➢ *Molecular Content of MSC-Derived Exosomes*

The regenerative properties of exosomes are due to the presence of a variety of molecules within them. Various growth factors like vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), fibroblast growth factor (FGF), and epidermal growth factor (EGF) are present in MSC-Derived Exosomes [13,32]. Apart from proteins, exosomes contain a variety of microRNAs which play a key role in the regulation of signalling pathways for wound healing, including PI3K/Akt, Wnt/β-catenin, TGF-β/Smad, NF-κB, and HIF-1α pathways [29,33].

➢ *Immunomodulatory Role of Exosomes*

Excessive inflammation and the chronic activation of M1 macrophages are characteristic features of chronic diabetic wounds. Exosomes isolated from MSCs downregulate inflammatory responses via inhibition of TNF-α, IL-1β, and IL-6 expression and induction of IL-10 [34]. Moreover, exosome-contained miRNAs facilitate M2 macrophage differentiation by suppressing the activation of the NF-κB signalling pathway, thus shifting the process of inflammation into the tissue regeneration phase [35]. The activation of the Nrf2/HO-1 signalling pathway and, as a consequence, reduction of the oxidative stress and prevention of apoptosis in cell culture has been observed in several experiments [28].

➢ *Angiogenesis and Neovascularisation*

Angiogenesis is a necessary step of wound healing. MSC exosomes induce endothelial cells' proliferation, migration, and tube formation via VEGF signalling pathways [23]. The increased expression of HIF-1α and activation of PI3K/Akt signalling pathways due to the presence of miR-126 and miR-210 in exosomes leads to enhanced neovascularisation and restoration of blood flow to ischemic diabetic wounds [36].

- In diabetes mellitus animal models, treatment with exosomes led to an increase in capillary density, collagen deposition, and granulation tissue formation compared with control groups [37].
- Conditioned Medium and MSC Secretome
- Conditioned medium (CM) is a culture medium obtained from MSC cultures that contain cytokines, growth factors, chemokines, extracellular vesicles, and soluble proteins called the MSC secretome [13]. The application of the secretome for therapy is preferable compared to cell therapy in terms of low immunogenicity, better storage, simplified manufacture, and no risks caused by cell transplantation [38].
- MSC-derived CM is composed of VEGF, HGF, FGF, TGF-β, EGF, PDGF, and anti-inflammatory cytokines contributing to tissue and wound regeneration [39]. Numerous studies showed that conditioned medium promotes fibroblast proliferation, collagen production, endothelial cell migration, and keratinocyte regeneration [40].
- Signalling Pathways of Molecular Regulation Induced by MSC-Derived Products
- Regenerative properties of MSC-derived exosomes and secretome involve activation of the following signalling pathways:
- PI3K/Akt pathway: stimulates angiogenesis and cell survival [36];
- Wnt/β-catenin pathway: promotes keratinocytes proliferation and tissue regeneration [29];
- TGF-β/Smad pathway: mediates collagen synthesis and remodelling of extracellular matrix [25];
- Inhibition of NF-κB pathway: regulates inflammation [35];
- HIF-1α signalling pathway: promotes hypoxia-mediated angiogenesis [36];
- Nrf2/HO-1 signalling pathway: decreases oxidative stress and apoptosis [28].

➢ *Cell-Free Therapy Benefits*

Unlike traditional transplantation of mesenchymal stem cells (MSCs), cell-free therapy using exosomes and secretomes derived from mesenchymal stem cells presents some benefits. They include minimal tumorigenicity, lack of ectopic tissue formation, and reduced immunogenicity, resulting in increased biosafety. Exosomes and secretomes are easy to preserve and transport, thus allowing for scale-up and standardisation. Besides, they are able to overcome biological barriers and retain stability in a physiological environment. What is more, they can be genetically engineered for delivering targeted treatment, which makes cell-free therapy an attractive alternative to traditional MSC therapy [15,31]. Despite these advantages, there are still difficulties related to exosome isolation methods, purification, dosing, scaling, quality assurance, and regulatory classification. The international recommendations offered by the International Society for Extracellular Vesicles (ISEV) highlight the significance of standardised characterisation of extracellular vesicle-based therapeutics [41]. In general, MSC-derived exosomes, secretome, and conditioned medium can be considered as prospective cell-free regenerative treatments that will reproduce many features of parental cells. Due to their anti-inflammatory, angiogenic, antioxidative, and regenerative properties, they can be applied for normal and diabetic wound healing treatment.

➢ *Differential Effects of MSCs and their Derivatives in Normal and Diabetic Wound Healing*

This process consists of hemostasis, inflammation, proliferation and remodelling. The stages in this process occur in a well-coordinated manner in normal individuals and end up in wound healing and restoration of tissue structure and function. On the other hand, wounds in diabetes mellitus patients have characteristics of inflammation, inadequate angiogenesis, hyperoxidation, matrix breakdown, and poor cellular functions that finally result in non-healing and

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chronic ulcers [1,4,16]. Therefore, the way that the mesenchymal stem cells and their products affect the wound healing process is different between normal and diabetic wound environments.

