Journal of Translational Medicine

REVIEW

Open Access

Mesenchymal stem cells-derived small extracellular vesicles and apoptotic extracellular vesicles for wound healing and skin regeneration: a systematic review and meta-analysis of preclinical studies

Yufan Zhu[1], Han Yang[1], Zhixin Xue[1], Haojing Tang[1], Xihang Chen[1*] and Yunjun Liao[1*]

Abstract

Background Studies examining the therapeutic potential of Mesenchymal stem cells-derived extracellular vesicles (MSC-EVs) in wound healing and skin regeneration have progressed rapidly. Prior to considering clinical translation, a systematic and comprehensive understanding of these experimental details and the overall impact of MSC-EVs on skin regeneration is necessary.

Methods 83 studies were identified in Web of Science, Embase, and PubMed that satisfied a set of prespecified inclusion criteria. A random effects meta-analysis was conducted for wound closure rate, scar width, blood vessel density and collagen deposition.

Conclusions Our findings demonstrate clear potential of MSC-EVs to be developed as therapy for wound healing and skin regeneration both in diabetic and non-diabetic animal models. Moreover, subgroup analyses demonstrated that apoptotic small extracellular vesicles (ApoSEVs) showed better efficacy than apoptotic bodies (ApoBDs) and small extracellular vesicles (sEVs) in wound closure outcome and collagen deposition, while sEVs displayed better than ApoEVs in revascularization. Among frequently used routes of administration, subcutaneous injection displayed a greater improvement to wound closure, collagen deposition and revascularization as compared to dressing/covering. Among easier-access source of MSCs, ADSCs demonstrated the best effect in wound closure rate and collagen deposition, as compared, BMMSCs displayed better in revascularization. Additionally, high heterogeneity observed in collection conditions, separation methods, storage methods, modifications, treatment dose, administration route, and frequency of MSC-EVs underscores the urgent need for standardization in these areas, prior to clinical translation.

Xihang Chen and Yunjun Liao are co-corresponding authors.

*Correspondence:
Xihang Chen
Xihangchen@hotmail.com
Yunjun Liao
yunjun1000@sina.com

Full list of author information is available at the end of the article

Protocol Registration PROSPERO CRD42024499172.
Keywords Extracellular vesicles, Mesenchymal stem cells, Skin regeneration, Wound healing, Meta-analysis

Introduction

Since their discovery in the 1970s, mesenchymal stem cells (MSCs)have demonstrated great potential in regenerative medicine applications. However, the clinical application of MSCs faces several challenges, including variability, scalability, delivery methods, ethical concerns and safety issues [1]. Recently, however, researchers have identified that MSCs release numerous extracellular vesicles (EVs) which serve as mediators of intercellular communication and exhibit biological activities similar to MSCs. These EVs are thought to promote cell proliferation, differentiation, and angiogenesis, while simultaneously inhibiting apoptosis, inflammation, and fibrosis during tissue regeneration and repair processes [2–6]. Encased within a phospholipid bilayer, EVs carry a diverse array of macromolecules, including proteins, lipids, and nucleic acids [7]. Traditionally, in the absence of functional definitions, EVs were categorized based on combinations of size, biogenesis, and biophysical separation processes. For example, apoptotic extracellular vesicles (ApoEVs), which include apoptotic small EVs (ApoS-EVs, < 1 μm in diameter) and apoptotic bodies (ApoBDs, 1–5 μm in diameter), are released from fragmented apoptotic cells. Small EVs (sEVs, <200 nm in diameter) form a nanosized subclass, comprising exosomes derived from the endosomal system (typically < 200 nm in diameter) and ectosomes originating from the plasma membrane, which span a broader size range.

As the primary barrier between the body and the external environment, the skin is susceptible to various injuries. With the increasing prevalence of skin-related health issues, particularly among diabetic and elderly populations, the search for effective treatment options is becoming more urgent. While both preclinical and clinical studies on the therapeutic potential of sEVs derived from MSCs in wound healing and skin regeneration have progressed rapidly [8–10], the therapeutic potential of MSC-derived ApoEVs has only recently been appraised, with just five preclinical studies included in this meta-analysis. Furthermore, it has been reported that mature osteoclast-derived ApoEVs exhibit better osteogenic potency compared to exosome [11]. Similarly, another study, found that fewer huMSCs were required for ApoEVs isolation, and superior endometrial regeneration was achieved following huMSCs-ApoEVs implantation [12] compared to exosome-based therapy. Though there're many meta-analysis related to the application of traditionally-defined sEVs in skin regeneration, the comparative study between sEVs and ApoEVs is rare. Therefore, this study utilized meta-research methods to compare the therapeutic efficacy of ApoEVs and sEVs derived from MSCs in wound healing and skin regeneration.

Given the variability in EVs methodologies, there is still no consensus on which interventional traits (e.g., MSCs source, route of administration, animal species and immunocompatibility) offer the greatest therapeutic benefit. To address this gap, we conducted subgroup analyses to identify specific EVs characteristics associated with enhanced therapeutic outcomes, with the goal of optimizing the clinical application of MSC-EVs therapy in the future.

Lastly, prior to considering clinical translation, a systematic and comprehensive understanding of these experimental details and the overall impact of MSC-EVs on skin regeneration is crutial. In our approach, we emphasized the importance of methodological rigor and reporting quality, aligning with established field guidelines, including the International Society for Cell and Gene Therapy (ISCT) criteria for MSC identification [13] and the Minimal information for Studies of Extracellular Vesicles (MISEV2023) [14].

results

Search results

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A search conducted on November 11th, 2023, across Web of Science, Embase, and PubMed yielded a total of 1803 articles. After pooling all articles into Endnote X9.3.3 software, 594 duplicates were removed. Titles and abstracts were screened to include articles investigating the therapeutic application of MSC-EVs EVs in skin repair, rejuvenation, and wound healing in mammalian models. We excluded 1008 studies that were in vitro studies, reviews, reports, commentaries, conference proceedings, or articles written in languages other than English. Full-text assessment of the remaining 201 articles resulted in the exclusion of 129 studies. Reasons for exclusion included: 20 studies did not characterize EVs by size and at least one EV protein marker, 63 studies did not characterize MSCs by differentiation potential or MSCs surface marker, 3 studies did not relate to skin regeneration and wound healing, 3 studies did not research articles, 8 studies exclusively using EVs not from MSCs, 7 studies exclusively using nanovesicles and 25 studies exclusively reporting in vitro findings. Additionally, an updated search conducted on June 15th, 2024, identified 11 additional studies, bringing the total number of eligible manuscripts for this systematic review to

83. The flow chart in Fig. 1 summarizes the study selection approach.

General characteristics of the included studies

The 83 studies deemed eligible for inclusion were published between 2015 and June 4th, 2024. Notably, approximately 82% ($n = 64$) of these studies were published in 2020 or later, indicating a surge in interest in MSC-EVs for promoting wound healing and skin regeneration. These studies originated from six different countries, with the majority (86.7%, $n = 72$) originating from China. Figure 2 depicts year of publication (2 A) and region according to the first author's affiliation (2B).

Characteristics of animal models

All studies utilized either a mouse ($N = 61$; 73.5%) or rat ($N = 22$; 26.5%) model (Fig. 2C). Non-diabetic wounds and diabetic wounds were investigated in 36 (43.4%) and 39 (47.0%) studies, respectively. 30 studies used streptozotocin (STZ)-induced diabetic models to represent type 1 diabetes, while 9 studies utilized genetically modified diabetic db/db mice to represent type 2 diabetes. Full-thickness excisional wounds were the most-studied models ($n = 75$; 90.4%), comprising dorsal wounds ($n = 60$), diabetic foot ulcer ($n = 3$) [15–17], and leg excisional wounds ($n = 4$) [18–21]. Other models ($n = 8$; 10%) include scleroderma ($n = 1$) [22], burns ($n = 1$) [23], photoaging ($n = 3$) [24–26], atopic dermatitis ($n = 2$) [27, 28], and frostbite injury ($n = 1$) [29] (Fig. 2D).

MSC-EVs methodology and interventional characteristics

Types and cellular origin of EVs

sEVs were the most-studies type of EVs ($n = 78$), of which 69 nomenclatures were exosome. As recommended by the nomenclature in MISEV 2023, exosome is a biogenesis-related term indicating origin from the endosomal system, which distinguishes exosome from ectosome. However, none of these studies assessed the putative markers of EV biogenesis pathways. Other types of EVs include ApoEVs ($n = 5$), of which 2 were ApoBDs [30, 31], 2 were ApoSEVs [32, 33] and 1 was both ApoSEVs and ApoBDs [34] (Fig. 3A).

