

Review

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Review

Advancements and Insights in Exosome-Based Therapies for Wound Healing: A Comprehensive Systematic Review (2018-June 2023)

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Abstract: Exosomes have shown promising potential as a therapeutic approach for wound healing. Nevertheless, the translation from experimental studies to commercially available treatments is still lacking. To assess the current state of research in this field, a systematic review was performed to examine the methodological heterogeneity among studies conducted over the past five years. Additionally, the review analyzed the suitability of animal models used and their relevance to human medicine. A PubMed search was performed for English-language, full-text available papers published from 2018 to June 2023, focusing on exosomes derived from mammalian sources and their application in wound healing, particularly those involving *in vivo* assays. Out of 531 results, 148 papers were selected for analysis. The findings revealed significant variability in terms of cell sources and types, biomaterials, and administration routes under investigation, indicating the need for further research in this field. Additionally, a comparative examination encompassing diverse cellular origins, types, administration pathways, or biomaterials is imperative. Furthermore, the predominance of rodent-based animal models raises concerns, as there have been limited advancements towards more complex *in vivo* models and scale-up assays. These constraints underscore the substantial efforts that remain necessary before attaining commercially viable and extensively applicable therapeutic approaches using exosomes.

Keywords: animal models; exosomes; skin regeneration; wound healing; systematic review

1. Introduction

The skin serves as the body's external protection against harmful agents, regulating the internal temperature and integrity, while maintaining homeostasis. Under normal conditions, the skin can regenerate itself, through a complex process, that comprehends four distinct phases: hemostasis, inflammation, proliferation, and remodeling. However, when this process fails or is disrupted, it can culminate in impaired tissue regeneration or prolonged wound healing, leading to the formation of chronic wounds [1–3].

Chronic wounds are characterized by a prolonged inflammation (lasting from 4 to 12 weeks), often associated with infections, microbial biofilms, and impaired response from epithelial cells [4]. These wounds are multifactorial and frequently occur in individuals with several diseases, including diabetes, infections and arterial/venous insufficiency [5].

The prevalence of chronic non-healing wounds is increasing due to factors such as population aging and aging-associated diseases, concomitant diseases, tumors and congenital defects, negatively impacting the quality of life of millions of people worldwide. Therefore, the socioeconomical and health care burden is also increasing [1–3].

Current therapies such as debridement, antibiotherapy and dressings remain insufficient, as they are not efficient and there is still a need for new treatments. In the last few years, regenerative medicine has gained popularity, and extensive research has been conducted on mesenchymal stem cells (MSCs) and their derivatives in several fields, including wound healing and skin regeneration.

MSCs are defined by the International Society of Cellular Therapy as similar to fibroblasts, adherent to plastic and with the ability to differentiate into three different cell lines, *in vitro* (chondrocytes, osteoblasts, and adipocytes). These cells should express the surface markers CD73, CD90 and CD105, while not expressing hematopoietic markers (CD14, CD45, CD34, CD19/HLA-DR and CD11b/CD79). These undifferentiated cells have the potential to repair different tissues as they undergo differentiation. Furthermore, MSCs can be obtained from different sources and species. In recent years, there has been a notable rise in the use of MSCs for wound healing purposes, with numerous studies showcasing promising outcomes utilizing cells obtained from diverse sources [1,2].

The use of MSC-derived products, such as secretome and exosomes, when compared to MSCs offers some advantages, including a reduced risk of tumorigenesis and minimal immune rejection [4], being therefore steadily rising. Exosomes are nano-vesicles secreted from the endosomal system (30-150nm) and represent one of the three major subpopulations of extracellular vesicles [6]. The other subpopulations include apoptotic bodies (>100nm) and microvesicles (100-1000nm). Exosomes are produced by several different cell types from different origins [7].

Several studies have shown that exosomes derived from MSCs have similar therapeutic properties, angiogenic ability and immune modulation as the cells from which they originate [3,8–10].

The aim of this systematic review was to assess the methodological heterogeneity in studies and furnish the scientific community with a comprehensive overview of the advancements made in this field over the past five years. Additionally, the review encompassed an analysis of the animal models used to evaluate the translational potential of the data to human medicine.

2. Data and Methods

This systematic review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The main goal of this study was to assess the methodology heterogeneity and provide insights into the progress of exosome research in wound healing over the past five years.

The research involved using the PubMed database, covering the period from 2018 to June 2023. The search query used the following keywords: “wound healing” [Title/Abstract] AND “exosomes” [Title/Abstract] NOT “review” [Title/Abstract], which initially retrieved 531 results.

All 531 publications underwent titles, abstracts and full-text articles examination.

The eligibility criteria included: 1) English language, 2) Full access to the publication, 3) Exosomes from mammalian sources, 4) Exosomes applications in wound healing, and 5) Use of animal models (*in vivo* studies).

Exclusion criteria were applied to filter out the studies that did not meet the research goals, such as: 1) *in vitro* studies, 2) review articles, 3) non-english language publication, 4) studies unrelated to wound healing, 5) no full access to the publication, and 6) studies not involving exosomes.

To ensure rigorous study selection, all authors participated in the process and conducted double-checks. Any discrepancies or disagreements were resolved through discussion and consensus. Duplicates were searched through Endnote software and data analysis was performed using an Excel form specifically designed by the authors.

Among the initial 531 studies, 383 were excluded based on the exclusion criteria mentioned above, resulting in 148 papers. These remaining papers underwent a thorough double-check by all authors.