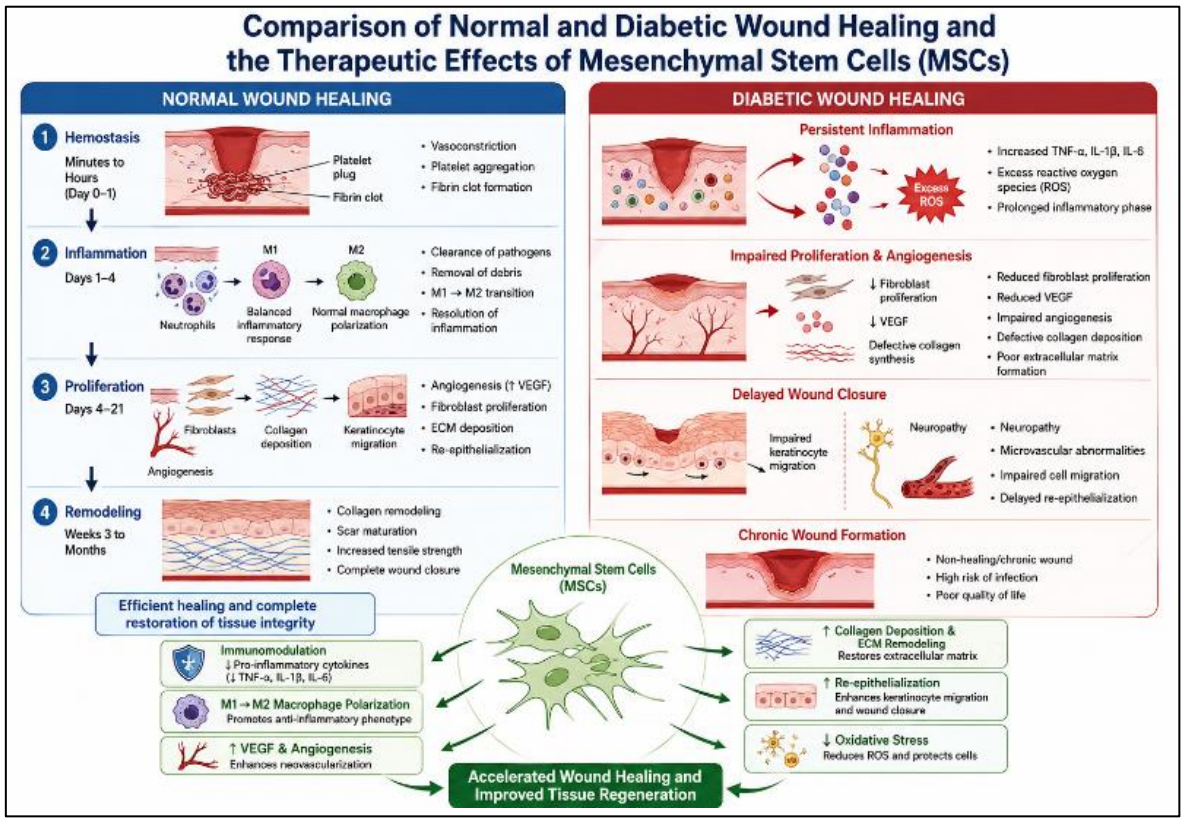

Fig 4 Comparison of Normal and Diabetic Wound Healing and MSC Therapy

➢ *Effects of Mesenchymal Stem Cells in Normal Wound Healing*

In acute injuries, the inflammatory phase occurs briefly and is self-limiting. MSCs induce faster conversion of the inflammatory stage to the proliferation stage through the production of anti-inflammatory growth factors and cytokines [10,11]. MSCs contribute to the development of angiogenesis through the production of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and hepatocyte growth factor (HGF). These growth factors promote the proliferation and development of new blood vessels [23,24]. Furthermore, TGF-β1 produced by the MSCs promotes migration of fibroblasts and collagen production [25]. A few animal studies have reported enhanced wound healing, increased capillary density, and better collagen fibre alignment after application of bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose-derived mesenchymal stem cells (ADSCs), and umbilical cord-derived mesenchymal stem cells (UC-MSCs) in a normal wound model [11,25,27]. Also, the exosomes released by the mesenchymal stem cells promote keratinocyte migration and epithelial regeneration, leading to improved tissue architecture and less scarring [36].

➢ *Physiological Characteristics of Diabetic Wounds*

Diabetes significantly affects the wound environment. High glucose levels stimulate the production of reactive oxygen species (ROS), activation of inflammation, endothelial dysfunction, angiogenesis, and extracellular matrix breakdown [4,5]. In diabetic wounds, there is a prolonged infiltration of neutrophils and macrophages, especially M1 macrophages. Increased levels of TNF-α, IL-1β, and IL-6 inhibit the fibroblasts from growing and hence tissue regeneration becomes difficult [42]. Moreover, there is dysfunction of HIF-1α and reduced expression of vascular endothelial growth factor (VEGF) which affects the angiogenesis process [43]. Additionally, high MMP activity and low TIMPs cause degradation of extracellular matrix proteins and growth factors and this hinders tissue remodeling [26].

➢ *Therapeutic Effects of MSCs in Diabetic Wounds*

Due to the fact that diabetic wounds demonstrate the presence of chronic inflammation and impaired angiogenesis, the beneficial effect of MSCs on the wound is greater than in the case of normal wounds. The immunoregulatory effects of MSCs are expressed through the promotion of M1 macrophages towards anti-inflammatory M2 macrophages by means of prostaglandin E2 (PGE2), IL-10, and TSG-6 secretion [12,21]. The mentioned process leads to reduction in TNF-α, IL-1β, and IL-6 expression and stimulation of pro-regenerative anti-inflammatory mediators [12]. MSCs' immunoregulatory effects serve as one of the key factors which positively affect diabetic wound healing. In addition, the hypoxic state of diabetic wounds allows benefiting from the angiogenic effects of MSCs. MSCs increase the expression of VEGF, angiopoietin-1, HGF, and IGF-1 due to

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the activation of HIF-1α and PI3K/Akt signaling pathways which promotes restoration of vascularization and oxygenation [23,24].

➢ *Impact of Mesenchymal Stem Cells on Diabetic Wounds*

Various experimental studies have shown that treatment involving MSCs promotes wound healing in diabetic wounds through wound closure, re-epithelialization, formation of granulation tissues, collagen synthesis, angiogenesis, and tensile strength of the newly formed tissues [11, 25]. Moreover, the MSCs alleviate oxidative stress and suppress apoptosis of the endothelial cells and fibroblast cells via nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway.

