Supporting wound healing by mesenchymal stem cells (MSCs) therapy in combination with scaffold, hydrogel, and matrix; State of the art

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Submission date: 07-Jun-2023 08:59PM (UTC+0800)
Submission ID: 2111022879
File name: 001-1-s2.0-S0344033823002753-main_1.pdf (1.76M)
Word count: 10122
Character count: 57604

Pathology - Research and Practice 248 (2023) 154575

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

Supporting wound healing by mesenchymal stem cells (MSCs) therapy in combination with scaffold, hydrogel, and matrix; State of the art

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ARTICLE INFO

Keywords:
Mesenchymal stem cells (MSCs)
Wound healing
Scaffold
Matrix
Hydrogel
Cell therapy

ABSTRACT

Non-healing wounds impose a huge annual cost on the survival of different countries and large populations in the world. Wound healing is a complex and multi-step process, the speed and quality of which can be changed by various factors. To promote wound healing, compounds such as platelet-rich plasma, growth factors, platelet lysate, scaffolds, matrix, hydrogel, and cell therapy, in particular, with mesenchymal stem cells (MSCs) are suggested. Nowadays, the use of MSCs has attracted a lot of attention. These cells can induce their effect by direct effect and secretion of exosomes. On the other hand, scaffolds, matrix, and hydrogels provide suitable conditions for wound healing and the growth, proliferation, differentiation, and secretion of cells. In addition to generating suitable conditions for wound healing, the combination of biomaterials and MSCs increases the function of these cells at the site of injury by favoring their survival, proliferation, differentiation, and paracrine activity. In addition, other compounds such as glycol, sodium alginate/collagen hydrogel, chitosan, peptide, timolol, and poly(vinyl) alcohol can be used along with these treatments to increase the effectiveness of treatments in wound healing. In this review article, we take a glimpse into the merging scaffolds, hydrogels, and matrix application with MSCs therapy to favor wound healing.

1. Introduction

Non-healing wounds affect a large population in the world annually and impose very heavy costs on the treatment system [1,2]. Wound healing is a complex and multi-step process, which, creating changes at any stage can make the wound healing longer or shorter and the amount

Abbreviations: ADM, Acellular dermal matrix; ADSC, Adipose-derived stem cells; ECM, Extracellular matrix; EGF, Epidermal growth factor; EPSCs, Epidermal stem cells; FGF, Fibroblast growth factor; FOXP3, Forkhead box P3; GVHD, Graft versus host disease; HA-CA, Catechol-modified hyaluronic acid; HLA, Human leukocyte antigen; IFN, Interferons; IL, Interleukin; KGF, Keratinocyte growth factor; MIP-1α, Macrophage inflammatory protein-1 alpha; MSCs, Mesenchymal stem cells; NK, Natural killer; NF-κB, Nuclear factor kappaB; PDGF, Platelet-derived growth factor; PGE2, Prostaglandin E2; TNF, Tumor necrosis factor.

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https://doi.org/10.1016/j.prp.2023.154575
Received 27 April 2023; Received in revised form 24 May 2023; Accepted 25 May 2023
Available online 26 May 2023

of scar remains from the wound [1,2]. Failure to heal the wound and the remaining scar from the wound can cause a lot of problems for the patient and cause mental illness and a lack of confidence for the patient [1]. Various methods are used in the treatment of wounds, and each of these methods has advantages and disadvantages and only some of them have enough effectiveness [3–5]. The different dressing is used to create a suitable environment for wound healing. These dry dressings can delay the healing of the wound and cause necrosis. The use of scaffolds, hydrogels, and cell-matrix because of their properties is capable of promoting wound healing in patients. The structure of these compounds can be changed according to the need and is suitable for wound healing and regeneration and cell growth, proliferation, differentiation, and migration [6–8]. In addition, to enhance function and efficiency, these compounds can also be combined with substances such as polyethylene glycol, sodium alginate/collagen hydrogel, chitosan, peptide, timolol, and poly (vinyl) alcohol (PVA) [9–14].

Nowadays, the use of stem cells in the treatment of wounds and regenerative medicine has been considered. Mesenchymal stem cells (MSCs) are separated from different sources and can enhance wound healing and reduce scarring with the properties of immunomodulation and secretion of exosomes and vesicles [2,15]. The wound environment can interfere with the growth, proliferation, and survival of stem cells [6,16]. Therefore, to increase survival and to create the appropriate conditions for the growth, reproduction, and differentiation of these cells, Scaffolds, hydrogels, and various compounds are used [16,17]. According to their structure, these compounds can provide a suitable environment for the survival and growth of cells and increase the function, efficiency, secretion of compounds, and migration of MSCs. The combination of MSCs with scaffold, hydrogel, and matrix along with other compounds can increase the performance of MSCs [9,11,18]. On the other hand, biomaterials with a direct effect on the wound environment can promote wound healing [6,16,17]. In this study, we intend to investigate the effect of using scaffolds, hydrogels, and matrix along with MSCs in wound healing.

