Int J Burn Trauma 2026;16(5):169-186
www.IJBT.org /ISSN:2160-2026/IJBT0173226

Review Article

Influence of macrophage-derived exosomes in wound healing: a systematic review and meta-analysis of animal studies

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Received April 11, 2026; Accepted July 8, 2026; Epub October 25, 2026; Published October 30, 2026

Abstract: Objectives: Long-term and acute skin lesions are relatively severe in terms of health and economy. Macrophage-derived exosomes are promising acellular therapeutics, but their subtypes and corresponding effects are unknown. This paper will systematically study the effect of polarisation on wound healing in animal models. Methods: 17 preclinical studies of macrophage-derived exosomes in wound healing were included in this meta-analysis, and the risk of bias was evaluated using the SYRCLE tool. Results: Our analyses Shows Differential Performance. M1 macrophage-derived exosomes significantly suppressed wound healing (SMD = -1.38, 95% CI [-2.29, -0.47], P < 0.05), whereas exosomes from M0 and M2 macrophages promoted healing (M0: SMD = 3.05, 95% CI [1.60, 4.50], P < 0.05; M2: SMD = 4.04, 95% CI [3.39, 4.69], P < 0.05). In addition, M2 exosomes promoted the healing of wounds by the following ways: they reduced Notch length (SMD = -6.46, 95% CI [-7.89, -5.03], P < 0.05), increased granulation tissue thickness (SMD = 10.84, 95% CI [7.13, 14.55], P < 0.05), and promoted collagen deposition (M0: SMD = 2.56, 95% CI [0.71, 4.41], P < 0.05; M2: SMD = 2.63, 95% CI [0.72, 4.54], P < 0.05), as well as microvessel density (M0 and M2: SMD = 5.02, 95% CI [1.85, 8.20], P < 0.05); preconditioning strategies further enhanced their efficacy, and pre-treatment or modification of exosomes can be used to improve their performance. Conclusions: M2 and M0 macrophage-derived exosomes promote wound healing, M1 exosomes inhibit it, and preconditioning further improves this effect.

Keywords: Macrophages, exosomes, wound healing, meta-analysis

Introduction

As the frequency and prevalence of diseases like inflammation, trauma, and tumors [1-3] increase, the number of wounds associated with these diseases has also gone up. Wounds have become an important clinical condition or complication that is the most prevalent and chronic [4]. In the meantime, as the trends of population aging and increasing obesity rates have been progressing, so has the prevalence of aging related diseases including diabetes, obesity, metabolic disorders, auto immune diseases and cardiovascular issues. Consequently, it has led to the emergence of impaired wound healing as a significant issue that not only impacts human health, but also the healthcare burden of global healthcare systems [5]. Estimates show that the problem of impaired wound healing is estimated to impact about 6.5 million individuals annually, and the healthcare systems use more than 25 billion dollars annually to treat chronic wounds [6]. The present wound management techniques consist of wound evaluation, debridement, antibiotic and other forms of dressing, skin substitutes, growth factors, negative pressure wound care, hyperbaric oxygen therapy and skin grafts or flap transplantation [7, 8]. Nonetheless, these methods of treatment cannot always cope with the underlying pathophysiological processes of wounds, which can often lead to the most inad-

https://doi.org/10.62347/ZBKK7105

equate outcomes, infections, and even more serious complications. Thus, the elaboration of effective and properly designed wound management strategies has gotten more and more significant.

Wound healing is a highly controlled process that comprises of hemostasis, inflammation, proliferation and remodeling. Close coordination of every step is crucial with any failure in one step greatly affecting the overall healing process [9, 10]. The interaction between several cell types is involved in this process and is guided by a complex and dynamic interaction among them [11, 12].

Macrophages are important regulators of all wound healing phases being pivotal in coordinating the inflammatory process and controlling crucial events in tissue regeneration due to their essential regulatory roles [9, 13]. Macrophages are very plastic and heterogeneous, thus are able to vary into different phenotypes in reaction to microenvironmental signals and, thereby, fulfill various functions [14]. Macrophages are usually divided into M1 and M2 phenotypes based on surface markers, as well as the cytokines they produce [15]. M1 macrophages, which have a pro-inflammatory phenotype, are the ones that are involved in the initial stages of inflammation, and are used to dispose of pathogens and necrotic debris. They also release a lot of cytokines, such as interleukin-1 beta (IL-1 beta), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). Excess of such cytokines can cause chronic inflammation and hinder wound healing process [16]. M2 macrophages, in contrast, are associated with the production of many anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta (TGF-beta). M2 macrophages are involved in clearing apoptotic cells and damping proinflammatory responses, thereby providing the wound with the optimal environment to resolve and regenerate tissues [17, 18].

Exosomes are a category of extracellular vesicles produced by eukaryotic cells through the endosomal pathway, and are usually between 30 and 150 nanometers in diameter [19]. Macrophage exosome secretion is also regulated by the fundamental pathway of multivesicular bodies (MVBs) biogenesis, trafficking and plasma membrane fusion, and can be polarized in secretion during physiological events like chemotaxis and immune synapse formation [20]. Exosomes can penetrate cell membranes and can be used to target particular recipient cells due to their long half-life and low immunogenicity [21]. The exosomes are also able to engage in intercellular communication, antigen presentation, and other physiological and pathological mechanisms through the delivery of miRNAs, proteins, and other molecules. They can regulate the polarization state, inflammatory response, and metabolic reprogramming of neighboring cells, thereby playing key roles in immune responses and the regulation of the inflammatory microenvironment [22].

Research has indicated that exosomes have great potential in facilitating tissue regeneration and healing, and can help in healing different tissues including bone, skin, tendons, and dental pulp [23-26]. Additionally, the surface engineering of exosomes and their use as vehicles of delivery confer on them greater specificity and therapeutic ability [27]. Most recent research is beginning to emphasize the critical involvement of macrophage exosome-derived exosomes in the regulation of immune regulatioregulationn [28-30]. Exosomes produced by different kinds of macrophages are also different in their immunomodulatory effects and have various functions in wound healing [31, 32]. However, the evidence for their function in the repair of wounds is still mostly at the preclinical stage and not well-established. Therefore, we have studied the impact of macrophage-derived exosomes on wound healing and skin regeneration in animal models systematically.

Materials and methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses [33] and was prospectively registered on the Open Science Framework (OSF) with the registration link: https://doi.org/10.17605/OSF.IO/HBQF2.

Search strategy

Three independent authors conducted an all-encompassing literature search with the key-

words “exosomes”, “macrophages” and “wound healing”, as well as their synonyms. Search for relevant papers in PubMed, Cochrane Library, Embase and Web of Science using MeSH terms, free-text terms and Boolean operators, and limit the search to studies published before March 1, 2026. The particular search strategy is shown in Supplementary Table 1. Search only contained studies on animals. In addition, the reference lists of the included articles were manually screened for any other potentially eligible studies. All of the retrieved articles were manually filtered further to select the final set of studies for this paper.

Inclusion and exclusion criteria

Inclusion criteria: (I) Studies involving animal models; (II) Studies that included both a control group (receiving either an inert solution, placebo, or no treatment) and an experimental group treated with macrophage-derived exosomes; (III) Studies reporting at least one of the following outcomes: wound healing rate, collagen deposition, neovascularization density, re-epithelialization, scar width, or levels of inflammatory markers; (IV) Studies that provided a description of the isolation and characterization methods for macrophage-derived exosomes.

Exclusion criteria: (I) Studies not based on animal experiments; (II) Studies lacking a control group that received an inert solution, placebo, or no treatment; (III) Studies published in Chinese; (IV) Case reports, reviews, or clinical trials; (V) Studies without available or extractable data.

Evaluation indicators and methods

Wound healing was evaluated primarily using five key indicators: wound closure rate, epidermal and granulation tissue thickness, collagen deposition and type I/III collagen ratio, and neovascularization density. First, the most intuitive evaluation indicator was wound size and closure rate. Based on wound healing photographs taken at different time points, and using the wound area on the day of modeling as a reference, the closure rate was calculated using the formula: $(Area_0 - Area_n)/Area_0 \times 100\%$, where $Area_0$ represents the wound area on the day of modeling, and $Area_n$ represents the wound area at different time points. For epidermal and granulation tissue thickness, sections stained with hematoxylin and eosin (H&E) were examined under a light microscope, and the thickness was measured at three to five randomly selected sites per section, expressed in millimeters. Collagen deposition was assessed using Masson’s trichrome staining, with quantitative comparison based on the area occupied by collagen, while the type I/III collagen ratio was expressed as the ratio of Col I to Col III. Finally, neovascularization density was evaluated by CD31 and α-SMA immunohistochemical staining, using the number of blood vessels per square millimeter as the evaluation indicator.

Data extraction

Two researchers carried out the literature search, article selection and methodological quality assessment independently in accordance with the above plan. All the studies that met the inclusion criteria were independently judged by the two reviewers, and any disagreement arose due to discussion with a third reviewer. The reviewers reached a consensus and, at this time, began the work of extracting, organising and verifying the data. If the original numerical data could not be presented in the manuscript text, then a plot was obtained through WebPlotDigitizer (https://apps.automeris.io/wpd/). The extracted data included: (1) General study details: first author, publication year, and study location; and (2) Animal model parameters: species, age (or weeks of life), and number of subjects; (3) Model details: method of model construction, wound site, and wound size; (4) Exosome information: source, extraction method, characterization and identification, pre-treatment or engineering strategies; (5) Treatment details: mode of administration, dosage and concentration, follow-up duration; (6) Wound healing-related outcomes: including wound closure rate, neovascularization, collagen deposition, re-epithelialization, scar width, and levels of inflammatory markers; (7) Reported adverse events.

Risk of bias assessment

Based on the SYRCLE risk of bias tool, all the included studies of interventional animal

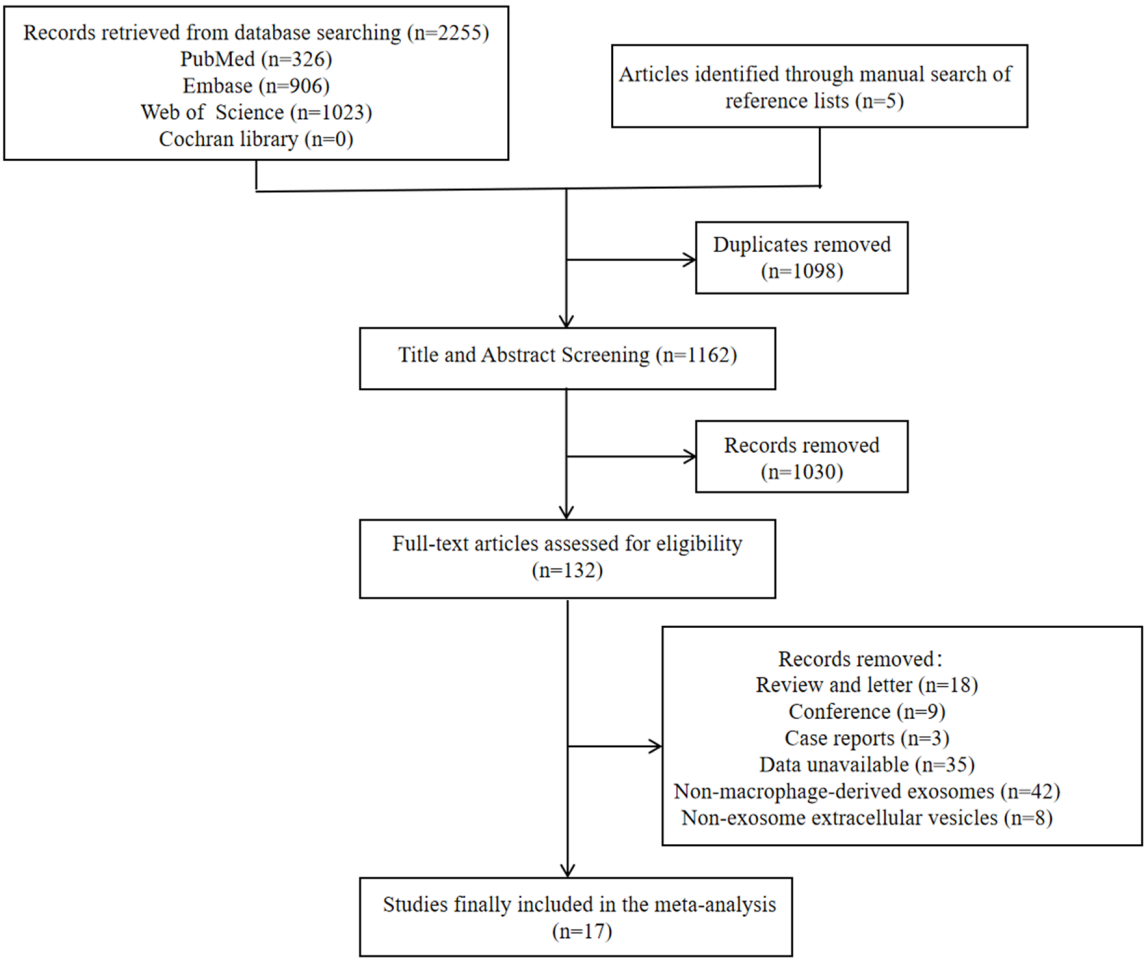


Figure 1. Diagram of the Literature Retrieval and Screening Procedure.

research were rated for a risk of bias. All kinds of biases in this study include selection bias, performance bias, detection bias, attrition bias, reporting bias, and other possible sources of error.