➢ *Role of MSC-Derived Exosomes in Diabetic Wound Repair*

MSC-derived exosomes appear to be an interesting non-cellular treatment approach able to imitate the effects of the parent MSCs. MicroRNAs from exosomes, such as miR-21, miR-126, miR-146a, and miR-210, play a role in controlling inflammation and angiogenesis in diabetic wounds [35,36]. They inhibit NF-κB activation, decrease levels of pro-inflammatory cytokines and stimulate macrophages toward M2 polarisation [34,35]. Moreover, miR-126 from exosomes initiates PI3K/Akt activation and endothelial cell proliferation and angiogenesis [36].

➢ *MSC-Derived Exosomes' Effects on Diabetic Wound Healing*

Several preclinical experiments conducted on animals with diabetes mellitus conditions showed that exosomes secreted from mesenchymal stem cells (MSCs) enhance wound healing by increasing capillary formation, inducing collagen synthesis, accelerating epithelial growth, decreasing inflammatory cell recruitment, and promoting wound healing [37]. Exosome treatment is more effective and safe when compared to the existing cellular treatment methods since the former is less immunogenic and not affected by the problems related to reduced cell survival and risks of cancer [15].

➢ *Effects of Oxidative Stress and Cellular Senescence*

The level of oxidative stress in wounds is significantly higher in the case of diabetic wounds compared to normal wounds. Uncontrolled ROS production causes mitochondrial dysfunction, DNA damage, cellular senescence and apoptosis [44]. MSCs and exosomes prevent oxidative damage by activating antioxidative signalling pathways like Nrf2/HO-1 and SIRT1 [28,45]. These mechanisms contribute to the maintenance of endothelial cells and increase the viability of fibroblasts and keratinocytes, thus improving tissue regeneration and preventing chronic inflammation.

➢ *Comparison of the Efficacy of Normal vs. Diabetic Wounds Healing*

Even though MSCs have a similar beneficial impact on both types of wounds, it can be assumed that their influence is significantly greater in diabetic ulcers since they act on the specific pathologies which cause chronic ulcers. While in the case of normal wounds, MSCs just accelerate physiological processes, in diabetic ulcers, they help to restore abnormal angiogenesis, suppress excessive inflammatory response, decrease oxidative stress, and remodel extracellular matrix [10,11]. Thus, it can be concluded that the efficacy of the stem cell therapy depends greatly on the microenvironment and pathologic characteristics of wounds. This information is crucial in order to develop an optimal treatment strategy.

➢ *Delivery Methods and Biomaterial-Based Approach for MSC and Exosome Therapy*

The therapeutic efficacy of mesenchymal stem cells (MSCs) and their derivatives greatly relies upon their survival, retention, engraftment, and the continuous secretion of bioactive factors at the injury site. However, although MSCs possess tremendous regeneration abilities, there are some shortcomings related to the administration of these cells, including low cell survival rate, rapid diffusion, low retention, and adverse microenvironment, especially when it comes to diabetic ulcers [46]. Therefore, many different methods of biomaterial-based delivery have been introduced.

➢ *Delivery Systems Based on Hydrogels*

Hydrogels represent three-dimensional polymeric network structures with high affinity to retain water, which is similar to the extracellular matrix. The biocompatibility, injectability, and ability to provide sustained release of biological cargo make hydrogels excellent delivery platforms for MSCs and exosomes [47]. Numerous natural hydrogels, including collagen, gelatin, alginate, hyaluronic acid, chitosan, fibrin, and decellularised extracellular matrix hydrogels, have shown positive results in wound-healing applications [48]. Synthetic hydrogels like PEG and PVA have also been applied due to their tunable degradation and mechanical properties [49]. The process of MSC encapsulation into hydrogels improves cell survival and protects cells from oxidative and inflammatory stresses [50]. The use of thermosensitive hydrogels containing MSCs in diabetic wound models leads to stimulation of angiogenesis, granulation tissue formation, collagen deposition, and re-epithelialization. Likewise, exosome-loaded hydrogels contribute to the controlled and prolonged delivery of extracellular vesicles and thereby increase their effectiveness and minimise degradation at the site of the wound [51].

➢ *Nanofibrous Scaffolds*

The structure of electrospun nanofibrous scaffolds resembles the structure of the natural extracellular matrix and provides an excellent medium for cell adhesion and proliferation [52]. Nanofibrous scaffolds can be created from biodegradable polymers such as polycaprolactone (PCL), polylactic acid (PLA), collagen, gelatin, silk fibroin, and chitosan [53]. MSCs attached to the nanofibrous scaffolds display increased proliferation, migration, and secretion of angiogenic factors. Moreover, exosomes and secretome components can be delivered by the scaffold-based system, effectively contributing to wound closure and vascularisation [54]. Research studies have revealed that nanofibrous matrices with MSCs improve collagen deposition, fibroblast proliferation, and epithelial regeneration in diabetic wound models.

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➢ *Scaffold-Free Cell Sheets*

The technology of cell sheet engineering presents an innovative method for transplants of intact cell layers without enzymatic detachment and artificial scaffolds. Cell sheets maintain the intercellular contacts and extracellular matrix proteins and increase the viability and functions of the cells [56]. MSC sheets derived from adipose tissue and bone marrow demonstrate better results of wound healing compared to traditional injections of cells [57]. These sheets stimulate vascularisation and collagen remodelling without cell loss after transplantation.

➢ *Oxygen-Releasing Biomaterials*

Tissue hypoxia is one of the critical factors affecting diabetic wounds because of poor blood circulation and impaired vasculature [43]. Oxygen-releasing biomaterials are used to overcome the problem of tissue hypoxia and support cellular metabolism [58]. The system contains oxygen-generating molecules such as calcium peroxide and magnesium peroxide incorporated in hydrogels or scaffolds for continuous oxygen release. The combination of oxygen-releasing biomaterials and MSCs leads to positive effects on neovascularisation, collagen deposition, and epithelial regeneration [59]. Increased oxygen availability supports MSC survival and VEGF and HIF-1α-dependent angiogenic factor secretion [60].