2. Wound healing

When a wound occurs in the body, a complex and multi-step process begins to repair this wound. Wound healing takes time and various conditions can change the healing process and speed of wound healing. If the conditions created for wound healing are suitable, it can shorten the healing time and reduce the amount of scarring and if the wound healing conditions are not suitable, it can make the wound healing time longer and the wound scar more. Factors causing inflammation at the injury site such as malignancy, old age, smoking, infections, oxidative stress factors, and some drugs are among the factors that prolong wound healing [19–22]. Among the factors that promote wound healing, we can mention the reduction of inflammation, an increase in growth factor, and a proper environment for the growth, proliferation, differentiation, and migration of cells to the injury site. Among the compounds that provide these conditions for cells and wounds, we can mention platelet-rich plasma, platelet lysate, autologous conditioned serum, scaffolds, hydrogels, matrix, cell therapy with various types of cells, especially MSCs [6,16,17,23–26]. Wound healing has three stages: Hemostasis and Inflammation, Proliferative Phase, and Maturation and Remodeling, and the mentioned compounds and cells accelerate these stages by creating suitable conditions.

2.1. Inflammatory phase

After creating a wound, the body reacts quickly and wound healing enters the inflammatory phase, which takes between 4 and 6 days. In this phase, first hemostasis and then inflammation occurs. In hemostasis, platelets come to the injured site and the coagulation cascade is activated. Various compounds such as fibrin, thrombin, growth factors, and cytokines are released at this stage [27]. Then the inflammation starts, which causes the destruction of bacteria and prevents infection when neutrophils enter the injury site. Monocytes and macrophages play an important role in the injury site and play a role in the transition from the inflammatory phase to the proliferative phase. Different types of growth factors and cytokines including epidermal growth factor (EGF), fibroblast growth factor (FGF), interferons (IFN), interleukin (IL), keratinocyte growth factor (KGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), thromboxane A2 (TXA2), and tumor necrosis factor (TNF) are released at the site of damage from platelet cells, endothelial cells, macrophages, lymphocytes, mast cells, keratinocytes, and fibroblasts. These compounds play a very important role in wound healing [28].

2.2. Proliferative phase

After passing through the inflammatory phase, the wound-healing process enters the proliferative phase. This phase occurs 4–14 days after creating a wound and encloses the stages of epithelialization, angiogenesis, granulation tissue formation, and collagen deposition. Epithelialization occurs with the migration and proliferation of epithelial progenitor cells to the injury site. Then angiogenesis occurs by endothelial cells and capillaries. Finally, with granulation and tissue deposition, a barrier is formed to prevent fluid leakage and infection. This phase is also highly dependent on cell secretions and a suitable environment for wound healing, which MSCs and bioactive materials can improve these conditions to a great extent [15,29,30].

2.3. Maturation and remodeling phase

From the 8th day, the wound enters the Maturation and Remodeling phase and it can last up to a year after the wound. This step is very important in wound healing, and if it is not done well, the wound will not have the necessary strength and integrity. Collagen deposition occurs at this stage, although if this is done more than usual, it can cause scarring and keloid in the injured area [19,28].

The mentioned steps for wound healing are not simple and it is a complex process that can have many changes according to conditions and factors. The treatments are used to accelerate and increase the quality of the wound-healing process. MSCs change these stages with their secretions, and scaffolds, hydrogels, and cell-matrix create suitable conditions, by improving the proliferation, differentiation, homing, and secretion of MSCs, they create moisture and suitable conditions to accelerate and improve wound healing stages. The use of compounds such as polyethylene glycol (PEG), sodium alginate/collagen hydrogel, chitosan, peptide, timolol, and PVA [9–14]. Along with the mentioned items can create a more appropriate combined treatment in wound healing.

3. Mesenchymal stem cells (MSCs)

MSCs are multipotent cells that can regenerate tissue in vitro and in vivo. Studies have shown the efficiency of these cells in the regeneration of different tissues such as the heart, bone, nervous system, and skin [31]. MSCs can be used systemically and locally. If used systematically, these cells can migrate to the desired location, although studies have shown that only a small number of these cells reach the desired location and a large part of them accumulates in the kidney and lung [32,33]. On the other hand, if these cells are used as a local injection, a large number of them remain in place and only a small amount of these cells enter the bloodstream [33,34]. Different biomaterials such as scaffolds, hydrogel, and matrix can be used to increase the survival of cells at the site of injury as well as to increase the growth, proliferation, and survival of cells. In studies, fibrin spray has been utilized to repair skin wounds, and scaffolds have been used to treat ischemia of heart tissue and diabetic wounds [35–38]. MSCs cells can promote wound healing and tissue regeneration by releasing growth factors and cytokines [39]. MSCs by