Statistical analysis

RevMan software (version 5.4) and R (version 4.3) were used to process the data in this study. Binary outcomes were presented as risk ratios (RRs) with 95% confidence intervals, and continuous outcomes were expressed in terms of standardized mean differences (SMDs) and their 95% CIs. The cutoff value of statistical significance is set at $P < 0.05$. I^2 statistics were used to evaluate the extent of heterogeneity in the studies. An I^2 value of less than 50% was considered low heterogeneity, and a fixed-effects model was used. Since $I^2 > 0.5$, there was considerable heterogeneity in the data, and thus a random-effects model was chosen. Subgroup analysis was conducted on different exosome sources, preconditioning and engineering alterations, as well as treatment durations.

Results

Search results

As of March 1, 2026, a total of 2,255 potentially relevant articles were identified from the aforementioned databases. After removing duplicates, titles and abstracts were screened, followed by full-text review. Ultimately, 17 studies met the inclusion criteria and were included in this meta-analysis [31, 34-49]. The detailed study selection process is illustrated in **Figure 1**.

Study characteristics

Table 1 shows the attributes of the animal experiments included here. Almost all of the studies have been released in the last five years, and research on this topic has been increasing. Most studies have used dorsal full-thickness skin wound models in rats or mice, and the wound sizes are generally between 5 mm and 20 mm. Among them, seven studies used non-diabetic wound models [35, 37, 38, 42, 44, 48, 49], and ten studies employed diabetic models [31, 34, 36, 39-41, 45-47]. One study used an oral mucosal wound model additionally [41].

Table 2 shows the attributes of exosome applications. Most of the included studies employed exosomes derived from M2-polarized macrophages [34-38, 41-47], six studies focused on M0-derived exosomes [39, 40, 42, 48, 49], and two involved M1-derived exosomes [42, 37]. Ultracentrifugation has been used more often in the isolation of exosomes, accounting for over 80% of the studies [34, 36-43, 46-48]. Some research has also employed ultrafiltration tubes or rapid extraction kits, and in some cases, size exclusion chromatography (SEC) has been used for subsequent purification [31, 44, 49]. A few studies have used commercial kits or precipitation-type methods [35, 45]. Characterisation of the exosomes involved, such as morphology, size and certain surface proteins, has been carried out. Eleven studies have encapsulated exosomes in biomaterial carriers such as hydrogels for wound treatment [34-36, 38, 41, 42, 45-47, 49], and one study used curcumin-loaded exosomes in combination with other drugs [39]. Eight studies have reported the concentration of exosomes used at doses of 0.8 μg/μL [49], 0.1 μg/μL [40], 0.5 μg/μL [50], 2 μg/μL [44, 48], and 1 μg/μL [37, 39, 40]. One study quantified exosomes by particle count and reported 5×10^8 particles/100 μL [45]. Six studies used exosomes in wound dressings [34-42], and ten were delivered subcutaneously [29, 31, 37-40, 44-46, 48]. The following are the follow-up times: 7-24 days. All studies that compared plain exosomes with biomaterial-assisted or engineered exosome groups were treated as independent comparisons in the meta-analysis.

Risk of bias and sensitivity analysis

All 17 studies were subjected to a bias risk assessment, and the results are shown in Supplementary Figure 1. Most studies have provided complete baseline data and show a low risk of bias in the baseline period. However, most of the studies did not report randomization; only six studies mentioned randomization, and none specified the way of randomization or whether allocation concealment was used. Only one of the studies has randomly selected the outcome data for analysis so far.

Funnel plots were also used to check for publication bias. As shown in Supplementary Figure 2, the studies in the exosome group were relatively evenly distributed. Egger's test gave a t-value of 1.94 (df = 10, P = 0.0807), and the estimated bias was 3.7823 (SE = 1.9465); thus, there was no significant publication bias in this group. At the same time, the linear regression test for Egger found a significant bias in the material-modified exosome group. However, as shown in the funnel plot (Supplementary Figure 3), only one study was significantly asymmetrical. Due to a small sample size, this study was not included in the analysis and, with the help of trim-and-fill, some of the data were corrected for possible bias. The corrected effect size was still statistically significant, and thus the results remained the same.

Meta-analysis

A total of 17 animal studies were included in the meta-analysis, and the main end points for wound healing were selected. They are: the rate of wound closure, collagen deposition, density of neovascularization, re-epithelialization, scar width and inflammatory marker levels. All of the above results were examined to determine whether macrophages from different phenotypes and in the presence of drugs could be treated by macrophage-derived exosomes.

Wound closure rate: 17 studies on the results of wound closure have been carried out using a total of 111 animals. Heterogeneity analysis shows that all I^2 values exceed 50%, thus indicating a relatively large amount of variation in the included studies. Thus, a random-effects

Table 1. The characteristics of animal experiments included in the study

Study	Country	Year	Species	Sex	Animal age (weeks)	Weight (g)	Sample sizes (treatment/control)	Experimental wound model	Wound dimensions (mm)	Diabetes (Yes/No?)
Banerjee A. et al. [34].	India	2024	Wistar albino rats	Male	8	250 ± 50	10/10	Back skin Wounds	20	Yes
Deng Y. et al. [49].	China	2025	SD rats	/	/	200-250	6/6	Back skin wounds	10	No
Dutta S. et al. [35].	Republic of Korea, China	2025	ICR rats	Male	3-4	/	5/5	Sbcutaneous back wounds	10	No
Jiang X. et al. [36].	China	2024	C57BL/6 mice	Male	6	/	5/5	Back skin wounds	8	Yes
Kim H. et al. [37].	Republic of Korea	2019	Balb/c mice	Male	5	/	4/4	Back skin wounds		No
Kwak G. et al. [38].	Republic of Korea	2022	Balb/c mice	Male	6	/	5/5	Back skin wounds	8	No
Li D. et al. [39].	China	2023	SD rats	Female	adult	180-200	6/6	Back skin wounds	15	Yes
Li M. et al. [40].	China	2019	SD rats	/	/	/	3/3	Back skin wounds	15	Yes
Li W. et al. [41].	China	2023	C57BL/6J mice	Male	6	18-22	6/6	Skin and oral wounds	Back: 10, Oral: 2	Yes
Liu J. et al. [42].	China	2024	Balb/c mice	/	8	20-25	8/8	Back skin wounds	8	No
Liu P. et al. [43].	China	2021	/	/	/	/	5/5	Back skin wounds	/	Yes
Lyu L. et al. [44].	China	2022	Balb/c mice	Male	8	20 ± 0.4	20/20	Back skin wounds	5	No
Meng H. et al. [45].	China	2025	Db/db mouse	Male	5-6	/	4/4	Back skin wounds	10	Yes
Xia W. et al. [31].	China	2023	Db/db mouse	/	/	/	6/6	Back skin wounds	8	Yes
Xiong Y. et al. [46].	China	2022	C57BL/6J mice	Male	6	/	6/6	Back skin wounds	10	Yes
Zeng J. et al. [47].	China	2023	SD rats	Female	8		3/3	Back skin wounds	9	Yes
Zeng T. et al. [48].	China	2025	SD rats	Male	7	200-250	6/6	Back skin wounds	/	No

SD rats: Sprague-Dawley rats; db/db mouse: diabetes mouse; STZ: streptozocin.

Table 2. The key features of exosome applications

Study	Country	Year	Sources of exosomes	Macrophage polarization induction methods	Exosome isolation and purification methods	Scaffold or payloads	Exosome concentration	Application methods	Frequency and duration	Control	Follow-up uration (days)	Experimental outcome measures
Banerjee A. et al. [34].	India	2024	M2	Raw264.7 IL-4 (40 ng/mL), 48 h	Ultracentrifugation	Hydrogels	/	Wound dressings	Once	Gauze	7, 21	Wound contraction
Deng Y. et al. [49].	China	2025	M0	Raw264.7	100 kDa ultrafiltration tube and total exosome isolation reagent from cell culture medium (Invitrogen, USA)	/	80 μg/100 μL	Wound dressings	Once	GelMA	3, 7, 14	Wound contraction, Epidermal thickness, Collagen volume fraction, CD31
Deng Y. et al. [49].	China	2025	M0	Raw264.7	Same as above	Mo and Gelatin	Same as above	Same as above	Same as above	Same as above	Same as above	Same as above
Dutta S. et al. [35].	Republic of Korea, China	2025	M2	Raw264.7 hydrogels	The precipitation method	Bioink	/	Wound dressings	Every 2 days	Untreated	7, 14	Wound contraction, Re-epithelialization, Epidermal thickness, Inflammation score, Fibrosis index

Jiang X. et al. [36].	China	2024	M2	Raw264.7 IL-4 (20 ng/ml), 2 d	Ultracentrifugation	/	/	Injection	Every 2 days	Saline	3, 7, 14, 21	Wound contraction, Thickness of granulation, Length of Wound area, Collagen, α-SAM, VEGF, Blood Flow volume
Jiang X. et al. [36].	China	2024	M2	Same as above	Same as above	Two-dimensional carbide (MXene)	/	Injection	Every 2 days	Same as above	Same as above	Same as above
Kim H. et al. [37].	Republic of Korea	2019	M1	(Bone marrow-derived hematopoietic precursors→M0→M1) M-CSF, 7d [M0] IFN-γ (40 ng/mL), 48 h [M1]	Ultracentrifugation	/	100 μg/100 μL	Subcutaneous injection	On day 1 and day 4	Saline	1, 4, 8, 12, 16, 20, 24	Relative wound area
Kim H. et al. [37].	Republic of Korea	2019	M2	IL-4 (20 ng/mL), 48 h [M2]	Same as above	/	Same as above	Subcutaneous injection	Same as above	Same as above	Same as above	Same as above
Kwak G. et al. [38].	Republic of Korea	2022	M2	(BMDMs→M0→M1→M2) M-CSF (10 ng/mL), 7d [M0] IL-4 (40 ng/mL), 24 h [M2]	Ultracentrifugation	/	/	Subcutaneous injection	Once	Saline	4, 8, 12, 16, 20, 24	Relative wound area, ARG1, Hair follicles, Adipocyte coverage
Kwak G. et al. [38].	Republic of Korea	2022	M2	Same as above	Same as above	Hydrogels	/	Same as above	Same as above	Same as above	Same as above	Same as above
Li D. et al. [39].	China	2023	M0	Raw264.7	Ultracentrifugation	Curcumin	200 μL	Subcutaneous injection	Once	PBS	7, 14, 21	Wound closure, Collagen, IL-6, α-SMA, CD31
Li M. et al. [40].	China	2019	M0	Raw264.7	Ultracentrifugation	/	100 ug/mL 1 mg/mL	Subcutaneous injection	Once	PBS	0, 7, 14, 21	wound contraction
Li M. et al. [41].	China	2023	M2	Raw264.7 IL-4 (20 ng/mL), 24 h	Ultracentrifugation	PANB/Au/AC	/	Wound dressings	Replace dressings on day 3, 6, 9	Untreated	Skin: 3, 7, 12 Oral: 7	Skin wound closure, Collagen density, CD31
Liu J. et al. [42].	China	2024	M0	Raw264.7	Ultracentrifugation	Hydrogels	50 μg/100 μL	Wound dressings	Once	GelMA	0, 3, 5, 7, 10, 14	Wound area, Notch length, Collagen, IHC score, MVD, CD31, α-SMA
Liu J. et al. [42].	China	2024	M1	LPS (100 ng/mL) and INF-γ (20 ng/mL), 48 h	Ultracentrifugation	Same as above	Same as above	Same as above	Same as above	Same as above	Same as above	Same as above
Liu J. et al. [43].	China	2024	M2	IL-4 (40 ng/mL), 48 h	Ultracentrifugation	Same as above	Same as above	Same as above	Same as above	Same as above	Same as above	Same as above
Liu P. et al. [43].	China	2021	M2	(BMDMs→M2) IL-4 (20 ng/ml), 24 h	Ultracentrifugation	/	/	/	/	PBS	3, 5, 7, 10, 14	Skin wound closure, Granulation tissue thickness, Epidermal thickness, CD31, Collagen deposition, Mean perfusion unit
Liu P. et al. [43].	China	2021	M2	Same as above	Ultracentrifugation	Hydrogels	/	/	/	Same as above	Same as above	Same as above

