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Systematic Review

Comparison of Effects Exosomes Derived from Mesenchymal Stem Cells and Other Cells on Wound Healing: A Systematic Review

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Abstract

Introduction: Exosomes stimulate tissue regeneration and can be a substitute customary therapies of wound healing. The study aimed to compare the wound healing effects of exosome derived from Mesenchymal Stem Cells (MSCs) and other cells in wounds.

Methods: We searched PubMed, MEDLINE, EMBASE, International Clinical Trials Registry Platform, Clinical Trials, Cochrane Library, Wiley, Google Scholar, ISI Web of Knowledge, and Scopus study design, study location, various types of cell origin, and the healing outcome of extracted exosome. Two reviewer authors independently investigated and assessed the titles and abstracts of all articles; the third reviewer determined disagreement between them. Data were documented about study design, study location, various types of cell origin, and the healing outcome of extracted exosome.

Results: A total of 2896 records were choice in an initial search for studies that used exosome for wound healing. Ultimately, 13 studies (seven articles applied MSC as origin of exosome, six studies used other cells expect MSCs as origin of exosome for wound healing) were included in this study. These articles were published from 2001 to December, 2023. This review study showed that MSC-derived exosomes have more wound-healing effects in angiogenesis, proliferation, collagen synthesis, and re-epithelialization. On the other hand, exosome with different cell origin has more wound-healing effects, such as proliferation, re-epithelialization, angiogenesis, and collagen synthesis.

Conclusion: Both MSC-derived exosomes and exosome with different cell origin, have great effects on the wound healing process. But, MSC-derived exosomes have better effects on the wounds that need to more angiogenesis and cell proliferation. Also, exosomes with different cell origin can have better effects on the wounds with more requirement of cell proliferation, and re-epithelialization.

Keywords: Exosome, Wound Healing, Stem Cell.

Introduction

As the largest organ, the skin protects the body from invading pathogens and injuries [1]. Boosting the wound-healing process is essential, concerning this organ being continually damaged by chronic and acute wounds [2]. This process involves several cellular and molecular events and cascades [3]. Four phases for skin injury healing are more challenging with some co-occurring; hemostasis, inflammation, cell proliferation, tissue remodeling, and scar maturation [4-9]. Exosomes are extra-cellular vesicles with various content depending on the origin of the cell type, e.g., proteins, mRNA, lipids, and microRNA. These vesicles are derived from the cells that fuse with the plasma membrane and are secret into the extra-cellular matrix. Different cells acquire exosomes via cell-type specific endocytosis or phagocytosis [2]. Several studies recommend that exosomes derived from other cell types be used to aid tissue repair due to their characteristics of non-immune rejection, easy control of concentration, homing effect, and high stability [5].

Anti-angiogenic proteins such as myeloperoxidase are expressed more in chronic wounds. Still, angiogenesis

stimulators such as superoxide dismutase extracellular are reduced compared to acute injuries [2].

In vivo, results show that eliminating bacterial infection, increasing angiogenesis, suppressing tissue inflammation, and oxidative damage can be better than monotherapy or individual antibiotics in treating wounds [4].

Mesenchymal stem cells (MSCs) can influence angiogenesis due to the secretion of pro-angiogenic factors. MSCs attend with noticeable anti-fibrotic activities, intermediated mainly by the release matrix metalloproteinase (MMPs). It makes them a practical and rational strategy to accelerate wound healing with a small scar. Subsequently, the principal healing properties of the MSCs be determined by their paracrine effects. MSCs-derived exosomes may also be a substitute alternative to skin regeneration and wound healing as an advanced cell-free procedure [5-15].

Injectable Surgical Fibrin Sealant (TISSEEL) improved skin wound healing by increasing collagen synthesis and skin structure regeneration. Platelets Exosome Product (PEP) improved angiogenesis by increasing the activity of vascular and epithelial cells. Transcriptome deconvolution, repair pathways including matrix regeneration and tissue growth, and neovascularization against in-treated wounds Only prioritized with TISSEEL [6].