modulating the regeneration environment can cause changes in wound healing stages and effective factors in this process such as tissue remodeling, immunomodulation, angiogenesis, and cell homing [40]. Therefore, instead of skin grafting, these cells can be used to promote wound healing and regeneration. MSCs can be isolated from different tissues such as bone marrow, adipose tissue, Wharton jelly, umbilical cord blood, and peripheral blood, and used for regeneration, although cells isolated from each tissue have advantages and disadvantages [41,42]. Cells isolated from adipose tissue do not change with the age of the donor, they can be used autonomously in elderly people, there are a large number of these cells in a small volume of adipose tissue, and it does not cause an immune reaction, and does not cause graft versus host disease (GvHD). Immaturity of isolated cells and no need for human leukocyte antigen (HLA) compatibility are the advantages of using stem cells with cord blood and Wharton's jelly and the small number of isolated cells and the need for cell culture to increase the number of these cells with the risk of causing changes in the cells are the disadvantages of MSCs with these sources [43]. MSCs derived from bone marrow are another widely used source. Ease of isolation and a large number of cells are the advantages of MSCs isolated from bone marrow and the maturity of the isolated cells and the possibility of causing GvHD is its disadvantage [41,43]. Although, mesenchymal stem cells isolated from adipose tissue source show higher immunomodulatory ability than stem cells isolated from bone marrow [44]. The immunomodulatory property of MSCs is related to the direct contact with the target cell and the secretion of various factors in a paracrine manner [45].

In vitro studies have shown that MSCs co-culture with activated lymphocytes can induce IL17-expressing lymphocytes, and co-culture of these cells with CD4 + lymphocytes can increase the expression of Notch1/forkhead box P3 (FOXP3) pathway and increase the percentage of CD4 cells. +CD25 FOXP3+ [46,47]. On the other hand, MSCs play a role in the activity of nuclear factor kappaB (NF-κB) by expressing Toll-like receptors (TLRs) 3 and 4 and can contribute to the response of T cells in cellular infections [48]. Human placenta MSCs (PMSCs) by expressing a high amount of programmed-death ligand 1 (PD-L1) and PD-L2 inhibit the proliferation of T cells and inhibit the cell cycle [49]. MSCs can inhibit natural killer (NK) cells. By increasing IL-12/IL-18-stimulated NK, MSCs increase IFN-γ from these cells and thus increase defense against infections at the site of injury and wound and increase tissue repair [50,51]. Compounds secreted from MSCs such as IL-6 inhibit the differentiation of monocytes towards the anti-inflammatory phenotype, and the production of prostaglandin E2 (PGE2) from MSCs causes the differentiation of monocytes into dendritic cells [52,53]. MSCs by secreting IL-10, IL-1β, IL-12, and Macrophage inflammatory protein-1 alpha (MIP-1α) as well as glucocorticoid and progesterone receptors and downregulation of IL-23 and IL-22 cause the differentiation of inflammatory macrophages M1 to anti-inflammatory macrophages M2 [54,55]. By reducing the possibility of infection and increasing the anti-inflammatory properties of the immune system, all the mentioned cases can create the conditions for wound healing and tissue repair [28,45]. Increasing angiogenesis is one of the other mechanisms that play a role in the effectiveness of MSCs in wound healing [56,57]. Studies have shown that MSCs can increase angiogenesis and increase the proliferation of epidermal stem cells (EPSCs) by increasing the expression of VEGF, p-STAT3, and SDF-1, as well as modulating the Notch signaling pathway, and thus promote better wound healing [56,57]. Various studies have used MSCs along with scaffold, hydrogel, and matrix for dermal regeneration. The results of these studies have shown an increase in the survival and function of seeded cells in biomaterial compounds at the wound site [16].

4. Combination therapy with biomaterials and MSCs

Using dry dressings can dehydrate the wound environment and cause necrosis, as a result, the compounds used should have softness, moisture, and proper absorption to be able to create a suitable microenvironment for tissue repair at the site of injury, a suitable environment for cells and release effective compounds in wound healing and prevent microbial contamination and infection in the injured area [58]. The advantages of using biomaterials are listed in Table 1. Recently, several compounds are used for better wound healing and increasing the function of cells used in wound healing. The compounds used are bioabsorbable and non-bioabsorbable and these compounds are used with or without cells at the site of injury [5,58]. Among the compounds used, we can refer to polyethylene glycol, sodium alginate/collagen hydrogel, chitosan, peptide, timolol, and PVA [9–14]. These compounds together with MSCs increase the proliferation, migration, and differentiation of MSCs and promote wound healing. The method of using and functioning of MSCs and biomaterials is shown in Fig. 1.

4.1. Scaffold

Various biosynthetic scaffolds have been used to improve wound healing. These scaffolds have been used together with cells or alone for wound healing. Various studies have suggested the use of seeded cells along with scaffolds. The combination of these scaffolds with MSCs has shown a suitable effect on wound healing [16,24]. Used scaffolds can support wound healing and also provide repair conditions for used cells [16].

