




Exosome therapy: A new remedy for wound healing

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ABSTRACT

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Wound healing is one of the most discussed challenges in medical science today. To date, several therapeutic methods have been proposed to repair wounds that do not heal properly, the most recent of which is treatment using extracellular vesicles, specifically "exosomes." Exosomes are nano-sized vesicles that are secreted from a wide range of cells and, due to the cargo they contain, can modulate target tissues through mechanisms critical for wound healing and can be used as a wound treatment. Exosomes derived from mesenchymal stem cells (MSCs) derived from various tissues hold promise for cell-free therapies to repair tissue damage. Extracellular vesicles play key roles in cell biology and may offer novel clinical diagnostics and therapies. They contribute to intercellular signaling and the maintenance of tissue homeostasis. The biogenesis of exosomes begins in the endosomal system. This varies depending on the origin of the extracellular vesicles, their physiological and pathological status, and even the exact site of cellular release. The clearance of exosomes from cells, tissues, and body fluids follows a different pattern. Advanced technologies in regenerative medicine have led researchers to use exosomes isolated from mesenchymal stem cells with high regenerative capacity in diseases. Exosomal cargo plays a key role in diagnosis and treatment by controlling the disease process. This narrative review summarizes evidence from major international scientific databases regarding the therapeutic role of exosomes in wound healing. Various in vitro studies have shown the safety, efficacy, and therapeutic potential of exosomes in wound healing. This review critically evaluates current evidence on exosome-based therapies for wound healing and highlights their therapeutic potential, limitations, and future translational challenges.

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1. Introduction

1.1 Background and Significance of Wound Healing

Wounds, as relatively common injuries, frequently occur on the skin of people in society, causing pain and social challenges for them. Therefore, there is a need to provide an effective treatment method for this problem [1,2]. So far, various biological, physical, and chemical regenerative methods have been proposed, such as laser, vacuum therapy, ultrasound therapy, bioengineered skin, and growth factor injections [3].

1.2 Exosomes as Novel Therapeutic Agents

Recently, the use of extracellular vesicles (EVs) as a drug delivery tool has received special attention due to their simple properties, derived from parental or host cells. Despite normal cellular homeostasis, EVs play a central role in the pathobiology of disease processes through intracellular signaling cascades [4]. Exosomes are one of the most prominent types of extracellular vesicles. These vesicles are secreted to establish intercellular communications [5]. They are distinguished from other extracellular vesicles by their smaller size (30-150 nm) and their type of formation [6]. Almost all cells, tissues, and body fluids, such as plasma, urine, saliva, tears, gastrointestinal (GI) secretions, semen, and breast milk, secrete exosomes (Figure 1) [4,7].

1.3 Exosome biology

Blood cells, especially platelets, are candidates for cell therapy, and their selection was made considering the role of these cells in repair processes [8]. Since the major inductive effect of these cells is caused by their secretory content to the outside of the cell, it has been

suggested that instead of using the cells directly, their purified extracellular vesicles should be used [6]. The structure of exosomes consists of a phospholipid bilayer membrane along with a variety of other lipids such as cholesterol and phosphatidylserine. Exosomes are also rich in lipid bilayer molecules such as glycosylphosphatidyl inositol-anchored protein (Lysobisphosphatidic acid (LBPA)) and flotillin [9].

In addition, a variety of proteins participate in their structure formation. Examples of these proteins include cytoskeletal proteins, membrane channels, and adhesion proteins. Exosomes also contain a variety of protein and nucleic acid cargoes. The protein content carried by exosomes includes enzymes such as Matrix MetalloProteinases (MMP), signaling proteins (Wnt4/3), heat shock proteins (hsp70/72/90), and growth factors (VEGF/TGF- β). Membrane transport and fusion proteins, chaperones, adhesion molecules, MHCs (Major Histocompatibility Complexes), cytoskeletal proteins, and lipid-associated proteins are considered to be the main exosomal proteins [4]. Apart from metabolic enzymes and signal transduction molecules such as G proteins and protein kinases, exosomes contain mRNAs (Messenger RNAs), miRNAs (microRNAs), non-coding RNAs (ncRNAs), and mitochondrial DNA in their composition. The first types of nucleic acids identified in exosomes were mRNAs and miRNAs [10]. In addition to proteins, nucleic acid cargoes directly and indirectly intervene in the development of wound healing by altering the expression levels of various proteins. miRNAs (miRNA-122 /miRNA let7c/miRNA-124) can be considered the most important exosomal nucleic acids. These short non-coding RNAs play a key role in inhibiting the expression of various proteins [11], and cells secrete them to induce or inhibit the expression of various genes [12].