The extracted information from the selected studies included PMID (PubMed Identification), paper title, publication date, corresponding author's country, cell species, cell type, biomaterial usage, administration route, animal models and exclusion criteria (when applicable).

GraphPad Prism version 8.0.1 was used to elaborate the graphical representations of the collected data.

Bias assessment was evaluated for each study regarding the adherence to MSCs minimal criteria and animal models were examined to determine external validity.

The selection process is summarized in Figure 1.

Through this systematic review, the study aimed to provide valuable insights and contribute to the understanding of exosome-derived treatments in wound healing, with potential implications for potential translation into human medicine.

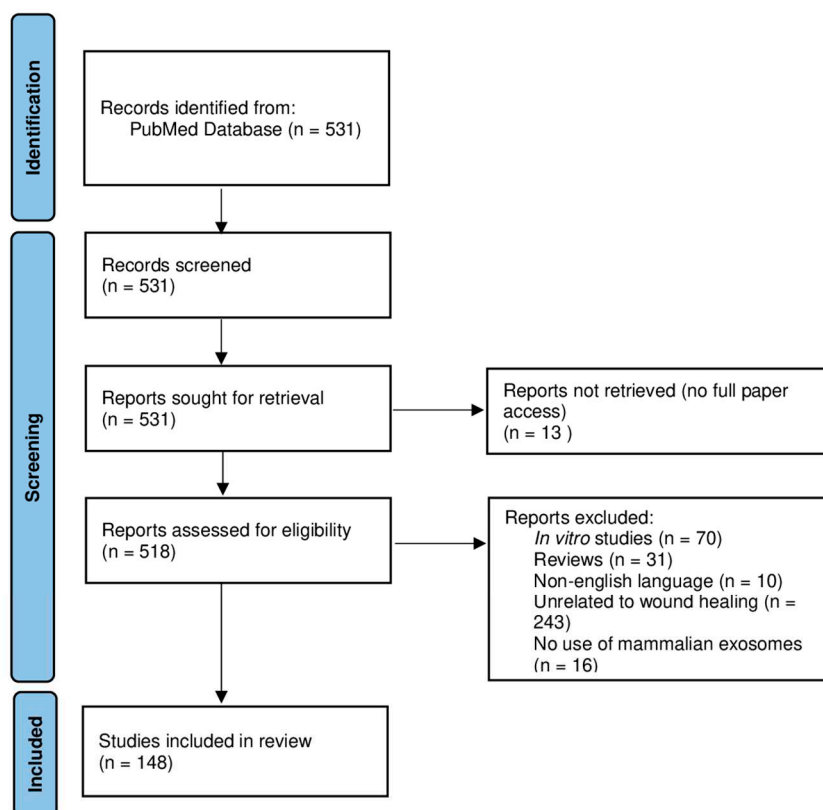


Figure 1. PRISMA Flow Diagram that summarizes the selection process.

3. Results

3.1. Retrieved Data

The following table summarizes the retrieved data from the selected 148 papers (Table 1).

Table 1. Summary of the retrieved data from the 148 papers.

Ref	Year	Country	Cell Source	Cell Type	Biomaterial	Administration Route	Animal Models
[11]	2019	China	Human	ADSC	Hydrogel	SC Injection	Mice
[12]	2020	China	Human	UCMSC	Hydrogel	SC Injection	Rat
[13]	2018	China	Human	UCMSC	x	SC Injection	Mice
[14]	2020	China	Human	BMSC	x	SC Injection	Rat
[15]	2022	China	Human	UVEC	Patch	Patch	Mice
[16]	2022	China	Human	ADSC	Hydrogel	Topical	Mice
[17]	2020	China	Human	BMSC	x	SC Injection	Rat
[18]	2021	China	Rat	BMSC	x	SC Injection	Rat
[19]	2021	China	Human	ADSC	x	SC Injection	Mice
[20]	2018	China	Human	ADSC	x	SC Injection	Rat
[21]	2022	China	Mice	BMSC	Hydrogel	SC Injection	Mice
[22]	2022	USA	Human	Epidermal	x	SC Injection	Mice
[23]	2020	USA	Mice	Keratinocyte	x	SC Injection	Mice
[24]	2022	China	Human	ADSC	x	SC Injection	Mice
[25]	2020	China	Human	BMSC	x	SC Injection	Rat
[26]	2022	China	Rat	BMSC	Hydrogel	Topical	Rat
[27]	2020	China	Human	Peripheral Blood	x	SC Injection	Mice
[28]	2020	India	Rat	ADSC	Scaffold	Scaffold	Rat
[29]	2022	China	Human	DPs	x	SC Injection	Mice
[30]	2019	China	Human	ADSC	Scaffold	Scaffold	Mice
[31]	2021	China	Human	UCMSC	x	EV Injection	Rat
[32]	2019	China	Human	BMSC	x	SC Injection	Mice
[33]	2022	Korea	Mice	BMSC	Hydrogel	SC Injection	Mice
[34]	2020	China	Human	ADSC	x	SC Injection	Rat
[35]	2020	China	Mice	BMSC	x	ID Injection	Mice
[36]	2021	China	Human	ADSC	x	SC Injection	Mice
[37]	2022	China	Human	Epidermal	Hydrogel	SC Injection	Mice
[38]	2022	Korea	Human	ADSC	x	SC Injection	Mice
[39]	2022	China	Human	ADSC	x	SC Injection	Mice
[40]	2019	Korea	Mice	BMSC	x	SC Injection	Mice
[41]	2020	China	Human	BMSC	x	SC Injection	Mice
[42]	2023	China	Mice	ADSC	Hydrogel	SC Injection	Mice
[43]	2021	China	Human	ADSC	Scaffold	Scaffold	Mice
[44]	2021	China	Mice	Serum	x	SC Injection	Mice
[45]	2022	China	Mice	Fibroblast	x	ID Injection	Mice
[46]	2018	China	Human	ADSC	x	SC and ID Injection	Mice
[47]	2019	China	Human	ADSC	x	SC Injection	Mice
[48]	2023	China	Human	Placenta	Patch	Patch	Mice
[49]	2019	China	Human	Embryonic	x	Topical	Mice
[50]	2022	China	Human	UCMSC	x	SC Injection	Mice
[51]	2022	China	Mice	ADSC	x	SC Injection	Mice
[52]	2021	China	Rat and Mice	Serum	x	SC Injection	Mice
[53]	2019	China	Human	Macrophage	x	SC Injection	Mice
[54]	2022	China	Human	UCMSC	x	Topical	Mice
[55]	2019	China	Macaque	iPSCs	x	Topical	Macaque
[56]	2022	China	Mice	ADSC	x	SC Injection	Mice
[57]	2022	China	Human	UCMSC	x	SC Injection	Mice