Silk fibril is a natural protein that is effective among other scaffolds and has many advantages such as low immunogenicity, non-toxicity, its similarity to natural extracellular matrix (ECM) due to its morphology and architecture and dynamic changes during the destruction of nanofibrils, it is a suitable compound for the proliferation and production of ECM in seeded cells [24,59]. Studies have shown that the use of scaffolds with pores of 20–125 micrometers can support skin regeneration, proliferation, adhesion, differentiation, and cell migration [17,60,61]. Millán-Rivero et al. [62] study showed that the use of Silk fibroin scaffolds along with Wharton jelly MSCs can be effective in the formation of dermis fibroblasts, neuroxemia, reduction of inflammation and regeneration of inflammation in the wound site.

The study by Wahl et al. [16] used different types of scaffolds to improve the performance of MSCs in vitro. The use of scaffolds was able to cause attachment, survival, seeding efficiency, metabolic activity, cellular distribution, paracrine release, and better angiogenesis at the injury site. To increase the efficiency of scaffolds, synthetic compounds such as sodium carboxymethylcellulose are used, which show sufficient protection for skin wound healing in Thickens burn wounds [63].

Sodium carboxymethylcellulose is a synthetic compound that is formed from the hydration of cellulose with sodium hydroxide and from

Table 1
Advantages of using matrix, scaffold, and hydrogel.

Biomimetic environment for cells
Creating a suitable environment for the growth and proliferation of cells
Helping the migration of cells and the survival of more cells at the site of injury
Increase secretion of cellular compounds
Can be used with different types of cells
Structural features
Having elasticity and stiffness similar to skin
Making structural changes appropriate to the wound and the wound environment
Creating changes in biological, chemical, and stiffness conditions
Simultaneous use with other compounds to increase performance
Wound regeneration
Creating a suitable environment for wound healing
Creating a suitable cover for the bottom surface
Maintaining the humidity of the environment and preventing the formation of tissue necrosis
Preventing wound contraction and creating hypertrophic scars
Immunogenicity
Use without inflammatory responses
Reducing the inflammation in the wound environment
Stability and durability
Possibility of one-time use and no need for continuous replacement

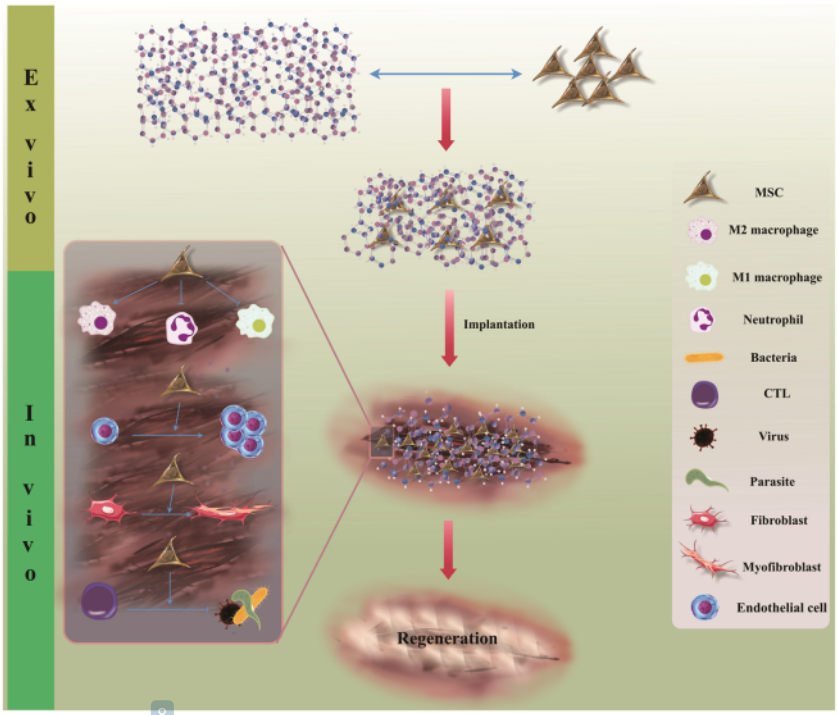

Fig. 1. Method of using and functioning of mesenchymal stem cells (MSCs) and biomaterials. Mesenchymal stem cells in combination with biomaterials can be used at the site of injury to elicit more favored outcome. Biomaterials provide conditions for wound healing by creating suitable conditions for cell growth, proliferation, and differentiation.

an alkaline pulp-catalyzed reaction with chloroacetic acid. In addition to protecting external bacteria in the wound, this compound has a very suitable ability to absorb and transfer liquids. However, the toxic effects of this compound on the body are still not well known [11]. In a study, Rodrigues et al. [11] investigated the efficacy of combining adipose-derived stem cells (ADSCs) with sodium carboxymethylcellulose scaffold in a mouse wound model. The results of this study showed that the combination of sodium carboxymethylcellulose with MSCs has no effect on membrane viability and can have genotoxicity in high doses. This combination has increased cell proliferation, epithelium thickness,

Table 2
Studies conducted on the combined treatments of mesenchymal stem cells (MSCs) and scaffold in wound healing.