Lyu L. et al. [44].	China	2022	M2	(PBMC→M0→M2) 50 ng/ml M-CSF, 7d [M0] IL-4 (20 ng/ml), 48 h [M2]	Initial isolation of exosome by PEG precipitation,Purification of exosome by SEC	/	200 ug/100 uL	Subcutaneous injection	Every 7 days	PBS	3, 7, 14	Skin wound closure, Width of scar, Collagen volume rate, TNF-α, IL-1β, IL-10, TGF-β, VEGF, Granulation tissue relative thickness, α-SMA, Vessel density in sarcomeres, The number of mature blood vessels in sarcomeres
Meng H. et al. [45].	China	2025	M2	Raw 264.7 IL-4	An exosome purification kit (Omiget, China)	Hydrogels	5E+8 particles/100 μL	Subcutaneous injection	/	PBS	3, 7, 10, 14, 21	Wound healing rat, CD86, CD206
Meng H. et al. [45].	China	2025	M2	Same as above	Same as above	/	Same as above	Same as above	/	same as above	same as above	Same as above
Xia W. et al. [31].	China	2023	M0	ATMs from lean mice	Ultracentrifugation (3000×g) combined with exosome quick extraction solution	/	100 μg/100 μL	Injection	From day 1 to day 5	PBS	5, 10, 15	Relative wound area, Microvessel density, TNF-α, CD86, CD206
Xiong Y. et al. [46].	China	2022	M2	(BMDMs→M2) M-CSF (50 ng/mL), 7d [M0] IL-4 (20 ng/mL) [M2]	Ultracentrifugation	Hydrogels	/	Injection	Every 2 days	PBS	3, 5, 7, 10,14	Skin wound closure, CD31, CD34, Granulation tissue thickness
Zeng J. et al. [47].	China	2023	M2	Raw264.7 IL-4 (100 ng/mL), 24 h	Ultracentrifugation	Microneedle	/	Wound dressings	Once, and received 808 nm NIR laser treatment on days 1, 3, and 5.	Untreated	1, 3, 5, 9, 14	Wound area, Inflammation cell, Collagen deposition area
Zeng T. et al. [48].	China	2025	M0	(THP-1→M0) Phorbol myristate acetate (PMA, 100 ng/mL)	Ultracentrifugation	/	200 μg/100 μL	Injection	/	PBS	4, 7	Wound closure, Length of wounds, Microvessel of density, Vessel volume

PMA: phorbol myristate acetate; BMDMs: Bone marrow cells→Bone marrow-derived macrophages; THP-1: Human acute monocytic leukemia cells; ATMs: Adipose tissue macrophage; M-CSF: monocyte-colony stimulating factor; PBMC: peripheral blood mononuclear cells; SEC: size exclusion chromatography.

model was used. Based on the above data, exosomes from M0 and M2 macrophages both promoted wound healing (SMD = 3.05, 95% CI [1.60, 4.50] for M0; SMD = 4.04, 95% CI [3.39, 4.69] for M2). Subgroup analysis also showed that material-assisted (exosomes loaded onto scaffolds or exosomes with loaded drugs) M2 exosomes were more effective than unmodified M2 exosomes in promoting wound healing (SMD = 4.81), and this difference was statistically significant; however, no significant change occurred in the M0 group (**Figures 2A** and **3A**). Exosome therapy also showed better results in treating diabetic wounds (**Figures 2B** and **3B**). H&E staining also showed that M2 exosomes significantly reduced wound width (Supplementary Figure 4). Exosomes from M1 macrophages did not promote the healing of wounds in a combined experiment. However, only two independent studies have been conducted so far, and the general research conditions are not well covered by them. Therefore, although the results show that M1 exosomes may be harmful to wound healing, more in-depth and well-designed experiments are still needed to verify and extend this.

Wound healing generally consists of three overlapping phases: the inflammatory phase, proliferative phase, and remodeling phase [51]. To further investigate the phase-specific effects of exosome therapy, the studies in this selection were divided into three groups according to when the intervention occurred: days 1-3 (inflammatory stage), days 4-10 (early recovery stage), and days 11-24 (late recovery stage). Based on the results, M2-derived exosomes promoted wound healing in all stages and were likely to have continuous therapeutic effects; they were probably anti-inflammatory and pro-regenerative (Supplementary Figure 5). Wound healing in the inflammatory stage indicates a reduction in inflammation, and at this time, tissue repair can occur more rapidly. Exosomes from M0 macrophages also had some positive effects at every stage of repair, but the degree of the effect was consistently lower than that for M2 exosomes (Supplementary Figure 6). M1-derived exosomes did not show a significant inhibitory effect during the early stage of healing, but rather showed an obvious suppressive effect in the late stage of healing (SMD = -2.46, 95% CI [-3.33, -1.59], P < 0.05), as shown in Supplementary Figure 7. Thus, they may interfere with tissue reconstruction and repair.

Epidermal and granulation tissue thickness: Among the included studies, only two evaluated epidermal thickness. Despite the limited evidence base, both studies consistently demonstrated that exosomes derived from M0 and M2 macrophages promoted epidermal formation, suggesting a potential beneficial role in cutaneous wound repair. Nevertheless, given the small number of available studies, further investigations are required to substantiate this finding. Regarding granulation tissue thickness, seven studies were included (n = 24). Heterogeneity analysis indicated no substantial heterogeneity among the studies (I^2 = 44.3%, *P* = 0.0959), thus a fixed-effects model was applied. The results demonstrated that exosome treatment significantly increased granulation tissue thickness in wounds (SMD = 10.84, 95% CI [7.13, 14.55]) as shown in **Figure 4**.

Collagen deposition and type I/III collagen ratio: Collagen deposition and remodelling are necessary for wound healing, and a certain proportion of both type I and type III collagen fibres is generated [52-54]. Seven studies have investigated collagen deposition to date, and a total of 13 comparisons have been incorporated into this analysis. Based on the above experiment, it is found that M0-derived exosomes and M2-derived exosomes were able to promote collagen synthesis more effectively than the control group. M0-derived exosomes had an SMD of 2.56 (95% CI [0.71, 4.41], P < 0.05), and M2-derived exosomes had an SMD of 3.50 (95% CI [0.21, 6.79], P < 0.05). As shown in **Figure 5**, M2 exosomes promoted more collagen deposition than M0 exosomes significantly (P = 0.0011). The ratio of type I/III collagen is a necessary condition for good collagen that prevents the formation of a scar. Only one study examined this ratio and, in doing so, used different time points and exosome strategies as independent comparisons. A total of four data points were added. As shown in **Figure 6**, both unmodified exosomes and material-assisted exosomes had a lower type I/III collagen ratio than the control (SMD = -4.92, 95% CI [-7.43, -2.41], P < 0.05). Furthermore, the proportion was relatively small in the later period of recovery compared with the beginning. Based on this result, it can

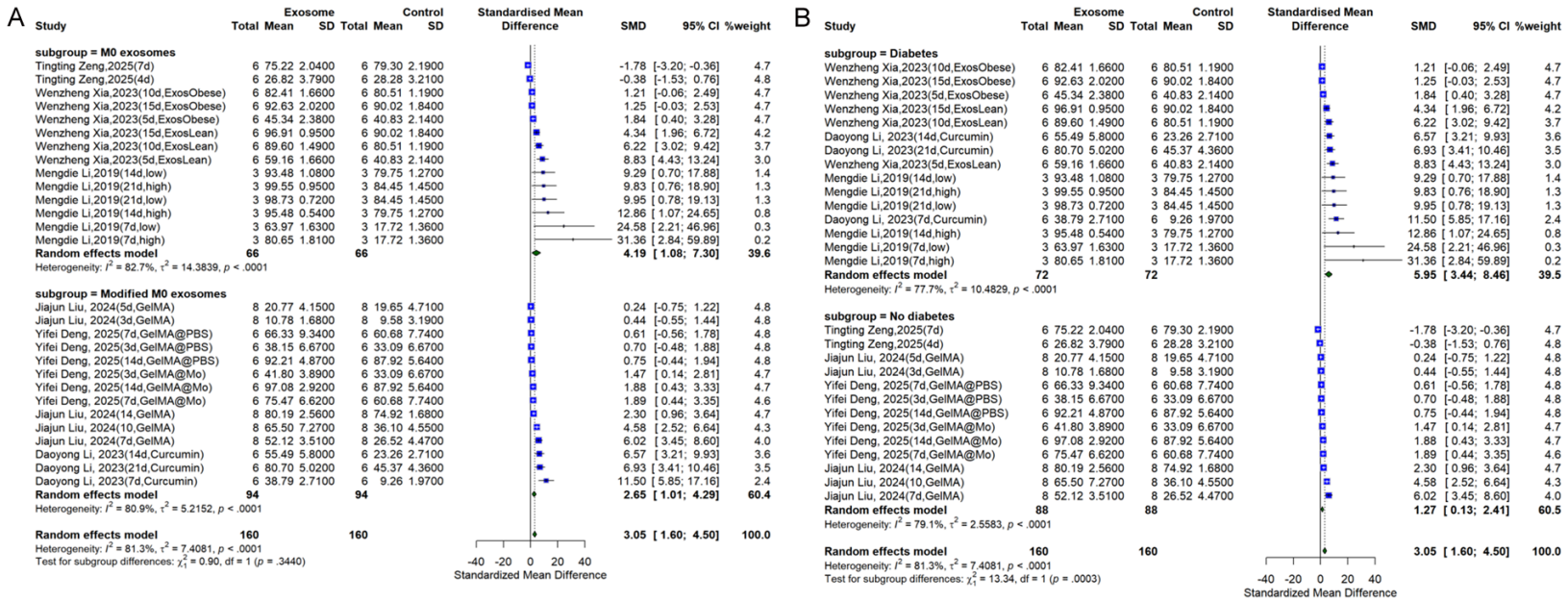


Figure 2. The forest plots of wound healing rates associated with M0 macrophage-derived exosomes. A. Subgroup analysis by exosome type (unmodified vs. modified exosomes); B. Subgroup analysis by diabetic status.

