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Biomimetic scaffolds loaded with mesenchymal stem cells (MSCs) or MSC-derived exosomes for enhanced wound healing

Alireza Ghasempour[1,2], Hamideh Dehghan[3], Mahmoud Mahmoudi[2,4] and Fahimeh Lavi Arab[2,4*]

Abstract

Since wound healing is one of the most important medical challenges and common dressings have not been able to manage this challenge well today, efforts have been increased to achieve an advanced dressing. Mesenchymal stem cells and exosomes derived from them have shown high potential in healing and regenerating wounds due to their immunomodulatory, anti-inflammatory, immunosuppressive, and high regenerative capacities. However, challenges such as the short life of these cells, the low durability of these cells in the wound area, and the low stability of exosomes derived from them have resulted in limitations in their use for wound healing. Nowadays, different scaffolds are considered suitable biomaterials for wound healing. These scaffolds are made of natural or synthetic polymers and have shown promising potential for an ideal dressing that does not have the disadvantages of common dressings. One of the strategies that has attracted much attention today is using these scaffolds for seeding and delivering MSCs and their exosomes. This combined strategy has shown a high potential in enhancing the shelf life of cells and increasing the stability of exosomes. In this review, the combination of different scaffolds with different MSCs or their exosomes for wound healing has been comprehensively discussed.

Keywords Mesenchymal stem cell, Exosome, Scaffold, Wound healing, Tissue engineering

Introduction

The skin is a versatile organ that serves multiple functions. It protects against physical and chemical hazards and ultraviolet radiation exposure, which occurs daily. Due to the harsh external environment, the skin frequently sustains damage, so it's not surprising that it has complex healing mechanisms to facilitate quick and effective recovery [1]. Managing wounds is a significant global challenge that places a substantial financial strain on governments worldwide. Hence, there has been extensive research into wound dressings that can aid in wound healing [2].

Mesenchymal stem cells (MSCs) are a potent approach to healing skin wounds due to their ability to differentiate,

*Correspondence:
Fahimeh Lavi Arab
laviaf@mums.ac.ir; fahime.lavi@gmail.com
[1]Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran
[4]Department of Immunology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

facile harvest, low immunogenicity, recruitment of other host cells, and secretion of growth factors and matrix proteins, making them an attractive treatment option. MSCs facilitate the movement of cells, the formation of new blood vessels, the development of epithelial cells, and the formation of granulation tissue, leading to faster wound closure [3]. Adhesion challenges and a high rate of cell death hinder the impact of therapies using stem cells. A promising approach to preserving stem cell activity and ensuring their protection involves a combined therapeutic strategy with advanced materials [4]. Combined treatments that use a set of scaffolds, cells, and biological elements are receiving attention today. Fabricated biological scaffolds provide a base for seeding stem cells and an environment supporting growth. In general, these designed scaffolds facilitate the transport and delivery of stem cells [5].

This study is a comprehensive review of investigations related to combining different scaffolds (including porous, hydrogel, nanofibrous, and 3D-printed scaffolds) with MSCs or MSC-derived exosomes. First, this review provides a proper overview of scaffolds' potential, and then it assesses the regenerative mechanisms of MSCs or MSC-derived exosomes combined with scaffolds for wound healing.

Wound healing process

Wounds are produced for various reasons, including surgery, burns, and diabetes [6]. These kinds of damage create two different wound types: acute and chronic [6, 7]. Acute wounds experience a sequence of molecular occurrences that ultimately lead to restoring structural stability. In contrast, chronic wounds do not heal because of underlying diseases like diabetes and are distinguished by abnormal developments, such as ongoing inflammation, enduring infections, and tissue death [7, 8]. Although the wound healing process is remarkably sophisticated and relies on the intricate interaction of various factors, it is typically divided into four overlapping yet separate stages: hemostasis, inflammation, proliferation, and remodeling [8, 9]. The various phases of wound healing are depicted in Fig. 1.

Hemostasis

The first steps after an injury depend on a sequence of serine protease occurrence to stop blood loss and accomplish hemostasis. This phase initiates when damage leads to blood leaking into the exposed wound area, activating the extrinsic clotting cascade and releasing various mediators [10]. It can be said that this phase includes initial hemostasis, secondary hemostasis, and vasoconstriction, which are three important stages [7, 11]. Following injury, the injured endothelium releases vasoconstrictors such as endothelin, which quickly constrict blood vessels to reduce bleeding. Catecholamines and prostaglandins in the bloodstream also regulate this constriction in response to the injury [7]. Additionally, platelet-derived growth factor (PDGF) induces mesenchymal cells, exceptionally smooth muscles in the vessel walls, resulting in contraction [11]. After vessel cut, the thrombogenic subendothelial matrix is exposed. Platelets attach to it and induce the inside-out signaling interactions, that yields integrin turning on and augments the binding of other platelets and the surrounding extracellular matrix (ECM) [7, 11]. Platelet degranulation liberates inflammatory mediators like interleukin (IL)-8, also known as CXCL8. This process also causes the release of IL-1α, IL-1β, IL-6, tumor necrosis factor (TNF)-α, transforming growth factor (TGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) and triggers the complement cascade [7, 10, 12]. Subsequent to obtained hemostasis, histamine is released by the triggered complement cascade, resulting in the dilation and leaking of capillaries, improving inflammatory cell migration into the wound area and completing the shift to the inflammatory stage of wound healing [10].

Inflammation

Soon after hemostasis, the wound inflammatory reaction activates. Neutrophils and macrophages, two prominent innate immune cells from resident populations or recruited via extravasation from nearby vessels, play a crucial role in this phase [12]. Damaged cells result in the recruitment of inflammatory cells, particularly neutrophils, through damage-associated molecular patterns (DAMPs), hydrogen peroxide (H_2O_2), lipid mediators, and chemokines [11]. Swelling, redness, and pain may occur during this stage [9].

The main function of neutrophils is to eliminate microbes. This function is done through the targeted release of reactive oxygen species (ROS), the creation of neutrophil extracellular traps (NETs), and antimicrobial molecules. This process relies on neutrophil elastase, peptidylarginine deaminase 4 (PAD4), and gasdermin D [12]. Additionally, neutrophils can pull matrix elements from neighboring organs into the wound, which can affect the wound healing procedure [12, 13]. Most neutrophils die after completing their functions and are eliminated through macrophage efferocytosis [12]. It is worth noting that the maintained and unsuitable presence of neutrophils in the injury area is a significant contributing cause of wounds that don't heal. For instance, extra NETs postponed wound healing in diabetic foot wounds [10].

During the initial phases of wound healing, macrophages exhibit a distinct pro-inflammatory state known as the classically activated macrophage or the M1 phenotype. DAMPs and other inflammatory signals generated at the wound location, including IFN-γ and TNF, induce