Type of wound	Cell source	Animal	Type of study	Material used	Outcome	Ref.
Full thickness wound	Human A-MSCs	Mouse	In vivo	Silk fibroin scaffold	Maintaining MSCs adherence, proliferation, and differentiation Decreasing wound area and improving tissue regeneration Increasing angiogenesis gene expression	[24]
Full thickness wound	Rat A-MSCs	Rat	In vivo	Sodium carboxymethylcellulose scaffold	Increasing the rate of cell proliferation Increasing the tissue granulation and epithelium thickness	[11]
Diabetic wound	Mice BM-MSCs	Diabetic mice	In vivo	3D scaffold	Enhancing the formation of granulation tissue, Promoting angiogenesis, and facilitating collagen deposition Decreasing M1-type macrophage formation and expression of pro-inflammatory cytokines (IL-6 and TNF-α) Promoting M2-type macrophage and anti-inflammatory cytokines (IL-4 and IL-10)	[118]
-	Human Adipose MSCs	-	In vivo	BioPiel (chitosan film), Smart Matrix (fibrin matrix), Integra DRT (collagenglycosamin glycan matrix), and Strattice (decellularized dermis)	Increasing cellular distribution, attachment, survival, metabolic activity, and paracrine release	[16]
Full-thicknessWound	Human Wj-MSCs	Mouse	In vivo	Silk fibroin scaffolds	Yielding neoangiogenesis Decreasing Inflammatory cell infiltration Increasing myofibroblast proliferation Facilitating epidermal regeneration	[62]

and tissue granulation, although, it did not affect collagen fiber and wound closure. This study showed that this compound can be used in lower concentrations as a safe compound for MSCs in wound healing. decellularized scaffold can be a suitable combination in wound healing due to its ability to mimic ECM. Navone et al. [24] used decellularized silk fibril scaffold combination with MSCs in wound healing and showed that this combination can increase cell growth, proliferation, and adhesion and improve wound healing. The studies conducted on scaffolds and the results of these studies are summarized in Table 2.

4.2. Hydrogel

In recent years, the use of hydrogels has gained attention due to their easy use, ability to encapsulate and seed cells in it, non-invasiveness, adaptability to the patient's body, ability to change shape, and easy molding [64–66]. Hydrogel compounds such as alginate, collagen, hyaluronic acid, chitosan, and gelatin are natural or synthetically prepared such as poly (ethylene glycol), poly (lactide-co-glycolide) polyacrylamide. Each of these compounds has advantages and disadvantages. Natural compounds have properties similar to ECM and are routinely used in regenerative medicine and tissue engineering. Although, these compounds have disadvantages such as the high cost of preparation, the heterogeneity of the structure, and the instability of these compounds. Synthetic hydrogels have both advantages and disadvantages. Among the advantages, their tenability, reproducibility, and the ability to design for specific purposes are the advantages of synthetic hydrogels and its toxicity for the host's body, the non-biological nature of the compounds, the insufficient mechanical properties, and less similarity to ECM are its disadvantages. Hydrogels can play a role in increasing cell growth, bone formation, and vascular anastomosis, and can be used to encapsulate cells and drug carriers [67, 68]. The studies conducted on hydrogel and the results of these studies are summarized in Table 3.

4.2.1. Fibrin

Fibrin is a compound that is naturally used as a scaffold for endothelial cells and leukocytes in tissue regeneration [69,70]. The use of fibrin has been able to solve the problems of infection in the injured area to some extent [71]. The advantages of fibrin are the possibility of designing and adjusting bulk stiffness gel, its degradability, and porosity for the proliferation and secretion of MSCs [72–75]. Compared to collagen which is found in mature tissues, fibrin gel can stimulate the release of repair factors and extracellular matrix to stimulate tissue repair [76].

The use of fibrin with its advantages has been able to solve some of the problems of dry dressings and prevent infection. In addition, with the changes that have been made in fibrin hydrogels, its use has been made easier and its properties have been improved. However, fibrin hydrogels still have problems such as relatively rapid shrinkage, low mechanical stiffness (which limits durability), and rapid degradation after placement in the wound site. To reduce these problems, fibrin hydrogels can be used with other compounds. The use of polyethylene glycol (PEGylated fibrin hydrogel) creates a highly hydrated hydrogel microenvironment by creating additional cross-linking between fibrin polyethylene glycol (PEGylated) (FPEG) during thrombin-mediated polymerization of fibrin, Which, provides the possibility of cell seeding in the matrix and causes the formation of blood vessels both in vitro and in vivo [77–79].

4.2.2. Silver sulfadiazine

Various compounds are used to control bacterial infection. Topical silver sulfadiazine (SSD) is one of these compounds, which, has a wide range of activity against Gram-positive and Gram-negative bacteria as well as fungal infections [80–82]. SSD interferes with the structure of enzymes by binding to the thiol group and ionizing with bacterial DNA. However, the frequent use of this combination, in addition to the need for multiple uses and continuous bandaging of the wound, brings the possibility of silver poisoning. The simultaneous use of this compound with hydrogels can control the release of this compound at the site of injury. The combination of antibacterial SSD and the natural biological activity of fibrin improves the regeneration of tissue and blood vessels in the wound [79,83].