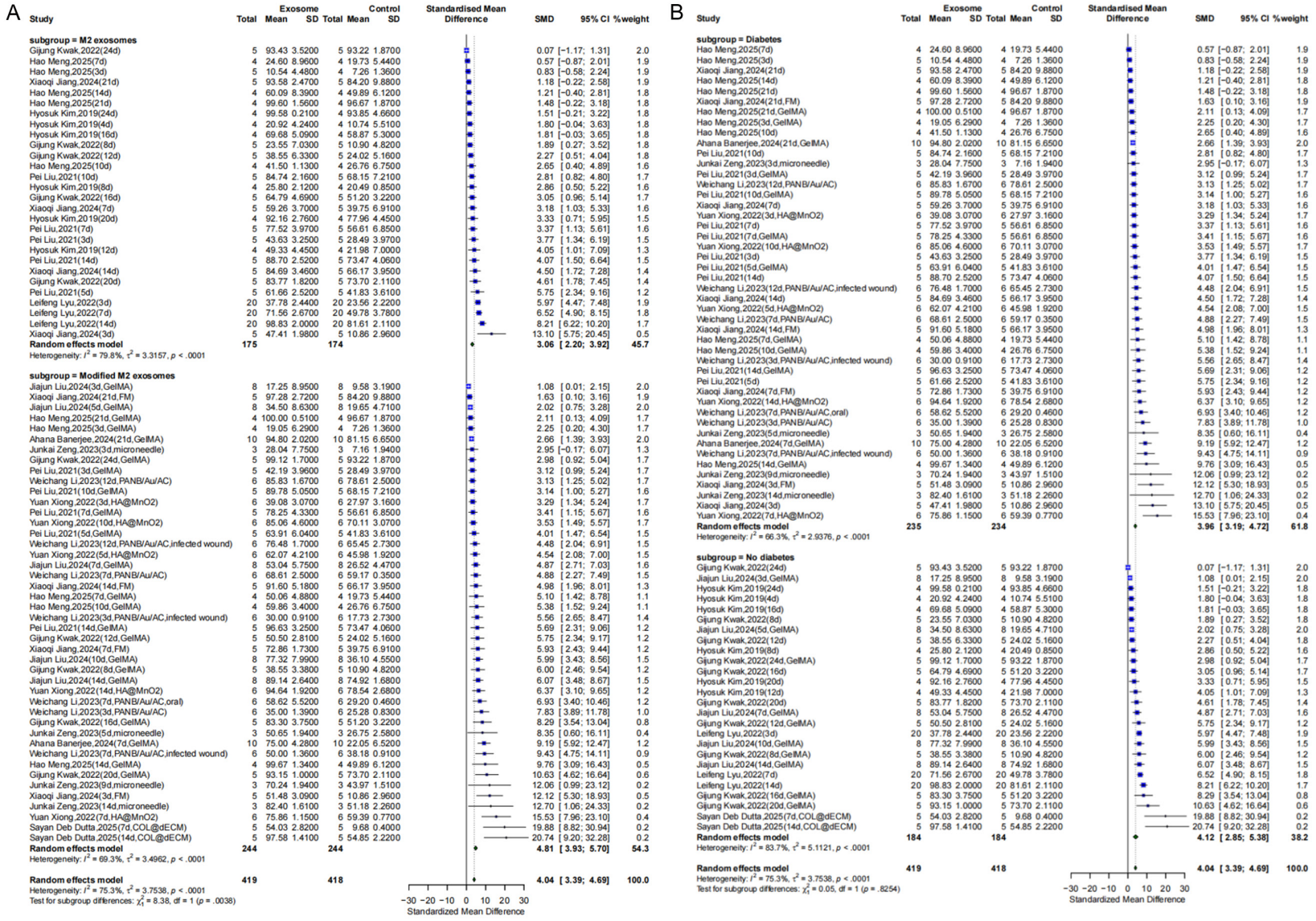


Figure 3. The forest plots of wound healing rates associated with M2 macrophage-derived exosomes. A. Subgroup analysis by exosome type (unmodified vs. modified exosomes); B. Subgroup analysis by diabetic status.

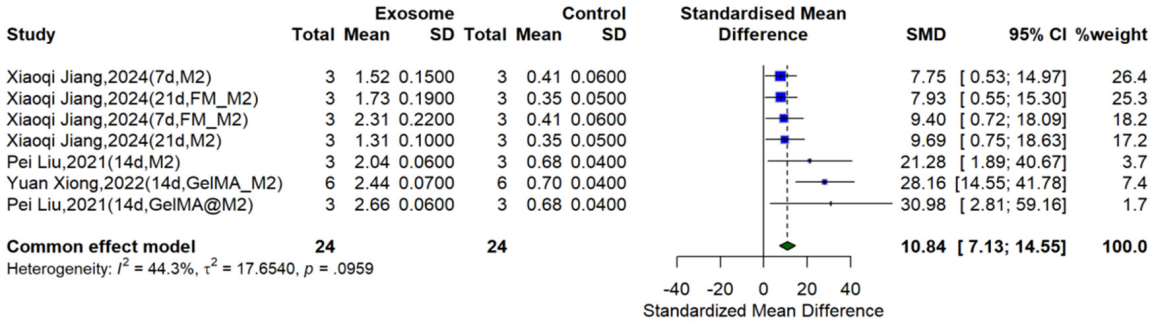


Figure 4. The forest plot of granulation tissue thickness in wound healing.

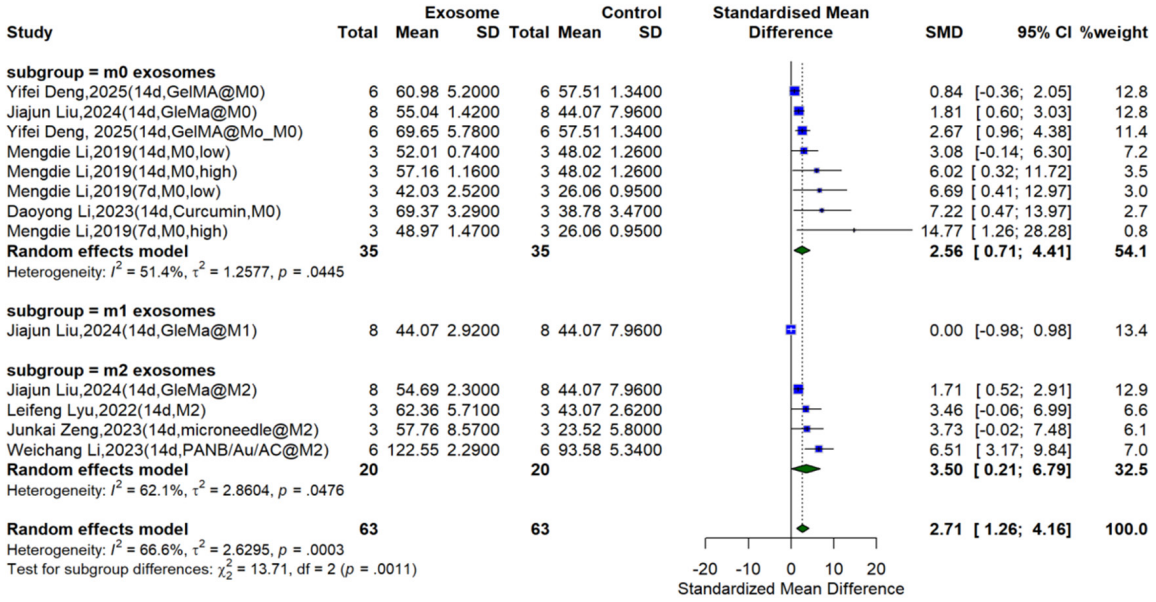


Figure 5. The forest plot of collagen deposition in wound healing.

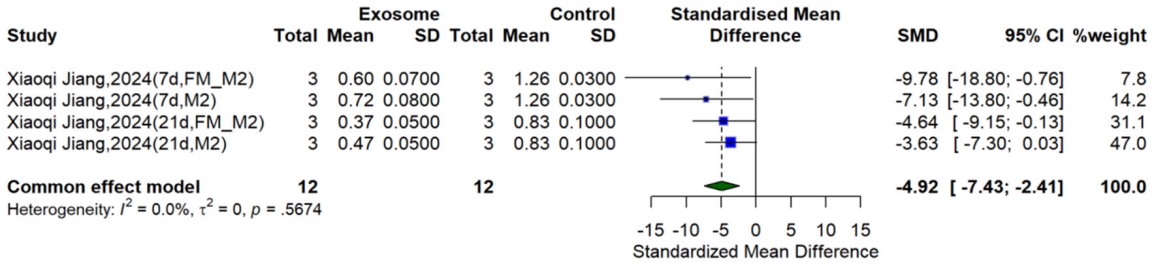


Figure 6. The forest plot of collagen type I/III ratio in wound healing.

be assumed that the treatment helped to switch from a type I collagen that is rich in early stages to a type III collagen that is more mature, thus helping to reduce scarring. Heterogeneity analysis showed that the I^2 value was 0%, and thus the studies were highly consistent. However, due to a small number of included studies and small sample sizes, more research is required to increase the cohort size and standardize protocols for verifying the reliability and clinical significance of the results.

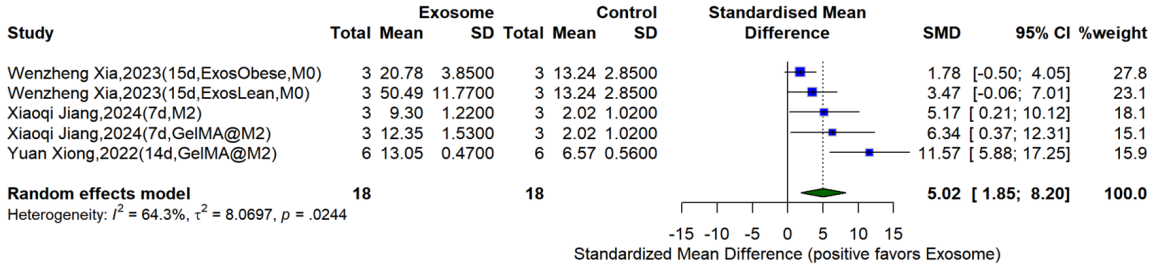


Figure 7. The forest plot of neovascularization density in wound healing.

Neovascularization density: Physiological wound healing relies on the coordinated progression of coagulation, inflammation, granulation tissue formation, and tissue remodeling, all of which are dependent on the oxygen and energy supplied by the microvascular network [55, 56]. The effect of exosomes on neovascularization density in wounds was reported in five studies involving a total of 36 subjects. As shown in **Figure 7**, exosome treatment promoted the formation of new microvessels at the wound site significantly (SMD = 5.02, 95% CI [1.85, 8.20], P < 0.05), and thus improved oxygen and nutrient supply to the healing tissue. A moderate level of heterogeneity was observed in the studies (I^2 = 64.3%, P = 0.0244), and this difference might be due to various reasons, such as different sources of exosomes, delivery methods or different times for treatment. However, all the studies have shown that there is a general increase, thus promoting angiogenesis during the healing of wounds through exosomes.

Discussion

Data were pooled from 17 studies in this meta-analysis and systematic review to examine the effect of exosomes released by different subtypes of macrophages on wound healing. Different organs in the human body have different functions for exosomes. Exosomes from M0 and M2 macrophages have all shown good effects on wound healing at different times, but M2-derived exosomes have had the best overall healing results. Exosomes from M1 macrophages, on the other hand, suppressed the late-stage tissue regeneration during wound healing. None of the included studies have reported any adverse effects of exosome therapy, so it has been found that macrophage-derived exosomes are a safe and effective healing system for wounds.

Exosomes are generated at the endosome and then mature in the early and late endosomes. Within the multivesicular bodies (MVBs), they develop as intraluminal vesicles (ILVs) and are eventually released outside the cell after the fusion of MVBs with the plasma membrane [57]. Exosomes have many types of proteins, lipids, and nucleic acids in their composition, and they also carry other features of the cells they originate from [58]; generally speaking, exosomes serve as messengers for intercellular communication and influence various other processes in the body, such as altering cell division and differentiation, regulating blood vessel growth, etc [59]. Most studies consider M0 macrophages to be unpolarized, and the M1 subtype is pro-inflammatory and associated with M2 macrophages that have an anti-inflammatory effect and promote tissue repair [14]. Exosomes from the above-mentioned distinct macrophage types have different sets of biological signals and can perform various functions according to their cell of origin [60]. Macrophage phenotypes have been linked to multiple disorders in bones through exosomes. Exosomes released by M0 and M2 macrophages can promote bone growth, but those from M1-polarised macrophages tend to suppress bone healing [61]. Research has also found that M2-derived exosomes contain a relatively higher amount of miR-365 than M1-derived exosomes [62]. Exosomes from M2 macrophages promote the transition of M1 macrophages to an M2-like phenotype in a PI3K/AKT pathway and thus enhance bone healing [63]. Exosomes of M2-like macrophages are also rich in IL-10 mRNA and have been found to inhibit bone loss in a murine model of periodontitis [64]. Exosomes from M0 and M2 macrophages in this study all showed good therapeutic effects at different stages of wound healing. Stimulate collagen production,

promote the growth of new blood vessels, encourage the formation of new epidermis and supporting granulation tissue, and speed up tissue healing. Pro-inflammatory M1 macrophage-derived exosomes are known to highly express miR-155, a pro-inflammatory microRNA that inhibits angiogenesis, increases myocardial injury, and damages cardiac repair [65]. Although there were no serious adverse effects in the inflammatory and early-healing periods, M1-Exos were relatively harmful in the late-healing stage. This is probably because of continuous release of pro-inflammatory factors that inhibit tissue repair and modify the immune microenvironment; thus, healing will be impaired. At the same time, exogenous M1-exosomes may continuously suppress the phenotype switching of macrophages, thus sustaining M1 dominance for a longer time and inhibiting matrix deposition and remodelling. This interpretation is in line with the damage to collagen organisation and new blood vessel formation at a later stage. Certainly, due to the small sample size of the included studies, we cannot exclude the possibility of biased results. Therefore, there is a risk of harm from M1-derived exosomes during tissue repair.