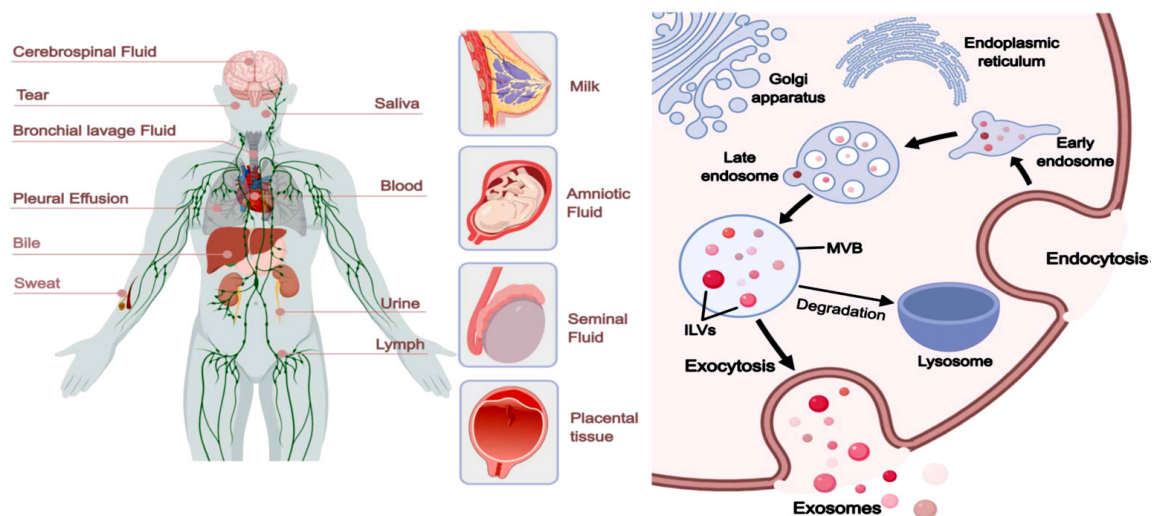


Figure 1. Biogenesis and sources of exosomes. Exosomes are found in every physiological fluid, including urine, blood, sweat, saliva, tears, bile, lymph, cerebrospinal fluid, semen, breast milk, amniotic fluid, and placenta. Exosome biogenesis involves the double indentation of the plasma membrane and the formation of a multivesicular body (MVB) containing intraluminal vesicles (ILV). ILVs are ultimately released as exosomes through the fusion of the MVBs with the plasma membrane and exocytosis [7].

Researchers have identified 9,769 proteins, 2,838 miRNAs, 3,408 mRNAs, and 1,116 lipids present in the exosome cargo [4,5]. Exosome secretion begins with the inward folding of the cell membrane to form an early endosome.

These vesicles then mature into multivesicular structures and absorb their contents. Although many are transported to lysosomes for recycling, secondary mature vesicles are released outside the cell as exosomes [13].

1.4 Challenges and limitations ahead

One of the challenges with exosomes is their extraction, as they are very small and cannot be purified using simple and common methods [6]. Exosomes are typically isolated from cell culture supernatants or biological fluids based on their physical, biochemical, and morphological characteristics. Isolation can be performed by several methods, such as ultracentrifugation, ultrafiltration, gradient ultracentrifugation, sedimentation, size exclusion chromatography, separation methods based on immunological properties, mass spectrometric immunoassay, magnetically activated cell sorting, and microfluidic-based techniques, each of which has its own advantages and disadvantages [6,10]. Ultracentrifugation is the most commonly used method for isolating exosomes. The complex proteins in exosomes are analyzed by processes such as Western blotting, flow cytometry, and mass spectrometry. In addition, high-precision fluorescence analysis of the sample is possible in the nanoparticle tracking method [14]. Given their size, appropriate specificity, and apparent role in many pathobiological processes, the therapeutic potential of exosomes is significant in the management of a variety of neurological disorders, infectious diseases, musculoskeletal disorders, cardiovascular disorders, and wound healing [4]. The use of exosomes in various fields, especially in wound healing, has shown significant effects. Several studies have shown that exosomes extracted from various cells, such as mesenchymal stem cells, can promote faster healing of acute and chronic wounds [15]. These nanovesicles play their role in wound healing by stimulating various processes, including extracellular matrix secretion, increased cell proliferation and migration, induction of angiogenesis, and regulation of inflammatory processes at the wound site [16].

1.5 Exosome sources

Mesenchymal stem cell-derived exosomes are of great interest due to their therapeutic and regenerative potential. Given the challenges of isolating exosomes from various body fluids, regenerative medicine practitioners are using MSC-derived exosomes to treat various disorders. Exosomal cargoes derived from mesenchymal stem cells exhibit intracellular signaling and communication with target tissues. Key sources of