Gil et al. [84] investigated wound healing and the antimicrobial effect of FPEG-based wound dressing for the controlled delivery of SSD entrapped in chitosan microspheres (CSM) (SSD-CSM-FPEG) on wounds with *Pseudomonas aeruginosa* infection. The result of this study showed the effectiveness of this combination in better wound healing and eliminating infection. However, no study has been done on the

Table 3
Studies conducted on the combined treatments of mesenchymal stem cells (MSCs) and hydrogel in wound healing.

Type of wound	Cell source	Animal	Type of study	Material used	Outcome	Ref.
Full thickness wound	Human ADSCs	Mice	In vivo	Catechol-functionalized hyaluronic acid	Increasing wound closure, epidermis regeneration, and skin thickness Increasing VEGF, IGF-1, FGF-2, ANG-1, PIK, and AKT expression	[102]
	Human bone marrow	-	In vitro	RGD-containing hydrogels LLP2A-tethered hydrogels	Promoting wound healing	[99]
Full thickness wound	Rat ADSCs	Diabetic rat	In vivo	Pluronic F-127	Accelerating wound closure and re-epithelialization Increasing expression of CD31, Ki67, VEGF, TGF-β	[98]
Full thickness wound	Human UCMSC-exo	Diabetic rat	In vivo	Pluronic F-127	Accelerating wound closure and re-epithelialization	[68]
Full thickness wound	Human UCMSCs	Rat	In vivo	Thermo-sensitive chitosan-based hydrogel	Accelerating wound closure, microcirculation, tissue remodeling, re-epithelialization, hair follicle regeneration Promoting collagen deposition and keratinocyte mature marker K1 expression Decreasing inflammatory factors secretion (TNF-α and IL-1β	[12]
Full thickness wound	Human UC-MSCs	mice	In vivo	Sodium alginate/ collagen	Promoting the formation of granulation Enhancing collagen deposition Increasing VEGF and TGF-β1 expression Reducing the production of TNF-α and IL-1β and higher release of IL-4 and IL-10	[14]
Diabetic wound	ADSCs	Diabetic Rat	In vivo	Hyperbranched multi-acrylated poly (ethylene glycol) Macromers (HP-PEGs)	Accelerating diabetic wound healing process by inhibiting inflammation Promoting angiogenesis and re-epithelialization	[13]

combination of these compounds with MSCs in wound healing to investigate its greater antibacterial effectiveness in wounds.

4.2.3. Poly (ethylene glycol)

PEG is one of the hydrogels with a biocompatible structure that is used in cell culture and tissue engineering scaffolds. PEG has been used in various studies to induce changes and improve function in various cells. Noiri et al. [85] have used PEG to modify the structure of MSCs to attach to endothelium surfaces. In another study, Xu et al. [13] used hyperbranched PEG to improve the function of adipose tissue-derived stem cells. The results showed that these cells have stemness properties, promote adipose tissue-derived stem cell secretions, and promote wound healing in animal model wounds. Lee et al. study [10] on the effect of poly (ethylene glycol-b-[DL-lactic acid-co-glycolic acid]-b--ethylene glycol) on muscle-derived stem cells showed the effectiveness of this combination and increased wound healing, wound closure, epithelium migration, and collagen deposition in the wound of diabetic mice. The use of PEG in combination with MSCs in wound healing needs more studies to determine its appropriate efficacy and non-toxicity.

4.2.4. Sodium alginate/collagen hydrogel

Collagen is the most abundant protein in the human body and mammals, which is widely used in tissue engineering and scaffolding due to its effects on cell growth and proliferation [14,86]. Collagen is divided into two fibrillar types including type I, II, and III collagen, and non-fibrillar type collagen type IV and collagen-like protein. Fibrillar collagen with its properties such as high tensile strength, biocompatibility, biodegradability, availability, and stability has found a suitable application in tissue engineering and wound healing [86–88]. Sodium alginate (SA) is a compound obtained from brown algae. This compound has a polysaccharide structure and is used in wound healing with hydrogel and scaffold due to its properties of high hydrophilicity, excellent biocompatibility, high hydrophilicity, and hemostatic capabilities [14,89]. In an in vitro study, Zhou et al. [18] showed the effectiveness of sodium alginate and collagen in preventing MSCs apoptosis. In another study, Zhang et al. [14] used sodium alginate/-collagen hydrogel together with UC-MSCs in wound healing, and their results showed the effectiveness of this combination in wound healing, collagen deposition, increased angiogenesis, and reduced inflammation at the wound site.