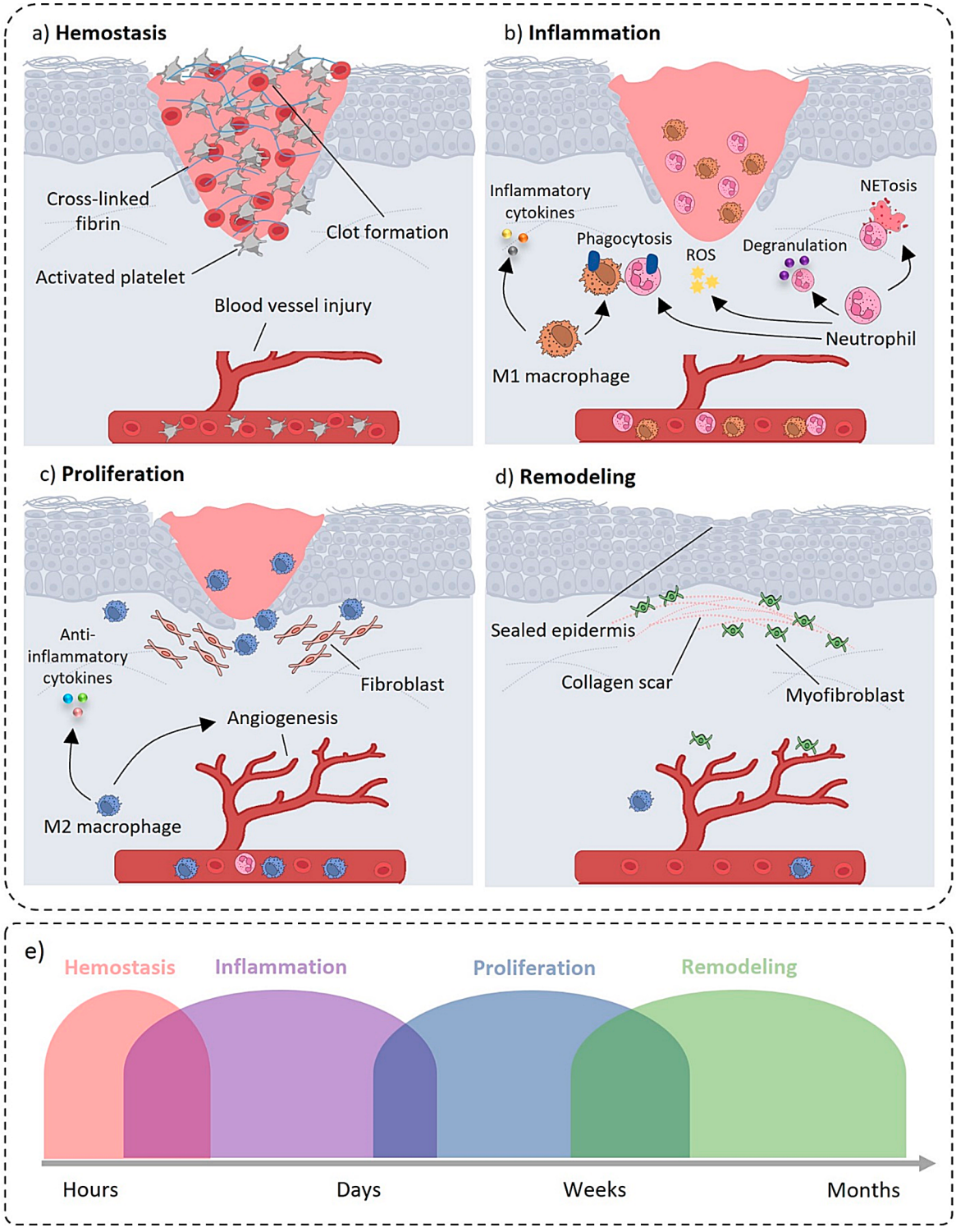

Fig. 1 The overview of wound healing phases. This figure illustrates the various biological changes that occurred at each phase, including hemostasis (**a**), inflammation (**b**), proliferation (**c**), and remodeling (**d**). Timeframe approximation for the wound healing phases is also shown (**e**)

the M1 phenotype [12]. This phenotype produces pro-inflammatory cytokines, including IL-1β, IL-6, IL-12, IL23, TNF-α, and chemokines, which enhance natural killer cells (NK cells), macrophages, and helper T cell reactions [10, 14].

Proliferation

During this phase, vascular channels were re-established, granulation tissue was formed, and the wound surface was re-epithelialized [10]. The resolution of inflammation results in the polarization of the pro-inflammatory phenotype into an anti-inflammatory type known as the alternatively activated macrophage or the M2 macrophage. Anti-inflammatory macrophages play a role in forming new blood vessels, and many of them during this phase are associated with increased microvessel density [11]. The process of forming granulation tissue, mainly consisting of type III collagen, fibroblasts, and new blood vessels, happens simultaneously as angiogenesis. Fibroblasts are the primary cells in creating granulation tissue, and specific molecules derived from macrophages can stimulate the production of molecules that aid in re-epithelialization in fibroblasts [7, 10]. Fibroblasts and pro-repair macrophages impact keratinocyte re-epithelialization. Re-epithelialization is triggered by EGF, keratinocyte growth factor (KGF), and transforming growth factor-α (TGF-α), which are secreted by platelets, keratinocytes, and activated anti-inflammatory macrophages [10]. In a feedback loop, keratinocytes induce fibroblasts via fibronectin, tenascin C, and laminin [10, 15].

Remodeling

Closure of various wounds is typically regarded as the conclusion of wound healing. However, wounds may undergo a remodeling or tissue maturation process for an extended period, lasting several months or even years [11]. This final stage involves the shift from granulation tissue to scar. This shift includes slowing down blood vessel growth and switching type III collagen in granulation tissue with more potent type I collagen [10, 11]. Scar tissue typically forms in adults, while embryonic wound healing takes place without scarring [7]. Fibroblasts evolve into myofibroblasts in reaction to mechanical tension and TGF-β signaling, which play a notable role in this phase by contracting the wound [10, 16]. Myofibroblasts also aid in remodeling by releasing matrix metalloproteinases (MMPs), which break down the collagen deposited during granulation tissue formation [10, 11]. When the wound healing process is terminated, myofibroblasts undergo apoptosis. If this does not happen, hypertrophic scars tend to create [11].

MSCs and MSC-derived exosomes: focus on wound healing

MSCs are spindle-shaped cells with the capacity for multipotent differentiation (into tri-lineages, i.e., osteogenesis, adipogenesis, and chondrogenesis) and self-renewal. They originate from different tissues, adhere to tissue culture plates, and exhibit specific cell surface markers [17–20]. MSCs are an excellent cell source for tissue regeneration due to their potential characteristics, including anti-inflammatory, immunoregulatory, immunosuppressive, and suitable paracrine effects [17, 18]. It was shown before that MSCs can be effective in bone regeneration, cartilage repair, central and peripheral nervous system rebuilding, liver regeneration, corneal reconstruction, and tracheal reconstruction [18].

MSCs can generate diverse cells associated with wound healing, such as dermal fibroblasts, endothelial cells, and keratinocytes [21]. Additionally, MSCs can decrease the production of MMPs due to their antioxidant and anti-apoptosis properties, resulting in inducing the proliferation of dermal fibroblasts [21, 22]. MSCs regulate fibroblast activity and prevent excessive collagen production, leading to decreased scarring through the MAPK/ERK pathway. Also, MSCs can enhance wound healing by promoting wound closure, suppressing inflammatory reactions, boosting the formation of new blood vessels, influencing cell growth, and managing the restructuring of the ECM. These MSCs can stimulate mononuclear cells to produce IL-10, which reduces inflammation and assists in the healing of wounds [23]. Evidence increasingly indicates that paracrine signaling is the primary mechanism through which MSCs boost wound repair [3]. Angiopoietin-1 (ANGPT1), basic-fibroblast growth factor (bFGF), EGF, insulin-like growth factor-1 (IGF-1), KGF, PDGF, TGF-β, and VEGF are essential to enhanced wound healing, which is secreted by MSCs [3, 23]. Furthermore, Exosomes secreted by MSCs effectively promote wound healing [23–25], which will be discussed further. On the other hand, MSCs even suppress the pro-inflammatory properties of myeloid cells, encompassing monocytes, macrophages, and granulocytes [3].

Despite significant progress in employing MSCs for skin tissue regeneration, it's important to consider the inherent limitations of MSC therapy. Hence, MSC-derived exosomes have achieved considerable interest as a novel "cell-free" method for skin wound healing [26]. MSC-derived exosomes are small membranous vesicles, typically 30–150 nm in diameter and round or oval shape. MSC-derived exosomes possess several profits over traditional MSC transplantation, including decreased vascular embolism risk due to their smaller size, reduced tumor formation possibility due to lack of self-replicating properties, and more preservation approaches [27]. These exosomes contain various molecular components,

such as lipids, proteins, DNA, and microRNA, that can target molecular pathways and biological events in recipient cells, such as endothelial cells, keratinocytes, and fibroblasts. They can also alter macrophage activation, promote angiogenesis, and boost the proliferation and migration of keratinocytes and dermal fibroblasts [28].

Biomimetic scaffolds for delivery of MSCs and MSC-derived exosomes

As discussed, MSCs could enhance wound healing notably, but their short life span in the wound site hinders the full completion of their repairing efficacy. This reason has initiated examinations to achieve the optimal system for MSC delivery. Existing cell-based therapies primarily focus on injections of cells administered intradermally or systemically. The systemic administration demonstrates that most cells are trapped in the lung and that only a tiny amount reaches the wound area. However, Intradermally administration to the wound edges remarkably enhanced wound healing [29]. On the other hand, traditional wound coverings like cotton, bandages, and gauze do not create a moist and dynamic condition for wound healing. Another issue is that these coverings may adhere to the wound, leading to pain for patients upon removal [30, 31]. Frequent replacement is also necessary, which could lead to additional trauma. Moreover, biological dressings, like pig skin, pose the potential for transmitting bacteria and viruses as well as facing immune system rejection [32]. Hence, the choice of materials is crucial in wound care. Materials that possess softness, moisture, and appropriate absorption are vital in creating a favorable microenvironment for tissue repair and supporting cell function [33].