➢ *Injectable Biomaterials*

Injectable biomaterials present minimally invasive methods for the delivery of MSCs and exosomes to irregular wounds. Injectable hydrogels can adjust to wound morphology and release the therapeutic factors continuously [47]. Recent research has found that injection of gelatin methacryloyl (GelMA), hyaluronic acid and chitosan-based systems helps increase retention and viability of transplanted MSCs [61]. Exosome-loaded injectable hydrogels have also been proven to facilitate wound healing in diabetes patients through stimulating angiogenesis and decreasing inflammation [62].

➢ *Smart Dressings and Responsive Biomaterials*

The advanced wound dressings have gone further than being just a protective barrier and have become an active platform for drug delivery. The smart biomaterials are able to react to pH values, enzyme presence, temperature and oxidative stress in the wound environment [63]. Responsive dressings and hydrogels can release MSC-exosomes and growth factors in accordance with pathological conditions in a wound. An intelligent system allows increasing efficacy and avoiding unnecessary release of biomolecules [64]. In addition, incorporation of antibacterial nanoparticles and antioxidants into smart dressings is important for preventing infections and oxidation in diabetic wounds [65].

➢ *Three-Dimensional Bioprinting*

3D bioprinting has proved itself to be one of the most promising technologies for designing biomimetic skin substitutes. Bioinks consisting of MSCs, extracellular matrix proteins and growth factors can be printed layer-by-layer in order to create tissue-engineered substitutes [66]. The 3D-bioprinted scaffolds stimulate vascularisation, fibroblast growth, and epidermis regeneration. Additionally, individual wound dressings can be produced in accordance with wound geometry [67]. Even though it is currently at an early stage of development, 3D bioprinting is predicted to become one of the key technologies in regenerative wound therapy and personalised medicine.

➢ *Delivery Systems for Exosomes*

One of the main disadvantages of the application of exosomes in therapy is the rapid decomposition and elimination of exosomes after administration, which affects the therapeutic efficiency of exosomes. In order to deal with this issue, researchers have created different types of delivery systems such as hydrogels, nanoparticles, liposomes, electrospun nanofibers, sprayable bandages, microneedle patches, and decellularised extracellular matrix scaffolds [68].

➢ *Challenges and Future Perspectives for Biomaterial-Assisted MSC Therapies*

While promising results have been obtained through biomaterial-assisted MSC therapies, there are several limitations that have slowed down their transition into clinical settings. These limitations include unstandardized biomaterial composition, variations in the rate of degradation and mechanical strength, absence of sufficient data regarding long-term safety of these biomaterials, manufacturing issues, regulatory problems, and the high cost of manufacture. It is important in future studies to focus on the synthesis of biomaterials that have a range of functions, including angiogenesis, antibacterial, antioxidative and immunomodulatory properties. The progress in the field of nanotechnology, gene editing, and computer-designed biomaterials could help in this regard.

➢ *Preclinical Data: Animal Models and Therapeutic Outcomes*

There is ample data proving the possibility of using mesenchymal stem cells (MSCs) and their derivatives in the treatment of acute and diabetic wound healing from preclinical studies. Various animal models, ranging from healthy rodents to STZ-induced diabetic rats and mice, genetically diabetic db/db mice, and porcine wound models, have been used to study the effects of MSC therapy and the mechanism of action. Enhanced wound healing, increased angiogenesis, increased collagen deposition, and decreased inflammation were observed after MSCs transplantation [11,25,69].

➢ *Animal Models Used in MSC-Based Wound Healing Studies*

The rodent model is still the most commonly used experimental system because of its cheapness, reliability, and possibility of genetic manipulation. The Streptozotocin-induced diabetic mice and rats are often used to study hyperglycemic-induced problems with wound healing and to mimic diabetic ulcers [70]. The genetically diabetic db/db mice are obese, insulin-resistant, and have chronic inflammation and mimic type 2 diabetic wounds [71]. Large animal models like pigs exhibit more anatomical similarity to

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human skin and are being increasingly employed in the translational evaluation of MSC therapy [72].

➢ *Bone Marrow-Derived Mesenchymal Stem Cells*

Bone marrow-derived mesenchymal stem cells (BM-MSCs) are the most thoroughly researched cell type in the regenerative medicine field. Wu *et al*. found that transplanted BM-MSCs accelerated wound closure, increased blood vessel density, and enhanced collagen production in full-thickness excisional wounds [25]. Histological analysis confirmed an increase in fibroblast proliferation and organization of the extracellular matrix. In the same way, Chen *et al*. showed that BM-MSCs paracrine factors promoted the recruitment of macrophages and endothelial cells, thus contributing to angiogenesis and granulation tissue development [23].

➢ *Adipose-Derived Mesenchymal Stem Cells*

ADSCs can serve as valuable alternatives because of their abundance and accessibility. ADSCs have potent immunomodulating and angiogenic properties and produce high amounts of VEGF, HGF, and FGF [73]. Kim *et al*. demonstrated that ADSC transplantation increased re-epithelialization and neovascularization in diabetic mice [74]. In addition, ADSCs increased collagen deposition and downregulated inflammatory cytokines, leading to wound closure.

➢ *Umbilical Cord-Derived Mesenchymal Stem Cells*

The advantage of using UC-MSCs is that their proliferative potential is higher compared to the adult MSCs and they also have lower immunogenicity. The strong angiogenic and anti-inflammatory properties of UC-MSCs provide good options for use in treating chronic wounds [75]. Several experiments have shown that UC-MSCs transplantation can induce VEGF expression, improve collagen production, and enhance wound healing in diabetes mellitus models [76].