Different Types of Macrophages produce exosomes with different effects on the repair of wounds, but this is not yet clear. Some problems in the in vivo application of exosome-based therapy include a low yield, a tendency to aggregate, a lack of stability, and rapid clearance or internalization by recipient cells [66-68]. According to a meta-analysis, engineered exosomes that are either modified with biomaterials or delivered via carrier systems have all shown improved results in wound healing. Therefore, through the application of advanced engineering strategies to functionally modify and precisely tailor macrophage-derived exosomes, it is hoped that the current deficiencies can be rectified and more stable and prolonged therapeutic effects achieved. The present studies on modifying exosomes mainly fall into three categories: preconditioning of donor cells, surface engineering of exosomes [69, 70], and loading them with anti-inflammatory factors or therapeutic drugs for targeted delivery [71, 72]. Exosomes have also been added to many composite systems, such as hydrogels, microneedles, 3D-printed scaffolds and microfluidic devices. The above strategies can extend the life cycle of exosomes and release them in a controlled manner for a prolonged period; thus, they will stay at the wound site for a longer time and improve overall therapeutic effects [73, 74]. However, at present, there is no internationally recognized standard for exosome purification, material safety or therapeutic efficacy, and the methods used to modify exosomes and load drugs are still facing numerous difficulties in practical application and clinical translation; thus, this is an urgent problem that needs to be addressed [75]. Future research will focus on building high-efficiency, standardized, controllable and biologically safe exosome engineering systems. Strengthened research is required at a large scale to ensure the reproducibility and biological effect of animal experiments, thereby promoting clinical application.

Some constraints of this study need to be mentioned. First, the relatively small sample sizes of the included experiments, variations in wound size among models, and inconsistencies in exosome concentration, administration frequency and duration, as well as modification or loading strategies, have all contributed to a significant heterogeneity among the studies. Many other studies have not detailed the risks of bias. Therefore, the reliability of the conclusions drawn from the different types of macrophage-derived exosomes on wound healing is relatively low. Second, this study sought to explore the impact of exosome treatment at various stages of wound healing, so the results of wound healing reported at different times in the original studies were also taken as independent data for analysis. However, in this way, the independence of the study cannot be ensured, and double counting will occur. To address this problem of methodology, I will take different periods in time and perform multiple rounds of tests to verify the stability of the results. The results indicate that although this strategy cannot exclude the possibility of multiple calculations, the general conclusions of the various analyses are in agreement and thus relatively stable. Thirdly, the conventional classification of macrophages into M0, M1 and M2 subtypes does not fully reflect the phenotypic diversity at different times in life and in disease [76]. For example, the four sub-types of the M2 macrophage population are M2a, M2b, M2c, and M2d, and they have different pheno-

types and biological activities [50]. The particular roles of exosomes from the above-mentioned precisely identified macrophage types in wound healing are still unknown and require further study. In addition, our subgroup analysis shows that there are still some considerable differences in the apparent macrophage phenotypes. Although the polarisation protocol is changed to add more cytokines, or different exposure times and culture media are used, the molecular composition of the exosomes may vary but remain too subtle to be detected by conventional surface markers. Therefore, in the future, more studies will be conducted to investigate the function of exosomes at the molecular level by proteomics and small RNA sequencing. Finally, animal models cannot reproduce all the various changes in the disease microenvironment that occur in humans. Therefore, there is an urgent need to optimize and refine the design of preclinical models to enhance their physiological relevance and predictive value for clinical outcomes.

Conclusion

Our meta-analysis provides preliminary evidence that exosomes derived from M0 and M2 macrophages promote wound healing, whereas those originating from M1 macrophages exhibit inhibitory effects. Subgroup analysis indicates that engineered exosomes incorporating biomaterials or delivered through support carriers have been enhanced therapeutically. Given the complex composition and multiple functions of exosomes, the dosage, frequency and time of their application need to be standardized. In the future, more research will be conducted on the basic information and reasons for exosome-mediated wound healing to develop more targeted, high-efficiency applications. Research is underway to improve the efficiency and controllability of delivery systems for exosomes by using biomaterials. A high-efficiency, standardized and mechanism-driven exosome engineering platform needs to be built to promote its successful clinical application.

Acknowledgements

This study was supported by the Natural Science Foundation of Chongqing (CSTB2024NSCQ-MSX0434), the Chongqing Outstanding Young Medical Talent Program (2024, Wenjie Zhong), the Graduate Innovation Research Project of Chongqing Medical University (KQY202511).

Disclosure of conflict of interest

None.

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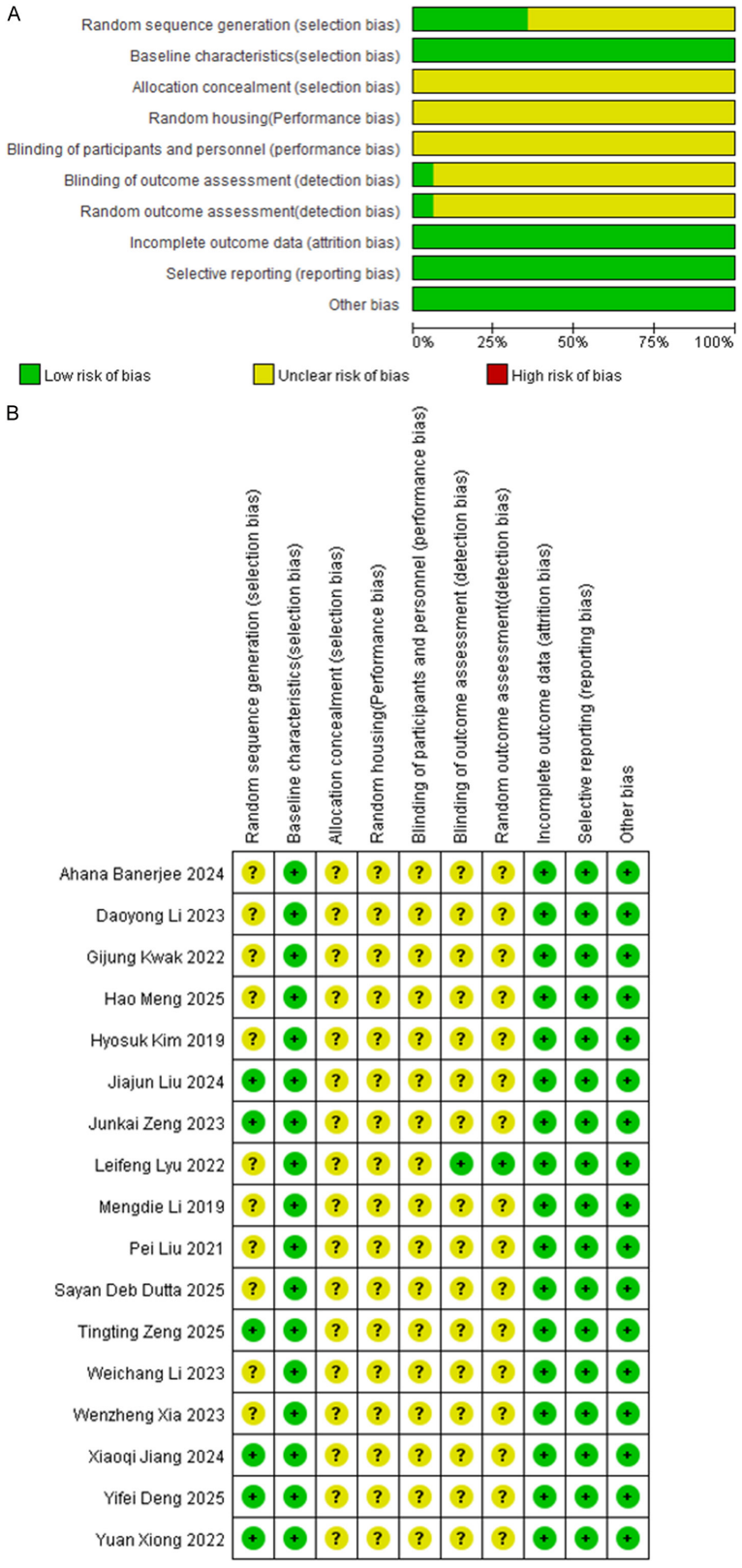
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Supplementary Table 1. Detailed search strategy

PubMed (Medline)	
#1	(Macrophages[MeSH Terms]) OR ((((((((((Monocyte-Derived Macrophages[Title/Abstract]) OR (Monocyte Derived Macrophages[Title/Abstract])) OR (Macrophage[Title/Abstract])) OR (Macrophages, Monocyte-Derived[Title/Abstract])) OR (Macrophage, Monocyte-Derived[Title/Abstract])) OR (Macrophages, Monocyte Derived[Title/Abstract])) OR (Monocyte-Derived Macrophage[Title/Abstract])) OR (Bone Marrow-Derived Macrophages[Title/Abstract])) OR (Bone Marrow-Derived Macrophage[Title/Abstract])) OR (Bone Marrow Derived Macrophages[Title/Abstract])) OR (Macrophage, Bone Marrow-Derived[Title/Abstract])) OR (Macrophages, Bone Marrow-Derived[Title/Abstract]))
#2	(wound healing[MeSH Terms]) OR (((((((wound healing*[Title/Abstract]) OR (Healing, Wound[Title/Abstract])) OR (Wound Repair[Title/Abstract])) OR (Wound Closure[Title/Abstract])) OR (Epithelialization[Title/Abstract])) OR "ulcer*"[Title/Abstract] OR "burn*"[Title/Abstract] OR "wound infection"[Title/Abstract] OR "laceration*"[Title/Abstract] OR "bedsore*"[Title/Abstract] OR "cavity wound*"[Title/Abstract] OR "surgical wound dehiscence"[Title/Abstract] OR "chronic wound"[Title/Abstract] OR "pressure ulcer*"[Title/Abstract] OR "diabetic foot ulcer*"[Title/Abstract] OR "necrotizing fasciitis"[Title/Abstract] OR "skin wound*"[Title/Abstract] OR "traumatic wound*"[Title/Abstract] OR "infected wound*"[Title/Abstract] OR "post-surgical wound*"[Title/Abstract] OR "healing defect"[Title/Abstract] OR "open wound*"[Title/Abstract] OR "epidermal regeneration"[Title/Abstract]))
#3	("exosomes"[MeSH Terms]) OR (((((((((exosome*[Title/Abstract]) OR (vesicle*[Title/Abstract])) OR (samll extral cellular vesicle*[Title/Abstract])) OR (microvesicle*[Title/Abstract])) OR (nanovesicle*[Title/Abstract])) OR (exosomal[Title/Abstract])) OR (microparticle*[Title/Abstract])) OR (exovesicle*[Title/Abstract])) OR (endosome*[Title/Abstract]))
#4	#1 AND #2 AND #3
326	
Embase	
#1	'exosome'/exp
#2	'exosome'/exp OR exosome OR exosome*:ab,ti OR 'small extracellular vesicle*':ab,ti OR endosome:ab,ti OR vesicle*:ab,ti OR microvesicle*:ab,ti OR nanovesicle*:ab,ti OR exosomal:ab,ti OR microparticle*:ab,ti OR exovesicle*:ab,ti
#3	'macrophage'/exp
#4	'macrophage'/exp OR macrophage OR macrophage*:ab,ti OR 'bone marrow derived macrophage*':ab,ti OR 'hemosiderin laden macrophage*':ab,ti OR histiocyte*:ab,ti OR 'hofbauer cell*':ab,ti OR 'lipid laden macrophage*':ab,ti OR 'lung alveolus macrophage*':ab,ti OR 'm1 macrophage*':ab,ti OR microglia*:ab,ti OR 'peritoneum macrophage*':ab,ti OR 'regulatory macrophage*':ab,ti OR 'tumor-associated macrophage*':ab,ti OR 'von-hansemann macrophage*':ab,ti
#5	'wound healing'/exp
#6	'wound healing'/exp OR 'wound healing' OR (('wound'/exp OR wound) AND ('healing'/exp OR healing)) OR 'wound healing*':ab,ti OR 'epiboly*':ab,ti OR 'granulation tissue*':ab,ti OR 'scar formation*':ab,ti OR 'wound healing impairment*':ab,ti OR 'wound repair':ab,ti OR 'wound closure':ab,ti OR 'epithelialization':ab,ti OR 'ulcer*':ab,ti OR 'burn*':ab,ti OR 'wound infection*':ab,ti OR 'laceration*':ab,ti OR 'bedsore*':ab,ti OR 'cavity wound*':ab,ti OR 'surgical wound dehiscence':ab,ti OR 'chronic wound*':ab,ti OR 'pressure ulcer*':ab,ti OR 'diabetic foot ulcer*':ab,ti OR 'necrotizing fasciitis':ab,ti OR 'skin wound*':ab,ti OR 'traumatic wound*':ab,ti OR 'infected wound*':ab,ti OR 'post-surgical wound*':ab,ti OR 'healing defect':ab,ti OR 'open wound*':ab,ti
#7	#1 OR #2
#8	#3 OR #4
#9	#5 OR #6
#10	#7 AND #8 AND #9
906	
Cochran library	
#1	MeSH descriptor: [Exosomes] explode all trees
#2	(exosome*):ti,ab,kw OR (vesicle*):ti,ab,kw OR (small extral cellular vesicle*):ti,ab,kw OR (microvesicle*):ti,ab,kw OR (nanovesicle*):ti,ab,kw
#3	(exosomal):ti,ab,kw OR (microparticle*):ti,ab,kw OR (exovesicle*):ti,ab,kw OR (endosome*):ti,ab,kw