mesenchymal stem cell-derived exosomes include bone marrow, adipose tissue, placental cells, umbilical cord cells, endometrial fluid, and amniotic fluid. MSC-derived exosomes contain cell surface markers such as CD29, CD44, and CD73. They play a critical role in biomechanisms involved in repair and regeneration, bioenergetics, immune regulation, intracellular communication, and tissue metabolism [5]. In a proteomic analysis, a total of 730 protein molecules were isolated in exosomes derived from MSCs from bone marrow. Some researchers have identified the presence of transcriptional signaling factors in exosomal cargo. Amniotic fluid exosomes are preferred over bone marrow-derived exosomes for clinical applications. Mesenchymal stem cells can be obtained from a wide range of body tissues and fluids, such as adipose tissue, bone marrow (BM), dental pulp, synovial fluid (SF), amniotic fluid (AF), placenta (PL), umbilical cord (UC), umbilical cord blood (UCB), and Wharton's Jelly (WJ) [2,17,18]. Since the properties and functions of MSCs depend on their origin, it is obvious that the properties and functional qualities of MSC exosomes will vary based on the origin of MSCs. Therefore, biological differences such as the origin of MSCs and the functionality of their exosomes should be considered for specific clinical applications. However, comparative studies of MSC exosomes based on their tissue origin are still limited [19]. Mesenchymal stem cells, as sources of exosomes, have both self-renewal and differentiation potential (into other cell types) [20]. Although exosomes derived from stem cells have received much attention recently and numerous studies have revealed the benefits of exosomes derived from them, exosome secretion is not limited to them, but a wide range of cells, including fibroblasts, keratinocytes, endothelial cells, and immune cells, secrete their own exosomes and, through them, create their own unique inductive effects [21].

1.6 Mechanisms in wound healing

In addition, blood cells such as white and red blood cells, platelets, and macrophages also secrete specific exosomes, each of which can have a positive effect on skin repair, especially in regulating the inflammatory phase [22]. Platelets are among the first cells to arrive at the wound site in the early days after wound formation and initiate a repair response. Their effects are not limited to the early stages, but platelets affect all stages of wound healing, including hemostasis, inflammation, cell proliferation, and matrix remodeling. Platelets at each stage release secretory packages to the outside, the most important of which are alpha granules, dense granules, lysosomal granules, microvesicles, and exosomes, each of which acts as an extracellular reservoir for the immediate or delayed release of growth factors, cytokines, adhesion proteins, and other signaling molecules (Figure 2) [16,23]. Although these substances can be secreted by themselves, secretion in vesicular forms (exosomes) can deliver them in higher

concentrations and with greater efficiency. One of the important criteria in wound healing is increased cell proliferation. Studies have shown that platelet exosomes have a beneficial ability to increase the proliferation of various cells, including fibroblasts, endothelial cells, and mesenchymal stem cells. Compared with normal cells, those treated with these exosomes show a noticeable difference in their proliferation ability within a period of 24 to 48 hours. Angiogenesis is another trait studied in the assessment of wound healing potential. The formation of new vascular tubes composed of dermal endothelial cells is of particular importance. Platelet exosomes induced the formation of these vessels at a higher rate than normal cells. Human dermal endothelial cells formed longer vascular channels than normal after 5 days of exosomal treatment [24].

Since reactive oxygen species (ROS) cause cellular and tissue damage [25,26] and also inhibit the growth and proliferation of skin cells, their production and presence at the wound site is one of the obstacles that slows down the healing process.

Therefore, it is necessary to neutralize them through a process. Platelet exosomes, especially when applied to the wound with a hydrogel, have the ability to reduce the effect of these substances. Another effect of platelet exosomes is the conversion of the pro-inflammatory

(M1) to the anti-inflammatory (M2) form of macrophages. Macrophages are one of the key elements of wound healing in all its stages. Their conversion from M1 to M2 forms plays an important role in the establishment of the hemostasis and inflammation phase. This feature indicates that macrophages are converted to the M2 form at a higher rate under the influence of this class of exosomes than in the normal state [27].

Studies on signaling pathways have shown that exosomes derived from platelet-rich plasma (PRP) primarily activate the YAP (YES-associated protein) signaling pathway. Thus, under the influence of TGF- β (Transforming Growth Factor- β), the Rho GTPase protein is activated, activating various signaling proteins downstream of it, which ultimately lead to the dephosphorylation of YAP.

Dephosphorylation will cause YAP to move into the nucleus and affect genes related to cell proliferation in fibroblasts. In addition to the YAP pathway, these exosomes can also activate the PI3K/Akt (phosphatidylinositol-3 kinase) and Erk1/2 (Extracellular signal-regulated kinases) pathways. These pathways are considered to be among the underlying mechanisms in endothelial cell proliferation and the angiogenesis process [28].