Ref	Year	Country	Cell Source	Cell Type	Biomaterial	Administration Route	Animal Models
[58]	2020	China	Human	ADSC	x	SC Injection	Mice
[59]	2022	China	Human	UCMSC	x	SC Injection	Rat
[60]	2020	China	Human	UCMSC	x	SC Injection	Mice
[61]	2020	China	Human	UVEC	Hydrogel	Topical	Rat
[62]	2022	China	Human	iPSCs	Hydrogel	Topical	Mice
[63]	2023	China	Mice	ADSC	x	SC Injection	Mice
[64]	2020	China	Human	Amniotic Membrane	x	SC Injection	Mice
[65]	2022	China	Human	UVEC	x	SC Injection	Mice
[66]	2021	China	Human	ADSC	x	Injection and Topical	Mice
[67]	2021	China	Human	UCMSC	Hydrogel	Topical	Mice
[68]	2019	China	Human	UVEC	x	SC Injection	Rat
[69]	2023	China	Human	UVEC	Hydrogel	Microneedle	Rat
[70]	2021	China	Human	UCMSC	Hydrogel	SC Injection	Rat
[71]	2020	China	Human	UVEC	Hydrogel	SC Injection	Rat
[72]	2022	China	Rat	BMSC	x	SC Injection	Rat
[73]	2022	China	Human	ADSC	x	SC Injection	Rat
[74]	2023	China	Human	UCMSC	x	SC Injection	Mice
[75]	2022	China	Mice	ADSC	Hydrogel	Topical	Rat
[76]	2022	China	Human	ADSC	x	SC Injection	Mice
[77]	2019	Japan	Human	Epithelial	x	Topical	Rat
[78]	2022	China	Human	DPs	x	SC Injection	Mice
[79]	2021	China	Rat	Dermal	x	SC Injection	Rat
[80]	2022	Portugal	Human	UCMSC	x	SC Injection	Rat
[81]	2022	China	Rat	Placenta and ADSC	x	SC Injection	Rat
[82]	2022	China	Human	UCMSC	Hydrogel	SC Injection	Mice
[83]	2021	China	Human	ADSC	x	SC Injection	Rat
[84]	2022	China	Human	UVEC	x	SC Injection	Mice
[85]	2019	China	Human	Fetal dermal	x	SC Injection	Mice
[86]	2020	China	Mice	BMSC	x	Topical	Mice
[87]	2023	Iran	Human	Fetal dermal	x	Topical	Rat
[88]	2022	Taiwan	Mice	ADSC and dermal	x	Topical	Mice
[89]	2020	China and Finland	Human	ADSC	x	IP Injection	Mice
[90]	2022	USA	Human	BMSC	x	SC Injection	Mice and Rat
[91]	2020	China	Human	BMSC	x	SC Injection	Mice
[92]	2021	China	Human	UCMSC	x	SC Injection	Rat
[93]	2022	China	Human	ADSC	x	SC Injection	Mice
[94]	2020	India	Rat	ADSC	Scaffold	Scaffold	Rat
[95]	2019	China	Human	Placenta	Hydrogel	SC Injection	Mice
[96]	2020	China	Human	BMSC	x	SC Injection	Rat
[97]	2023	China	Rat	BMSC and plasma	Hydrogel	Topical	Rat
[98]	2021	China and Finland	Human	ADSC	x	IP Injection	Mice
[99]	2021	China	Human	UCMSC	x	SC Injection	Mice
[100]	2020	China	Human	Epidermal	x	SC Injection	Rat
[101]	2020	China	Human	ADSC	Hydrogel	Topical	Rat