Paracrine factors and exosomes secreted from fat-derived stem cells can cause faster wound healing. Exosomes are cell-derived nanovesicles that carry microRNAs and growth factors, and their effect on wound healing and angiogenesis has been proven. They stimulate cell proliferation and migration, sufficient collagen synthesis and regeneration, and increase recovery. They get injured. According to a hypothesis, reducing hypoxia and oxidative stress increases collagen regeneration and re-epithelial regeneration, and induction of angiogenesis; It happens with the function of the oxidant scaffold that releases oxygen and exosomes and causes better healing of the diabetic wound. In the following, we predicted that the exosomes derived from EDSCs induce more migration of fibroblasts and keratinocytes and increase cell survival in hyperglycemic conditions, which ultimately causes faster wound closure [7-10].

Exosomes are extra-cellular vesicles with various content depending on the origin of the cell type, e.g., proteins, mRNA, lipids, and microRNA. Therefore, this study aimed to compare the wound healing effects of exosome derived from Mesenchymal Stem Cells (MSCs) and other cells in wounds.

Methods

Online databases such as PubMed, MEDLINE, EMBASE, International Clinical Trials Registry Platform, Clinical Trials, Cochrane Library, Wiley, Google Scholar, ISI Web of Knowledge, and Scopus were searched. Terms and keywords were included exosome, wound, injury, healing, damage, gene, cell, inflammation, fibroblast cell, mesenchymal stem cell, stem cell and burn.

Exclusion criteria were included non-wound damage, unused of exosome for healing, studies that were only brief, lack of cell data, clinical studies without preliminary results.

Two reviewer authors independently searched and assessed the titles and abstracts of all studies; the third reviewer resolved difference between them.

Data were documented concerning study design, study location, various types of cell origin, and the healing outcome of extracted exosome.

Results

A total of 2896 records were choice in an initial search for studies that used exosome for wound healing.

Ultimately, 13 studies (seven articles applied MSC as origin of exosome, six studies used other cells expect MSCs as origin of exosome for wound healing) were included in this study. These articles were published from 2001 to December, 2023.

We studied the full text of the articles, and 13 articles were included in the systematic review (Figure 1).

This review study showed that MSC-derived exosomes have more wound-healing effects in angiogenesis, proliferation, collagen synthesis, and re-epithelialization. On the other hand, exosome with different cell origin has more wound-healing effects, such as proliferation, re-epithelialization, angiogenesis, and collagen synthesis (Table 1).