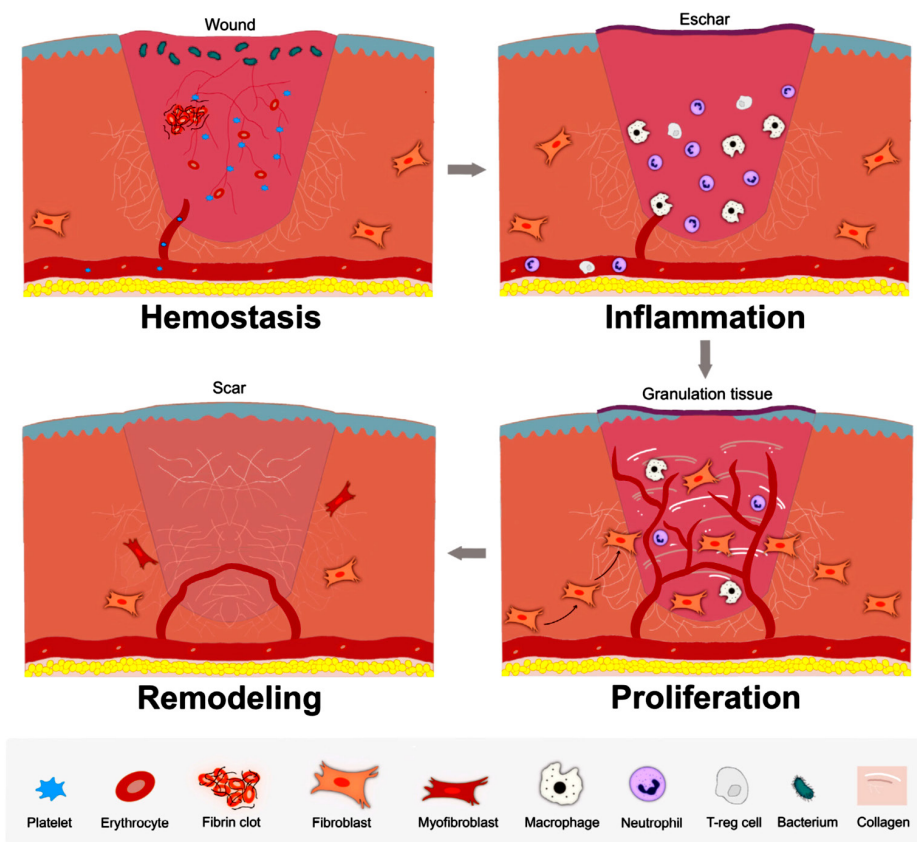


Figure 2. Stages of wound healing. In the hemostatic stage, platelets aggregate to prevent bleeding into the wound, and an initial fibrin clot is formed. In the inflammatory stage, local and systemic immunity responds by recruiting and activating neutrophils and macrophages to neutralize invading bacteria and pathogens. In the proliferative stage, granulation tissue is formed with abundant blood vessels, re-epithelialization, proliferation and migration of fibroblasts, and synthesis of extracellular matrix. In the remodeling stage, the wound is completely closed by matrix deposition and remodeling, and a scar may form [23].

One of the topics of interest in exosome-based therapy is the loading of other drugs into exosomes and the use of the desirable properties of exosomes in drug delivery, as well as the combination of the effect of natural exosome content with a synthetically loaded drug.

It has been suggested that loading curcumin onto exosomes can create positive synergy in wound healing. Macrophage exosomes loaded with curcumin can reduce inflammation and eliminate ROS in damaged tissue, while simultaneously increasing cell proliferation and migration in it. Other therapeutic methods can play a complementary role in improving the function of these exosomes [29].

Erythrocytes, as the main and most abundant blood cells, account for a major share of blood exosomes. Most studies on erythrocyte exosomes have been conducted in relation to blood stored in blood banks. Examination of these cells shows that with the passage of time after the start of storage, the size of erythrocytes as well as their membrane function decreases. In addition to reasons such as increased ROS production, one of the main causes of this decrease is considered to be the frequent secretion of exosomes. As expected, the secretion of these vesicles increases dramatically in pathological conditions. In addition to the general components present in all types of exosomes, erythrocyte exosomes also contain other specific components, including the membrane protein BAND3, the enzyme carbonic anhydrase, and modified hemoglobins [30].

Over 78 different miRNAs have been identified in red blood cell exosomes, with miR125-b-5p, miR4454, and miR451a accounting for the majority of them. The role of these miRs in regulating the immune response and stimulating macrophages and dendritic cells has been demonstrated [12]. Dendritic cells are a group of immune cells found in the blood that originate from the bone marrow and play a role in innate immunity. These cells are antigen presenters to T lymphocytes. They activate T lymphocytes in inflammatory conditions in two ways, directly and indirectly. In the direct method, dendritic cells express MHC-II peptide complexes that bind to T cells, and in the indirect method, secreted MHC-IIs are transferred to the dendritic cells of other cells. These cells activate the dendrites of other dormant cells by transferring MHC-II via exosomes, thereby further activating T lymphocytes [31,32]. By activating T lymphocytes and converting macrophages into an anti-inflammatory form, these exosomes have been able to balance the inflammatory phase and heal the wound caused by myocardial infarction [33,34].

Studies have shown that neutrophil exosomes contain contents that have antibacterial effects, so they can be important in cleaning damaged tissue. Also, if these exosomes are loaded with growth factors, in addition to their antibacterial effect, they can directly affect wound healing [35,36]. Exosomes have also been identified for T/B lymphocytes, mast cells, and other blood cells, each of which has been implicated in fighting various

diseases. Since these cells are generally associated with the promotion of immunogenic and inflammatory processes, they all have the potential to exhibit wound healing effects, which warrants further research into their effects [36].

Exosomes play a crucial role in intercellular communication and may influence disease progression. Recent studies are evaluating the diagnostic and therapeutic aspects of exosomes for various systemic disorders. Detecting substances (intracellular and extracellular) carried by these nanoparticles and promoting their immunological uptake through surface proteins will assist in pathological diagnosis. The spectrum of diseases in which exosomes play a key role in their diagnosis includes cerebrovascular disease, diseases related to the central nervous system, and neoplasms associated with kidney, liver, and lung disease [37].