Three-dimensional scaffolds are generally porous, biocompatible, and biodegradable structures, which could create appropriate microenvironments by providing mechanical, physical, and biochemical stimuli to promote optimal cell growth and function. The functionality of 3D structures during biomedical applications is directly affected by their porosity and pore size. Open, porous, and interconnected networks are crucial for cell nutrition, proliferation, and migration during tissue vascularization and the development of new tissues. Porous surfaces also simplify mechanical interlocking between the structures and surrounding tissue, enhancing the implant's mechanical steadiness. Furthermore, the network structure of the pores promotes the formation of new tissue [34]. As illustrated in Fig. 2, these scaffolds possess various benefits for enhancing the wound healing process, such as gas exchange, absorbing exudates, providing a moist condition for cell migration, and reducing excessive oxidative reactions.

The use of MSCs in wound healing faces challenges such as storage problems, tumorigenesis, rejection by the immune system, and embolism risk [35–37]. Since MSC exosomes mediate the biological effects of MSCs and contain paracrine factors of SCs, they may have the same biological functions as MSCs and be effective in wound healing. MSC-derived exosomes contain metabolites, proteins, DNA and non-coding RNAs, and cytokines, including VEGF, TGF-β1, IL-6, and IL-10 [38]. In one study, miR-223 was found in MSC-derived exosomes to regulate inflammation and induce wound healing by influencing the pknox1 gene and the polarization of macrophages [39].

The content of MSCs-derived exosomes is taken up by receptor cells such as fibroblasts, keratinocytes, immune cells, and endothelial cells and accelerates wound healing. The rapid excretion of exosomes and the relatively short half-life under in vivo conditions are among the challenges for the clinical application of exosomes [40]. In many studies, multiple doses of exosomes are used to maintain an appropriate local concentration of exosomes. However, it should be borne in mind that this work is limited due to the cost of preparing exosomes and the pain and discomfort caused by the injection [41]. Among other problems with the use of MSCs-derived exosomes in wound healing, it can be mentioned that given the prolonged process of wound healing, especially in diabetic wounds, the use of MSC-derived exosomes is associated with challenges such as maintaining the viability, function, and stable release of exosomes [42].

Scaffolds with a highly porous structure are crucial for maximizing the flow of nutrients [42]. In recent years, it has been found that hydrogels release exosomes slowly and sustainably and can accelerate wound healing [38]. In the study by Shi et al., a multifunctional hydrogel with gallic acid-conjugated chitosan and partially oxidized hyaluronic acid was designed for the sustained release of hypoxic BMSCs-derived exosomes. The covalent bond between the amine group of the proteins on the exosome surface and the hydrogel structure, as well as the hydrogen bonds in the hydrogel network, are probably responsible for the durability and stability of the exosomes in the hydrogel. The slow degradation of the hydrogel causes the exosomes to be gradually released into the wound environment. By slowing the release rate of exosomes into the wound environment, inappropriate physical interaction of exosomes with other substances present in the wound is prevented [41]. Wu and colleagues designed a wound dressing of chitosan hydrogel and ADMSC-Exo using a physical mixing method. This study showed that the degradation rate of chitosan hydrogel is always lower than the release rate of exosomes, which means that the release of the exosomes does not only depend on the degradation of the hydrogel but is rather due to the diffusion of the exosomes from the hydrogel space [43].

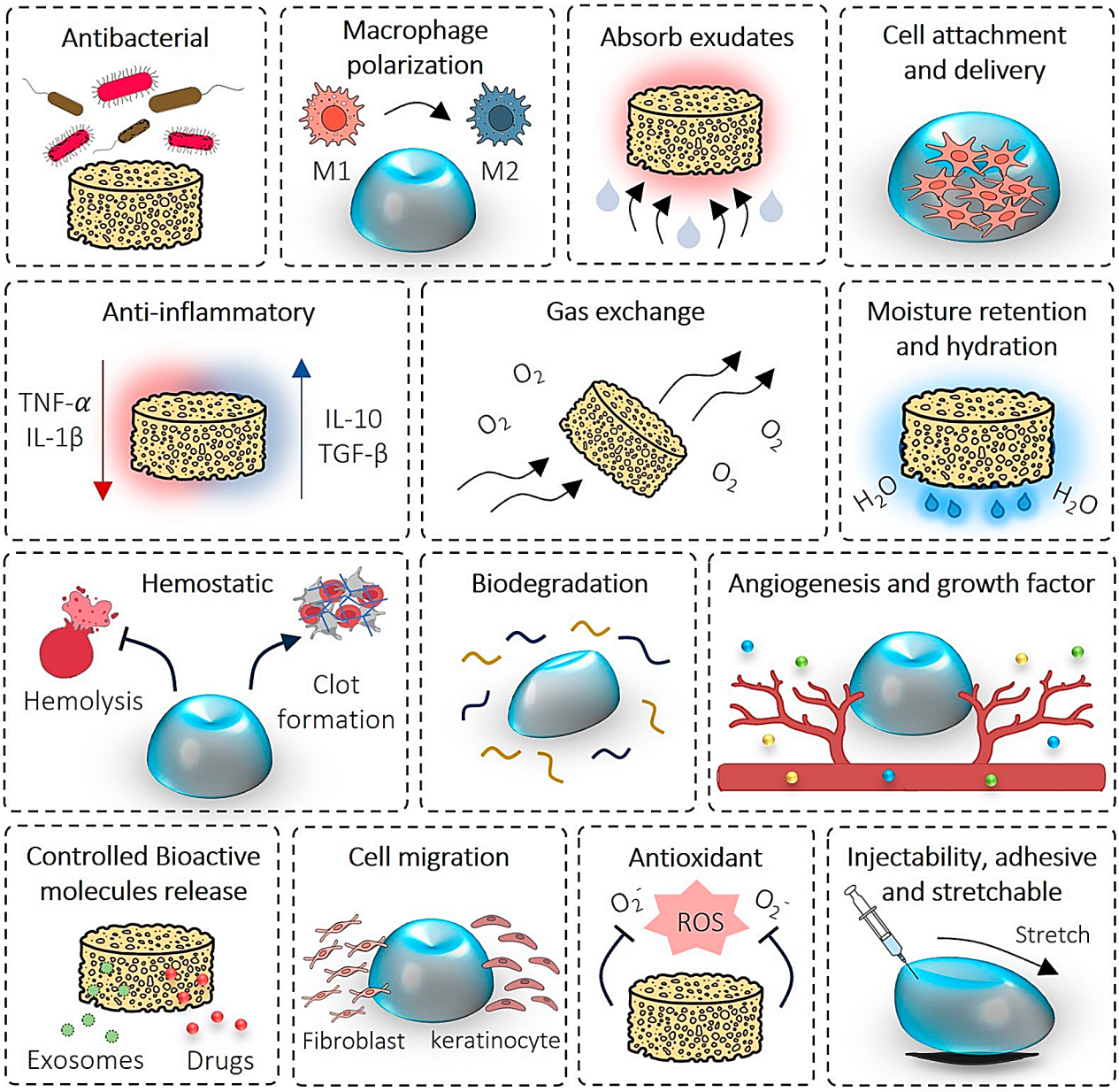

Fig. 2 This schematic illustrates the benefits and characteristics of different types of scaffolds. It's important to note that the porous scaffold and the hydrogel scaffold are represented as models of the four mentioned scaffolds, and some of the same characteristics can be attributed to the other two types of scaffolds, including nanofiber scaffolds and 3D printed scaffolds

Scaffolds can regulate the cell's physical, chemical, and mechanical maintenance, as they are similar in structure to the ECM [44, 45]. Scaffolds must be cytocompatible to attach well to cells to protect better and stabilize MSCs and MSC-derived exosomes through appropriate interactions such as covalent bonds and electrostatic interactions between the scaffold and MSCs or MSC-derived exosomes [41, 46]. The large pore size and high porosity result in high permeability of the liquid and allow sufficient transfer of nutrients, oxygen, and metabolic waste, improving the conditions for the growth and migration of MSCs [43, 47]. In addition, this leads to faster degradation of the scaffolds and allows the MSCs and their derived exosomes to interact with the targeted ablated tissue [38, 44]. For instance, Various scaffolds based on chitosan can offer MSCs an appropriate environment. Because MSCs can stick to chitosan, either present on the scaffold's surface or in the holes found in the biomaterials, chitosan scaffolds are a suitable delivery route for MSCs. Because of this adhesive capability, MSCs can multiply on the scaffold's surface [48].

Figure 3 illustrates the creation and secretion of exosomes from MSCs and their interaction with target cells. Furthermore, it demonstrates the advantages of using scaffolds for exosome loading and delivery.

The current review focused on four distinguished scaffolds, including porous, hydrogel, nanofibrous, and 3D-printed scaffolds. We investigated their interaction with various types of MSCs or MScs-derived exosomes, aiming to enhance wound healing.