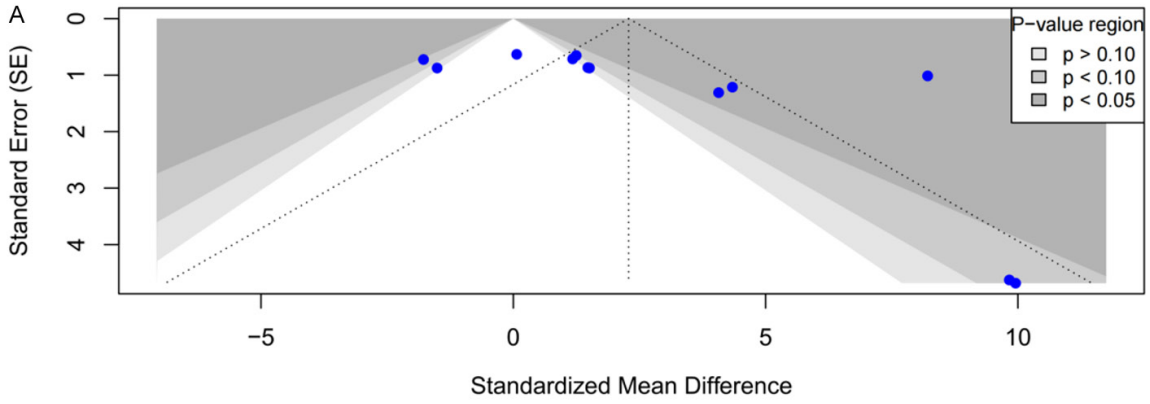
#4	#1 or #2 or #3
#5	MeSH descriptor: [Macrophages] explode all trees
#6	(epithelioid cell*):ti,ab,kw OR (foam cell*):ti,ab,kw OR (Giant cells, Foreign-Body):ti,ab,kw OR (Giant cells, Langhans):ti,ab,kw OR (Histiocyte*):ti,ab,kw
#7	(Kupffer Cell*):ti,ab,kw OR (Macrophages, Alveolar):ti,ab,kw OR (Marcrophages, Peritoneal):ti,ab,kw OR (osteoclast*):ti,ab,kw OR (Tumor-Associated Macrophage*):ti,ab,kw
#8	#5 or #6 or #7
#9	MeSH descriptor: [Wound Healing] explode all trees
#10	(cicatrix):ti,ab,kw OR (Re-Epitheliazation):ti,ab,kw OR (wound repair*):ti,ab,kw OR (wound closure):ti,ab,kw OR (epitheliazation):ti,ab,kw
#11	(ulcer*):ti,ab,kw OR (burn*):ti,ab,kw OR (wound infection):ti,ab,kw OR (laceration):ti,ab,kw OR (bedsore*):ti,ab,kw
#12	(cavity wound*):ti,ab,kw OR (surgical wound dehiscence):ti,ab,kw OR (chronic wound*):ti,ab,kw OR (diabetic foot ulcer*):ti,ab,kw OR (necrotizing fasciitis):ti,ab,kw
#13	(skin wound*):ti,ab,kw OR (traumatic wound*):ti,ab,kw OR (infected wound*):ti,ab,kw OR (post-surgical wound*):ti,ab,kw OR (healing defect):ti,ab,kw
#14	(open wound*):ti,ab,kw AND (epidermal regneration):ti,ab,kw
#15	#9 or #10 or #11 0r #12 or #13 or #14
#16	#4 and #15
#17	#16 and #8
0	

Web of science	
#1	TS=(exosome*) OR TS=(vesicle*) OR TS=(microvesicle*) OR TS=(nanovesicle*) OR TS=(microparticle*) OR TS=(exovesicle*) OR TS=(samll extral cellular vesicle*) and Preprint Citation Index (Exclude - Database)
#2	TS=(“wound healing*” OR “ulcer*” OR “burn*” OR “wound infection” OR “surgical wound dehiscence” OR “laceration*” OR “bedsore*” OR “cavity wound*” OR “wound healing” OR “Healing, Wound” OR “Wound Repair” OR “Wound Closure” OR “Epithelialization” OR “ulcer*” OR “burn*” OR “wound infection” OR “laceration*” OR “bedsore*” OR “cavity wound*” OR “surgical wound dehiscence” OR “chronic wound” OR “pressure ulcer*” OR “diabetic foot ulcer*” OR “necrotizing fasciitis” OR “skin wound*” OR “traumatic wound*” OR “infected wound*” OR “post-surgical wound*” OR “healing defect” OR “open wound*” OR “epidermal regeneration”) and Preprint Citation Index (Exclude - Database)
#3	TS=(“Macrophages” OR “Monocyte-Derived Macrophages” OR “Monocyte Derived Macrophages” OR “Macrophage” OR “Macrophages, Monocyte-Derived” OR “Macrophage, Monocyte-Derived” OR “Monocyte-Derived Macrophage” OR “Bone Marrow-Derived Macrophages” OR “Bone Marrow-Derived Macrophage” OR “Bone Marrow Derived Macrophages” OR “Macrophage, Bone Marrow-Derived” OR “Macrophages, Bone Marrow-Derived” OR “Kupffer Cells” OR “Alveolar Macrophages” OR “Osteoclasts” OR “Tumor-Associated Macrophages” OR “Foam Cells” OR “Giant Cells” OR “Dendritic Cells”) and Preprint Citation Index (Exclude - Database)
#4	#1 AND #2 AND #3 and Preprint Citation Index (Exclude - Database)
1023	



Supplementary Figure 1. Risk of bias. A. Summary of bias risk. B. Graph showing bias risk.

A



B

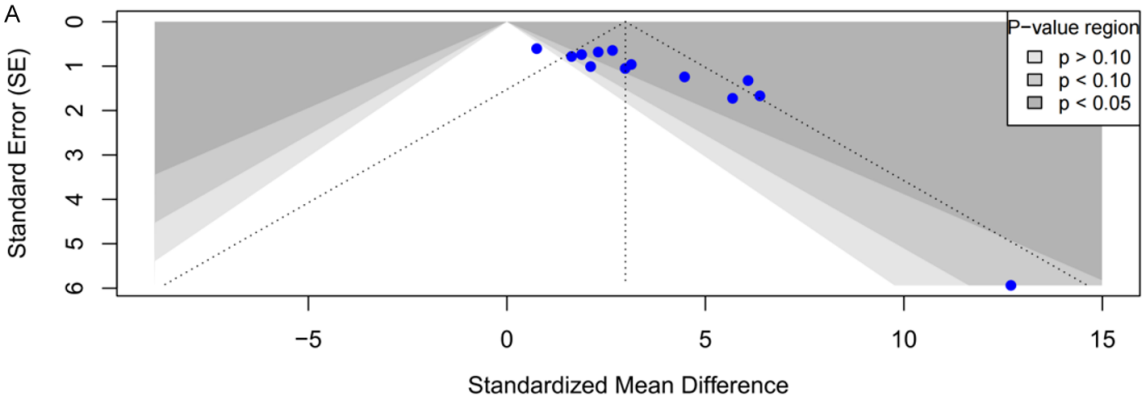
```
> # Egger's test for funnel plot asymmetry
> metabias(meta_result, method.bias = "linreg")
Linear regression test of funnel plot asymmetry

Test result: t = 1.94, df = 10, p-value = 0.0807
Bias estimate: 3.7823 (SE = 1.9465)

Details:
- multiplicative residual heterogeneity variance (tau^2 = 6.9788)
- predictor: standard error
- weight:    inverse variance
- reference: Egger et al. (1997), BMJ
```

Supplementary Figure 2. Publication bias and Egger's linear regression test in exosome research. A. Publication bias Funnel plot of exosomes group. B. Egger's linear regression test.

A



B

```
> # Egger's test for funnel plot asymmetry
> metabias(meta_result, method.bias = "linreg")
Linear regression test of funnel plot asymmetry

Test result: t = 4.86, df = 11, p-value = 0.0005
Bias estimate: 3.4408 (SE = 0.7077)

Details:
- multiplicative residual heterogeneity variance (tau^2 = 0.9450)
- predictor: standard error
- weight:    inverse variance
- reference: Egger et al. (1997), BMJ
```