Exosomes are used as a vector or carrier molecule to elicit biological responses. Extracellular vesicles are derived from various cell types and tissues. When delivered to specific diseased tissue (wound), under specific conditions, EVs promote tissue repair and homeostasis. Extracellular vesicles derived from mesenchymal stromal cells exhibit proliferative, trophic, anti-inflammatory, immunomodulatory, and therapeutic properties. They support neoangiogenesis and cell proliferation [38]. The advantages of exosomal cargoes over stem cells in terms of clinical and therapeutic potential have been identified, including the absence of the inherent risk associated with cell-based therapies, including stem cells, the absence of proliferation potential and risk of malignancy, the absence of immune response to infections and cancers, and targeted action at the desired site [39].

The versatility of extracellular vesicles enhances intracellular signaling capabilities and their movement across cell membranes to restore micromolecular homeostasis. Apart from these benefits, exosomes also offer neuroprotective and regenerative capabilities by crossing the blood-brain barrier in neurological diseases [40]. Exosome delivery routes and modes of action are analyzed, and the challenges they face are highlighted. The most common route is intravenous (IV), which is a rapid route despite its clearance in the liver and kidneys. This method is widely used for conditions including orthopedic, neoplastic, cardiac, and vascular injuries. The intramuscular (IM) route is used primarily in neuromuscular and musculoskeletal conditions, while the subcutaneous (SC) route is used in cosmetic applications. The IM or SC route is chosen due to the ease of the injection site and volume. The intraspinal route is preferred in neurodegenerative conditions such as Alzheimer's, Parkinson's, and Creutzfeldt-Jakob disease. Topical aerosol sprays are used in wound healing. This route is preferred for hair growth and rejuvenation in age-related treatments [41]. There are currently no exosomal products approved by the Food and Drug Administration (FDA) for human use in the

United States. According to the FDA, exosomes require studies that effectively demonstrate safety and efficacy, along with product purity and disease-treating potency. Exosome-based therapies are under the Investigational New Drug (IND) stage of development and require approval from regulatory agencies before clinical trials can begin. The regulatory framework assesses safety standards for microbial and viral contamination and requires Good Manufacturing Practices (GMP), Good Laboratory Practice (GLP), Good Distribution Practice (GDP), Good Clinical Practice (GCP), and Good Storage Practice (GSP) standards for the production and quality control of the relevant treatments to regulate the conduct of clinical trials [42].

According to the Center for Biologics Evaluation and Research (CBER), exosomes are considered biologics. Depending on the type, the framework established for biologics also applies to exosomes. For example, an antitumor vaccine using exosomes would be regulated under the same regulations as cancer vaccines. The functional class of an EV-based therapeutic determines its drug class. Accordingly, the International Extracellular Vesicle Society classifies EV-based therapeutics as biologics with the following properties: Therapies derived from unmodified cells, therapies derived from genetically engineered cells (without transgenes), therapies derived from exosomes, and gene-modified cells with transgenes, which are classified as gene therapy products, and native exosomal therapies used as drug delivery systems, which serve as carriers for chemical and biological compounds and are considered as biologic drugs [43].

The amount of extracellular vesicles can be obtained by measuring the total amount of proteins, lipids, or RNAs, as EVs are composed of all of these molecules. These methods do not provide information about the number of extracellular vesicle particles. Several methods are available to measure the number and size of particles, including nanoparticle tracking analysis (NTA), resistive pulse sensing (RPS), and dynamic light scattering (DLS), with NTA being the most widely used method. NTA determines the number and size of particles by tracking the Brownian motion of single particles in an aqueous solution. However, NTA has a low resolution for dispersed samples. In addition, NTA cannot distinguish extracellular vesicles from other nanoparticles, such as protein beads [44]. Recently, instruments for fluorescence NTA have been introduced that detect fluorescently labeled EVs with specific antibodies. Quantification of extracellular vesicles remains very challenging.

New technologies and instruments have been introduced, including: nanoflow cytometry, direct random optical reconstruction microscopy, ExoCounter with optical disk technology, and imaging flow cytometry [45-48]. In order to investigate and identify extracellular vesicles, proteins associated with exosomes have been reported in studies, such as tetraspanins (CD63, CD9, and CD81), annexins,

flotillin, Alix protein (ALG-2-interacting Protein X), and Tumor Susceptibility Gene 101 protein (TSG101) [49].

These proteins are considered specific markers for exosomes because they are highly enriched in these proteins compared to the cells of origin [49,50]. Furthermore, since Alix and TSG101 proteins are involved in the formation of multivesicular bodies, their presence is essential to support the endocytic origin of exosomes [49].

For quality control, at least semiquantitative methods for the detection of these proteins in exosomes are recommended. Enzyme-Linked Immunosorbent Assay (ELISA) and flow cytometric analysis are both suitable for GMP-compliant and academic laboratories. Although Western blotting has been widely used in academic laboratories, it is limited by the lack of proper quantification and validation [51]. The purity of extracellular vesicles is also a critical quality control criterion. A simple way to monitor the purity of extracellular vesicles is the particle-to-protein, protein-to-lipid, or RNA-to-particle ratios. The absence of intracellular proteins, such as histones, lamin A/C (HSP90B1), GRP94 (Glucose-regulated protein 94), Golgin subfamily A member 2 (GOLGA2), GM130 (Golgi Matrix protein 130), and cytochrome C (CYC1), is another important criterion for determining the purity of extracellular vesicles or exosomes. These proteins are not enriched in exosomes due to their precise cellular location. Impurities from the cell culture process, including antibiotics and serum, should also be analyzed to monitor the removal of potentially hazardous substances [52].