Porous scaffolds

Sponge scaffolds with extensive porosity and a consistently interconnected pore structure are produced using natural or synthetic polymers and various methods, including porogen leaching, gas foaming, and freeze-drying [5, 49]. These scaffolds have suitable porosity to simplify gas and micronutrient exchange and absorb exudates. For example, in a study by Cui et al., collagen-tussah silk fibroin hybrid scaffolds were synthesized using the freeze-drying method for loading BMSCs. The various scaffolds possess good porosity, ranging from 63.51 to 94.68%. Also, the scaffolds' water vapor transmission rate (WVTR) was around 52–64% [50]. Khandan-Nasab et al. presented an alginate/pullulan/hyaluronic acid scaffold with an average pore size of 100 µm, which was profitable for cell attachment and migration. The attachment of adipose-derived MSCs to the scaffolds was assessed by employing field emission scanning electron microscopy

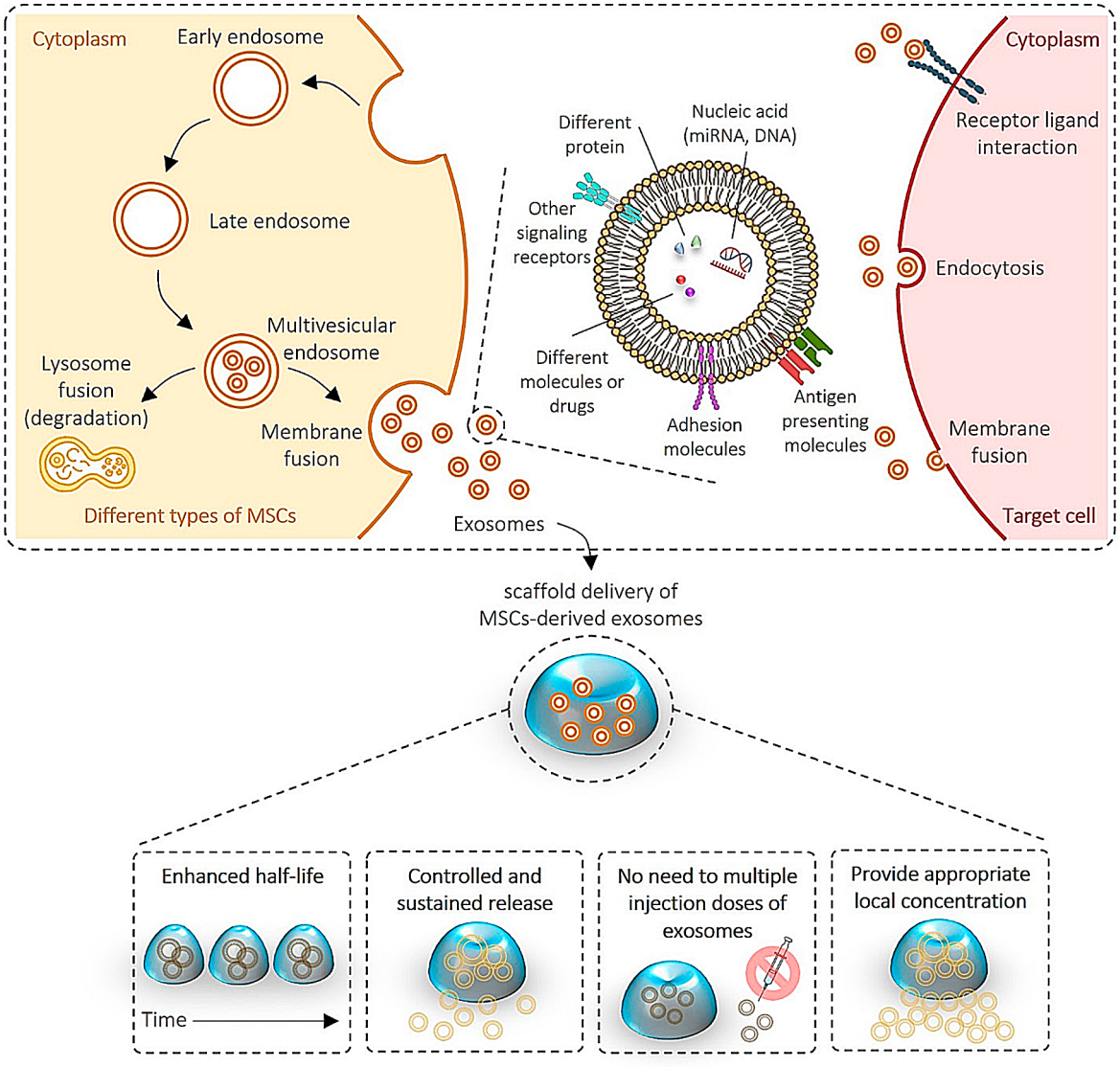

Fig. 3 How exosome is formed and its possible interaction with target cells is given in this schematic. Also, the possible benefits of using scaffolds for exosome delivery have been shown

(FE-SEM) and 4′,6-diamidino-2phenylindole (DAPI) fluorescent staining. The scaffold exhibited a significant capacity for cell attachment. It revealed the uniform morphology of 1-day cultured cells on the surface, which were evenly dispersed and connected with a high density in the porous framework [30]. The fabrication method for sponge and hydrogel scaffolds differs, leading to variations in the water content percentage within the scaffold. Also, sponge scaffold fabrication is more time-consuming than hydrogel, and its surface and structure need adjustment based on the cell type and host tissue. Overall, sponge scaffolds possess a uniform interconnected pore network that supplies an appropriate condition for cell attachment, migration, and nutrient transition [29].

Hydrogel scaffolds

Hydrogel structures are a type of polymeric materials, which their hydrophilic nature allows them to maintain notable amounts of water within their 3D structures [51]. Hydrogels have garnered significant interest in wound healing treatment, as they can sustain cell viability at the implantation site and are versatile in their production [29]. Hydrogels can also affect cell adhesion, proliferation, and differentiation due to their hydrophilic properties [52]. Hydrogels can be fabricated employing both natural and synthetic polymers. Natural polymer-based hydrogels show some benefits over synthetic polymer-based hydrogels regarding biocompatibility, cellular interactions, and degradation. However, their range of applications is limited by their restricted mechanical strength. This limitation can be addressed in synthetic polymer-based hydrogels by manipulating the structure or functional groups of the polymer chains [5, 53]. For instance, since regulating biomaterial degradation rates in vivo is crucial, Martin et al. use hydrolytically degradable ester linkages to fabricate manufactured hydrogels with tunable in vivo degradation kinetics for temporally regulated carry of MSCs. The degree of in vivo hydrogel degradation can be managed by modifying the proportion of ester to amide linkages in the structure macromers. These hydrolytic hydrogels degrade at speeds that allow unhindered skin wound healing while improving the local existence of MSC in comparison to the broadly employed protease-degradable hydrogel [54].

The formation of cracks often compromises the beneficial properties of traditional hydrogels. Hence, functional hydrogels have been engineered to address this drawback by possessing self-healing or self-repairing capabilities [55]. Injectable and self-repairing hydrogels can adjust to varying wound forms and dynamics. Additionally, self-repairing hydrogels have benefits over conventional dressings in terms of excellent flexibility, adhesion, and hydrophilicity [56]. Bai et al. present a new self-healing hydrogel fabricated by crosslinking N-carboxyethyl chitosan and adipic acid dihydrazide with hyaluronic acid-aldehyde in situ. The ability to self-heal was shown to repair structural and functional damage, preserving the integrity of network structures and the gel's mechanical properties. The bone marrow MSCs could adhere and proliferate well in this multifunctional hydrogel, demonstrating suitable protection and delivery properties for treating diabetic foot ulcers (DFUs) [55]. In another study, methylcellulose-chitosan hydrogel loaded with placental MSCs-derived exosomes was designed by Wang et al. A macroscopic test verified the self-healing property, which indicated after the fusion of the two dyed pieces of hydrogel, the formed hydrogel was robust sufficiently to bear the tensile force without breaking [57].

Nanofibrous scaffolds

The production of fibrous scaffolds mainly involves employing electrospinning to create 3D structures of microscale or nanoscale fibers that resemble the structure of natural human tissues very well [5, 29]. Electrospun nanofibers play a crucial role in wound healing. Their unique structure, with a relatively large surface area, ability to closely imitate the native ECM, tunable waterproofness and breathability, customizable drug delivery process, great inter-pore connectivity, and the potential to cause no scarring, make them an effective tool in this process [58, 59]. The high surface-area-to-volume ratio feature enables cell adhesion, but small pore size may inhibit cell migration. Therefore, the design must be customized for the particular cell type [29]. Several factors impact the diameter and morphology of electrospun nanofibers, encompassing polymeric solution features, processing parameters, and environmental circumstances. Electrospinning process parameters, such as viscosity/concentration, applied voltage, and flow rate, are an important class of these factors [60].