➢ *MSC-Derived Exosomes*

It has been shown recently that exosomes derived from MSCs replicate several regenerative abilities of the parent cells. Zhang *et al*. showed that exosomes from induced pluripotent stem cell-derived MSCs facilitated wound healing via collagen deposition and angiogenesis [36]. According to Shabbir *et al*., MSC-derived exosomes were able to induce proliferation and migration of fibroblasts and endothelial cells, resulting in enhanced tissue regeneration [37]. Also, exosomes' application decreased the levels of inflammatory cytokines and induced M2 macrophage polarisation in diabetic wound models [35].

➢ *Secretome and Conditioned Medium*

MSC-conditioned medium (CM) includes various components such as cytokines, chemokines, extracellular vesicles, and growth factors.

Walter *et al*. demonstrated that conditioned medium accelerated wound healing by enhancing fibroblast migration and collagen synthesis [40]. Similar findings were observed in diabetic animal models, where conditioned medium improved angiogenesis and suppressed inflammatory responses [38].

➢ *Biomaterial-Assisted MSC Therapy*

Several studies have shown that combining MSCs with biomaterials enhances therapeutic efficacy. Rustad *et al*. demonstrated that hydrogel-mediated delivery improved MSC survival and significantly enhanced diabetic wound healing [50]. Likewise, Wang *et al*. reported that exosome-loaded self-healing hydrogels promoted collagen deposition, angiogenesis, and epithelial regeneration in diabetic wounds [51]. These findings indicate that biomaterials can protect transplanted cells and provide sustained release of exosomes and growth factors, thereby maximising therapeutic outcomes.

Table 3 Representative Preclinical Studies Investigating MSCs and their Derivatives in Wound Healing

Study	Animal Model	MSC Source	Delivery Method	Major Findings
Wu *et al.,* 2007 [25]	Mouse excisional wound	BM-MSCs	Local injection	Increased angiogenesis and collagen deposition
Chen *et al*., 2008 [23]	Mouse wound model	BM-MSCs	Injection	Enhanced macrophage recruitment and vascularisation
Sasaki *et al*., 2008 [27]	Murine wound model	BM-MSCs	Local administration	Accelerated re-epithelialization
Kim *et al*., 2007 [74]	Diabetic mice	ADSCs	Injection	Enhanced wound closure and neovascularisation
Zhang *et al*., 2015 [36]	Rat wound model	iPSC-MSC exosomes	Local injection	Increased collagen synthesis and angiogenesis
Shabbir *et al*., 2015 [37]	Mouse wound model	MSC exosomes	Topical application	Increased fibroblast proliferation

➢ *Summary of Preclinical Findings*

In general, all the preclinical data presented above clearly show the promising efficacy of MSCs and their derivatives for the treatment of skin injuries and promotion of wound healing. Specifically, all these studies reveal that MSCs and their products have a significant ability to accelerate the process of wound healing and stimulate the formation of new blood vessels via the stimulation of VEGF and HIF-1α-mediated pathways. Besides, MSCs promote the proliferation of fibroblasts, collagen deposition, and ECM remodelling; therefore, they facilitate the formation of granulation tissue and improve the tissue tensile strength. The

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enhanced process of epithelialization and the restoration of skin structure were observed in many works.

Moreover, MSCs can suppress excessive inflammation and induce macrophages to acquire the M2 anti-inflammatory phenotype. Antioxidant and antiapoptotic effects of these cells reduce oxidative stress and increase cell survival in the wound microenvironment. In general, all this evidence shows that there is a set of multiple mechanisms that ensure tissue regeneration and improvement of healed tissue by MSCs and their secretome. The convincing results obtained from preclinical models have become the basis for the development of clinical applications of MSC-based therapies for diabetic foot ulcers and other chronic wounds.

- *Clinical Evidence and Human Trials*

However, despite the wealth of pre-clinical evidence regarding the ability of MSCs and their products to induce tissue regeneration, there has been relatively little translation into clinical settings. The vast majority of clinical applications have utilised MSCs for diabetic foot ulcers (DFUs), critical limb ischemia, and chronic non-healing wounds. Although existing data suggest that the use of such therapy is fairly safe and might considerably increase wound healing and regeneration, a high heterogeneity of results hampers the drawing of firm conclusions [69,70].

- *Application of MSCs in Chronic Wounds: Clinical Evidence*

One of the most difficult complications of diabetes mellitus, diabetic foot ulcers, causes many problems, including severe morbidity, hospitalisations, and amputations of limbs [3]. Standard treatments are usually unable to ensure full wound healing since they cannot correct the inflammatory and vascular abnormalities [5].

The potential of mesenchymal stem cells obtained from multiple sources, such as bone marrow, adipose tissue, umbilical cord, and placenta tissues, has been tested in clinical trials of Phases I and II in chronic wound healing and diabetic foot ulcers. In order to achieve optimal efficacy and maximise cell retention in the wound, multiple modes of administration of these cells have been used. These include intramuscular and perilesional injection, intravenous administration, and topical administration. Moreover, novel delivery methods utilising biodegradable scaffolds and hydrogels have been designed to maximize cell retention and paracrine factor release [71]. Such methods have exhibited a good safety profile and served as the foundation for future clinical testing of MSC therapies. In most clinical trials, improvement was seen in wound closure, vascularisation, and tissue regeneration with minimal side effects.

- *Clinical Studies of Bone Marrow-Derived MSC*

One of the early studies utilising autologous bone marrow-derived MSC was done by Dash *et al*. and showed a considerable reduction in the size of the ulcer and faster wound closure after local delivery [69]. Procházka *et al*. evaluated bone marrow-derived cell therapy on diabetic foot ulcers and found improved tissue oxygenation, vascularisation, and wound closure rates [72]. A similar improvement was seen when Lu *et al*. administered autologous bone marrow-derived MSCs through the intramuscular route in their study group [73].