Ref	Year	Country	Cell Source	Cell Type	Biomaterial	Administration Route	Animal Models
[102]	2018	China	Human	Plasma	Sponge	Sponge	Rat
[103]	2021	China	Human	UCMSC and ADSC	x	SC Injection	Mice
[104]	2019	Iran	Human	Menstrual Blood	x	ID Injection	Mice
[105]	2020	China	Human	Saliva	x	SC Injection	Mice
[106]	2023	China	Human	ADSC	Hydrogel	SC Injection	Mice
[107]	2021	China	Human	Peripheral Blood	x	SC Injection	Mice
[108]	2021	China	Mice	Plasma	x	SC Injection	Mice
[109]	2018	Japan	Human	iPSCs	x	SC Injection	Mice
[110]	2022	USA	Mice and Human	Plasma	x	Topical	Mice
[111]	2023	China	Human	UCMSC	x	Topical	Mice
[112]	2020	China	Human	Amnion	x	SC Injection	Rat
[113]	2022	China	Human	Keratinocyte	x	SC Injection	Mice
[114]	2022	China	Mice	ADSC	Hydrogel	SC Injection	Rat
[115]	2021	China	Mice	Dermal	x	ID Injection	Mice
[116]	2022	USA	Mice	Skin	Sponge	Sponge	Mice
[117]	2023	China	Human	UCMSC	x	SC Injection	Mice
[118]	2019	China	Human	BMSC	x	SC Injection	Rat
[119]	2021	China	Human	Amniotic Fluid	x	SC Injection	Rat
[120]	2022	China	Human	ADSC	x	SC Injection	Mice
[121]	2018	China	Human	Amniotic Fluid	x	SC Injection	Mice
[122]	2021	China	Human	ADSC	x	SC Injection	Rat
[123]	2020	China	Human	Peripheral Blood	x	Injection	Mice
[124]	2022	China	Rat	ADSC	Hydrogel	Topical	Rat
[125]	2020	China	Human	UCMSC	Nanoparticles	EV Injection	Rat
[126]	2023	Korea	Human	UCMSC	x	Injection and Topical	Mice and Rat
[127]	2022	China	Human	Gingival	x	SC Injection	Mice
[128]	2021	China	Human	UCMSC	Hydrogel	Topical	Rat
[129]	2022	China	Human	BMSC	x	EV Injection	Mice
[130]	2023	China	Human	Keratinocyte	x	SC Injection	Mice
[131]	2021	China	Human	DPs	x	Topical	Mice
[132]	2020	China	Human	UCMSC	Dressing	Topical	Mice
[133]	2023	China	Human	UCMSC	x	SC Injection	Mice
[134]	2021	China	Human	Embryonic Dendritic	x	SC Injection	Rat
[135]	2022	China	Mice	epidermal T cells	x	SC Injection	Mice
[136]	2021	USA	Mice	Skin	Sponge	Topical	Mice
[137]	2023	China	Human	Epidermal	x	SC Injection	Mice
[138]	2022	China	Human	UVEC	x	SC Injection	Mice
[139]	2019	Portugal	Human	UCMSC	Hydrogel	Topical	Mice
[140]	2023	China	Mice	Macrophage	x	Topical	Rat
[141]	2021	Portugal	Human	UCMSC	Hydrogel	Topical	Mice
[142]	2023	China	Human	UCMSC	x	SC Injection	Mice

Ref	Year	Country	Cell Source	Cell Type	Biomaterial	Administration Route	Animal Models
[143]	2021	China	Human	BMSC	x	SC Injection	Mice
[144]	2018	USA	Mice and Human	BMSCs, Skin and Gingiva	x	SC Injection	Mice
[145]	2023	China	Mice	ADSC	x	SC Injection	Mice
[146]	2023	China	Human	Plasma	x	SC Injection	Mice
[147]	2023	China	Human	Hair follicle	x	SC Injection	Mice
[148]	2020	China	Human	ADSC	x	SC Injection	Mice
[149]	2023	China	Rat	ADSC	x	SC Injection	Rat
[150]	2023	China	Mice	BMSC	Dressing	Topical	Rat
[151]	2020	China	Human	Peripheral Blood	x	SC Injection	Mice
[152]	2023	China	Rat	BMSC	Hydrogel	SC Injection	Mice and Rat
[153]	2019	Korea	Human	Fibroblast	x	Topical	Mice
[154]	2020	China	Human	ADSC	x	SC Injection	Mice
[155]	2023	USA	Human	Placenta	x	Topical	Mice
[156]	2023	China	Human	ADSC	x	SC Injection	Mice
[157]	2021	Egypt	Dog	BMSC	Hydrogel	Topical	Dog
[158]	2021	China	Human	ADSC	x	SC Injection	Mice

3.2. Scientific data production and publication distribution between 2018 and June 2023:

All 148 papers selected were comprehensively analyzed to assess the temporal distribution of its publication across the five-year timeframe (Figure 2). In 2018, a total of 7 papers were published (4,7%). The subsequent year, 2019, witnessed a notable increase in publications, with 16 papers accounting for 10.8% of the selection. The publication rate continued to rise in 2020, reaching 30 papers (20,3%). In 2021, 29 papers were published (19,6%). The most significant publication rate occurred in 2022, with 42 papers published (28,4%). Up until June 2023, 24 additional papers have already been published, indicating that the year will probably surpass previous records (16,2%). These data demonstrate that there has been a continuous and stable increase in scientific investment in this research area, with the number of works carried out and published results increasing continuously.

Publications per year

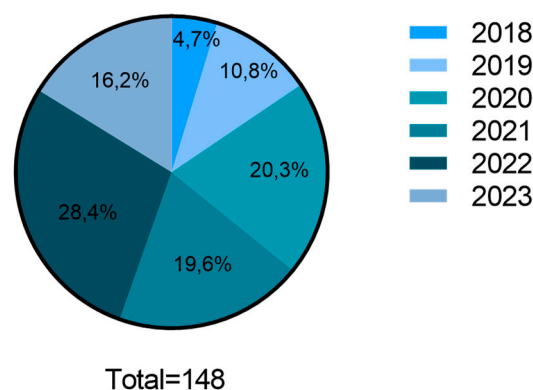


Figure 2. Graphical representation of publication distribution per year, from 2018 to June 2023.