2. Research background

2.1 Preclinical and clinical evidence

In preclinical studies reported on MSCs exosomes, MSCs were isolated from different tissues/cells as follows: bone marrow (51%), umbilical cord/placental tissue (23%), adipose tissue (13%), derived from Embryonic Stem Cells (ESCs) or induced Pluripotent Stem Cells (iPSCs) (8%), and others (5%) [2,5,53,54].

In total, 77 clinical trials have been registered among researchers worldwide in various pathologies. Out of the 77 trials, 11 clinical trials have been completed, and the positive diagnostic and therapeutic effects of exosome-based therapy in various cancers, neurodegenerative and hematological diseases have been proven [55].

In clinical studies conducted on the skin of 11 volunteers, it was found that after 30 days, the wounds created on the skin of all individuals as a result of treatment with these exosomes were completely closed, without leaving any scars [24].

In one study, PRP exosomes were examined along with a hydrogel, and the results obtained indicated that the latter combination increased cell proliferation and migration. As a result of these exosomes, the expression of the growth factors EGF (Epidermal Growth Factor),

VEGF (Vascular Endothelial Growth Factor), IGF-1 (Insulin-like Growth Factor 1), and TGF- β 1 (Transforming Growth Factor-Beta 1) increased, which collectively are considered indicators of the induction of regenerative processes in the skin [56].

A recent study investigated the effect of macrophage exosomes immobilized on a microneedle structure. This immobilization would allow for the gradual release of exosomes into the damaged tissue and their longer-lasting effect. Also, a mild heat shock could stimulate endothelial cell proliferation. Therefore, in this study, a light-sensitive polydopamine hydrogel substrate was used in the wound area, which, upon irradiation with an 808 nm laser, creates a mild thermal shock in the wound area (approximately 40°C). The combination of exosomes immobilized on microneedles with thermal shock has shown greater regenerative effects than the normal state (control) and the separate use of each of these methods, indicating the effectiveness of this type of combined treatment in skin regeneration [57].

Hitoshi et al. (2018) showed that exosomes from stimulated stem cells were more effective than the stem cells themselves in fibroblast migration and wound closure. The scratching method was used to induce fibroblast migration in this study [58].

While numerous studies highlight the therapeutic potential of exosomes, particularly those derived from mesenchymal stem cells (MSCs), for wound healing, a more analytical approach is warranted. The existing findings, though promising, are often presented in isolation without comprehensive and critical comparative analysis.

For instance, the differential effects of MSC-derived exosomes from various tissue sources (e.g., bone marrow, adipose tissue, umbilical cord) on wound repair require more profound investigation to ascertain which source offers the greatest efficacy across different clinical scenarios.

Furthermore, the reported mechanisms of action (such as promoting angiogenesis, modulating inflammation, and stimulating cellular proliferation) sometimes present variations across studies that should be systematically compared and evaluated. Such analysis is crucial for accurately assessing the overall effectiveness and reliability of this therapeutic modality.

3. Research methodology

This manuscript presents a structured narrative review of the literature on the therapeutic role of exosomes in wound healing, conducted according to a predefined search strategy and selection framework. Relevant studies were identified through searches of major scientific databases using predefined keywords related to exosomes, extracellular vesicles, mesenchymal stem cells, and wound healing.

3.1 Search Strategy

In this study, we conducted a comprehensive literature search using the following keywords and their

combinations: ('exosomes' OR 'extracellular vesicles') AND ('wound healing' OR 'tissue repair' OR 'cutaneous regeneration'). Searches were performed in the following databases: PubMed, Scopus, and Web of Science. The search was limited to articles published between 2000 and 2025 and available in English.

3.2 Study Selection Criteria

3.2.1 Inclusion Criteria

Studies focusing on the therapeutic application of exosomes or extracellular vesicles (EVs) in wound healing. Studies involving human or animal models, including in vitro, in vivo, and clinical trials. Articles published in peer-reviewed journals.

3.2.2 Exclusion Criteria

Studies not directly related to wound healing or exosome therapy. Articles not published in English. Studies with unclear or poorly characterized exosome isolation and therapeutic protocols. Duplicate articles and unrelated content in the articles were removed and excluded from the reference set, and the targeted findings were categorized.

3.3 Study Selection Process

The retrieved articles were initially screened by title and abstract to identify potentially relevant studies. Full texts of the selected articles were then reviewed for eligibility based on the inclusion and exclusion criteria. Studies that met the criteria were included in the final narrative synthesis. A total of 152 articles were identified, of which 22 were excluded based on title/abstract screening, and a further 14 were excluded after full-text review, resulting in a final inclusion of 116 studies.