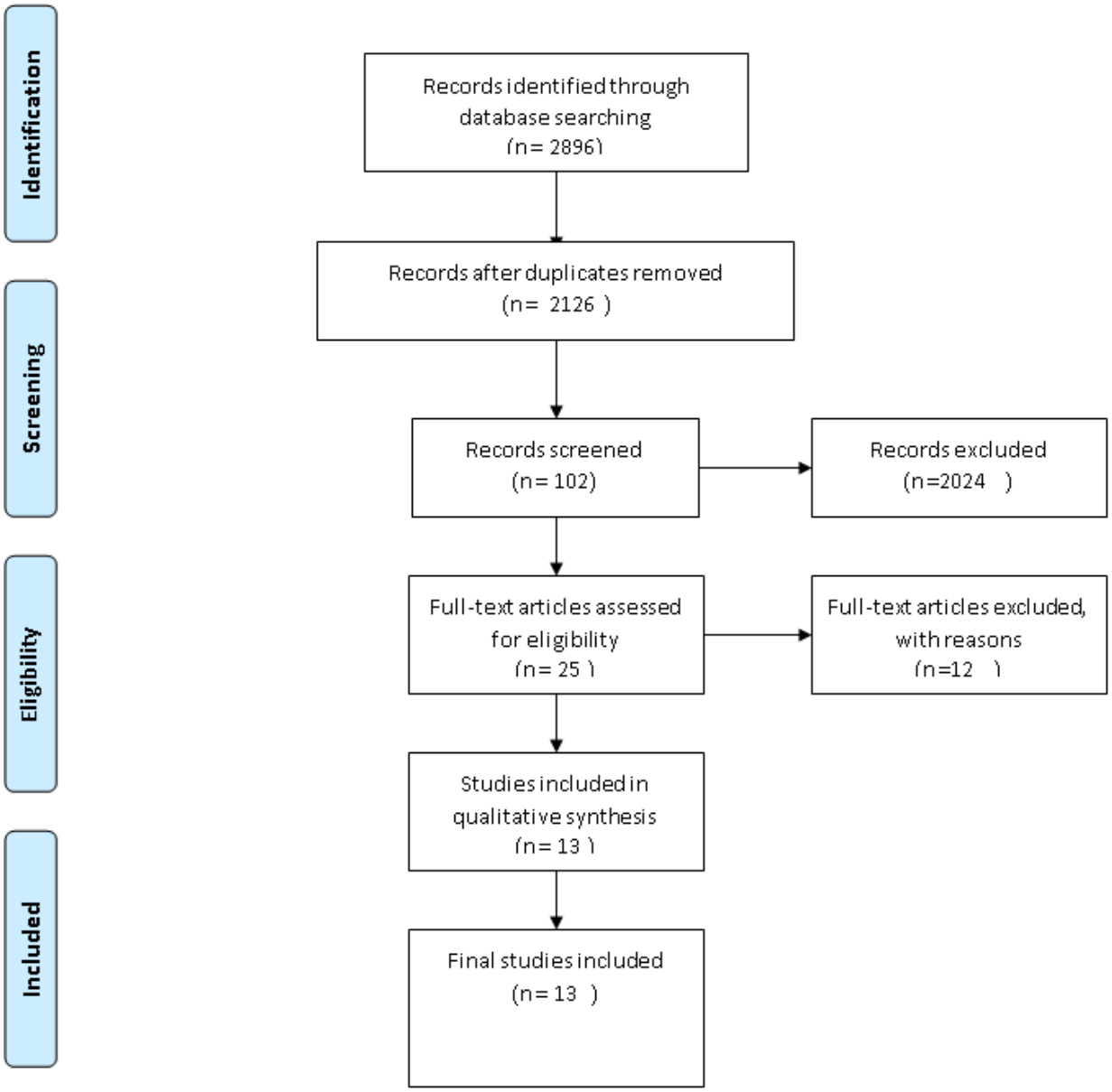

Figure 1: PRISMA Flow chart of the study

He X, et al. [1] conducted a study on the effect of macrophages on the wound-healing process. This study found that the early depletion of macrophages slows wound healing, and bone marrow mesenchymal stem cells and jaw bone marrow MSCs cause Macrophage polarization to promote M2 and improve wound healing. Mechanistically, the exosomes derived from MSCs increase the polarization of macrophages, and the exosomes that reduced the M2 phenotype of macrophages decreased. The results showed that MSCT with the transfer of transferable microRNA causes M2 polarization and heals wounds faster with angiogenesis, differentiation, wound contraction, and tissue remodeling [1].

Liu W, et al. [2] investigated the effect of exosomes derived from melatonin-pretreated mesenchymal stem cells) MT-Exo (and found that these exosomes accelerate the healing of diabetic wounds by suppressing the inflammatory response, angiogenesis, and collagen synthesis in vivo [2].

Sun B, et al. [12] conducted a study on an integrated Exosome-Reductive COF nanoagent for faster healing

of diabetic febrile wounds. This study showed that by increasing angiogenesis and eliminating bacterial infection and the synergistic effect of oxidative suppression, infectious diabetic wounds can be treated faster than single antibiotics [12].