The geographical distribution of scientific publications in the field of exosome application in wound healing was examined, focusing on the corresponding author's country over a 5-year timeframe (Figure 3). China emerged as the country with the highest scientific publication rate in

this field, with 122 publications (82,4%). The United States of America (USA) followed with 8 publications (5,4%), South Korea with 5 publications (3,4%) and Portugal with 3 publications (2,0%). Other countries have lower publication rates: Japan recorded 2 publications (1,4%), as did Iran (1,4%) and India (1,4%). Similarly, Egypt and Taiwan each had 1 publication (0,7%). Additionally, a collaboration between China and Finland resulted in 2 publications (1,4%).

Papers per Country

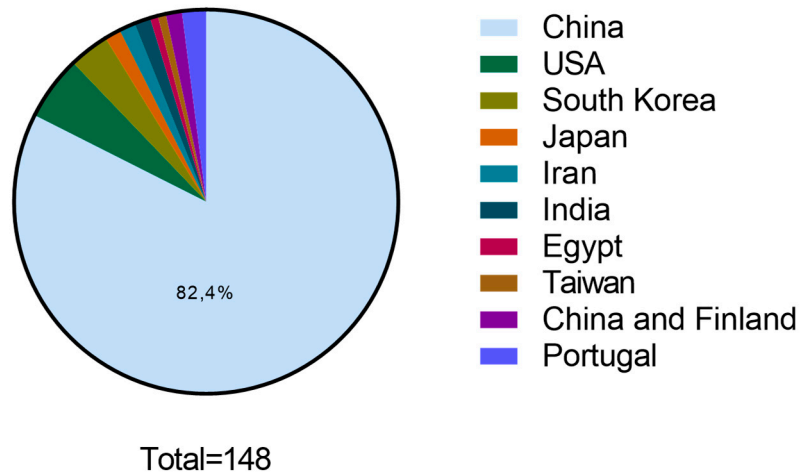


Figure 3. Graphical representation of publication distribution per corresponding authors country (2018- June 2023).

3.3. Cell source and type

Cell source was analyzed as seen in Figure 4. Among the papers analyzed, human tissues were the preferred cell source for exosome extraction (73,6%). Then, rodent-derived cells corresponded to 23%, with 15,5% from mice and 7,4% from rat. The other sources, although less frequent, consisted of dog (0,7%) and macaque (0,7%). Furthermore, 1 study compared mice and rat-derived exosomes (0,7%), while 2 independent studies compared both mice and human-derived exosomes (1,4%).

Cell Source

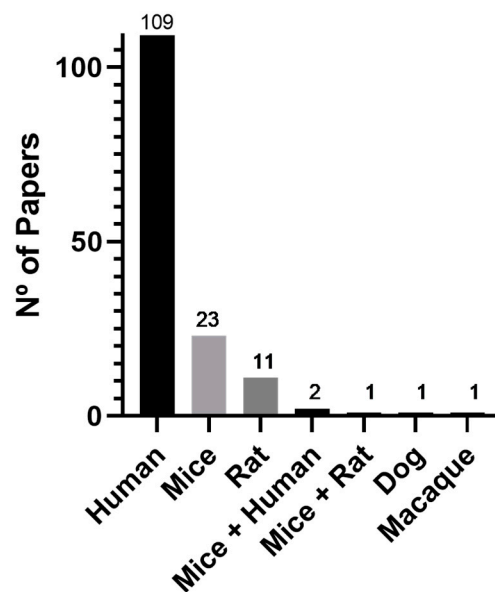


Figure 4. Graphical representation of cell tissue source distribution in scientific literature between 2018 and June 2023.

According to the data presented in Table 2, the most commonly used to extract exosomes in humans is the adipose tissue (ADSC) with 26,6%, followed by the UCMSCs (umbilical cord mesenchymal stem cells) with 22,9%, and the BMSCs (bone marrow derived mesenchymal stem cells) with 10,1%. Other tissues still present considerable percentages of use, such as placenta (2,8%), peripheral blood (3,7%), epidermal (3,7%), DP (dental pulp derived mesenchymal stem cells) (2,8%) and umbilical vein (7,3%). Regarding mice, adipose tissue emerges as the preferred source (30,4%), followed by bone marrow (26,1%). In rats, both adipose tissue and bone marrow (36,4%) are favored as primary sources for exosome extraction. These results are in agreement with the general scientific literature related to the use of cell-based therapies, where adipose tissue, bone marrow and umbilical cord are the most explored tissues and the respective MSCs are the most studied and characterized cells both for their direct use and of their secretion products.

Table 2. Summary of the most used cell types of the most common species.

	Human (109 studies)	Mice (23 studies)	Rat (11 studies)
BMSC	11 (10,1%)	6 (26,1%)	4 (36,4%)
ADSC	29 (26,6%)	7 (30,4%)	4 (36,4%)
UCMSC	25 (22,9%)	X	X
UVECS	8 (7,3%)	X	X
DP	3 (2,8%)	X	X
Epidermal	4 (3,7%)	X	X
Peripheral Blood	4 (3,7%)	X	X
Placenta	3 (2,8%)	X	X
Others	22 (20,2%)	10 (43,5%)	3 (27,3%)

3.4. Biomaterials and Administration Route

As seen in Figure 5, the analysis of biomaterials used in all 148 papers revealed that the majority of studies chose to use exosomes without any biomaterial (73,6%). However, when a biomaterial was selected, hydrogels were the most commonly used (18,2%). Other biomaterials were also employed in several studies, such as scaffolds (2,7%), patches (1,4%), sponges (2,0%), nanoparticles (0,7%) and dressings (1,4%).