4.2.5. Chitosan-based hydrogel

Among the appropriate cell and drug carriers, chitosan/sodium glycerol phosphate (CS/GP) based hydrogels can be mentioned, which POgood biodegradability and biocompatibility [90,91]. CS/GP has a unique heat-sensitive effect that makes it suitable for injectable hydrogels. With all the mentioned advantages, this composition has disadvantages such as poor mechanical properties, and insufficient deformation rate, which needs to be improved [90,91]. This goal is possible by adding compounds such as collagen, graphene, and nanocrystal cellulose [92,93]. The use of modified compounds in combination with MSCs can be effective in accelerating wound healing [12]. Xu et al. [12] showed in their study that the use of thermo-sensitive chitosan-based hydrogel encapsulated hUC-MSCs can lead to better wound healing, wound closure, re-epithelialization, and reduction of inflammation at the wound site.

4.2.6. Pluronic F-127

Pluronic F-127 (PF-127) is a unique, synthetic, hydrogel biocompilation and heat-sensitive (at low temperatures in liquid and high temperatures in semi-solid gel), which is also known as Poloxamer 407, and its use has been approved by the FDA [94,95]. The thermal properties of PF-127 make it a suitable compound in the wound environment to be able to perform properly in this environment, can adhere to the target site, and exert its biological function with bioactive compounds [68,94]. The function and structure of this compound can prolong the release time of therapeutic proteins and increase the half-life of the drug and serum. In addition, PF-127 can absorb secretions from the surface of the wound and has a mild inflammatory effect, which can help maintain moisture and promote wound healing [96,97]. All the mentioned properties make PF-127 a suitable compound for increasing the performance and effectiveness of MSCs and MSC-EXO. Studies have shown that the use of MSC-EXO in combination with PF-127 can increase wound closure, and tissue regeneration, and increase the expression of genes and growth factors related to angiogenesis in the injury site [68]. In addition, in another study conducted by Lin et al. [98] on the effectiveness of ADSCs in combination with PF-127, similar results were obtained, which showed the efficiency and performance of PF-127 in increasing the function of cells and exosomes secreted from it in wound healing.

4.2.7. Peptide

Various peptides are used to increase the growth and proliferation of MSCs and wound healing. The peptide with the amino acid sequence arginine-glycine-aspartic acid (RGD) is one of the most widely used amino acid sequences, which bind to αVβ3 and α5β1 integrins, which are related to fibronectin, vitronectin, and ECM proteins, cause the differentiation of stem cells and changes in the extracellular signal [99,100]. D- and L-enantiomers of Cys-Ala-Gly (CAG) a tripeptide that can cause changes in the proliferation, mechanical properties, and wound healing of MSCs [99]. CAG is another tripeptide derived from collagen type IV and can promote the growth, adhesion, and proliferation of endothelial cells and wound healing [100]. Studies have shown that the use of these compounds in combination with hydrogels can promote the differentiation and adhesion of MSCs, smooth muscle cells, and endothelial cells along with changes in ECM proteins, which can improve wound healing [99,100].

4.2.8. Hyaluronic acid

Hyaluronic acid is a polysaccharide compound that plays a role in wound healing, cell proliferation, differentiation, migration, and ECM organization and metabolism. Hyaluronic acid is found in various tissues such as skin, eyes, cartilage, and joints [101,102].

Hyaluronic acids with high molecular weight can prevent cell migration and proliferation, although hyaluronic acids with low molecular weight, especially 150–250 kD, can promote wound healing by supporting cell proliferation, cell migration, and angiogenesis [103, 104]. Hyaluronic acid has biocompatibility, matrix structure similarity, and drug delivery capabilities, which has led to the wide use of this compound for biomedical and pharmaceutical applications [26]. To increase the performance and increase reversibility of hyaluronic acid, changes have been made in it so that it can promote wound healing and improve the performance of the cells that are used in combination. In the study of Eke et al. [105], by using 40 s of UV rays, they created a crosslink between methacrylated gelatin (GelMA) and methacrylated hyaluronic acid (HAMA) and increased the performance of the hydrogel and prolonged the reversibility of this compound and the better performance of ADSCs. The study of Pak et al. [102] also showed that Catechol-modified hyaluronic acid (HA-CA) hydrogel, in addition to better biocompatibility and tissue adhesion, causes better survival and performance of stem cells than hyaluronic acid hydrogel. These studies showed that hydrogel alone and in combination with different materials and improving the performance of hydrogel can promote wound healing and protect stem cells in wound healing.

4.3. Matrix

Matrix is composed of an insoluble scaffold such as collagen, fibronectin, and elastin. These matrices increase cell growth, proliferation, and migration by maintaining cell signals, cytokines, and growth factors [106]. If these biological compounds are natural substances, there is a risk of disease transmission and immunogenicity, although the use of

processing methods can eliminate some of these diseases, they are still not completely effective. One of the ways to reduce the risk of disease transmission is the use of acellular matrix [107]. The use of acellular dermal matrix (ADM) in wound healing, healing damaged tissue, regenerating epidermis, revascularization, and improving the function and survival of the cells used in the damaged area [108]. The use of ADM can improve the performance of MSCs and can promote reepithelialization, and facilitate angiogenesis and skin regeneration in deep extensive burns and full-thickness skin wounds [3,109].