The animal sources of MSCs used included human ($n = 58$; 69.9%), mouse ($n = 9$; 10.8%), rat ($n = 4$; 4.8%) [35–38], canine ($n = 1$,1.2%) [27] and unknown ($n = 11$, 13.3%). MSCs were derived from a variety of tissue sources including adipose tissue ($N = 32$; 38.55.%), umbilical cord ($N = 19$; 22.9%), bone marrow ($N = 16$; 19.3%), dermal ($n = 1$;1.2%) [39], fetus skin($n = 1$; 1.2%) [40], oral mucosa lamina($n = 3$;3.6%) [41–43], exfoliated deciduous teeth($n = 1$; 1.2%) [44], synovium($n = 2$;2.4%) [45, 46], orbicularis oculi muscle($n = 1$; 1.2%) [47], hair follicle($n = 1$; 1.2%) [48], placenta($n = 1$; 1.2%) [49], amniotic($n = 2$; 2.4%) [50, 51], menstrual blood($n = 1$; 1.2%) [52], and induced pluripotent stem cells (iPSCs) ($n = 2$; 2.4%) [28, 53] (Fig. 3B).

Characterization of MSCs

Based on the ISCT guidelines [13], a total of 66 studies (79.5%) met al.l three criteria for MSCs characterization, demonstrating the ability to adhere to plastic, exhibit in vitro multi-lineage differentiation capacity, and express surface markers. Additionally, 17 studies (20.5%) met two out of all the three criteria for MSCs characterization, demonstrating the ability to adhere to plastic and either exhibit in vitro multi-lineage differentiation capacity or express surface markers.

EVs collection conditions

Since serum contains EVs, 42 studies (50.6%) collected sEVs from serum-free medium. Others prepared culture medium with EV-depleted FBS ($n = 22$; 26.5%) or chemically defined medium ($n = 2$;2.4%) [45, 53]. sEVs were collected after conditioning periods of 24 h ($n = 10$), 48 h ($n = 42$), 36 h($n = 1$) [54], or 72 h ($n = 4$). Regarding the preparation of ApoEVs, one study utilized culture medium containing 0.3 μ of staurosporine [33], while three studies used 0.5μM staurosporine [30–32], both added to the conditioned medium for 12 h. One study administrating ApoEVs used three methods, including adding 0.5μM staurosporine, 0.5μM H_2O_2 or exposed to ultraviolet light for 12 h [34]. Additionally, 20 studies (24.4%) did not disclose the duration of cell culture conditioning before harvest.

EVs separation techniques

There is no gold standard separation technique for various types of EVs, and EVs separation methods varied considerably across the studies (Supplementary Fig. 1). Ultracentrifugation ($n = 81$, 97.6%) was the most widely used technique, albeit with various centrifugation protocols. Ultrafiltration by membranes of pore size 0.22 μm ($n = 46$, 55.4%), 0.45 μm ($n = 2$, 1.3%) [34, 55], 30 kDa($n = 1$, 1.3%) [42], or 100 kDa ($n = 5$, 6.0%) [18, 21, 43, 56, 57] was often done as an adjunct to other separation steps. Commercial precipitation-based isolation kits [23, 40, 43, 58–61], size exclusion chromatography (SEC) [42], and tangential flow filtration (TFF) [27] were used in 7, 1, and 1 study respectively. 1 study used PEG-6000 to achieve a final concentration of 8% [16]. 54 studies (65.1%) combined two or more separation techniques to achieve higher purity. 4 studies of ApoEVs all only used ultracentrifugation as separation technique [30–33]. One study administrating ApoEVs [34] also used 0.45 μm filter and 0.22 μm to separate ApoSEVs (<1 μm) into small (<0.22 μm), medium (0.22–0.45 μm), and large (>0.45 μm) size subtypes, though the subsequent

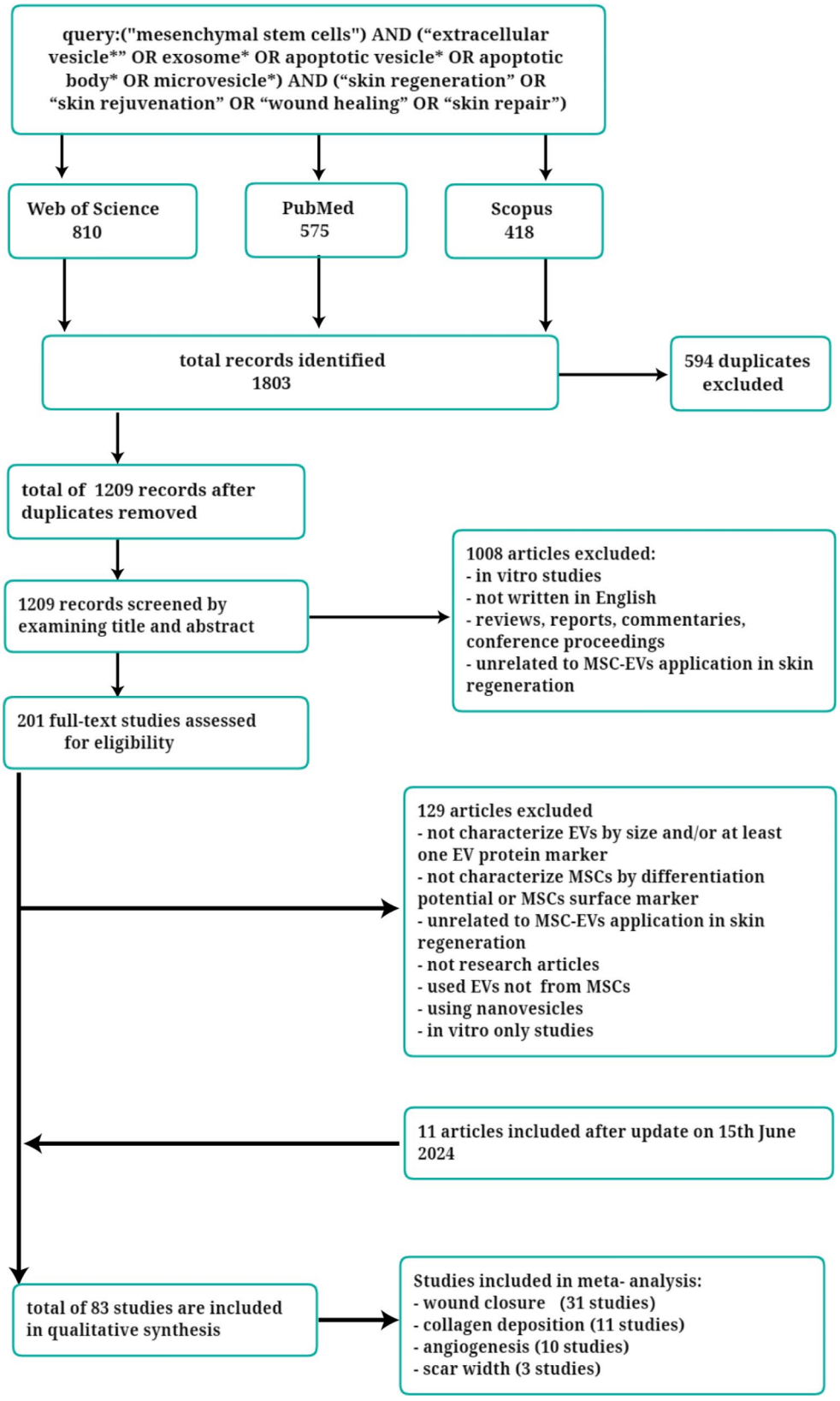

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram detailing study screening and selection