Bian D, et al. [4] conducted a study on using mesenchymal stromal cells and the effect of exosomes derived from them, which in vivo reports proved that MSC-based therapies are effective for accelerating the healing process of skin wounds with angiogenesis, skin cell migration, and re-epithelialization [4].

Shi A, et al. [6] produced a suitable product for chronic wound healing and complete skin regeneration by combining clinical grade platelet exosome product(PEP) with surgical injectable fibrin sealant(TISSEEL). Due to its stability at room temperature, this product can produce a bioactive transforming growth factor beta to guide regenerative events. It can promote wound healing with cell proliferation, migration, tube formation, skin organoid, matrix remodeling, neovascularization, and tissue growth [6].

Xiong Y, et al. [9] conducted a study on multifunctional hydrogel that can release exosomes at the right time and accelerate the oxidative healing of diabetic wounds with fibroblast growth factor. They showed that these in vivo and in vitro results show rapid healing of diabetic wounds. The released FGF-2 enhanced epithelization efficiently, and The released ExosM2@miR-223 simulated enduring angiogenesis [9].

Wang M, et al. [10] produced a multi-purpose dressing to heal diabetic wounds and increase angiogenesis. This dressing is made of heat-sensitive polysaccharide, an injectable adhesive that can stably release exosomes. Finally, this multifunctional dressing positively affected the healing of wounds related to vascular disorders and diabetic wounds [10].

Ahmadpour F, et al. [15] conducted a study that evaluated the fibroblast cell derived exosome on the burn wound healing. They showed that inflammation and granulation were higher in the exosome groups. Also, the re-epithelialization and collagen deposition was higher.

Shiekh PA, et al. [16] conducted research on the wound dressing of OXOB antibacterial cryogel and exosome-releasing antioxidant cryogel and found that OXBand reduces oxidative stress, increases neovascularization, increases the speed of re-epithelialization and wound closure, and increases collagen deposition. This positive result on the wound can lead to the developing of a new treatment strategy for healing diabetic wounds [16].

Kim H, et al. [7] studied the phenotypic change and conversion of M1 to M2 macrophages and found that this direct conversion at the wound site increases re-epithelialization, collagen deposition, and angiogenesis. Changing the phenotype of macrophages caused by exosomes can cause a balance between macrophages. As a result, it is a new and helpful treatment method for treating wounds and skin inflammations [7].

Zhou et al. [8] researched the effects of exosome interaction between keratinocytes and macrophages and found no significant difference in re-epithelialization. Also, an increase in re-epithelial value was seen in the group of macrophages that provide inflammatory markers in the granulation tissue [8].

Yang J, et al. [13] demonstrated that MSC-derived exosomes in both in vivo and in vitro, promoting cell proliferation and angiogenesis [13].

Table 1 :Included articles in the study.