- *Clinical Studies of Umbilical Cord and Adipose-Derived MSC*

Umbilical cord-derived MSCs have high proliferation and low immunogenicity, which make them ideal candidates for allogeneic application [67]. Moon *et al*. proved that allogeneic transplantation of umbilical cord blood-derived MSC improved wound healing and granulation tissue formation without any significant adverse events [74]. Allogeneic adipose-derived stem cells (ADSCs) have also shown promising results. Lee *et al*. found increased angiogenesis and wound closure rates in diabetic patients with ADSC treatment [75].

- *Meta-Analyses and Systematic Reviews*

A number of meta-analyses have considered the effectiveness and safety of stem cell therapy for diabetic foot ulcers. In particular, Xie *et al*. examined randomised controlled trials and showed that stem cell therapy was associated with increased rates of ulcer healing and decreased likelihood of amputations in comparison with standard therapy [76]. Qiu *et al*. noted improvement of ankle-brachial index, transcutaneous oxygen pressure and ulcer closure after stem cell therapy [77]. Similarly, Gao *et al*. found that MSC treatment led to an increase in the proportion of completely healed wounds without increased incidence of adverse effects [78]. Nevertheless, the authors noted the necessity of further large multicenter randomised trials since most existing studies suffer from small sample sizes and heterogeneity of the treatment.

- *Safety Profile*

According to current data, the majority of MSC-based therapies are safe and well tolerated. Adverse events, which are usually mild and transient, include: Pain at the site of injection; Local edema; Mild fever; Transient inflammation [69]. Neither tumorigenicity, ectopic tissue formation, nor significant immune rejection were observed within the follow-up period [79]. Immunological non-reactivity of MSCs is primarily due to the lack of MHC class II antigens and co-stimulatory molecules [3].

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➢ *Limitations of Current Clinical Evidence*

Table 4 Current Limitations and Challenges in the Clinical Translation of MSC-Based Therapies for Wound Healing

Limitation	Description	Implications
Small sample sizes	Most clinical studies include fewer than 50 patients, limiting statistical power and the ability to generalise findings [76].	Reduced reliability of efficacy and safety outcomes; larger multicenter trials are needed.
Heterogeneity of cell sources	Studies employ MSCs derived from bone marrow, adipose tissue, umbilical cord, and peripheral blood, resulting in considerable biological variability [70].	Direct comparison among studies is difficult, and the optimal cell source remains uncertain.
Variability in treatment protocols	Significant differences exist in cell dose, frequency of administration, delivery route, use of biomaterials, and duration of follow-up [78].	Lack of consistency complicates interpretation of clinical outcomes and hinders meta-analyses.
Lack of standardisation	No universally accepted protocols are available for cell isolation, expansion procedures, potency assays, quality control, and storage conditions [80].	Reproducibility and large-scale manufacturing remain major challenges for regulatory approval.
Limited long-term follow-up	Most clinical studies have follow-up periods of less than two years, providing insufficient data regarding long-term efficacy and safety [79].	The durability of therapeutic effects and potential late adverse events remain unclear.

Table 5 Representative Clinical Studies of MSC Therapy in Chronic Wounds and Diabetic Foot Ulcers

Study	Cell Source	Patients	Route of Administration	Major Outcomes
Dash *et al*., 2009 [69]	BM-MSCs	Chronic ulcers	Local injection	Significant wound closure
Procházka *et al*., 2010 [72]	BM-MSCs	DFU patients	Intramuscular injection	Improved tissue oxygenation
Lu *et al*., 2011 [73]	BM-MSCs	Critical limb ischemia	Intramuscular injection	Reduced amputation rates
Moon *et al*., 2019 [74]	UC-MSCs	Diabetic wounds	Local administration	Enhanced granulation tissue
Lee *et al*., 2019 [75]	ADSCs	DFU patients	Injection	Increased angiogenesis
Gao *et al*., 2022 [78]	Meta-analysis	Multiple studies	Various	Improved healing rates

➢ *Overall Clinical Outcomes*

A growing body of research based on clinical trials provides evidence that MSC therapy positively affects wound healing and regeneration of tissues. It is suggested that MSC-based therapies can effectively speed up wound healing, increase blood supply, and angiogenesis, resulting in better oxygen and nutrient delivery to the injured area. Moreover, application of MSC therapy can be linked to an increase in the number of granulation tissue and decreased risk of limb amputation in patients suffering from diabetic foot ulcers and chronic ischemic lesions. Besides, treatment with MSCs results in improved quality of life and functional recovery of patients. It is important to note that Phase I and Phase II clinical trials have confirmed a good safety profile of MSC therapy without any treatment-related serious adverse events. However, there is still insufficient evidence to translate into regular clinical use, which highlights the necessity of conducting adequately planned phase III multicenter randomized control trials with appropriate methodology. Overall, clinical findings indicate the translational potential of MSCs and their derivatives for regenerative treatments of chronic wounds and diabetic foot ulcers.

➢ *Safety Profile of MSC Therapy*

It has been found that clinical use of mesenchymal stem cells (MSCs) and their derivatives is characterized by a satisfactory safety profile. MSCs demonstrate a lower degree of immunogenicity compared to embryonic stem cells due to their weak expression of major histocompatibility complex class II (MHC-II) molecules and co-stimulatory molecules such as CD40, CD80, and CD86 [79,81]. Therefore, there is no risk of immune rejection associated with the administration of allogeneic MSCs. There have been cases of only mild and transient side effects during the administration of MSCs, such as pain, swelling, redness, and low fever [69]. Meta-analysis did not show the existence of increased numbers of severe side effects, infections, malignancies, and deaths among MSC-treated patients [78,79]. Lalu *et al.* conducted systematic reviews of over 1,000 individuals who showed no significant toxicity or adverse effects following MSC treatment [79]. In line with this, Thompson *et al*. also supported the safety profile of MSC treatments in several applications [82]. However, long-term safety still lacks complete knowledge since most of the studies used follow-up periods below five years. Hence, post-market surveillance and cohort studies for long-term safety are needed.