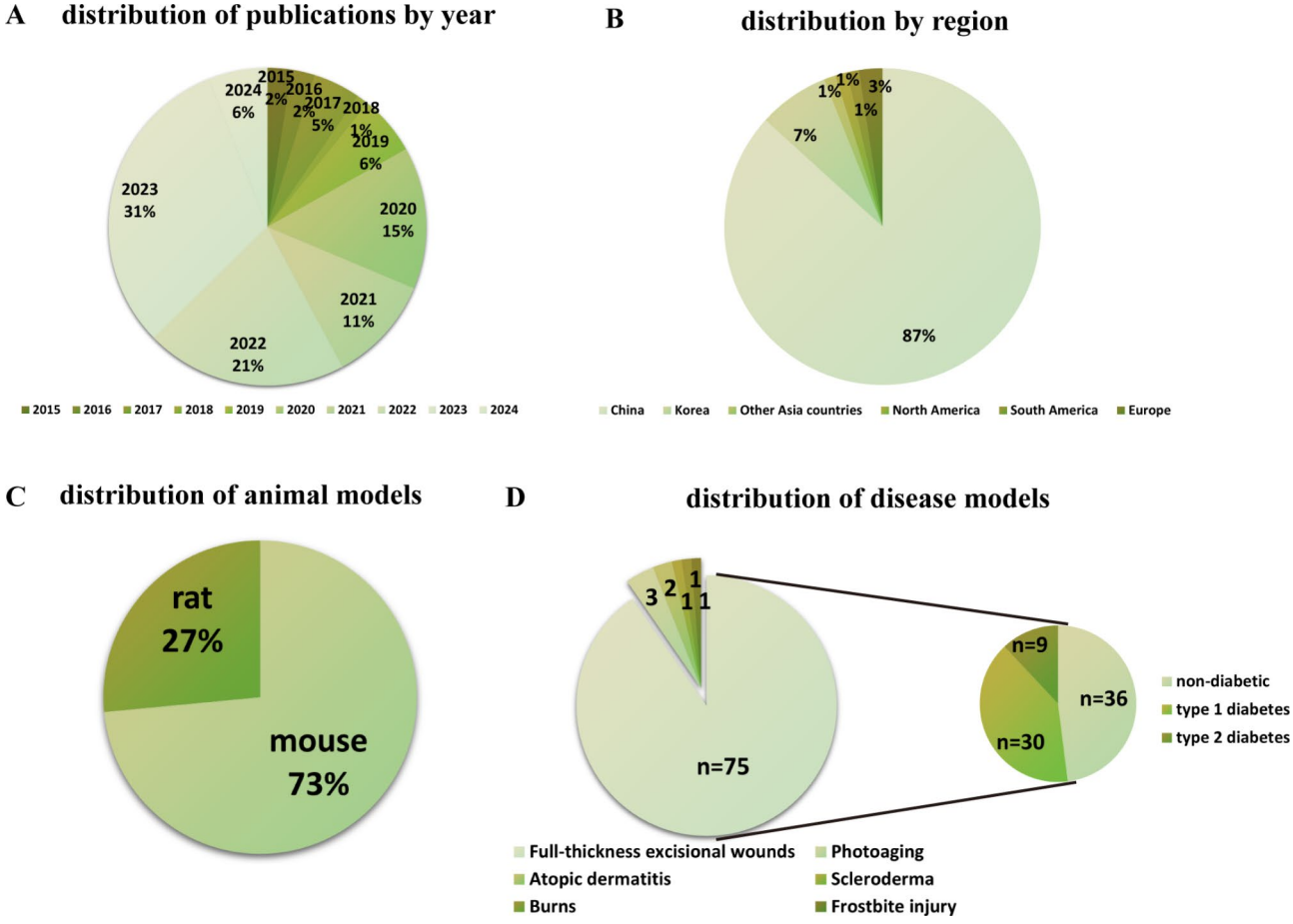

Fig. 2 An overview of study characteristics, including distribution of **(A)** publication year, **(B)** region, **(C)** animal models, and **(D)** disease models

research found that there was no difference in efficacy of the three subtypes in vitro.

EVs storage before use

60 studies (72.3%) reported storage temperature and/or medium of collected EVs. Among these, 47 studies stored collected EVs in -80℃, while only one study stored them in -20℃ [62]. Regarding the suspension medium, 46 studies utilized 100 µl ($n=6$) [30–32, 34, 51, 59], 200 µl ($n=8$) [22, 36, 39, 46, 54, 61–63], 500ul ($n=3$) [18, 19, 21] of PBS for storage, with some studies employing other unknown volumes. Additionally, one study used PBS containing phosphatase and protease inhibitor cocktails [36]. Furthermore, one study reported the thawing method before use: frozen EVs were thawed completely at 4℃ and were not refrozen [27]. However, no study reported the number of freeze-thaw cycle and the pre-separation storage conditions.

Characterization of EVs preparations

EVs were characterized by protein quantification (N = ;4554.2%), size distribution ($N=82$; 98.8%), morphological analysis ($N=82$; 98.8%) and surface marker expression ($N=83$; 100%) in most studies. A diverse array of characterization procedures was used in the studies we reviewed (Supplementary Fig. 1b). The determination of size distribution involved various techniques, including nanoparticle tracking analysis (NTA) ($n=57$;68.7%), dynamic light scattering (DLS) ($n=17$; 21.8%), atomic force microscopy (AFM) ($n=2$; 2.6%) [25, 52], and tunable resistive pulse sensing (TRPS) ($n=1$; 1.3%%) [42]. For morphology assessment, transmission electron microscopy (TEM) was predominantly used ($n=75$; 90.4%), while a smaller proportion of studies utilized scanning electron microscopy (SEM) ($n=7$; 9.0%) [30–32, 35, 50, 52, 64] and cryo-TEM ($n=1$; 1.3%) [43]. Protein quantification was primarily conducted using bicinchoninic acid assay (BCA) ($n=41$; 49.4%), with a few studies employing ELISA kit ($n=2$; 2.6%) [52, 65] or Bradford assay ($n=2$; 2.6%) [66]. 4 studies reported 584.71 µg/mL [67], 710 µg/ml [68], 2 µg/µL [69], and 1 µg/µL [70], respectively. Notably, most studies did not report EVs total protein yield, except for one study which documented a yield of 100 µg from 20 ml human adipose mesenchymal stem cells (ADSCs) (10^9 cells) collection medium [71]. RNA quantification was conducted using the Qubit

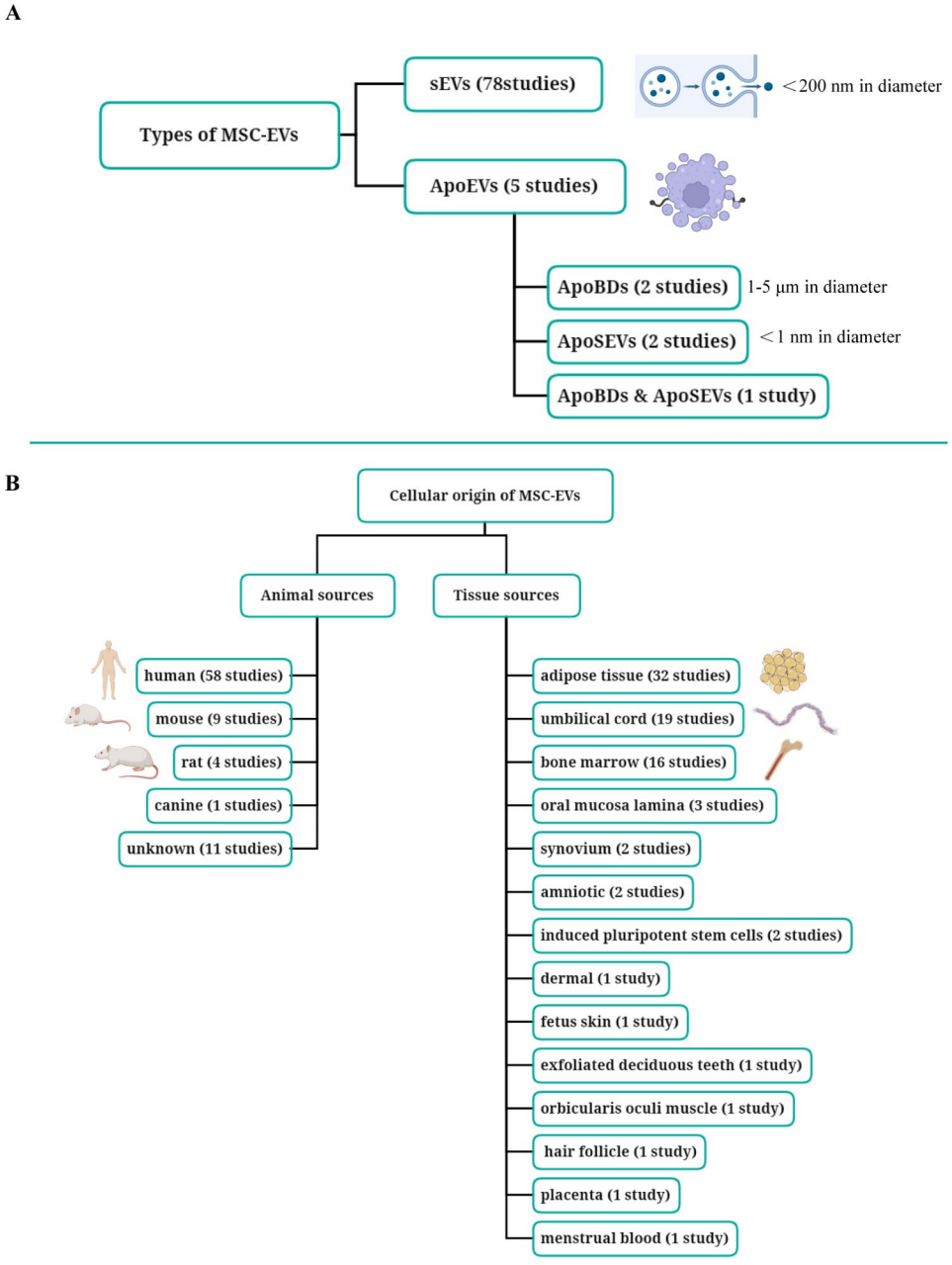

Fig. 3 Distribution of **(A)** types and **(B)** cellular origin of MSC-EVs across the included studies

RNA Assay Kit in two studies (2.5%) [23, 72]. However, the exact protein quantification data of ApoEVs were not reported in any related studies reviewed. Therefore, comparing the protein or RNA yield of sEVs and ApoEVs presents a challenge. Nevertheless, according to a study, the quantity of ApoSEV particles and protein produced by ADSCs undergoing apoptosis was significantly higher compared to the number of EVs secreted by normal ADSCs within a 24-hour period [33]. Specifically, an equal number of ADSCs generated six times more ApoSEV particles and four times more protein than normal EVs within a 12-hour period [33].