4. Discussion

This manuscript is a narrative review that synthesizes and critically discusses the current evidence on the therapeutic role of exosomes in wound healing. As the spectrum of exosome therapies expands, the International Society of Extracellular Vesicles (ISEV) and the European Network on Microvesicles and Exosomes in Health and Disease (ME-HaD) have developed specific guidelines to promote their use. The provisions of the standard operating protocols should be followed in the collection, processing, testing, quality control, and manufacturing of exosomes for clinical use. With the help of these policies, the potential of extracellular vesicles can be exploited with appropriate standards for therapeutic-clinical applications [59]. Since biological medicinal products include a range of different drugs, therapeutic exosomes were classified as advanced therapy medicinal products (ATMPs) in 2007 [60].

This category is further divided into subgroups of biological pharmaceutical products due to their

biological, physicochemical, and immunochemical properties, which include cell therapy, gene therapy, and tissue engineering products [43]. The production of clinical-grade extracellular vesicles with excellent manufacturing processes and quality control is important for the development of EV-based therapeutics. Furthermore, proper quality control is crucial for reproducible studies in academic settings. The Ministry of Food and Drug Safety of South Korea has issued the world's first guideline for extracellular vesicle therapeutic products, titled Guidelines for the Evaluation of Quality, Non-Clinical, and Clinical Usefulness of Extracellular Vesicle Therapeutic Products. Typical quality control criteria include determination of quantity, size, identity, and purity [52]. Potency assays are the most important quality control measure that predicts the efficacy of EVs in vivo. Regulatory authorities such as the FDA have recommended the appropriate use of potency tests for cell and gene therapy products [51]. In general, the effects of extracellular vesicles on wound healing can be examined in two parts: 1) hemostasis and clot formation after wound formation and 2) formation and induction of an immune response in the inflammatory phase. After a wound is formed on the skin, the first stage of healing is the formation of a clot to prevent bleeding. One of the main processes in clot formation is the conversion of fibrinogen to fibrin, which is carried out by the enzyme thrombin [61]. Research has shown that red blood cell exosomes can increase and activate this enzyme. Red blood cells contribute to the formation of clots at the site of bleeding and promote hemostasis by increasing the production of active thrombin and, subsequently the production of insoluble fibrin [30].

The second stage after homeostasis is inflammation and the recruitment of the immune system to the site of injury. Exosomes play a role in both the initiation and modulation of inflammation in the immune system. They contain the cytokines IL-13, IL-10, IL-5, and IL-1Ra, all of which are involved in the transition from the inflammatory phase. On the other hand, they increase the survival and proliferation of B and T lymphocytes, as well as monocytes. These exosomes significantly increase the levels of IFN- γ (Interferon Gamma), IL-17, and IL-9, which promote the development of T helper 1/9/17 lymphocytes. They help regulate the immune response by creating dual effects on the immune system and, subsequently, enable proper wound healing [22]. Mast cells, dendritic cells, oligodendrocytes, red blood cells, platelets, and white blood cells secrete their own exosomes under both physiological and pathological conditions [30]. Nowadays, considering that platelets exert their major effect through their secretory content, a new method has been invented in which, instead of directly applying these cells to the wound site, the plasma in which the platelets have secreted their exosomes is separated by centrifugation and a PRP is prepared for application to wounds [62].

PRP exosomes have successfully demonstrated their

in vitro-clinical studies and regenerative competence. Although the use of this method has a slight increase in price compared to routine wound treatment in clinics, which is due to the preparation steps, the use of PRP has significantly reduced the duration of hospitalization of patients and increased the likelihood of healing [63]. The effect of combining gel with PRP exosomes on macrophage transformation has also been investigated. In this study, the pro-inflammatory and anti-inflammatory factors of macrophages in the normal state and also in response to exosomal stimulation were examined, and it was observed that pro-inflammatory cytokines such as IL-1 β and TNF- α (Tumor Necrosis Factor alpha) were expressed in greater amounts than in the stimulated state. In contrast, anti-inflammatory cytokines, especially IL-4 and IL-10, were expressed more in the exosome-stimulated sample. This evidence suggests that PRP exosomes combined with the gel were able to induce macrophages to undergo a phase change [56,64]. Macrophage transformation (from the undifferentiated M0 form to the pro-inflammatory M1 and anti-inflammatory M2 forms) is driven by the induction of other cells. For example, under the influence of TNF- α and IL-12, these cells become pro-inflammatory, while IL-10, IL-4 and IL-13 push them towards the anti-inflammatory form. Macrophages not only receive effects from exosomes from other cells, but also secrete exosomes themselves in the blood in abundance, which vary depending on their form. For example, M1 exosomes contain more miR326 than M2, while M2 exosomes contain more miR365. Through these exosomes, macrophages can alter the expression of matrix metalloproteinases as well as inflammatory enzymes and cytokines, which is clearly important in wound healing [65,66]. Studies of the effect of exosomes on wound healing have shown that exosomes derived from M2 macrophages have the ability to enhance angiogenesis in damaged tissue. Studies on them have proven that treatment of human umbilical vein endothelial cells (HUVECs) with M2 exosomes improves angiogenesis-related traits, including proliferation, migration, and tube formation of these cells. VEGF, the most commonly known factor for measuring angiogenesis, was significantly increased after the addition of these vesicles. According to the results of the studies, they exert this effect by activating the Akt/mTOR (mammalian Target Of Rapamycin) signaling pathway. M2 exosomes are rich in miR-21, which can inhibit the expression of PTEN (Phosphatase and TENsin homolog deleted on chromosome 10), which in turn stimulates Akt/mTOR, ultimately leading to an increase in the rate of angiogenesis. Also, applying this exosome to mouse skin was effective, as it completely closed the wound within 15 days after wounding, leaving a much smaller scar [67,68]. These exosomes have also shown anti-inflammatory effects. Various factors and cytokines are involved in the initiation and termination of the inflammatory phase. Measurement of some pro-inflammatory factors, such