Prakashan et al. reported that polycaprolactone-gelatin nanofiber scaffolds, with average fiber diameters ranging from 200 to 300 nm, were suitable for the adhesion, proliferation, and migration of bone marrow-derived cells. This nanofiber scaffold demonstrated profitable effects for wound healing [61]. Abdollahi et al. conducted a study to investigate the combined impact of cellular nanofiber composite scaffolds on chronic wounds, particularly diabetic ulcers. They used a nano extrusion device to create a nanoporous membrane with biodegradable polymers. Nano-bioscaffolds delivered human adipose-derived MSCs and placenta-derived MSCs to the wound sites. MSCs were attached to the structure using the collagen coating technique. Following diver physicochemical evaluations, the scaffold demonstrating outstanding characteristics was utilized to treat full-thickness diabetic wounds. The scaffold's SEM and AFM analysis displayed even nanofibers with diameters ranging from

100 to 130 nm and a surface roughness of less than 5 nm, respectively. When adhered to the scaffold, MSCs exhibited a typical spindle-shaped or fibroblast-like morphology. The scaffold also demonstrated the expected characteristics, such as swelling, hydrophilicity, biodegradation rate, and biocompatibility [62]. Nanofibers can also be combined with hydrogel in a bilayer wound dressing. In these structures, nanofibers and hydrogels work together to accelerate wound healing. The nanofibers in the top layer offer mechanical protection for the scaffolds and the ability to retain fluids and oxygen permeability. Meanwhile, the hydrogel layer serves as a 3D substrate for cell growth and delivery, leading to the regeneration of new tissue. Hence, Lashkari et al. reported polycaprolactone/gelatin nanofibers, which electrospun directly on the designed collagen/alginate hydrogel to be seeded with adipose-derived MSCs. Their findings revealed that re-epithelialization, neovascularization, and collagen remodeling were improved in cell-seeded bilayer scaffolds and nanofibers compared to the control group [59].

3D-printed scaffolds

3D bioprinting is an additive manufacturing approach based on computer-made designs that create biocompatible 3D structures. These cutaneous replacements outperform traditional skin regeneration methods due to their superior automation and standardization for clinical applications and their precise incorporation of living cells, growth factors, and other biomolecules. The benefits of 3D printing technology to fabricate skin scaffolds include incorporating interconnected macro/microporosity, utilizing various bioinks, and creating a precise geometric structure aligning with the tissue defect [63]. Also, the extensive design freedom, precise and reproducible outcomes, and the accessibility of cost-effective printers drive the growing fascination with 3D bioprinting [64].

Fabricating these scaffolds using 3D bioprinting needs bioinks, which are bioprintable materials. A variety of natural polymers and synthetic-based biopolymers have been utilized as bioinks [63]. For example, Wu et al. bioprinted an efficient biological scaffold using gelatine and sodium alginate loaded with adipose-derived MSCs and nitric oxide to assess its effectiveness in enhancing severe burn wound healing. The findings demonstrated that cells were evenly distributed within the hydrogel. Moreover, SEM images proved that the grid-like constructs of scaffolds and cells grew both inside and on the surface of the fabricated hydrogel. Also, the cumulative nitric oxide release exhibited prolonged and sustained release of nitric oxide. Finally, the scaffold revealed enhanced wound healing by boosting epithelialization, collagen deposition, and neovascularization [65]. Within additional investigation, Hu et al. employed an extrusion-based cryogenic 3D printing approach to produce decellularized small intestinal submucosa incorporated with mesoporous bioactive glass and bone marrow MSCs-derived exosomes for accelerated diabetic wound healing [38].

Biomimetic scaffolds combination with MSCs or MSC-derived exosomes: role in wound healing

Figure 4 summarizes the repair mechanisms of loaded scaffolds. Tables 1 and 2, respectively, show the studies, including the combined treatment of scaffolds with MSCs or scaffolds with MSC-derived exosomes.

Immunomodulatory, anti-inflammatory and macrophage polarization

Immune cells and factors are crucial in the wound healing process. They commence the inflammatory process, aid in wound cleansing, play a role in angiogenesis and stem/progenitor cell effects such as proliferation and differentiation, and eventually enhance following tissue healing [8, 89]. However, when the immune system is not regulated correctly, it can result in ongoing inflammation and postponed healing [8]. Su et al. showed that exosome-functionalized polyethylenimine-modified electrospun fibers (Exo-PEF) could elevate the existence of Tregs in more increased than twofold quantity in compression to untreated wounds on day 7. Also, immune responses induced in lymph nodes and spleen demonstrated reduced IFN-γ^+ $CD4^+$ T cells on day 7 in lymph nodes and on day 14 in spleen. The hypertrophy of the lymph nodes in the Exo-PEF group was evident by day 14, suggesting immune activation in the lymph nodes. Increased IL-4, 5, 10, and 13 were also observed [89].

Wound inflammation is a complex process that significantly impacts healing. Prolonged inflammation can result in overly scarring, making developing effective wound healing drugs challenging [94]. Because of this great importance, most of the studies focused on the topic of this review showed the anti-inflammatory effects of scaffolds containing MSCs or their exosomes. For instance, enzyme-linked immunosorbent assay (ELISA) revealed increased IL-10 and TGF-β1 and decreased IL-1β and IL-6 when using sodium alginate/gelatin hydrogels loaded with adipose-derived MSCs for diabetic wounds [52]. TNF-α and IL-6 immunohistochemistry assay in a study by Zhou et al. showed a reduction of these inflammatory cytokines when using Pluronic F-127 hydrogel that encapsulated human adipose-derived MSCs-exosomes [86].

Since macrophage polarization towards M2 is essential for wound healing, studies have well revealed the polarization ability of scaffolds loaded with MSCs or MSC-derived exosomes. For example, it was observed that M2 phenotype macrophages ($Arg1^+$/$CD206^+$ cells)