Biomaterials used in Publications

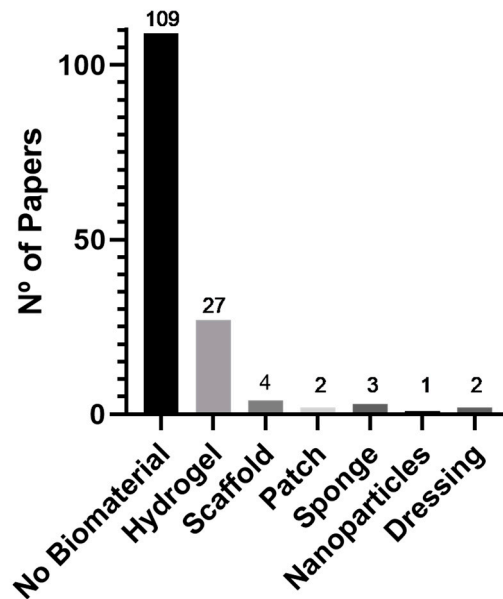


Figure 5. Graphical representation of the biomaterials used in publications related to wound healing between 2018 and June 2023.

In the analysis of these 148 papers, the administration route of exosomes was analyzed and compared to the selected biomaterials, as illustrated in Figure 6. The preferred method, regardless of the presence of biomaterials, was via subcutaneous (SC) injection at the wound margins (66,2%). Within this route, subcutaneous injection without a biomaterial (57,8%) was the most common approach, while the association with a biomaterial was only 8,8%.

Topical administration was used 25,7%, with 16,9% involving the use of a biomaterial and 8,8% without one. Other administration routes included intradermal (ID) injection (2,7%), intraperitoneal (IP) injection (1,4%) and endovenous (EV) injection (2,0%). There were also 2 papers that compared topical and subcutaneous injections (1,4%), while 1 study compared topical and intradermal injections (0,7%).

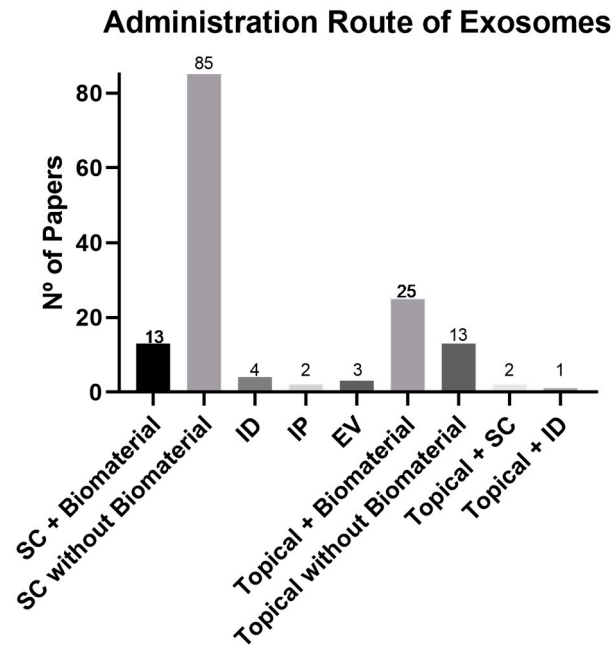


Figure 6. Graphical representation of the administration route of exosomes used in wound healing between 2018 and June 2023. EV – Endovenous, ID – Intradermal, IP – Intraperitoneal, SC - Subcutaneous.

3.5. Animal Models

Among the studies included in the analysis, rodents were used in the majority, accounting for 96,6% of the total (143 studies), with mice comprising 66,9% (99 studies) and rats 29,7% (44 studies). Also, two studies used both mice and rats (1,4%), while one study used a non-human primate model (0,7%) and the last used a canine model (0,7%). Figure 7 provides a visual representation of the distribution of in vivo models used in the selected studies.

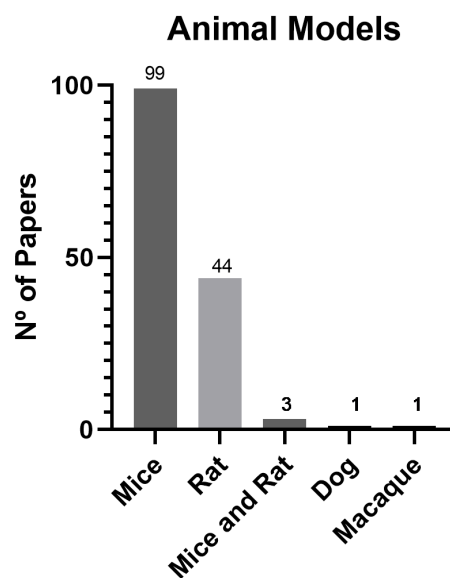


Figure 7. Graphical representation of the animal models used in wound healing between 2018 and June 2023.

4. Discussion

4.1. Scientific data production and publication distribution between 2018 and June 2023:

The publication rate regarding the use of exosomes for wound healing has shown a significant increase in the last five years, with 2022 marking the highest publication rate to date. Based on the count of 24 publications as of June, 2023 is expected to surpass previous records.

This notable increase in scientific publications reflects the recent emergence and promising outcomes of exosome-based therapies in wound healing. It is expected that even more valuable data will be published in the next years.