➢ *Malignant Transformation and Genetic Instability*

One of the key issues with the use of stem cell therapy is the risk of malignant transformation. Even though MSCs have high proliferation ability, existing studies show that they lack similar tumorigenic capabilities compared to embryonic stem cells or induced pluripotent stem cells [83].

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While these cells have proven therapeutic applications, extended in vitro cultivation of mesenchymal stem cells can result in the degradation of their biological attributes. There is evidence that extended cell culture can lead to chromosomal abnormalities, cellular senescence, genetic instability, and changes in differentiation capabilities – all of which can reduce the efficiency and safety of the therapeutic action of the cells [84]. These issues indicate that strict quality control practices should be implemented and followed during the whole process of cell isolation, culturing, storage, and clinical use. Notably, MSC-derived exosomes and secretome-based therapies have further benefits since there will be no risks related to cell viability and uncontrolled proliferation [15].

➢ *Regulatory Considerations*

Despite favourable results obtained preclinically and clinically, to date, there is no product based on MSCs that has been approved by the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) for use in diabetic wound healing [87]. The MSCs are categorised as ATMPs in Europe and HCT/Ps according to the FDA regulations [88].

Table 6 Regulatory Requirements for MSC-Based Therapies

Regulatory Requirement	Rationale
Safety	Ensure the absence of adverse effects
Efficacy	Demonstrate therapeutic benefit
Reproducibility	Achieve consistent outcomes
Quality control	Ensure product quality
Manufacturing consistency	Minimize batch-to-batch variability
Potency assays	Verify biological activity
Sterility and stability	Ensure product safety and shelf life.

Despite these requirements, variability in cell sources, lack of standardised protocols, and difficulties in defining potency markers continue to pose significant challenges to regulatory approval [87].

➢ *Heterogeneity of MSC Sources*

Although there are many advantages of therapies using mesenchymal stem cells (MSCs), there are still many issues that limit their successful translation into the clinic. Bone marrow-, adipose tissue-, umbilical cord-, placental-, and dental pulp-derived mesenchymal stem cells (MSC) have different biological properties, which makes it difficult to achieve standardisation [80]. Variations in cell culture parameters such as serum, number of passages, oxygen, and cryopreservation affect the potency and secretion of MSC [89]. There is a lack of universally accepted potencies for MSC-derived exosomes and secretomes [90]. Moreover, large-scale production of cell products in GMP-compliant facilities is expensive and technically challenging [91]. One more limitation of MSC therapy is low survival and engraftment rates, since hypoxia, oxidative stress, and inflammation in the microenvironment cause rapid death of cells and less than 1% of the transplanted cells survive [46].

➢ *Donor Variability*

Table 7 Donor Variability

Challenge	Description
Heterogeneity of MSC Sources	MSCs derived from bone marrow, adipose tissue, umbilical cord, placenta, and dental pulp exhibit distinct biological properties, complicating standardisation [80].
Variability in Culture Conditions	Differences in serum supplementation, passage number, oxygen concentration, and cryopreservation methods can significantly influence MSC potency and secretory profiles [89].
Lack of Potency Assays	Reliable and standardised assays for MSC-derived exosomes and secretome products have not yet been universally established [90].
Manufacturing and Scale-Up Challenges	Large-scale production under Good Manufacturing Practice (GMP) conditions remains costly and technically demanding [91].
Poor Cell Survival and Engraftment	Hypoxia, oxidative stress, and inflammatory microenvironments result in poor survival of transplanted MSCs, with less than 1% remaining viable after several days [46].
Donor Variability	Age, metabolic status, diabetes, obesity, and underlying diseases can affect MSC functionality and therapeutic efficacy [92].
Heterogeneous Clinical Protocols	Variations in cell dose, injection frequency, delivery methods, biomaterial combinations, and patient selection criteria hinder direct comparisons among studies [80].
Exosome Standardization	Lack of standardised methods for exosome isolation, characterization, storage, dosing, and purity assessment limits clinical application [41].
Cost and Accessibility	High manufacturing and quality-control requirements increase production costs and restrict accessibility, particularly in low-resource settings [91].

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➢ *Future Directions*

The future of research in this area should focus on the standardisation of MSCs' isolation, expansion, and characterization to improve reproducibility and facilitate the regulatory process. The establishment of validated potency assays along with the completion of large multicenter randomized controlled trials is necessary for providing robust evidence on the effectiveness and safety of MSC-based therapies. Additionally, improvements in exosome isolation and purification methods, along with genetic engineering and preconditioning, could further optimize their performance. The combination of MSCs with biomaterials and tissue engineering techniques provides a promising tool to enhance their performance. Lastly, artificial intelligence-guided personalized therapy along with the conduction of long-term safety studies and post-marketing surveillance is necessary to maintain the advantages of these therapeutic modalities.

IV. DISCUSSION

In the current systematic review, the biological properties, efficacy, and translational capacity of MSCs and their derivatives in both healthy and diabetic wound repair have been comprehensively studied. In general, the existing evidence suggests that MSCs possess numerous therapeutic effects via immunomodulation, angiogenesis, extracellular matrix remolding, antioxidant effects, and paracrine actions. All of these biological activities are especially beneficial in the case of diabetic wounds due to chronic inflammation, poor vascularization, oxidative stress, and improper tissue remodeling.

➢ *Mechanistic Insights into MSC-Mediated Wound Repair*

At first, the healing function of MSCs was explained through their ability to differentiate. Nevertheless, recent evidence showed that the differentiation process makes only a small contribution to wound healing, while paracrine signaling takes place dominantly [9,10]. Growth factors, cytokines, chemokines, and vesicles secreted from MSCs coordinate functions of fibroblasts, keratinocytes, endothelial cells, and immune cells, which leads to tissue regeneration [11,13]. The key mechanisms of action in MSC-based therapy are related to the polarization of macrophages. Diabetic wounds show high levels of M1 macrophages' activation and inflammatory cytokines including TNF-α, IL-1β, and IL-6 [42]. MSCs polarize M2 macrophages using IL-10, prostaglandin E2, TSG-6, and TGF-β, reducing inflammation and promoting tissue regeneration [12,21]. In addition, these immunomodulatory effects have been described in previous reviews by Shi *et al*. and Vizoso *et al*. [12,13].