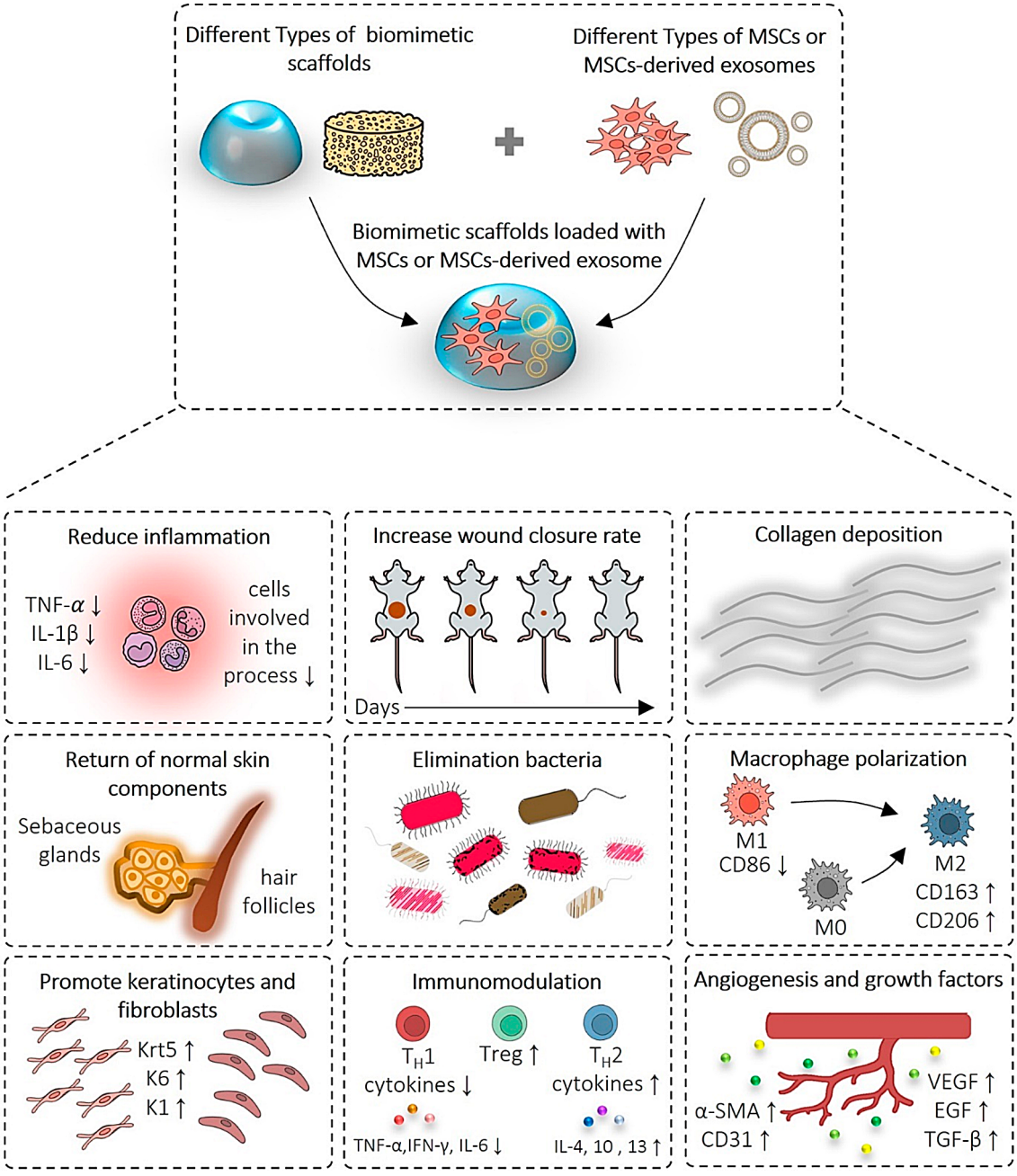

Fig. 4 Main reported roles of biomimetic scaffolds loaded with MSCs or MSCs-derived exosomes in different cutaneous wound healing. It's important to note that the porous scaffold and the hydrogel scaffold are represented as models of the four mentioned scaffolds

significantly enhanced, while M1 phenotype macrophages ($iNOS^+/CD80^+$ cells) decreased when using hypoxic MSCs-derived exosomes loaded multifunctional hydrogel. This may be due to the collaborative inhibition of SREBP2 activity in macrophages by the miR-4546-5p from hyBMSC-Exos and the hydrogel's antioxidant properties [41]. MSC spheroids induced by Biotin-^{D}FYIGSR hydrogel increased M2 marker CD206 and decreased M1 marker iNOS, revealing polarization of M1 macrophages to the M2 subtype [66]. In another study, bone marrow MSCs-Ladan 3D radially and vertically aligned nanofiber scaffolds could enhance M2 type macrophage (CD206 marker) and decrease M1 type macrophage (CCR7 marker) in 7 days [76].

Angiogenesis and growth factors

The related studies assayed hallmark proteins associated with vascular expansion, including CD31, α-SMA, and VEGF. Xu et al. designed hydrogel based on gelatin methacrylate and chitosan-catechol that encapsulated

Table 1 The studies used various MSC-laden scaffolds for wound healing

Type of MSCs	Main component	Types of wound/ study model	Highlighted results	Year	Ref.
Adipose or placenta-derived MSCs	Chitosan, collagen, hyaluronic acid, chondroitin sulfate	Full-thickness diabetic wounds/ male Wister rats	Wound closure rate ↑ Collagen density ↑ Inflammatory cells ↓	2024	[62]
Bone marrow derived MSCs	Polycaprolactone, gelatin	Full-thickness skin wound/ female New Zealand white rabbits	Wound contraction ↑ Re-epithelialisation ↑ Granulation ↑ Fibroblast formation and vascularization ↑ Hair follicle growth ↑ Haemorrhage ↓ Inflammation ↓	2024	[61]
Human umbilical cord-derived MSCs	Biotin-DFYIGSR peptide derivative,	Full-thickness diabetic wounds/ male C57BL/6 mice	Wound area ↓ MPO and iNOS ↓ CD206 and IL-10 ↑ TNF-α and IL-1β ↓ Ki67, CD31 and VEGFA ↑ Krt5 ↑	2024	[66]
Adipose-derived MSCs	Chitosan, polyvinyl alcohol	Diabetic mice	Wound area ↓ Granulation tissue ↑	2024	[67]
Adipose-derived MSCs	Sodium alginate, gelatin	Diabetic full-thickness excisional wounds/ male Sprague-Dawley rats	Collagen deposition ↑ EGF, PDGF, and VEGF ↑ CD31 ↑ IL-1β and IL-6 ↓ IL-10 and TGFβ1 ↑ IL-13 and IL-4 ↑ F4/80 and CD163 M2 macrophage ↑	2023	[52]
Bone marrow and adipose MSCs	Collagen, fibrin	Full-thickness burn wound infected by *Pseudomonas aeruginosa*/ male Balb/c mice	Bacterial count ↓ Acceleration in wound closure ↑ Major return sebaceous glands and hair follicles ↑	2023	[68]
Bone marrow MSCs	poly(ethylene glycol)-4maleimide	Diabetic full-thickness wounds/ diabetic mice (db/db)	Wound closure rate ↑ Epidermal thickness ↑ $Ly6C^{mid}F4/80^{+}$ double-positive monocytes and $F4/80^{+}$ macrophages ↑	2023	[54]
Adipose-derived MSCs	Collagen, alginate, polycaprolactone, gelatin	Full-thickness wounds/ male Wistar rats	Wound closure rate ↑ Collagen organization ↑ Re-epithelialisation ↑	2023	[59]
Adipose-derived MSCs	Alginate, pullulan, hyaluronic acid	Full-thickness wounds/ male balb-c mice	Wound closure rate ↑ Epidermal proliferation ↑ Re-epithelization ↑ Collagen content ↑	2023	[30]
Human umbilical cord MSCs	Fibrin	Full-thickness skin wounds/ female-specific pathogen-free class BALB/c mice	Wound closure rate ↑ Re-epithelization ↑ EGF ↑ TGF-β1 ↑ VEGFA ↑	2023	[32]
Human umbilical cord MSCs	Gelatin methacrylate, chitosan-catechol	Diabetic full-thickness wounds/ db/db diabetic mice	Wound closure rate ↑ TNF-α and IL-1β↓ α-SMA and CD31 double positive stained vessels ↑ VEGF ↑ Hair follicle ↑ Collagen deposition ↑	2022	[4]
Adipose-derived MSCs	β-chitin	Full-thickness cutaneous wounds/ Sprague–Dawley rats	Wound healing rate ↑ VEGFR and α-SMA ↑ Collagen I and collagen III ↑ TGF-β1, P-smad3, P-smad2 and TIMP1 ↑	2022	[69]

Table 1 (continued)

Type of MSCs	Main component	Types of wound/ study model	Highlighted results	Year	Ref.
Human umbilical cord MSCs	Sodium alginate, collagen	Full-thickness excision/ male C57/BL6 mice	Wound healing rate ↑ Collagen deposition ↑ EdU and K6 ↑ TGF-β1 ↑ α-SMA, CD31 and VEGF ↑ iNOS, TNF-α and IL-1β ↓ NLRP3 and caspase-1 ↓	2021	[70]
Adipose-derived MSCs	Gelatine, sodium alginate, S-Nitroso-N-acetyl-D, L-penicillamine	Full-thickness burn wounds/ male Balb/c mice	Wound area ↓ Re-epithelialisation ↑ Collagen deposition ↑ CD31 ↑	2021	[65]
Wharton's jelly MSCs	PF-127 hydrogel, sodium ascorbyl phosphate	Diabetic full thickness cutaneous wound / male Sprague Dawley rats	Residual wound area ↓ Dermis thickness ↑ Hair follicles ↑ Scar width ↓ CD86-positive M1 macrophages ↓ CD163-positive M2 macrophages ↑ CD31 ↑ Ki-67-positive proliferating cells ↑	2021	[71]
Gingival MSCs	Alginate, gelatin	Full-thickness wound/ male and female C57BL/6 mice	Original wound area ↓ TNF-α ↓ IL-10 ↑ CD31 ↑	2021	[72]
Adipose-derived MSCs	Collagen, alginate	Full-thickness burns/ male rats	Number of neutrophils ↓ Neovascularization ↑ Collagen deposition ↑	2021	[73]
Adipose-derived MSCs	Gelatin, poly(n-isopropyl acrylamide)	Ear full-thickness model/ Albino rabbits	Residual wound area ↓ Epithelium thickness ↑ Collagen density ↑ CD31 ↑	2020	[74]
Buccal fat pad-derived MSCs	Chitosan, polyvinyl alcohol, Carbopol, polycaprolactone, curcumin	Full-thickness wound/ male mice	Wound healing rate ↑	2020	[75]
Bone marrow derived MSCs	Collagen, tussah silk fibroin	Full-thickness wound/ Sprague Dawley rats	Re-epithelialisation ↑ α-SMA ↑	2020	[50]
Bone marrow derived MSCs	Poly(ε-caprolactone), pluronic-F-127	Diabetic full-thickness/ Male TALLYHO type 2 diabetic mice	Collagen deposition ↑ Newly formed blood vessels and CD31 ↑ Re-epithelialisation ↑ CD206 M2 macrophages ↑ CCR7 M1 macrophages ↑ IL-6 and TNF-α ↓ IL-4 and IL-10 ↑	2020	[76]
Bone marrow MSCs	N-carboxyethyl chitosan, adipic acid dihydrazide, hyaluronic acid-aldehyde	Diabetic foot wound/ male Sprague Dawley rats	Residual wound area ↓ TGF-β1, VEGF, and bFGF ↑ Inflammatory cell ↓ Neovascularization ↑ Ki67 ↑ CD86 positive cells ↓ CD163 positive cells ↑ Sebaceous glands and Hair follicles ↑	2020	[55]
Human umbilical cord MSCs	Chitosan, glycerol phosphate sodium, cellulose	Specific-pathogen-free-class Sprague Dawley rats	Wound closure rate ↑ TNF-α and IL-1β ↓ Collagen deposition ↑ K1 ↑	2019	[77]
Adipose-derived MSCs	Polycaprolactone, fibrinogen, acellular dermal matrix, collagen	Full-thickness wound/ Wistar rats	Wound closure rate ↑ Re-epithelialisation ↑ Collagen density ↑ CD31 ↑	2019	[78]