In addition, China stands out as the leading country regarding publication rate, which demonstrates the high importance this topic in this country. However, there remains a gap in research development and publication in this field, in other countries, particularly in Europe and America. It is essential to encourage research and publication in these regions, in order to promote advancements in the field of exosome-based therapy worldwide.

4.2. Cell source and type

Among the preferred tissue source for exosome production, human-derived cells accounted for 73,6% of the studies, followed by rodent-derived cells at 23%, with 15,5% from mice and 7,4% from rat.

Within the human-derived cells, the most commonly used tissue is the adipose tissue (26,6%), followed by the umbilical cord (22,9%) and the bone marrow (10,1%). In mice, adipose tissue emerges as the preferred source (30,4%), followed by bone marrow (26,1%). In rats, both adipose tissue and bone marrow (36,4%) are favored as primary sources for exosome extraction.

Given that the ultimate objective of most studies is the development of exosome-based therapies for human medicine, the retrieval of exosomes from human tissues appears to be a logical approach. However, the significant heterogeneity within the tissues, poses challenges in comparing results, as researchers have not reached an understanding of the most efficacious treatment option.

The preferred use of ADSCs (adipose tissue derived mesenchymal stem cells) is probably due to their low ethical issues, easy extraction, and cost-effectiveness. ADSCs have shown potential in wound healing, by increasing vascularization, fibroblasts migration and differentiation, and upregulating macrophages chemotaxis [2,159,160].

BMSCs have also demonstrated great potential in wound healing, increasing angiogenesis and reducing wound contraction [160]. Additionally, BM-MSCs have garnered significant attention as the most extensively investigated subset of MSCs and have been recognized for their relatively low immunogenicity [2].

UCMSCs have also shown their wound healing potential, as they can differentiate into epidermal tissue and are easier to harvest than BM-MSCs [1,2].

The variation observed in exosomes derived from different species and tissues still needs further research and understanding. The goal should be to identify the most effective sources and optimize and standardize the isolation processes to ensure consistent and reliable outcomes. By doing so, the scientific community can more accurately make comparisons between studies and advance towards the development of efficacious therapeutic approaches.

In addition, it is valuable to explore alternative sources of exosomes beyond those currently described, as it may uncover potential benefits and characteristics, broadening the range of therapeutic options.

Overall, while human-derived exosomes remain the preferred choice due to their ultimate clinical relevance, efforts should be made to refine the current methodologies and promote collaborations between research groups to better understand the most effective exosome-based treatments.

4.3. Biomaterials and Administration Route:

In most studies, exosomes were administered via SC injection in the wound margins, either without a biomaterial (57,8%) or in combination with a biomaterial (8,8%). This delivery method offers ease, speed, and localized treatment administration. Considering that most skin wounds are created on the animal's dorsum, incorporating biomaterials can be difficult, requiring prior development and testing. SC injection of MSCs has also demonstrated great results regarding wound closure, angiogenesis and re-epithelization. Alternatively, topical administration is also used (25,7%), as it is less invasive and less painful than the injection methods [161].

However, when a biomaterial was selected it was predominantly a hydrogel (18,2%). Other biomaterials were also applied in several studies, including scaffolds (2,7%), patches (1,4%), sponges (2,0%), nanoparticles (0,7%) and dressings (1,4%).

The combination of biomaterials aims to improve the therapeutic functionality of exosomes by stabilizing them and prolonging their release at the wound site, thereby preventing rapid entry into blood circulation and systemic dilution. Hydrogels, specifically, offer several advantages in wound healing, such as antibacterial activity, facilitation of tissue adhesion, protection against UV radiation, hemostatic capacity, promotion of spontaneous regeneration and easy injectability. They can also provide a 3D environment and mimic the extracellular matrix, while maintaining proper moisture levels at the wound site. Therefore, the use of exosomes associated with hydrogels has shown to improve wound healing, enhancing re-epithelization and vascularization [4,162].

Hydrogels based on chitosan or methylcellulose are considered great options for diabetic wound treatment and have been used in some of the selected studies. These polymers have good biodegradability, biocompatibility and are nontoxic. Geng et al, developed a loaded carboxyethyl chitosan hydrogel loaded with bone marrow derived exosomes to improve chronic diabetic wound healing. It increased angiogenesis and neovascularization, reduced local inflammation and improved wound healing in diabetic rats [26].

Pluronic F-12 hydrogels have also been used in selected studies, as they are injectable, biocompatible and thermosensitive. Zhou et al used a pluronic F-12 hydrogel combined with adipose tissue-derived exosomes to improve re-epithelization, angiogenesis, collagen synthesis and enhanced wound healing and cellular proliferation in mice [16]. Yang et al, also used a similar hydrogel combined with human umbilical cord-derived exosomes with increased wound closure rate and granulation tissue in rats [12].

Gelatin methacryloyl (GelMA) hydrogels were also chosen in different studies, due to their mechanical properties and ability to retain exosomes for a prolonged time. Zhao et al, used Human Umbilical Vein Endothelial Cells (HUVECs) derived exosomes in association with a GelMA hydrogel and demonstrated an improvement of angiogenesis and collagen maturity in rats [55]. Hu et al, used a similar hydrogel with ADSCs-derived exosomes and showed an improvement of wound healing with an increased blood vessel regeneration, proliferation and migration, in mice [42].

Several studies have combined hydrogels and MSCs, with promising results in skin regeneration. The use of BMSCs seeded into hydrogels improved angiogenesis and accelerated wound healing, in mice [163]. Another study demonstrated reduced scar formation, improved angiogenesis, collagen, granulation and re-epithelization in rabbits, using ADSCs combined with an hydrogel [164].