C

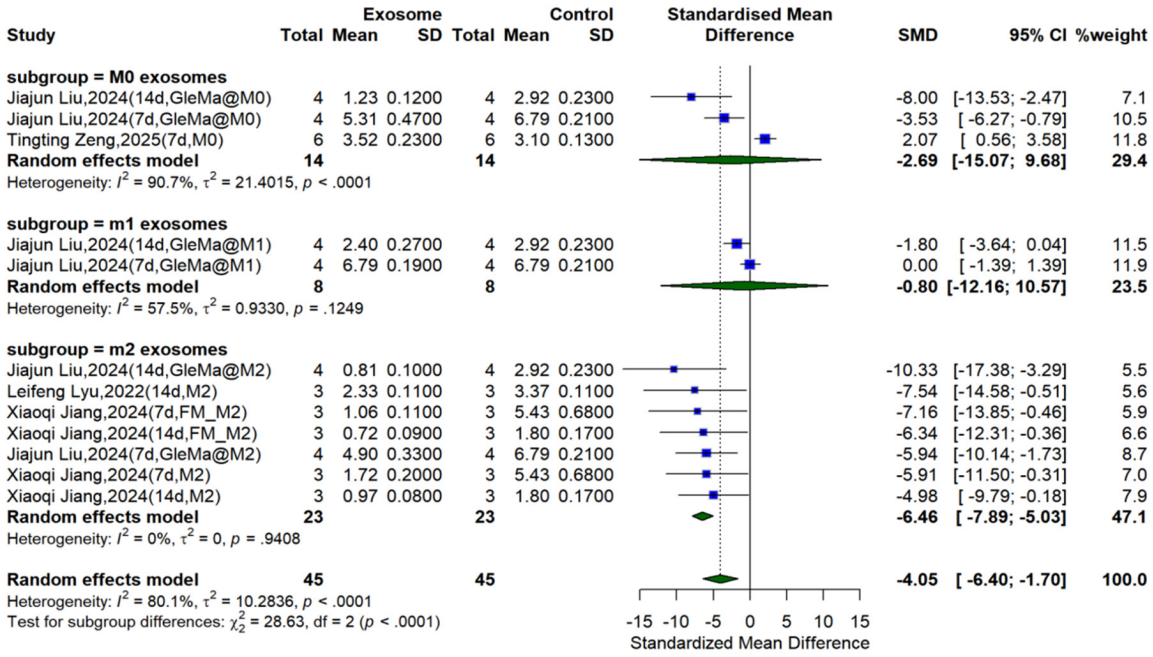
```
Number of studies: k = 18 (with 5 added studies)
Number of observations: o = 212 (o.e = 106, o.c = 106)

                         SMD           95%-CI    t p-value
Random effects model 2.0956 [0.6300; 3.5612] 3.02  0.0078

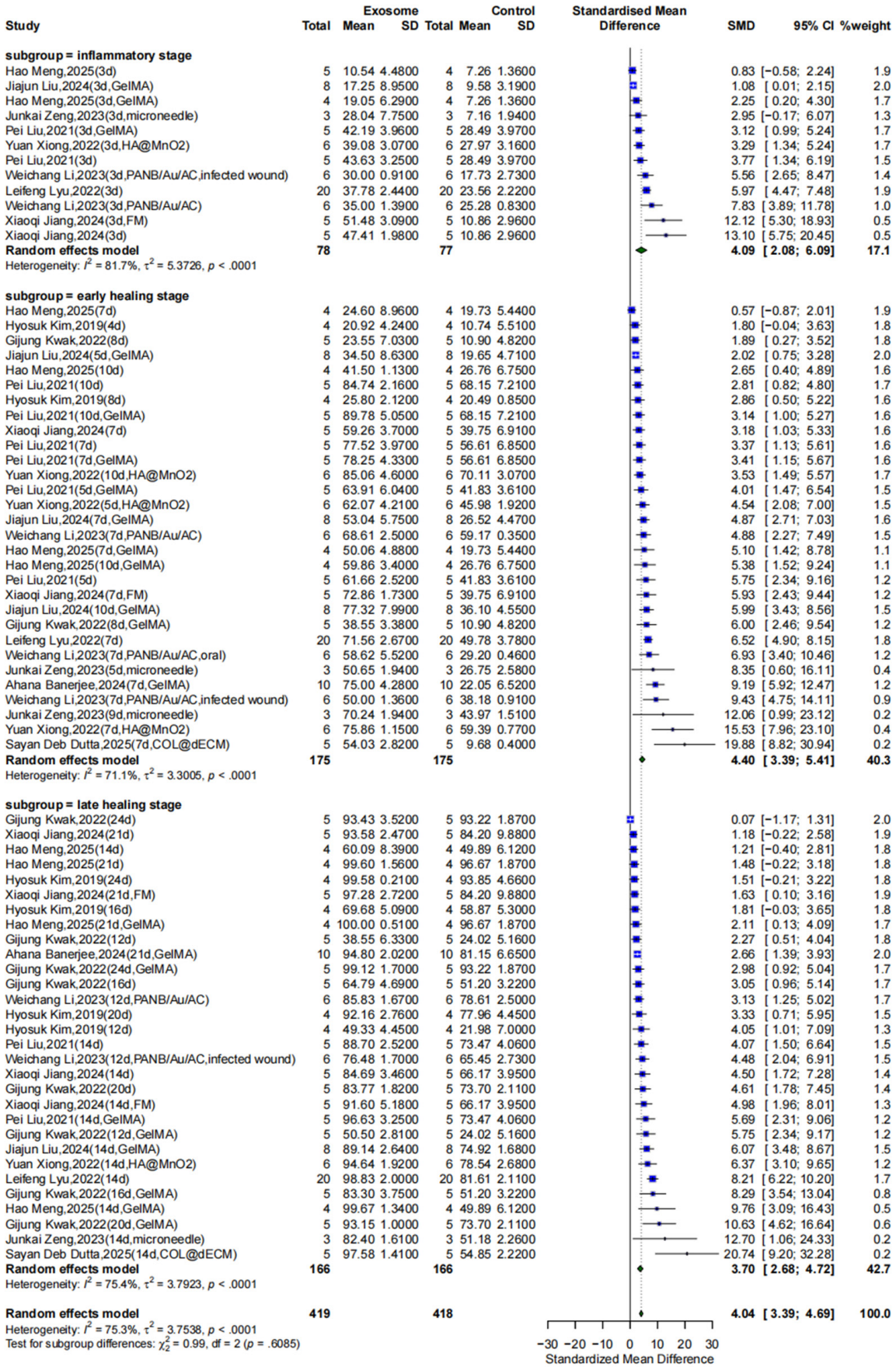
Quantifying heterogeneity (with 95%-CIs):
 tau^2 = 4.6939 [2.5117; 26.9928]; tau = 2.1665 [1.5848; 5.1955]
 I^2 = 73.3% [57.5%; 83.3%]; H = 1.94 [1.53; 2.45]

Test of heterogeneity:
     Q d.f.  p-value
 63.75   17 < 0.0001
```

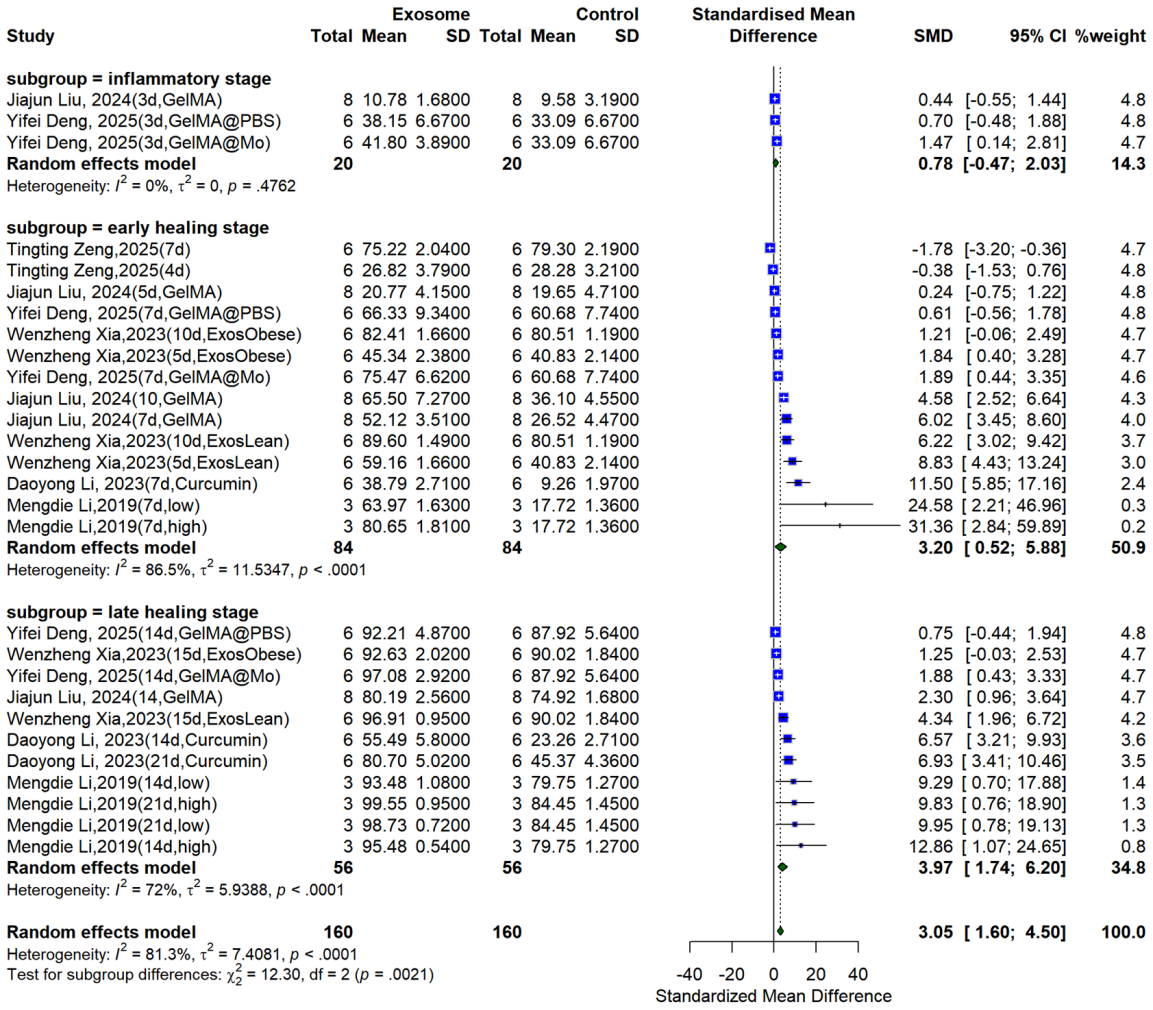
Supplementary Figure 3. Bias analysis and correction in material-modified exosome studies. A. Publication bias Funnel plot of material-modified exosomes group. B. Egger's linear regression test. C. Corrected meta-analysis.



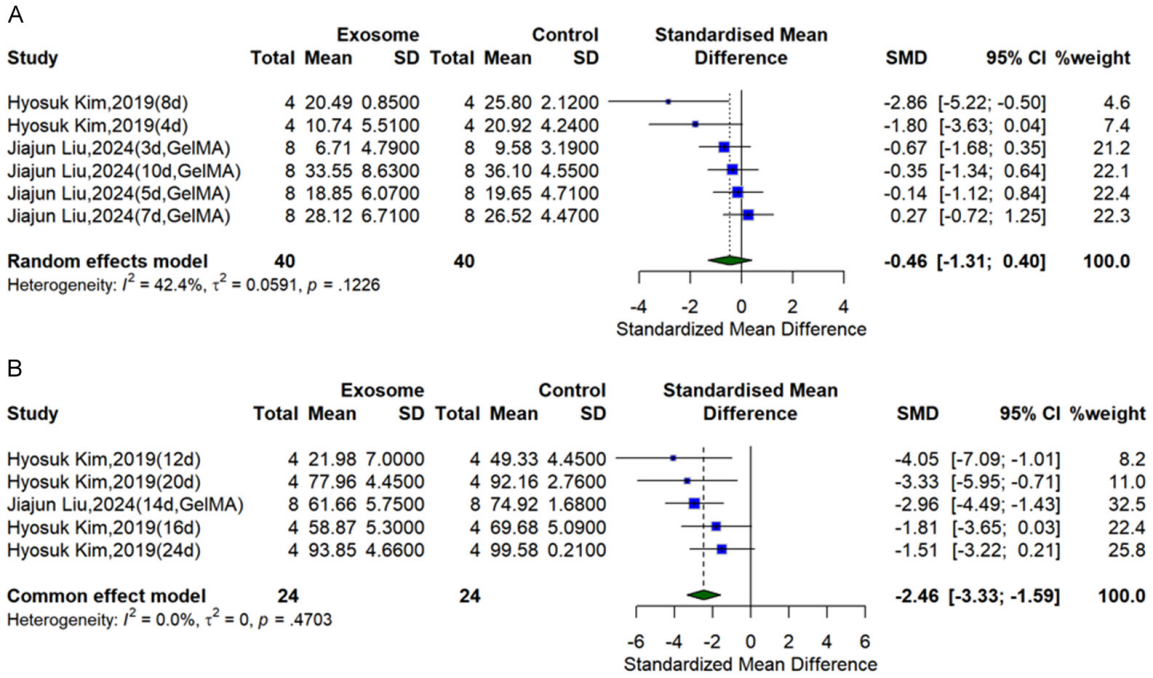
Supplementary Figure 4. The notch length (mm) of wound.