as TNF- α and IL-6, and comparison of the values in the normal state and the treatment state with M2 exosomes revealed a significant decrease in them under the effect of treatment, which confirms the hypothesis that M2 exosomes cause wound healing by affecting the inflammatory phase [64,68]. M2 exosomes not only affect other cells but also target macrophages themselves. M2 macrophage exosomes have the ability to switch macrophages from an inflammatory phase to an anti-inflammatory phase, inducing a positive self-regulatory effect [69]. Although the use of blood cells, especially platelets, has shown its effectiveness, issues such as short lifespan after incorporation into the wound site, complex growth requirements, and the risk of tumor formation when using stem cells have prevented the introduction of the aforementioned method as a definitive treatment [70-72]. Although exosome biology provides the mechanistic foundation for their regenerative potential, the therapeutic value of exosomes in wound healing should ultimately be judged by their clinical applicability. Current evidence suggests that exosomes may enhance angiogenesis, suppress excessive inflammation, and promote re-epithelialization and extracellular matrix remodeling; however, most findings remain preclinical. Major translational barriers include the lack of standardized isolation and characterization protocols, variability in exosome source and cargo, uncertainty regarding optimal dosing and delivery routes, and limited long-term safety data. In addition, the absence of large, well-controlled clinical trials has made it difficult to determine whether the promising outcomes observed in experimental models can be reliably reproduced in patients with acute or chronic wounds. Addressing these limitations will be essential for advancing exosome-based therapies from bench to bedside. The use of exosomes still faces challenges, including how to isolate them and the amount of exosome yield from cells. Although the methods used to extract exosomes have been relatively successful in research settings, their applicability for commercial and clinical exosomes is questionable. The extent and quality of a treatment's recovery compared to the usual state is an important indicator of its efficacy for clinical applications. Although blood exosomes have been shown to be effective in wound healing on their own, some research suggests that their use in combination with other drugs and therapies can enhance their effectiveness and promote faster wound healing.

The efficacy of macrophage, platelet, and erythrocyte exosomes in wound healing has been well studied. However, the information available about them is still controversial. With further study of the various exosomes secreted from different tissues, exosome therapy may be a promising strategy for treating and healing a variety of wounds. Despite these promising findings, substantial translational challenges remain. These include the lack of standardized isolation and characterization protocols, variability in exosome cargo

depending on cell source, uncertainties regarding optimal dosage and delivery routes, and limited long-term safety data. Addressing these challenges through multicenter clinical trials, reproducible manufacturing standards, and robust regulatory frameworks will be essential for successful clinical translation of exosome-based wound therapies.

5. Conclusion

Despite the significant potential of exosomes in accelerating and enhancing the wound healing process, the path toward achieving effective and reliable clinical applications is fraught with numerous challenges. At the extraction and purification stage, obtaining sufficient quantities of exosomes with high purity from various cellular sources is a complex process that requires continuous optimization to ensure the final products are free from cellular contaminants and unwanted proteins. Furthermore, the limitations of current separation methods, such as ultracentrifugation or ultrafiltration, often lead to the loss of some exosomes or damage to their delicate structure, which can negatively impact their biological activity. Another challenge pertains to standardization and analysis; the absence of uniform protocols for quantifying, assessing biological activity, and accurately characterizing exosomes makes it difficult to evaluate the results of different studies and hinders their comparability. Finally, challenges in clinical translation and regulation, including ensuring safety and efficacy in animal and human models, obtaining necessary approvals from regulatory bodies like the FDA, and developing sustainable and cost-effective methods for large-scale production, are significant hurdles that must be overcome before widespread clinical use of this therapeutic approach.

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Declaration of artificial intelligence (AI) in the writing process

The authors declare whether AI or AI-assisted technologies were used during the preparation of this manuscript. If used, AI tools were employed solely to improve language quality, grammar, readability, and organizational structure. The authors carefully reviewed and edited all AI-generated content and take full responsibility for the accuracy, integrity, and originality of the final manuscript. No AI tool was used to generate, analyze, or interpret scientific data or images, or to draw scientific conclusions. The use of AI-assisted technologies complies with current publication ethics recommendations and journal policies.

Authors' contributions

MA, PA, AA, MNB, MMMR: Writing original draft. MA, PA: Writing–review and editing. MMMR: Final Editing and Supervision. All authors read and approved the final version of the manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

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