These findings emphasize the importance of carefully selecting the biomaterials and administration route to optimize the therapeutic effects of exosomes in wound healing.

4.4. Animal Models

The results showed that rodents are the main animal models in studies involving exosome-based therapies in wound healing (96,6%). These findings are consistent with Al-Masawa et al previous findings up until March 2021 [3].

The use of small animal models has several advantages such as researchers' familiarity, easy handling, affordability, and availability. However, there are also limitations associated with these

models, including skin thickness, fast hair growth cycles, follicular pattern and wound size [165]. Rodents exhibit a thin epidermis and loose skin adherence, along with dense hair that has been suggested to potentially enhance the wound healing rate. In addition, these animals lack apocrine and eccrine glands, but possess a subcutaneous panniculus carnosus muscle, that enhances rapid wound contraction. Moreover, they also have stronger immune systems and have endogenous sources of vitamin C, which plays a significant role in wound healing [166,167].

Although rodent models are frequently used in the initial stages of new therapies approaches, it is necessary to scale-up to more complex animal models to better reflect the similarities between such models and the human species. The main goal of most researchers is to develop new treatments options for non-healing chronic wounds and make them commercially available to the human population. Therefore, the consistent use of rodents in 96,6% of studies over the last five years limits the broader application of this data.

Although the use of exosome-based therapies has been showing promising results over last few years, the inclusion of larger animal models, such as ovine, swine, dog and non-human primates is crucial. In addition, it is important to fulfill the 3Rs principle (replace, reduce and refine) regarding animal use, implying that research data should evolve until commercialization becomes possible [168,169].

However, these more complex models present challenges, as they are more expensive, more difficult to handle and require large set-ups. Pigs, for instance, are regarded as standard models for wound healing research due to the resemblance of their skin to that of humans. They also present physiological and anatomical similarity to the human species. Nonetheless, to date, no studies have been conducted on this particular species. Non-human primates, although sharing greater similarity with humans, are rarely used mainly due to ethical concerns [165,166].

The porcine model has been used in wound healing research, with promising results. In particular, the administration of BMSC and ADSC intradermally into partial-thickness wounds enhanced local epithelization and improved wound appearance, when compared to the control [170,171]. This suggests that the use of this cells can accelerate the wound healing process.

Martinello et al, used the ovine model in wound healing and achieved great results. The local injection of peripheral blood MSCs in the wound margins revealed improved re-epithelization, proliferation, neovascularization and contraction, with higher wound closer rate [172].

In dogs, the use of MSCs to treat chronic wounds has also demonstrated great potential. UCMSCs have been used in association with a PVA hydrogel showed significant progress in wound regeneration and decreased local ulceration [173]. Other study, using ADSc also improved re-epithelization, reduced local inflammation, promoted epidermal and dermal regeneration in both acute and chronic wounds [174]. In the selected study using a dog model, Bahr et al used BM-MSCs derived exosomes in association with a carboxymethylcellulose hydrogel. The results were promising, as the treatment enhanced wound healing with no scarring, with organized collagen deposition and increased dermal fibroblasts [157].

Lu et al, used autologous and allogeneic iPSCs derived exosomes to improve wound healing in macaques. It demonstrated an increased angiogenesis, collagen deposition, epithelial coverage and wound closure rate [55].

While acknowledging the differences among animal models, current approaches in wound healing remain highly relevant. However, it is crucial to increase the use of diverse and more complex animal models to bridge the gap between current findings and their practical application in the human species [175].

5. Conclusions

This comprehensive systematic review highlights the great potential of exosomes as therapeutic options for non-healing chronic wounds. Despite their promising role, the methodology associated with the use of exosomes-based therapies in wound healing remains highly heterogeneous. Further research endeavors are imperative to facilitate the commercial availability and clinical application of these treatments.

The considerable variability in cell sources, types, biomaterials, and administration routes under investigation shows the urgent need of further research in this field. Moreover, the lack of comparative studies exploring different cell sources/types, administration routes or even biomaterials is a critical gap that must be addressed. Furthermore, the predominant use of rodent-based animal models raises concerns, as limited progress has been made in advancing toward more complex in vivo models that closely resemble human physiology.

This study also has certain limitations, primarily due to the potential bias associated with study design and methodology of the included studies. To address these limitations, it is crucial that future research incorporates measures to mitigate bias, such as randomization, blinding and standardized protocols.

To achieve a commercially viable and widely accessible range of therapeutic options, several key objectives must be pursued in the future. Standardizing methodologies is paramount to ensure more reliable and comparable results. In addition, the inclusion of more complex animal models that closely mimic the human species will enable effective translation of research outcomes. These collective efforts will drive the field closer to its ultimate goal of achieving large-scale production and widespread availability of exosome-based therapeutic option for wound healing.

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Abbreviation:

ADSC	Adipose Tissue derived Mesenchymal Stem Cells
BMSC	Bone Marrow derived Mesenchymal Stem Cells
DPs	Dental Pulp derived Mesenchymal Stem Cells
EV	Endovenous
ID	Intradermal
IP	Intraperitoneal
iPSCs	Induced Pluripotent Stem Cells

MSCs	Mesenchymal Stem Cells
PMID	PubMed Identification
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SC	Subcutaneous
UCMSC	Umbilical Cord Mesenchymal Stem Cells
UVEC	Umbilical Vein Endothelial Cells

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