According to the MISEV 2023 [14], only 46 studies (55.4%) adequately characterized their EVs-featured protein. It is noteworthy that 44.9% ($n=37$) of studies did not report the assessment of at least one positive cytosolic marker and 62.8% ($n=52$) of studies did not report the major components of non-EV co-isolated structures to assesses purity from common contaminants. Moreover, in the case of ApoEVs, five studies solely detected ApoEVs as positive for apoptosis markers like Annexin V, Caspase-3, or cleaved Caspase-3, while neglecting the EVs-featured protein [30–34]. Lastly, no study provided

additional marker information on possible intracellular origins of separated EVs.

Modification of MSC-EVs

Modifications to EVs were conducted in 60 studies (72.3%), involving alterations to parent cells ($N = 33$; 42.3%), modifications to EVs directly ($N = 25$; 30.1%) and co-treatments ($N = 2$;) (Supplementary Fig. 2). Among alterations to parent cells, 12 studies implemented various culture conditions for parent cells, including incubation in hypoxic environments ($N = 2$) [19, 73], three-dimensional spheroids culture ($N = 2$) [47, 65], selenium treatment [59], education by exosomes from neonatal and adult serum [74], lipopolysaccharide (LPS) treatment [20], interferon-gamma (IFN-γ) treatment [75], melatonin treatment [76] and 3,2'-Dihydroxyflavone (3,2'-DHF) treatment [77]. Additionally, one study cultured MSCs in bioreactor culture system (perfusion bioreactor culture incorporating 3D-Printed Scaffolds) inducing an ≈40-80-fold increase in EVs production [65]. 21 studies genetically modified parent cells, with 20 studies utilizing lentivirus transduction, and one study employing gene knockout mice [39]. One study introduced miR-146a to exosomes directly by electroporation [60]. 22 studies loaded EVs into biomaterial scaffolds. Hydrogels were the most preferred choice ($n = 20$). The remaining studies utilized bioengineered micro-porous three-dimensional amniotic membrane-scaffold (AMS, $n = 1$) [78] and porous microspheres ($n = 1$) [41]. Among the hydrogels, six studies utilized synthetic hydrogels: Pluronic F-127 based (PF-127, $n = 4$) [31, 32, 79, 80], and gelatin methacryloyl (GelMA) hydrogel ($n = 3$) [33, 34, 81]. Eight studies employed natural hydrogels: chitosan-based ($n = 3$) [16, 46, 61] or incorporated with silk ($n = 1$) [42], hydroxyethyl cellulose ($n = 2$) [45, 66], alginate-based nanohydrogels ($n = 2$) [35, 82] and hyaluronan hydrogel($n = 1$) [49]. One study used chitosan-PF-127 composite hydrogel [80]. Dual-crosslinked hydrogel [33, 36], extracellular matrix hydrogel [10] and conductive hydrogel [70] were investigated in two, one and one study respectively. One study loaded polydopamine nanoparticles into EVs [81] and one study added sEVs into composite nanoparticles [61]. Additionally, two studies used co-treatments with tert-butylhydroquinone (tBHQ, $n = 1$) [37] or metformin($n = 1$) [70].

MSC-EVs administration and dosage regimen

The two most common routes of administration for MSC-EVs delivery were subcutaneous injection ($N = 38$; 45.8%) and local administration (dressing/covering) ($N = 19$; 22.9%). Dosing units varied considerably, including absolute protein amount ($N = 60$ 72.3%), particle number ($N = 7$; 9.0%) [16, 27, 47, 66, 68, 73, 77], or amount of EVs released by a certain number of MSCs ($N = 5$; 6.4%) [22, 27, 64, 83, 84]. The two most frequently used doses were 100 μg of EVs protein content in 100 μL PBS ($n = 13$; 16.7%) and 200 μg EVs in 100 μL PBS ($n = 9$; 10.8%) [17–19, 21, 26, 29, 57, 85, 86]. For studies administrating ApoEVs, four studies applied a dose of 50 μg protein content [30–33] and noe study applied a dose of 150 μg protein content [61]. The majority of studies delivered a single dose of therapy ($n = 49$; 59.0%). Studies with multiple administrations used a median value of 3 doses (ranged from 2 to 42 doses) (Supplementary Fig. 3).

Quality of reporting in MSC-EVs research

The quality of reporting across the studies was generally low, particularly regarding EV characterization and in vivo experiments. For EV characterization, critical details such as concentration (protein amount, particle number or amount of EVs released by a certain number of MSCs), positive cytosolic marker and possible intracellular origins of EVs were poorly reported. For in vivo experiments, 16 studies (19.3%) didn't disclose the sample size, and no study indicated how the sample size for animal models was calculated. 8 studies didn't reveal the administered dose [15, 36, 45, 59, 61, 76, 80, 87], and 7 studies didn't specify the treatment dose with exact EVs concentration but only mentioned the solution volume [46, 67, 70, 81, 82, 88, 89]. In terms of outcome reporting, only 18 studies (21.7%) provided actual numerical data. Furthermore, most studies did not report the absolute p-value and confidence interval of the measured outcomes, indicating a lack of comprehensive statistical analysis.

Meta-analysis

The meta-analysis included 31 full-thickness excisional wounds model studies, comprising 490 animals from 20 diabetes and 11 non-diabetes model studies, that disclosed the number of animals used in the experiments and characterized their EVs preparation as required by MISEV2023. Considering the limited number of studies, all 5 studies administrating ApoEVs were included.

Primary outcome: wound closure outcome

31 studies were eligible for meta-analysis of wound closure outcome. The analysis revealed a significant improvement in wound closure rate for wounds treated with MSC-EVs compared to controls (SMD = 3.60, 95% CI: 3.23 to 3.96, $p < 0.00001$), as illustrated in Fig. 4. The heterogeneity index was relatively high ($I^2 = 83\%$), indicating substantial variability in MSC-EVs cell source, preparation, and dosage regimen among the studies. Similarly, meta-analyses conducted separately for diabetic and non-diabetic groups also demonstrated significant effectiveness of MSC-EVs therapy in accelerating wound closure in both models (SMD = 3.59, 95% CI: 3.16 to 4.03, $p < 0.00001$; SMD = 3.60, 95% CI: 2.95 to 4.26, $p < 0.00001$