Angiogenesis is also one of the mechanisms that contribute to wound healing. MSC-secreted VEGF, HGF, FGF, and angiopoietins activate the proliferation of endothelial cells and neovascularization via PI3K/Akt and HIF-1α pathways [23,24]. This effect is especially relevant for diabetic wounds with poor neovascularization and tissue hypoxia [43]. Moreover, MSCs restore extracellular matrix balance via the regulation of matrix metalloproteinases and stimulation of collagen production by means of TGF-β signaling pathways [25,26]. The antioxidant properties of MSCs resulting from Nrf2/HO-1 and SIRT1 pathways also play an important role in the promotion of cell survival and tissue regeneration [28,45].

➢ *Comparison with Previous Reviews*

Most of the previous reviews mainly focused on either stem cell therapies or exosome therapies [11,13,15]. In contrast, the current review provides a comparative analysis of normal and diabetic wound healing, including both stem cell and exosome approaches. In particular, Hu *et al*. paid attention to the role of MSCs in skin wound healing but gave little consideration to biomaterials and translation into clinical practice [11]. In turn, Vizoso *et al*. drew attention to the therapeutic benefits of the secretome of MSCs but did not pay sufficient attention to diabetic wound pathology [13]. Recent reviews increasingly pay attention to the use of extracellular vesicles and biomaterials; however, only a few works have combined all these aspects in one review [15,41]. Our results corroborate previous observations proving that MSC-derived exosomes and secretome have similar beneficial properties to those of their parent cells.

➢ *Cell-Based Versus Cell-Free Therapies*

Despite the encouraging regenerative capacity of mesenchymal stem cell (MSC) therapy, there are some drawbacks, such as poor engraftment, donor-to-donor variability, immunogenicity, and issues related to the risk of developing cancer that still prevent the clinical use of such therapies [83]. The need to overcome the mentioned barriers has led to the development of cell-free therapies utilising exosomes and secretomes isolated from MSCs. They replicate the properties of MSCs but offer benefits like reduced immunogenicity and tumorigenicity, easy transportability and storage, the possibility to be used off-the-shelf and more flexible manufacturing process [15]. But there is still the need to overcome some barriers, such as lack of standardisation of isolation and characterisation process, uncertainty about the appropriate dosage, the inability of proper purification, and regulation problems of product registration [41,90].

➢ *Role of Biomaterials in Enhancing Therapeutic Efficacy*

Biomaterial-assisted delivery systems have emerged as critical tools for improving the survival and retention of transplanted cells and exosomes [46,47]. Hydrogels, nanofibrous scaffolds, cell sheets, oxygen-releasing biomaterials, and 3D-bioprinted constructs have demonstrated significant benefits in preclinical studies [50,51]. These platforms provide structural support and sustained release of therapeutic factors while protecting transplanted cells from oxidative stress and inflammatory injury. Future multifunctional biomaterials incorporating antimicrobial, antioxidant, angiogenic, and immunomodulatory properties may substantially improve clinical outcomes.

➢ *Clinical Implications*

Current clinical studies suggest that MSC-based therapies are safe and may accelerate healing of diabetic foot ulcers and chronic wounds [77,78]. Meta-analyses have reported improved wound closure rates and reduced

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amputation risk compared with conventional therapies [76,77]. Importantly, no significant increase in severe adverse events has been observed [79]. However, the reliability of the evidence available is restricted owing to smaller sample sizes, variations in methodology, and shorter follow-up periods. As such, MSC treatments have yet to be included in wound management guidelines.

➢ *Strengths of this Review*

The strengths of the current systematic review are numerous. It gives an extensive review of mesenchymal stem cells (MSCs) and their progenies and provides a comparative analysis of wound healing in healthy subjects and diabetics. Both mechanistic, preclinical, and clinical evidence have been incorporated to provide a general picture of the issue under investigation. Moreover, the involvement of biomaterial-assisted delivery systems, regulatory issues, translational aspects, as well as the recent advancements in extracellular vesicles and tissue engineering, are discussed in the article. The utilisation of PRISMA methodology and risk-of-bias analysis adds to the methodological quality of the research.

➢ *Perspectives for the Future*

Future work should be focused on the standardisation of protocols for isolating, expanding and characterising MSCs, as well as optimising dosages and modes of their administration for maximising their therapeutic potential. The development of validated assays that would measure the potency of MSCs and their engineering using gene editing techniques and pre-conditioning methods may further increase the effectiveness of such cells. Moreover, combining the therapy based on stem cells with biomaterials and tissue engineering, including three-dimensional bioprinting, seems to be one of the approaches for increasing the effectiveness of treatments. The future developments in terms of artificial intelligence and precision medicine may enable personalised treatment, while multicenter RCTs with prolonged follow-ups are needed to prove the long-term safety and efficacy of MSC-based therapy. Finally, establishing international standardised regulations for the manufacturing of such preparations will play an important role in their clinical implementation.

V. CONCLUSION

Mesenchymal stem cells (MSCs) and their progenies constitute highly promising regenerative modalities in terms of facilitating wound healing in the case of diabetic ulcers marked by chronic inflammation, defective angiogenesis, and oxidative stress. The underlying mechanism of their action is mostly paracrine and involves immunomodulation, angiogenesis, extracellular matrix remodelling, and antioxidative pathways. Cell-free preparations such as extracellular vesicles and exosomes provide several benefits in comparison to cell-based treatments and help to circumvent problems associated with inadequate engraftment and safety issues. While preclinical and early clinical studies reported positive results, there is still much work to be done in order to standardise and regulate the application of this treatment.

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