Study | Exosome Total Mean SD | Control Total Mean SD | Standardised Mean Difference | SMD 95% CI %weight
subgroup = inflammatory stage
Hao Meng,2025(3d) 5 10.54 4.4800 4 7.26 1.3600 0.83 [−0.58; 2.24] 1.9
Jiajun Liu,2024(3d,GelMA) 8 17.25 8.9500 8 9.58 3.1900 1.08 [0.01; 2.15] 2.0
Hao Meng,2025(3d,GelMA) 4 19.05 6.2900 4 7.26 1.3600 2.25 [0.20; 4.30] 1.7
Junkai Zeng,2023(3d,microneedle) 3 28.04 7.7500 3 7.16 1.9400 2.95 [−0.17; 6.07] 1.3
Pei Liu,2021(3d,GelMA) 5 42.19 3.9600 5 28.49 3.9700 3.12 [0.99; 5.24] 1.7
Yuan Xiong,2022(3d,HA@MnO2) 6 39.08 3.0700 6 27.97 3.1600 3.29 [1.34; 5.24] 1.7
Pei Liu,2021(3d) 5 43.63 3.2500 5 28.49 3.9700 3.77 [1.34; 6.19] 1.5
Weichang Li,2023(3d,PANB/Au/AC,infected wound) 6 30.00 0.9100 6 17.73 2.7300 5.56 [2.65; 8.47] 1.4
Leifeng Lyu,2022(3d) 20 37.78 2.4400 20 23.56 2.2200 5.97 [4.47; 7.48] 1.9
Weichang Li,2023(3d,PANB/Au/AC) 6 35.00 1.3900 6 25.28 0.8300 7.83 [3.89; 11.78] 1.0
Xiaoqi Jiang,2024(3d,FM) 5 51.48 3.0900 5 10.86 2.9600 12.12 [5.30; 18.93] 0.5
Xiaoqi Jiang,2024(3d) 5 47.41 1.9800 5 10.86 2.9600 13.10 [5.75; 20.45] 0.5
Random effects model 78 77 4.09 [2.08; 6.09] 17.1
Heterogeneity: I^2 = 81.7%, τ^2 = 5.3726, p < .0001
subgroup = early healing stage
Hao Meng,2025(7d) 4 24.60 8.9600 4 19.73 5.4400 0.57 [−0.87; 2.01] 1.9
Hyosuk Kim,2019(4d) 4 20.92 4.2400 4 10.74 5.5100 1.80 [−0.04; 3.63] 1.8
Gijung Kwak,2022(8d) 5 23.55 7.0300 5 10.90 4.8200 1.89 [0.27; 3.52] 1.8
Jiajun Liu,2024(5d,GelMA) 8 34.50 8.6300 8 19.65 4.7100 2.02 [0.75; 3.28] 2.0
Hao Meng,2025(10d) 4 41.50 1.1300 4 26.76 6.7500 2.65 [0.40; 4.89] 1.6
Pei Liu,2021(10d) 5 84.74 2.1600 5 68.15 7.2100 2.81 [0.82; 4.80] 1.7
Hyosuk Kim,2019(8d) 4 25.80 2.1200 4 20.49 0.8500 2.86 [0.50; 5.22] 1.6
Pei Liu,2021(10d,GelMA) 5 89.78 5.0500 5 68.15 7.2100 3.14 [1.00; 5.27] 1.6
Xiaoqi Jiang,2024(7d) 5 59.26 3.7000 5 39.75 6.9100 3.18 [1.03; 5.33] 1.6
Pei Liu,2021(7d) 5 77.52 3.9700 5 56.61 6.8500 3.37 [1.13; 5.61] 1.6
Pei Liu,2021(7d,GelMA) 5 78.25 4.3300 5 56.61 6.8500 3.41 [1.15; 5.67] 1.6
Yuan Xiong,2022(10d,HA@MnO2) 6 85.06 4.6000 6 70.11 3.0700 3.53 [1.49; 5.57] 1.7
Pei Liu,2021(5d,GelMA) 5 63.91 6.0400 5 41.83 3.6100 4.01 [1.47; 6.54] 1.5
Yuan Xiong,2022(5d,HA@MnO2) 6 62.07 4.2100 6 45.98 1.9200 4.54 [2.08; 7.00] 1.5
Jiajun Liu,2024(7d,GelMA) 8 53.04 5.7500 8 26.52 4.4700 4.87 [2.71; 7.03] 1.6
Weichang Li,2023(7d,PANB/Au/AC) 6 68.61 2.5000 6 59.17 0.3500 4.88 [2.27; 7.49] 1.5
Hao Meng,2025(7d,GelMA) 4 50.06 4.8800 4 19.73 5.4400 5.10 [1.42; 8.78] 1.1
Hao Meng,2025(10d,GelMA) 4 59.86 3.4000 4 26.76 6.7500 5.38 [1.52; 9.24] 1.1
Pei Liu,2021(5d) 5 61.66 2.5200 5 41.83 3.6100 5.75 [2.34; 9.16] 1.2
Xiaoqi Jiang,2024(7d,FM) 5 72.86 1.7300 5 39.75 6.9100 5.93 [2.43; 9.44] 1.2
Jiajun Liu,2024(10d,GelMA) 8 77.32 7.9900 8 36.10 4.5500 5.99 [3.43; 8.56] 1.5
Gijung Kwak,2022(8d,GelMA) 5 38.55 3.3800 5 10.90 4.8200 6.00 [2.46; 9.54] 1.2
Leifeng Lyu,2022(7d) 20 71.56 2.6700 20 49.78 3.7800 6.52 [4.90; 8.15] 1.8
Weichang Li,2023(7d,PANB/Au/AC,oral) 6 58.62 5.5200 6 29.20 0.4600 6.93 [3.40; 10.46] 1.2
Junkai Zeng,2023(5d,microneedle) 3 50.65 1.9400 3 26.75 2.5800 8.35 [0.60; 16.11] 0.4
Ahana Banerjee,2024(7d,GelMA) 10 75.00 4.2800 10 22.05 6.5200 9.19 [5.92; 12.47] 1.2
Weichang Li,2023(7d,PANB/Au/AC,infected wound) 6 50.00 1.3600 6 38.18 0.9100 9.43 [4.75; 14.11] 0.9
Junkai Zeng,2023(9d,microneedle) 3 70.24 1.9400 3 43.97 1.5100 12.06 [0.99; 23.12] 0.2
Yuan Xiong,2022(7d,HA@MnO2) 6 75.86 1.1500 6 59.39 0.7700 15.53 [7.96; 23.10] 0.4
Sayan Deb Dutta,2025(7d,COL@dECM) 5 54.03 2.8200 5 9.68 0.4000 19.88 [8.82; 30.94] 0.2
Random effects model 175 175 4.40 [3.39; 5.41] 40.3
Heterogeneity: I^2 = 71.1%, τ^2 = 3.3005, p < .0001
subgroup = late healing stage
Gijung Kwak,2022(24d) 5 93.43 3.5200 5 93.22 1.8700 0.07 [−1.17; 1.31] 2.0
Xiaoqi Jiang,2024(21d) 5 93.58 2.4700 5 84.20 9.8800 1.18 [−0.22; 2.58] 1.9
Hao Meng,2025(14d) 4 60.09 8.3900 4 49.89 6.1200 1.21 [−0.40; 2.81] 1.8
Hao Meng,2025(21d) 4 99.60 1.5600 4 96.67 1.8700 1.48 [−0.22; 3.18] 1.8
Hyosuk Kim,2019(24d) 4 99.58 0.2100 4 93.85 4.6600 1.51 [−0.21; 3.22] 1.8
Xiaoqi Jiang,2024(21d,FM) 5 97.28 2.7200 5 84.20 9.8800 1.63 [0.10; 3.16] 1.9
Hyosuk Kim,2019(16d) 4 69.68 5.0900 4 58.87 5.3000 1.81 [−0.03; 3.65] 1.8
Hao Meng,2025(21d,GelMA) 4 100.00 0.5100 4 96.67 1.8700 2.11 [0.13; 4.09] 1.7
Gijung Kwak,2022(12d) 5 38.55 6.3300 5 24.02 5.1600 2.27 [0.51; 4.04] 1.8
Ahana Banerjee,2024(21d,GelMA) 10 94.80 2.0200 10 81.15 6.6500 2.66 [1.39; 3.93] 2.0
Gijung Kwak,2022(24d,GelMA) 5 99.12 1.7000 5 93.22 1.8700 2.98 [0.92; 5.04] 1.7
Gijung Kwak,2022(16d) 5 64.79 4.6900 5 51.20 3.2200 3.05 [0.96; 5.14] 1.7
Weichang Li,2023(12d,PANB/Au/AC) 6 85.83 1.6700 6 78.61 2.5000 3.13 [1.25; 5.02] 1.7
Hyosuk Kim,2019(20d) 4 92.16 2.7600 4 77.96 4.4500 3.33 [0.71; 5.95] 1.5
Hyosuk Kim,2019(12d) 4 49.33 4.4500 4 21.98 7.0000 4.05 [1.01; 7.09] 1.3
Pei Liu,2021(14d) 5 88.70 2.5200 5 73.47 4.0600 4.07 [1.50; 6.64] 1.5
Weichang Li,2023(12d,PANB/Au/AC,infected wound) 6 76.48 1.7000 6 65.45 2.7300 4.48 [2.04; 6.91] 1.5
Xiaoqi Jiang,2024(14d) 5 84.69 3.4600 5 66.17 3.9500 4.50 [1.72; 7.28] 1.4
Gijung Kwak,2022(20d) 5 83.77 1.8200 5 73.70 2.1100 4.61 [1.78; 7.45] 1.4
Xiaoqi Jiang,2024(14d,FM) 5 91.60 5.1800 5 66.17 3.9500 4.98 [1.96; 8.01] 1.3
Pei Liu,2021(14d,GelMA) 5 96.63 3.2500 5 73.47 4.0600 5.69 [2.31; 9.06] 1.2
Gijung Kwak,2022(12d,GelMA) 5 50.50 2.8100 5 24.02 5.1600 5.75 [2.34; 9.17] 1.2
Jiajun Liu,2024(14d,GelMA) 8 89.14 2.6400 8 74.92 1.6800 6.07 [3.48; 8.67] 1.5
Yuan Xiong,2022(14d,HA@MnO2) 6 94.64 1.9200 6 78.54 2.6800 6.37 [3.10; 9.65] 1.2
Leifeng Lyu,2022(14d) 20 98.83 2.0000 20 81.61 2.1100 8.21 [6.22; 10.20] 1.7
Gijung Kwak,2022(16d,GelMA) 5 83.30 3.7500 5 51.20 3.2200 8.29 [3.54; 13.04] 0.8
Hao Meng,2025(14d,GelMA) 4 99.67 1.3400 4 49.89 6.1200 9.76 [3.09; 16.43] 0.5
Gijung Kwak,2022(20d,GelMA) 5 93.15 1.0000 5 73.70 2.1100 10.63 [4.62; 16.64] 0.6
Junkai Zeng,2023(14d,microneedle) 3 82.40 1.6100 3 51.18 2.2600 12.70 [1.06; 24.33] 0.2
Sayan Deb Dutta,2025(14d,COL@dECM) 5 97.58 1.4100 5 54.85 2.2200 20.74 [9.20; 32.28] 0.2
Random effects model 166 166 3.70 [2.68; 4.72] 42.7
Heterogeneity: I^2 = 75.4%, τ^2 = 3.7923, p < .0001
Random effects model 419 418 4.04 [3.39; 4.69] 100.0
Heterogeneity: I^2 = 75.3%, τ^2 = 3.7538, p < .0001
Test for subgroup differences: χ^2_2 = 0.99, df = 2 (p = .6085)
−30 −20 −10 0 10 20 30
Standardized Mean Difference

Supplementary Figure 5. The wound healing rates at different stages (inflammatory stage, early healing stage, late healing stage) after M2 exosomes treatment.



Supplementary Figure 6. The wound healing rates at different stages (inflammatory stage, early healing stage, late healing stage) after M0 exosomes treatment.



Supplementary Figure 7. The wound healing rates at different stages (inflammatory stage, early healing stage, late healing stage) after M1 exosomes treatment. A. Inflammatory stage and early healing stage. B. Late healing stage.