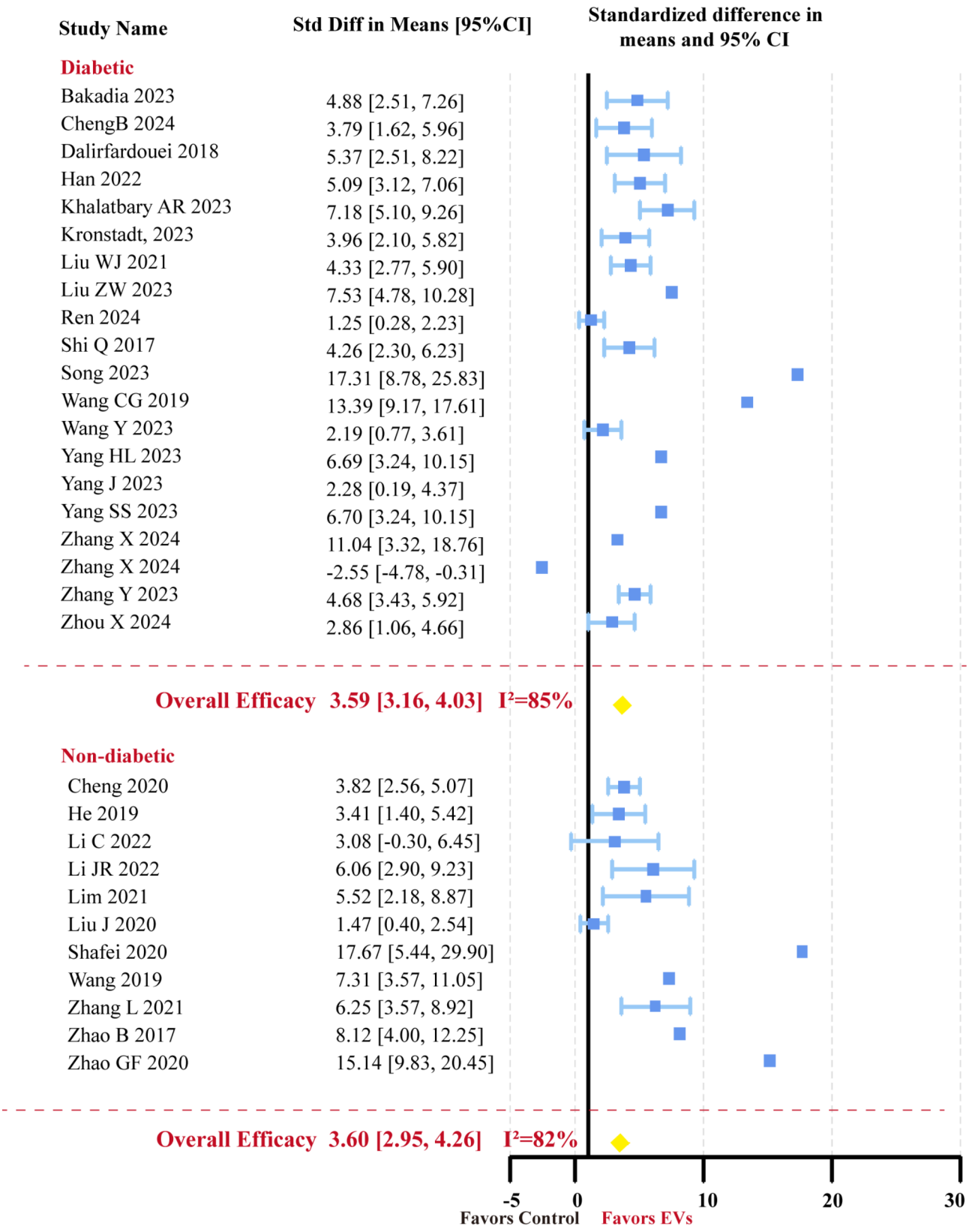

Fig. 4 Forest plot of mean difference of wound closure rate of 31 studies following MSC-EVs interventions in diabetic or non-diabetic wound healing model in comparison to placebo controls. The diamond represents the pooled SMD. I^2 value represents the statistical heterogeneity. MSC-EVs interventions were effective in promoting wound closure both in diabetic and non diabatic groups (SMD = 3.59, 95% CI: 3.16 to 4.03, $p < 0.00001$; SMD = 3.60, 95% CI: 2.95 to 4.26, $p < 0.00001$ in diabetes and non-diabetes models, respectively)

in diabetes and non-diabetes models, respectively). Heterogeneity remained high within subgroups regardless of the disease model (I^2 = 85%, and 82% in diabetes and non-diabetes models, respectively). Subgroup analysis demonstrated that sEVs consistently result in a superior efficacy in promoting wound closure, particularly both in diabetic and non-diabetic groups whereas the efficacy of ApoEVs is highly variable and similar to control treatments from pooled analysis (Figs. 5 and 6). MSC tissue source (p = 0.04 both in diabetic and non-diabetic groups) may be associated with greater EVs efficacy as EVs derived from hair follicle mesenchymal stem cells (FMSCs) and AECs (Amniotic Epithelial Cells, exhibit characteristics of both embryonic and mesenchymal stem cells) demonstrated better outcomes, in diabetic and non-diabetic groups respectively. However, the study number of FMSCs and AECs was limited, and among the most frequently used MSCs, ADSCs demonstrated the best effect in wound closure rate both in diabetic and non-diabetic groups. Engraft may showed superior benefits compared to the other routes of administration, though the related study number was limited. Among the most frequently used routes of administration, subcutaneous/intradermal injection showed better efficacy than dressing/covering. Xenogeneic administration of MSC-EVs also showed a greater promotion in wound closure compared to xenogeneic delivery (P = 0.002 both in diabetic and non-diabetic groups). Species (P<0.00001 both in diabetic and non-diabetic groups) may be associated with greater EVs efficacy as rat models demonstrated better outcomes.

However, it's important to note that only four studies used ApoEVs in diabetic group and only two studies used ApoEVs in non-diabetic group, which may cause the conclusions obtained on the use of ApoEVs risky and not very consistent. As one research reported, mature osteoclast-derived ApoEVs showed better osteogenic potency than exosome [11]. In another study, fewer huMSCs were needed for ApoEVs isolation, and better endometrial regeneration was obtained after the huMSCs-ApoEVs implantation, compared with exosomebased therapy [12]. These results were contradictory to our meta-analysis result above. Therefore, to draw more reliable conclusion, a subtypes meta-analysis was conducted for mice wound healing studies administering EVs with similar modification, treatment dose and administration route (Fig. 7). In diabetic group, the efficacy of 50 μg of ApoBDs protein without modification (SMD: 26.16, 95%CI: 21.65 to 30.67) is similar to 100 μg of sEVs protein without modification

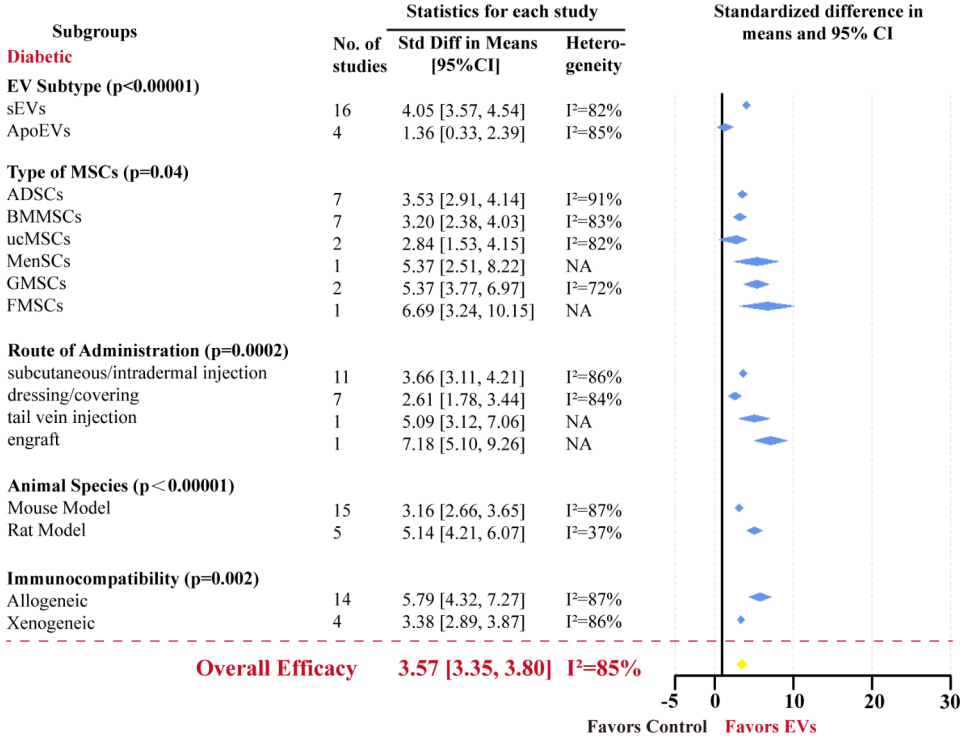

Fig. 5 Subgroup analysis of MSC-EVs for wound closure rate in diabetic wound healing model. Each row represents pooled estimate data from studies within that subgroup. Data is presented as a forest plot with SMD and 95% confidence intervals. I^2 value represents the statistical heterogeneity within each subgroup. Effect sizes > 0 favours MSC-EVs treatment and < 0 favours control. The 'Overall Efficacy' is a pooled estimate effect of MSC-EVs on wound closure rate from all studies combined. ADSCs: adipose mesenchymal stem cells; BMMSCs: bone marrow mesenchymal stem cells; ucMSCs: umbilical cord mesenchymal stem cells; MenSCs: menstrual blood mesenchymal stem cells; GMSCs: gingival mesenchymal stem cells; FMSCs: hair follicle mesenchymal stem cells