Table 1 (continued)

Type of MSCs	Main component	Types of wound/ study model	Highlighted results	Year	Ref.
Bone marrow MSCs	Graphene oxide, L-(+)-Ascorbic acid, L-tryptophan, Acellular dermal matrix	Full-thickness skin wound/ diabetic Male ICR mice	Wound closure rate ↑ Granulation tissue ↑ Regenerated collagen ↑ VEGF and α-SMA ↑ TGF-β ↑ Number of neovascular and vessel diameter ↑	2019	[79]
Bone marrow MSCs	N-Isopropylacrylamide, hyperbranched poly (amidoamine)	Full-thickness skin wound/ specific-pathogen-free-class C57 mice	Wound closure rate ↑ Re-epithelialisation ↑ α-SMA ↑ BrdU, Keratin 6 and K1 ↑ Collagen deposition ↑ FGF and TGF-β1 ↑	2018	[80]
Bone marrow MSCs	Unsaturated arginine-based poly(ester amide), chitosan derivative	Third-degree burn wounds/ female C57BL/6 J mice	Wound closure rate ↑ Re-epithelialisation ↑ Granulation tissue ↑ CD31 ↑ IL10 and CD206 ↑ TNF-α and iNOS ↑	2018	[81]

human umbilical cord-MSCs, which showed potency to increase CD31, α-SMA, and VEGF for diabetic wounds [4]. Also, sodium alginate/gelatin hydrogels loaded with adipose-derived MSCs demonstrated high potential for promoting PDGF, VEGF, and EGF, which can affect angiogenesis. Immunohistochemical staining was also shown that CD31 was enhanced on day 14 in diabetic wounds [52]. In a study by Liu et al., an Adipose-derived MSC-loaded β-chitin nanofiber hydrogel was developed. The study showed that the expressions of TGF-β1, P-smad3, P-smad2, and TIMP1 in the ADSCs+hydrogel treatment were more elevated than those of the ADSCs treatment. The examinations eventually indicated that ADSC-loaded β-ChNF hydrogel and ADSCs can regulate the TGFβ/smad signaling pathway to facilitate neoangiogenesis [69].

Tissue remodeling

Primary components of the dermal ECM are type I and III collagens, which play a crucial role in wound healing. Hence, polypeptide-based FHE hydrogel containing adipose-derived MSC exosomes could promote type I and III collagen levels in the wound [93]. Proliferating cell nuclear antigen (PCNA) can also indicate cell proliferation status. PCNA and Ki67 were raised when extracellular matrix hydrogel@exosomes accelerated diabetic wound healing [85]. MSC spheroids induced by Biotin-DFYIGSR hydrogel could promote the density of Krt 5 (basal keratinocyte marker cytokeratin 5). Also, Krt 10 (spinous keratinocyte marker cytokeratin 10) staining demonstrated that mature spinous layers only reproduced in this 3D culture group [66].

Overall, collagen deposition, re-epithelialisation, epidermal proliferation, dermis thickness, granulation tissue, and scar width were the most frequently analyzed areas, as shown in Tables 1 and 2.

Hemocompatibility

An ideal hydrogel-based hemostatic system should stop bleeding quickly, have adequate adhesion to wet tissues, have mechanical power to preserve blood pressure and have a hemolysis rate ≤ 5% [95]. Geng et al. revealed that when creating a rat liver haemorrhage model, MSC-Exos@CEC-DCMC HG attached to the bleeding zone repressed the bleeding blood and shrank the bleeding time, demonstrating that MSC-Exos@CEC-DCMC HG exhibited outstanding haemostatic effects. The overall amount of blood lost was significantly less than that of the control group [87]. Also, in the study of Prakashan et al., the nanofiber+BMSCs group exhibited decreased haemorrhage compared to the BMSCs and nanofiber groups [61].

Antioxidant

ROS are vital in facilitating the normal wound healing process. Maintaining the proper equilibrium between low and high ROS levels is crucial. Potential new treatments focus on developing antioxidant dressings that can help control this balance [96]. When the wound is formed, vasoconstriction and the blood coagulation cascade occur, both facilitated by ROS. While a physiological amount of ROS is helpful for wound healing, excessive production of these molecules can hinder the normal wound healing process [97]. Excessive ROS in the wound microenvironment impairs endothelial function and inhibits neovascularization [66].

In a study by Shi et al., the ROS level in high-glucose-exposed bone marrow-derived macrophages after using CG-OHA or CG-OHA@Exo hydrogels was considerably

Table 2 The studies used various MSC-derived exosome-laden scaffolds for wound healing

Source of Exosome	Exosome size (nm)	Main component of scaffold	Types of wound/ study model	Highlighted results	Year	Ref.
Adipose-derived MSCs	~100	Chitosan, β-sodium glycerophosphate	Full thickness/ male Sprague-Dawley rats	Wound closure rate ↑ Hair-covered area ratio ↑ Collagen deposition rate ↑ CD31 ↑	2024	[43]
Hypoxic bone marrow MSCs	~50–150 (with a peak at 141)	Gallic acid, chitosan, oxidized hyaluronic acid	Full-thickness diabetic wound / male db/db diabetic mice	Wound closure rate ↑ Thickness of epidermal and dermal ↑ Collagen deposition ↑	2024	[41]
Human umbilical cord MSCs	~100–120	Gallium, chitosan, silk	Diabetic full thickness skin defect/ male Sprague-Dawley rats	Wound closure rate ↑ Rate of re-epithelialization ↑ Collagen deposition ↑ IL-6 and TNF-α ↓	2024	[82]
Adipose MSCs	~50–120	Type I collagen, platelet-rich plasma	Full-thickness skin wound/ male BALB/c mice	Wound healing rate ↑ TNF-α and IL6 ↓ CD80/F4/80 + M1 macrophages ↓ VEGF and VE-cadherin ↑ α-SMA and CD31 ↑	2023	[42]
Adipose MSCs	~80	Amniotic membrane	Diabetic full-thickness skin wound/ male Wistar rats	Wound closure rate ↑ Formation of epidermis and dermis ↑ Collagen density ↑ TGF-β, bFGF, and VEGF ↑ IL-1β and TNF-α ↓ M1 macrophages ↓	2023	[83]
Umbilical cord MSCs	~126	Gelatin methacryloyl hydrogel	laser-injured skin wound / Male BALB/c mice	Wound closure rate ↑ KI67 ↑ VEGF ↑ CD31 ↑ Epidermal thickness ↑ Fibroblast ↑ Collagen density ↑ Inflammatory cell ↓	2023	[84]
Adipose MSCs	~108	ECM hydrogel from porcine left ventricular myocardium	Full-thickness cutaneous wound/ BALB/c mice	Wound closure rate ↑ Collagen density ↑ Granulation tissue ↑ Hair follicles ↑ Ki67 ↑ PCNA ↑ CD31 ↑ TNF-α & IL-6 ↓	2023	[85]
			Diabetic full-thickness skin wound / Diabetic ICR mice	Wound closure rate ↑ Collagen density ↑ Granulation tissue ↑ Ki67 ↑ PCNA ↑ CD31 ↑ TNF-α & IL-6 ↓		
Human adipose-derived MSCs	~30–100	PF-127 hydrogel	Full-thickness wound/ male ICR mice	Ki67 positive cells ↑ α-SMA and CD31 ↑ Wound closure rate ↑ collagen I and collagen III ↑ KRT1 ↓ AQP3 ↑ TNF-α and IL-6 ↓ CD68 ↓ CD206 ↑	2022	[86]