Authors	Year	Type of Origin cell	Type of wound	Results of wound healing
Zhou X. et al. [8]	2020	Keratinocyte	Murine dorsal wound-edge	The treated group indicated significant rise in pro-inflammatory markers in the granulation tissue compared to control group.
Shi A, et al. [6]	2021	Human Dermal Fibroblasts (FBs)	Rabbit ischemic wound	Exosome promoted vascular and epithelial cell activity increasing angiogenesis to restore mature skin function and blood flow.
He X, et al. [1]	2019	MSC	Skin Wound-Healing Model	This study showed appear stimulate angiogenesis and differentiation.
Xiong Y, et al.[9]	2021	MSC	Diabetic wounds	The M2-derived Exosomes (M2 Exos) stimulate angiogenesis.
Wang M, et al. [10]	2019	Adipose Stromal Cell	Diabetic wound	This study showed that new dressing enhanced the wound healing by motivating the angiogenesis process.
Kwak G, et al. [11]	2022	MSC	Animal model for cutaneous wound	This study showed promoting angiogenesis.
Sun B, et al. [12]	2022	MSC	Diabetic wound	This study demonstrated promoting angiogenesis and eradicating bacterial infection.
Yang J, et al. [13]	2020	MSC	Diabetic wound	Both in vivo and in vitro, exosomes promoting cell proliferation and angiogenesis.
Liu W, et al. [2]	2020	MSC	Diabetic wound	MT-Exo stimulated the healing by preventing inflammation, thus further facilitating angiogenesis and collagen synthesis in vivo.
Qiu X, et al. [14]	2020	MSC	Cutaneous wound healing model	They showed that the exosomes promoted their functions to enhance angiogenesis.
Nooshabadi VT, et al. [5]	2020	Easy-accessible stem cells	Cutaneous wound healing model	This study showed that EXO have high wound closure ability with a great degree of re-epithelialization.
Ahmadpour F, et al.[15]	2023	Fibroblast	Burn wound healing model	Inflammation and granulation were higher in the exosome groups. Also, the re-epithelialization and collagen deposition was higher.
Shiekh PA, et al. [16]	2023	Adipose-derived stem cells	Diabetic and infectious wound	This study revealed faster re-epithelialization, enhanced collagen deposition, increased neo-vascularization, and decreased oxidative stress compared to control wounds.

Discussion

This review study showed that MSC-derived exosomes have more wound-healing effects in angiogenesis, proliferation, collagen synthesis, and re-epithelialization. On the other hand, exosome with different cell origin has more wound-healing effects, such as proliferation, re-epithelialization, angiogenesis, and collagen synthesis.

Collagen production and cellularization of the wound skin in the saline group were significantly reduced compared to those treated with MSC-derived exosomes. Regeneration and re-epithelialization of the ECM fundamentally depend on promoting the migration of cell types such as keratinocytes and skin fibroblasts by exosomes [19].

Acceleration and enhancement of angiogenesis occur by releasing proangiogenic mediators by M2 macrophages. MDO macrophages produce proangiogenic factors such as FGF, VEGF, and EGF during the proliferation phase of wound healing. In addition, IL-19 enhanced angiogenesis in the ischemic state by directly regulating macrophage polarization [20].

Mesenchymal stem cells HWJ-MSC secrete exosomes. These exosomes help angiogenesis and wound healing in the body by activating β-catenin and transferring Wnt4 [21].

Rapid re-epithelialization of this tissue and positive regulation of collagen 1, CK19, and PCNA expression occurs with the effect of HWJ-MSC exosomes on the wound. Also, exosomes contain Wnt4, which helps to promote proliferation and migration of skin cells and β-catenin nuclear transfer [21].

Angiogenesis is supported by mesenchymal stem cells with paracrine effects and cell contact communication. Mesenchymal stem cells secrete proangiogenic factors, which include VFGF, bEGF TGF-β, placental growth factor (PGF), PDGF, IL-6, angiopoietin-1, and monocyte chemotactic protein-1 (MCP-1) [22]. Also, some studies have shown that MCP-1, VEGF, and IL-6 cause angiogenesis in vivo [23].

Mesenchymal stem cells express VEGF, one of the most important proangiogenic factors that may differentiate mesenchymal stem cells [24]. VEGF regulates the differentiation and migration of endothelial cells and accelerates the endothelialization of angiogenesis in the tissue by absorbing endothelial cells [25].

MSCs secrete HGF, and they contribute to promoting therapeutic angiogenesis in wound tissue and also treat vascular disorders [26]. MSCs seeded on the scaffold could significantly lessen the quality of regenerated skin, improve reepithelization and neo-angiogenesis, attenuate collagen deposition, and ultimately sustain a greater return of SGs and hair follicles, mainly by releases of paracrine factors [27].

AT-MSCs have a positive effect on suppressing TNFα-dependent inflammation myofibroblast differentiation as well as establishing granulation tissue, stimulating TGF-β1-mediated angiogenesis, intensifying M2 macrophage population [27].