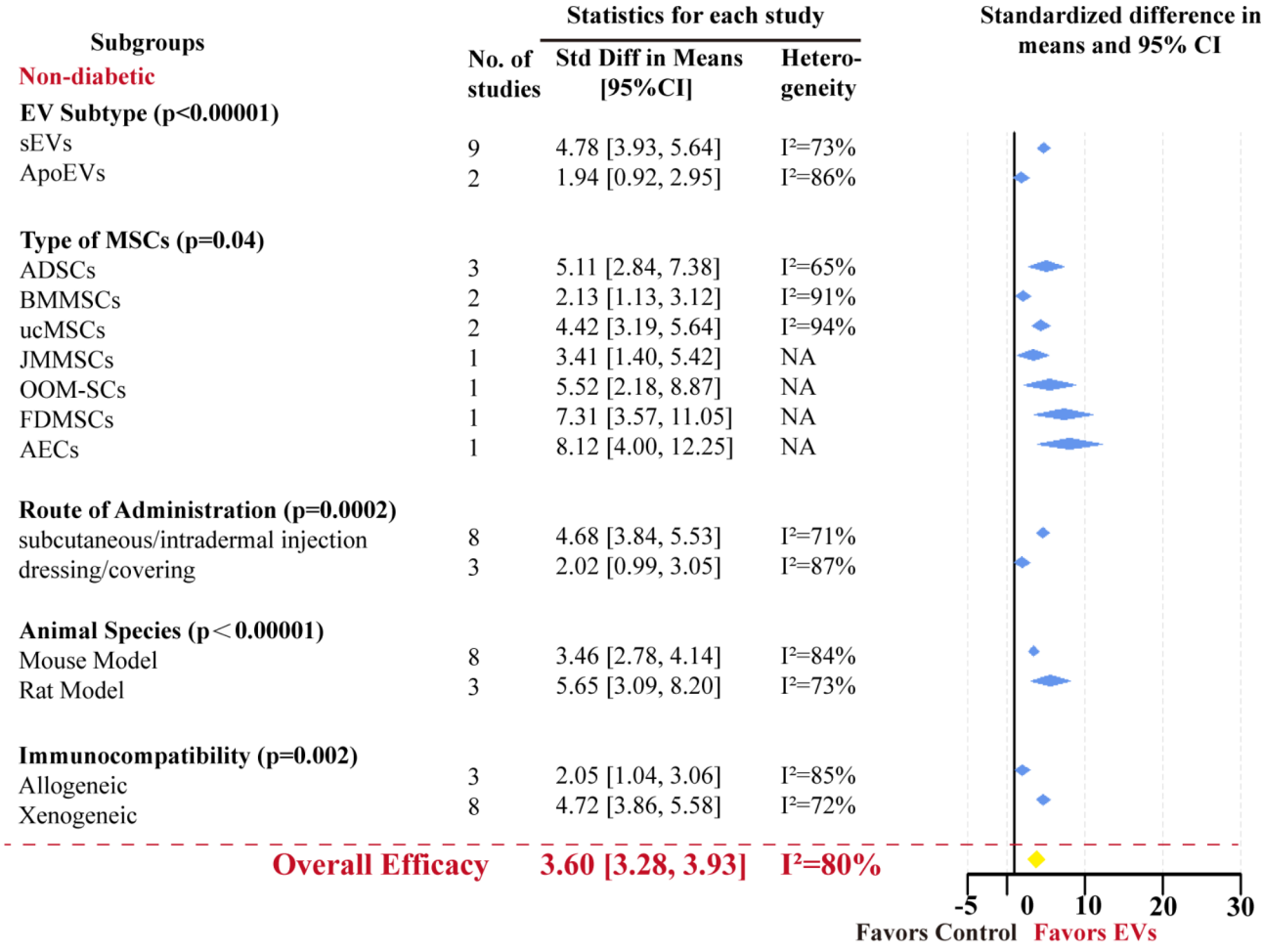

Fig. 6 Subgroup analysis for wound closure rate in non-diabetic wound healing model. Each row represents pooled estimate data from studies within that subgroup. Data is presented as a forest plot with SMD and 95% confidence intervals. I^2 value represents the statistical heterogeneity within each subgroup. Effect sizes > 0 favours MSC-EVs treatment and < 0 favours control. The 'Overall Efficacy' is a pooled estimate effect of MSC-EVs on wound closure rate from all studies combined. ADSCs: adipose mesenchymal stem cells; BMMSCs: bone marrow mesenchymal stem cells; ucMSCs: umbilical cord mesenchymal stem cells; JMMSCs: jaw bone marrow mesenchymal stem cells; OOM-SCs: facial tissue-derived orbicularis oculi muscle stem cells; FDMSCs: fetus skin-derived mesenchymal stem cells; AECs: amniotic epithelial cells

((SMD: 26.60, 95%CI: 25.14 to 28.06). 200 μg of sEVs protein demonstrate a reduction in effect size as compared to 50 μg and 100 μg dose whereas the result was reversed in non-diabetic group. In diabetic group, PF-127 hydrogel containing 50 μg of ApoBDs protein (SMD: 5.51, 95%CI: 2.20 to 8.81) showed similar efficacy with PF-127 hydrogel containing 100 μg of sEVs protein (SMD: 7.84, 95%CI: 44.34 to 11.35). Hyaluronan hydrogel containing 50 μg of ApoBDs protein (SMD: 23.74, 95%CI: 20.00 to 27.49) demonstrate a significant increasement in effect size as compared to the PF-127 hydrogel modification. Similarly, in non-diabetic group, GelMA containing 50 μg of ApoSEVs protein (SMD: 32.31, 95%CI: 28.86 to 35.77) also demonstrate a significant increasement in effect size as compared to the PF-127 hydrogel modification (SMD: 16.21, 95%CI: 8.90 to 23.34). Importantly, GelMA containing ApoBDs (SMD: -7.46, 95%CI: -10.99 to -3.93) showed a significant reduction in effect size compared to ApoSEVs. In conclusion, ApoSEVs showed better efficacy than ApoBDs and sEVs. Subcutaneous injection as route of administration displayed a greater improvement to wound closure as compared to dressing/covering. Lastly, the effect size of sEVs treatment varied considerably and seemed was not dose-respondent.

Secondary outcome: blood vessel density, collagen deposition and scar width

In addition to wound re-epithelialization and cell proliferation, collagen deposition, revascularization and inhibition of scar information were also essential parts of wound healing and skin regeneration. Therefore, secondary outcomes considered for wound healing studies included blood vessel density, collagen deposition and scar width.

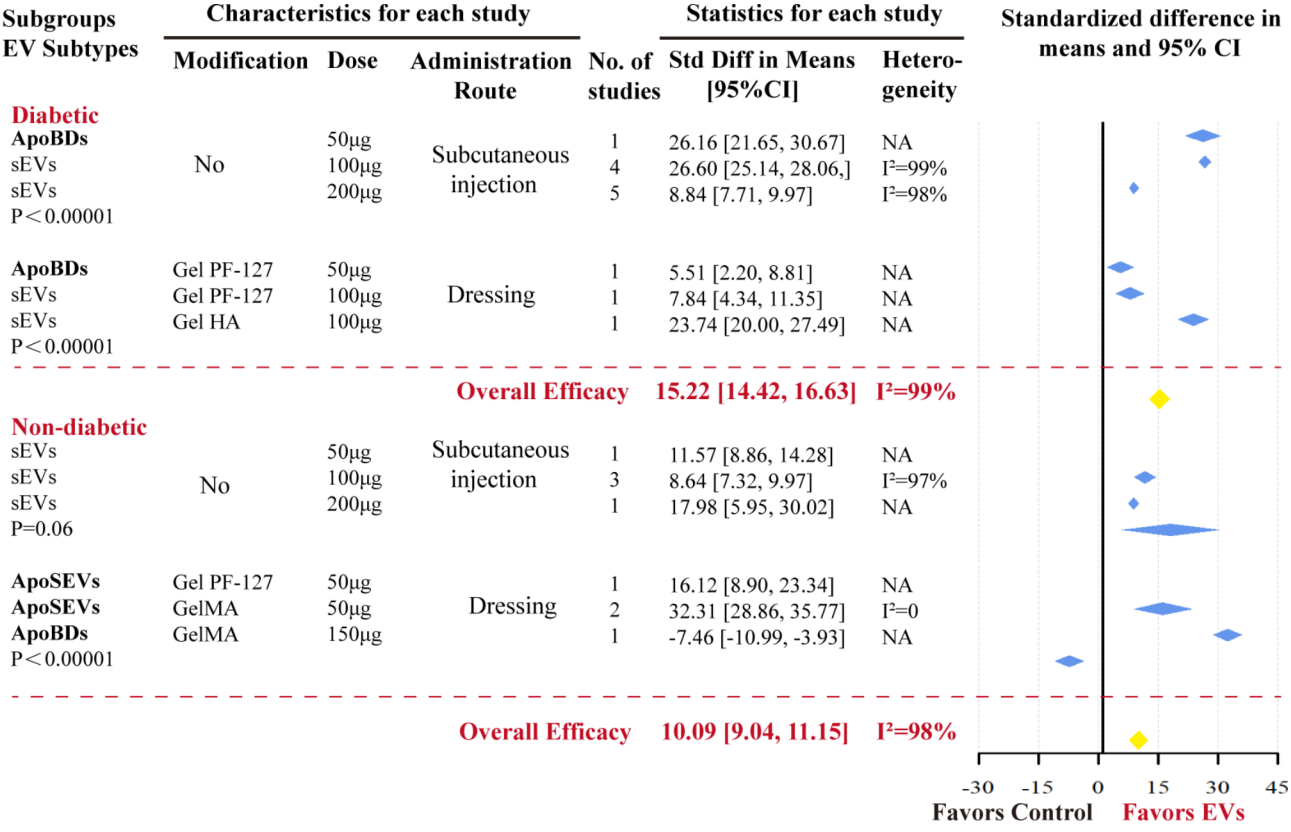

Fig. 7 Subgroup analysis for wound closure rate in diabetic and non-diabetic wound healing model. Subgroup analysis is conducted for mice wound healing studies administering MSC-EVs with similar modification, treatment dose and administration route. Each row represents pooled estimate data from studies within that subgroup. Data is presented as a forest plot with standardized mean difference and 95% confidence intervals. I^2 value represents the statistical heterogeneity within each subgroup. Effect sizes > 0 favours MSC-EVs treatment and < 0 favours control. The 'Overall Efficacy' is a pooled estimate effect of MSC-EVs on wound closure rate from all studies combined