Table 2 (continued)

Source of Exosome	Exosome size (nm)	Main component of scaffold	Types of wound/ study model	Highlighted results	Year	Ref.
Bone marrow MSCs	~50–150	Carboxyethyl chitosan, dialdehyde carboxymethyl cellulose	Diabetic wound/ Sprague-Dawley rats	Wound closure rate ↑ Collagen deposition ↑ INOS ↓ CD206 ↑ IL-6 and IL-1β ↓ CD31 ↑ Bleeding blood ↓	2022	[87]
Adipose MSCs	-	β-chitin	Full-thickness cutaneous wounds / Male Sprague-Dawley rats	Wound closure rate ↑ Re-epithelialization ↑ Collagen deposition ↑ Aldoa ↑ Actn2 ↑	2022	[88]
Mouse bone marrow MSCs	~76.7 ± 25.4	Polycaprolactone, polyethylenimine	Full-thickness skin wounds /female Balb/c mice	Wound closure rate ↑ IL-4, IL-10, and IL-13 ↑ TNF-α and IFN-γ ↓ α-SMA ↑	2021	[89]
Human umbilical cord MSCs	~60.1 ± 4.7	Poloxamer 407, carboxymethyl chitosan	Full-thickness dermal defects/ Female Sprague-Dawley rats	Wound closure rate ↑ Granulation tissue and epidermis-like cell arrangement ↑ Collagen deposition ↑ IL-1β and TNF-α ↓	2021	[90]
Human umbilical cord MSCs	~47.3	Silk fibroin, silk sericin	Full-thickness wound/ C57BL/6J mice	Wound closure rate ↑ Angiogenesis ↑ TNF-α ↓ $CD68^+$ cells ↓	2021	[91]
BMSC	~50–150 nm	Small intestinal submucosa, mesoporous bioactive glass	Diabetic full-thickness dorsal cutaneous wound / Sprague-Dawley rat	Wound closure rate ↑ Re-epithelialization ↑ Collagen deposition ↑ CD31 ↑ VEGF ↑ α-SMA ↑	2021	[38]
Umbilical cord-derived MSCs	~30–150	Pluronic F-127	Diabetic full-thickness skin wound/ Male Sprague-Dawley rats	Wound closure rate ↑ New hair follicle formation ↑ Collagen deposition ↑ CD31 ↑ Ki67 ↑ VEGF and TGFβ-1 ↑	2020	[92]
Placental MSCs	~62.5	Methylcellulose, chitosan	Diabetic full-thickness skin defect/ male C57BLKS-Leprdb mice	Wound closure rate ↑ Tissue thickness ↑ Fibroblasts ↑ Collagen deposition ↑ VEGF ↑	2020	[57]
Adipose MSCs	~60–80	Pluronic F-127,Oxidized hyaluronic acid-Poly-ε-L-lysine	Diabetic full-thickness wounds/-	Wound closure rate ↑ Collagen deposition ↑ α-SMA ↑ Ki67 ↑ Re-epithelization ↑ Scar tissue ↓ Granulation tissue ↑	2019	[93]

lower than in the control and exo groups. There is no notable discrepancy in ROS levels between the CG-OHA and CG-OHA@Exo groups, demonstrating that the hyBMSC-Exos has a negligible influence on CG-OHA hydrogel's antioxidant activity [41]. Also, MSC spheroid formation generated by the Biotin-^{D}FYIGSR hydrogel can eliminate and scavenge ROS in HUVECs and RAW264.7 cells, as well as in diabetic wounds [66]. Jiao et al. designed a combination therapy for diabetic wound healing using Wharton's jelly MSCs embedded in PF-127 hydrogel plus sodium ascorbyl phosphate. To investigate the role of mitochondria in the WJMSCs embedded in PF-127, oxidative stress and mitochondrial injury were analyzed employing the CM-H2DCFDA fluorescence experiment. The percentage of SOD-positive cells in the WJMSCs+PF-127 group was much higher than in the

WJMSCs group. Subsequently, with SAP supplementation, the percentage pointedly declined [71].

Antibacterial

The antimicrobial properties of MSCs have been demonstrated recently via both direct and indirect pathways. They enhance the elimination of bacteria by activating the host's natural immune cells (indirect) and releasing antimicrobial peptides (AMPs) (direct). These cells also can enhance antibiotic sensitivity [68]. However, due to the antibacterial properties in some biomimetic scaffolds, an increase in antibacterial activity has been seen in the combination of scaffolds and cells. For example, collagen-fibrin scaffolds containing AD-MSCs and BM-MSCs demonstrated substantial potential in treating infected burn wounds caused by *Pseudomonas aeruginosa* [68]. Shi et al. measured the inhibition zone and found that the gallium/chitosan/silk scaffold and gallium/chitosan/silk/exosome scaffold exhibited significant antibacterial ability against S. aureus and E. coli compared to the control group. However, no significant difference existed between a scaffold containing exosomes and a scaffold without exosomes. The SEM image demonstrated damage and collapse on both bacteria's surfaces [82]. Another study revealed that bone marrow MSCs-derived exosome-loaded carboxyethyl chitosan-dialdehyde carboxymethyl cellulose hydrogel has heightened antibacterial impacts by notably hindering bacterial growth in comparison to untreated diabetic wounds on the 10th day [87].

Future prospective

The studies' results related to this review's topic were promising, but here are some suggestions that will help increase our insights into the effects of these scaffolds loaded with MSCs or their exosomes in wound healing. For example, these biomimetic scaffolds can be used for co-delivery purposes, combining a cell with a drug, an exosome with a drug, or a cell with an exosome simultaneously, which may increase the wound healing potential. Employing pre-conditioned MSCs with drugs or metabolites that transform their phenotype to anti-inflammatory and immunomodulatory may be helpful for combining in the biomimetics scaffolds for wound healing. Exosomes derived from these pre-conditioned MSCs may be beneficial for such therapy. Another aspect to consider when using these scaffolds is their hemocompatibility. Hence, clot formation is essential for wound healing, so it is better to analyze clot tests. Few studies have evaluated the potential for clotting and coagulation of MSCs-loaded or exosome-loaded scaffolds, and future studies are strongly recommended to investigate this property. Tests that show the anti-hemolysis of these scaffolds are also necessary. Since immune cells such as Treg, $CD8^+$, Th17, Th1, mast cells, and Langerhans cells play roles in wound healing, future studies should evaluate the effect of MSCS-loaded or exosome-loaded scaffolds on these cells. Another aspect to consider when using these scaffolds is their impact on neuropathy, which is closely associated with impaired wound healing in diabetes.

Conclusion

This review has comprehensively investigated using of four porous, nanofibrous, hydrogel, and 3D-printed scaffolds to load MSCs or MSC-derived exosomes for wound healing. The outcomes demonstrated that these scaffolds effectively increase the retention time of MSCs or increase the stability of MSC-derived exosomes in the wound area. Also, these scaffolds, having suitable properties such as anti-inflammatory, antioxidant, and antibacterial, improve wound healing with the help of synergism with MSCs or MSC-derived exosomes. These scaffolds provide an optimal environment for MSCs or MSC-derived exosomes to exert their regenerative effects, such as angiogenesis. Overall, the combined treatments have yielded promising results, offering dressings that overcome the limitations of conventional dressings and demonstrate the necessary efficiency for wound healing.

Abbreviations

MSCs	Mesenchymal stem cells
PDGF	Platelet-derived growth factor
ECM	Extracellular matrix
IL	Interleukin
TNF-α	Tumor necrosis factorα
TGF	Transforming growth factor
EGF	Epidermal growth factor
VEGF	Vascular endothelial growth factor
DAMPs	Damage-associated molecular patterns
ROS	Reactive oxygen species
PAD4	Peptidylarginine deaminase 4
NK cells	Natural killer cells
KGF	Keratinocyte growth factor
TGF-α	Transforming growth factor-α
TGF-β	Transforming growth factor-β
MMPs	Matrix metalloproteinases
ANGPT1	Angiopoietin-1
bFGF	Basic-fibroblast growth factor
IGF-1	Insulin-like growth factor-1
WVTR	Water vapor transmission rate
FE-SEM	Field emission scanning electron microscopy
DFUs	Diabetic foot ulcers
ELISA	Enzyme-linked immunosorbent assay
PCNA	Proliferating cell nuclear antigen
Krt 5	Basal keratinocyte marker cytokeratin 5
Krt 10	Spinous keratinocyte marker cytokeratin 10
AMPs	Antimicrobial peptides
NETs	Neutrophil extracellular traps

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