Studies have shown that the use of a dermal matrix for the carrier of ADSCs can increase survival, and differentiation and promote wound healing [110]. In Qi et al. study [25], MSCs seeded in ADM were used for wound repair, which in addition to the survival of MSCs, increased angiogenesis, re-epithelialization, and wound regeneration. The studies conducted on matrix and the results of these studies are summarized in Table 4.

4.3.1. Timolol

Timolol is one of the drugs used to heal skin wounds. Timolol alone or in combination with other compounds has been used in several studies for wound healing [111]. Wound tissue can produce catecholamines, which inhibit wound epithelialization, keratinocyte migration, fibroblast phenotype change, increased neutrophils at the injury site, and as a result, increases inflammation and inflammatory cytokines at the wound site [4,112]. Timolo, as a beta-adrenergic antagonist, helps wound healing by inhibiting the effects of catecholamines, induces the secretion of IL-6 by MSCs, and repeals the effects of epinephrine and bacterial TLR activators [4,113]. Yang et al. [4] used the combination of dermal matrix, human MSCs, and timolol in the treatment of diabetic rat wounds, and the results of the study showed a reduction in inflammation at the wound site and promotion of wound healing. In another study, the use of dermal matrix, human MSCs, and timolol in porcine wounds showed the promotion of wound healing and the lack of immunogenicity of human MSCs in porcine [114].

4.3.2. Polyvinyl alcohol

Polymers are widely used in tissue engineering due to their mechanical and physical properties and the ability to make required changes in their composition and structure. Polyvinyl alcohol (PVA) is a synthetic polymer that is used in regeneration studies and soft tissue replacement due to its porous structure, tannable properties, high water content, and biocompatibility [115,116]. Studies have shown that the use of pure PVA has little effect on wound healing, this PVA is combined with various drugs and growth factors to increase its performance and efficiency [9,117]. In a study, Ha et al. [9] investigated the effect of combining PVA with human fibroblast-derived matrix and MSCs as an engineered ECM patch on a mouse full-thickness wound model. The results of the study showed, in addition to increasing cell growth, proliferation, and migration, promoting wound healing, collagen deposition, and neovascularization. The used engineered ECM patch can provide special conditions for wound healing with its regenerative properties.

5. Conclusion

In this study, the studies conducted on the combination therapy of scaffolds, matrix, and hydrogels with MSCs were reviewed. Scaffolds, matrices, and hydrogels are biomaterials that increase the growth, proliferation, and differentiation of cells by providing moisture and suitable conditions, as a result of increasing wound healing and reducing scars. MSCs, with their functions and secretions, cause wound healing. Studies have shown that the combination therapy of biomaterials with MSCs, in addition to increasing the proliferation, differentiation, and homing of these cells, promotes wound healing and lowers scars. Using other compounds such as glycol, sodium alginate/collagen hydrogel, chitosan, peptide, timolol, and PVA along with these treatments can also be effective. Although the compounds used are different and the studies conducted on each of these combinations are few, hence there is a need for more studies to investigate the sufficient effectiveness and side effects of these compounds.

Ethics approval and consent to participate

Not applicable.

Funding

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 4
Studies conducted on the combined treatments of mesenchymal stem cells (MSCs) and matrix in wound healing.

Type of wound	Cell source	Animal	Type of study	Material used	Outcome	Ref.
Diabetic wound	Human AMSCs	Mice	In vivo	Decellularized adipose matrix hydrogel	Increasing MSCs adhesion, survival, and proliferation Increasing MSCs paracrine activity with increased secretion of hepatocyte growth factor Accelerating wound closure and neovascularization	[119]
Full thickness wound	Human BM-MSCs	Mice	In vivo	Decellularized extracellular matrix, human fibroblast-derived matrix, polyvinyl alcohol	Accelerating wound closure, and tissue regeneration Promoting collagen deposition and neovascularization	[9]
Full thickness wound	Human MSCs	Porcine	In vivo	Dermal matrix and timolol	Promoting wound re-epithelialization Supporting angiogenesis	[114]
Full thickness wound	Human MSCs	Mice	In vivo	Dermal matrix and timolol	Increasing CCL2 and CD31 expression Reducing cytokine IL-1β and IL6 levels and neutrophil numbers Promoting wound healing	[4]
Full thickness wound	Human ADSCs	Mice	In vivo	Dermal matrix	Increasing cell survival and differentiation Promoting wound healing	[110]
Full thickness wound	Human BM-MSCs	Mice	In vivo	Denatured acellular dermal matrix	Promoting angiogenesis and re-epithelialization Supporting skin appendage regeneration	[25]
Full thickness wound	Human ADSCs	Mice	In vivo	Hydrogel biological scaffold from human decellularized adipose matrix (hDAM)	Accelerating wound closure Increasing neovascularization Sustaining cell adhesion, survival, and proliferation	[119]

Availability of Data and Materials

Not applicable.

Acknowledgment

This study was supported by the Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2023R259), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

Consent for publication

Not applicable.

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