Changes to collagen deposition measured by collagen volume fraction was reported in 11 studies for examining the influence of MSC-EVs interventions (a total of 166 animals; 8 studies used diabetes models, and 3 used non-diabetes models). Overall, MSC-EVs administration was associated with a significant improvement in collagen deposition (SMD = 2.60, 95% CI: 1.96 to 3.24; SMD = 5.16, 95% CI: 2.95 to 4.26, $p < 0.00001$ in diabetes and non-diabetes models, respectively) (Fig. 8). Similarly, subgroup meta-analyses in diabetic and non-diabetic groups demonstrated that MSC-EVs therapy was significantly more effective than control in promoting collagen deposition in both models (SMD = 3.27, 95% CI: 2.55 to 3.99, $p < 0.00001$; SMD = 5.16, 95% CI: 3.85 to 6.47, in diabetes and non-diabetes models, respectively). Heterogeneity was high in diabetes models ($I^2 = 86\%$) and non-diabetes models (($I^2 = 84\%$). From subgroup analysis (Fig. 9), collagen volume fraction was increased to a greater extent ($P < 0.00001$) by delivery of ApoSEVs as compared to sEVs and ApoBDs. However, the study number of ApoSEVs and ApoBDs was limited, with only two and one respectively. A subtypes meta-analysis was conducted for mice wound healing studies administering EVs with similar modification, treatment dose and administration route and couldn't draw an exact conclusion (Figure S4). When considering MSCs tissue source and route of administration, ADSCs and subcutaneous/intradermal injection displayed a greater improvement ($p<0.00001$). Xenogeneic administration of MSC-EVs also showed a greater improvement in collagen volume fraction compared to allogeneic delivery ($p<0.00001$). Species ($p<0.00001$) was associated with greater EVs efficacy as rat models demonstrated better outcomes (Fig. 9).

Ten studies assessing blood vessel density (number of blood vessels/mm2) to evaluate the effect of MSC-EVs transplantation on angiogenesis were eligible for meta-analysis (7 diabetes model studies of 116 animals; 3 non-diabetes model studies of 40 animals). Overall, MSC-EV administration was associated with a significant impact in supporting blood vessel development (SMD: 5.39, 95%CI: 4.50 to 6.29; SMD: 3.50, 95%CI: 2.32 to 4.68, in diabetes and non-diabetes models, respectively). The heterogeneity index was low ($I^2 = 30\%$) in diabetic group, but moderate ($I^2 = 65\%$) in non-diabetic group (Fig. 8). Subgroup analysis (Fig. 10) demonstrated that blood vessel density was increased to a greater extent ($P < 0.00001$) by delivery

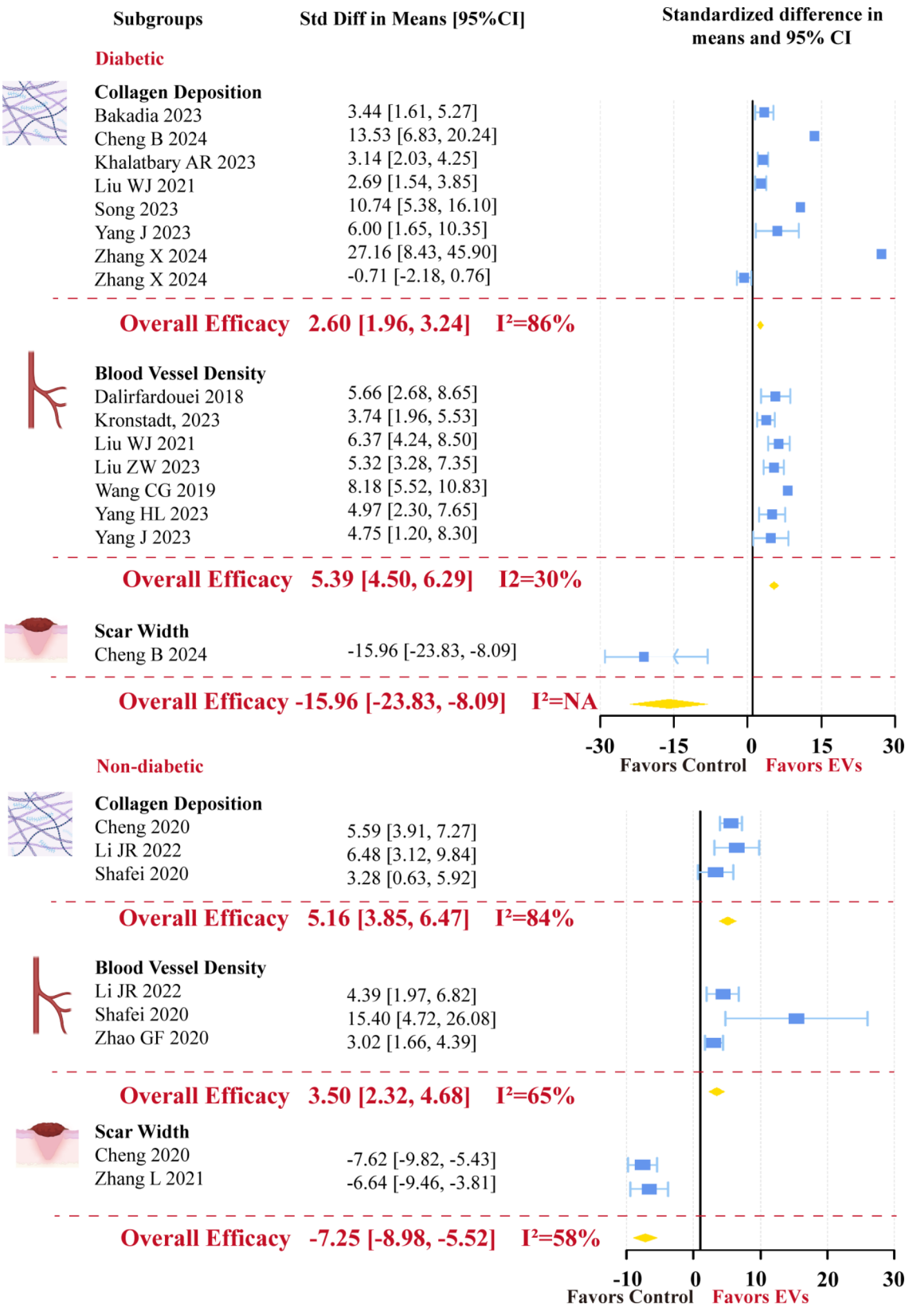

Fig. 8 Forest plot of different secondary outcomes in diabetic and non-diabetic wound healing model. Data is presented as a forest plot with SMD and 95% confidence intervals. The diamond represents the pooled SMD. I^2 value represents the statistical heterogeneity. The 'Overall Efficacy' is a pooled estimate effect of MSC-EVs on secondary outcomes (collagen deposition, blood vessel density, or scar width) from all studies combined