MSC spheres in stiffer gels produced more anti-inflammatory factors, PGA2, and angiogenic factor VEGF than normal MSCs, improved macrophage polarization, and stimulated endothelial proliferation. And increase angiogenesis in vivo [28].

Exosomal miRNAs, including miR-21, -125b, -145, -23a are secreted from HWJ mesenchymal stem cells and prevent myofibroblast accumulation and scar formation by blocking the TGFβ2/SMAD2 pathway and reducing collagen deposition [29].

Masson's trichrome staining showed collagen deposition and angiogenesis in HA@MnO2/FGF-2/Exos hydrogel-treated wounds. Collagen slowly replaced granulation tissue, and mice treated with HA@MnO2/FGF-2/Exos hydrogel had more organized collagen strands [9].

HA@MnO2/FGF-2/Exos hydrogel increased the antibacterial activity and improved the function of HUVECs and HSFs. After integrating FGF-2 and ExosM2@ miR-223, the hydrogel increased angiogenesis, granulation tissue development, collagen accumulation, ROS reduction, and regeneration, all of which accelerated Diabetic wound healing [9].

Exosomes derived from human umbilical cord mesenchymal stem cells boost the migration and proliferation of skin cells through Wnt4-mediated β-catenin nuclear translocation [30].

MSCs can increase the rate of proliferation of target cells by expressing growth factors, especially epidermal growth factors such as HGF and EGF [31].

MSCs might generate a lot of angiopoietin-1 and VEGF, indicating that stem cells enhance wound healing by secretion of angiogenesis-inducing molecules and differentiation [32].

M2 polarization of macrophages in vascular conditions contributes to collagen synthesis and angiogenesis in diabetic wounds. They release proangiogenic mediators from M2 macrophages promotes angiogenesis [33,20].

IL-19 causes direct regulation of macrophage polarization, and this can enhance angiogenesis of an ischaemic state [34].

lithium-containing biomaterials might encourage the upregulation of miR-130a in hBMSC-derived exosomes, thus improving the endothelial cells and angiogenesis [35].

MSC exosomes are stimulated by the ischemic limbs of a murine model to increase microvessel density, blood perfusion, and expression of angiogenesis-related biomolecules [36].

IL-6 induces prosurvival, pro-growth and proangiogenic, and MCP-1 is a chemoattractant for angiogenesis [37].

M2-EXO load more various cytokines than M1-EXO: CC11, CCL24, CCL27, IL4, CXCL12, Bfgf, CCL22, MFG-E8. CCL11 increases angiogenesis by activating the PI3K/Akt pathway [38] and CCL27 can boost skin regeneration by accumulating bone marrow-derived keratinocytes.

RM2 Mφs can contribute to promoting the migration ability of fibroblasts by depending on MMP-2-mediated proteolysis, which is similar to M2 Mφs [39]. VEGF is too important for angiogenesis to be expressed in vascular endothelial cells through autocrine mechanisms and paracrine [39]. The growth factors are the precarious controlling themes of the healing progression as they chemo-attract inflammatory cells and fibroblasts to the wound site and effect cellular proliferation [40].

Conclusion

Both MSC-derived exosomes and exosome with different cell origin, have great effects on the wound healing process. But, MSC-derived exosomes have better effects on the wounds that need to more angiogenesis and cell proliferation. Also, exosomes with different cell origin can have better effects on the wounds with more requirement of cell proliferation, and re-epithelialization.

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Conflict of Interest Disclosures

We confirmed that there is no conflict of interest.

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Authors' Contributions

Concepts, data gathering, data analysis, writing and editing: Fathollah Ahmadpour, Mahdyar Momeni

Ethical Statement

The Baqiyatallah University of Medical Sciences Ethics Committee confirmed the study's proposal with the code: IR. BMSU.REC1398.204.

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