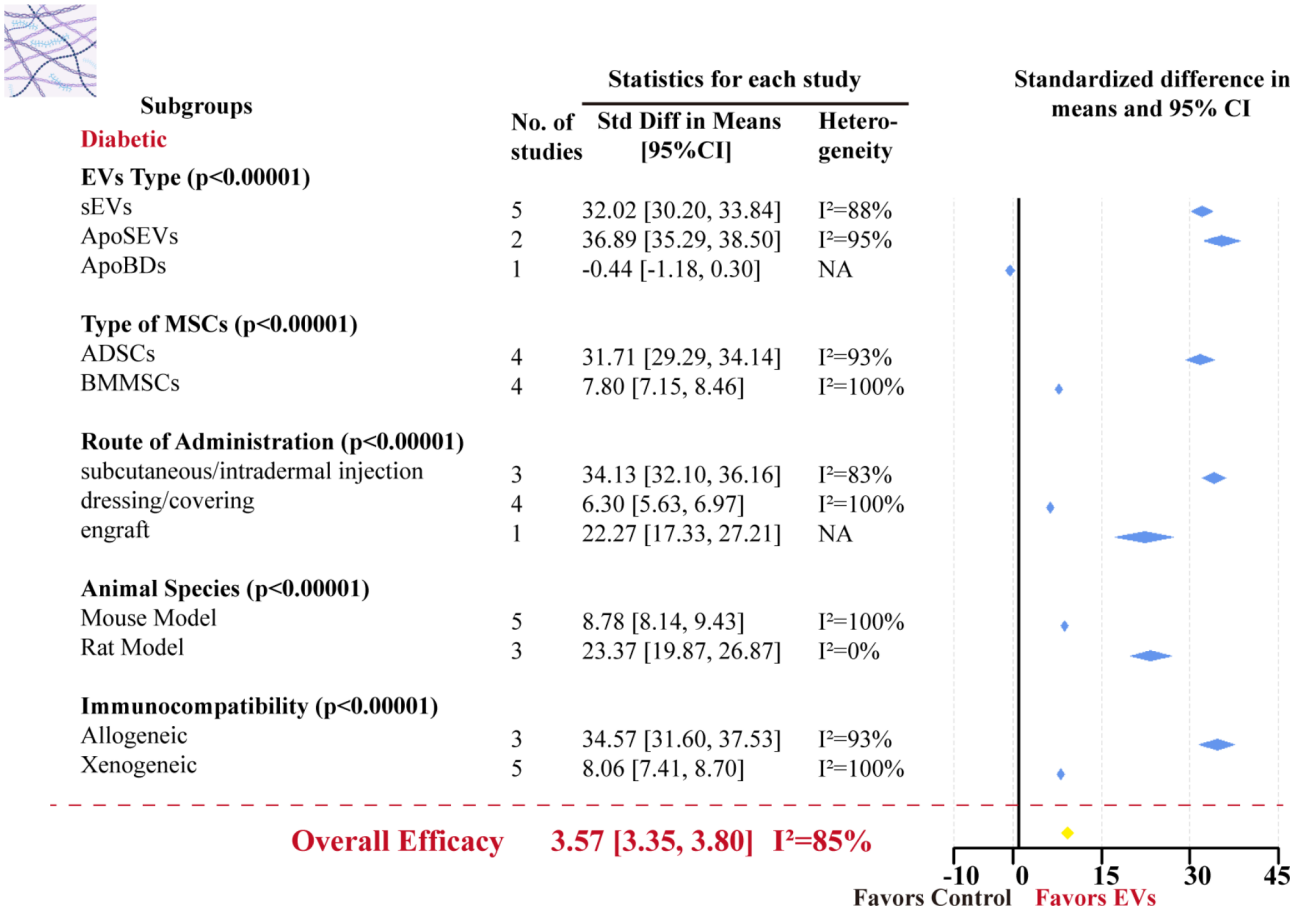

Fig. 9 Subgroup analysis for collagen deposition in diabetic wound healing model. Each row represents pooled estimate data from studies within that subgroup. Data is presented as a forest plot with SMD and 95% confidence intervals. I^2 value represents the statistical heterogeneity within each subgroup. The 'Overall Efficacy' is a pooled estimate effect of MSC-EVs on collagen deposition from all studies combined

of sEVs as compared to ApoEVs. However, it's necessary to note that the number of studies employing ApoEVs was limited, with only one. A subtypes meta-analysis was conducted for mice wound healing studies administering EVs with similar modification, treatment dose and administration route and couldn't draw an exact conclusion (Figure S5).When considering MSCs tissue source and route of administration, FMSCs and subcutaneous/intradermal injection displayed a greater improvement (p<0.00001). Additionally, BMMSCs demonstrated better effect than ADSCs. Lastly, similar to the results above, xenogeneic administration of MSC-EVs (p < 0.00001) and rat models (p < 0.00001) also demonstrated better outcomes (Fig. 10).

The meta-analysis of 3 studies assessing scar width (in μm) revealed promising results regarding the impact of MSC-EVs interventions (SMD =-15.96, 95% CI: -23.83 to -8.09, p < 0.0001 I^2 = NA; SMD = -7.25, 95% CI: -8.98 to -5.52, p < 0.00001, I^2 = 58%, in diabetes and non-diabetes models, respectively) (Fig. 8).

No harmful events were reported across any of the included studies, indicating the safety of MSC-EVs interventions in the context of promoting wound healing and skin regeneration.

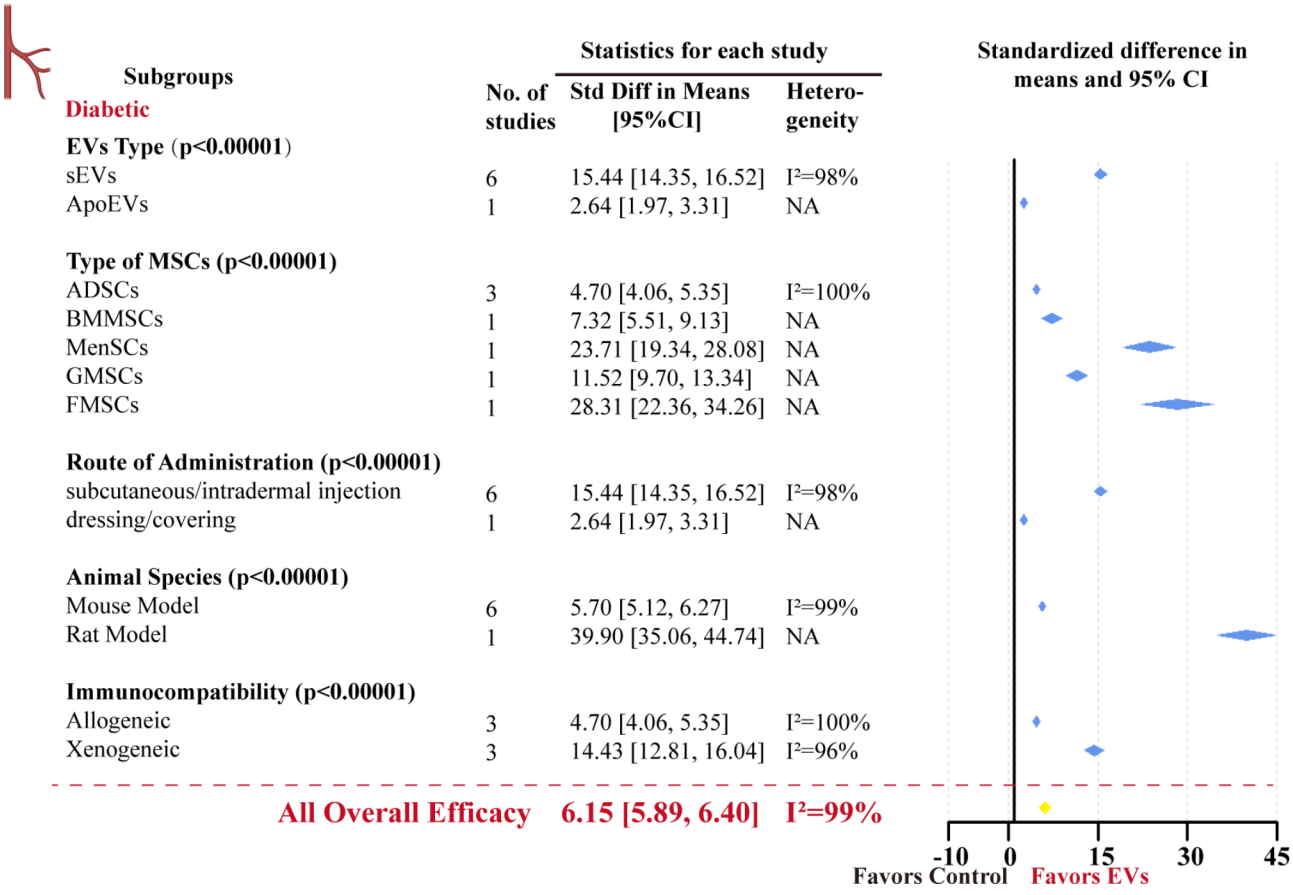

Fig. 10 Subgroup analysis for blood vessel density in diabetic wound healing model. Each row represents pooled estimate data from studies within that subgroup. Data is presented as a forest plot with SMD and 95% confidence intervals. I^2 value represents the statistical heterogeneity within each subgroup. The 'Overall Efficacy' is a pooled estimate effect of MSC-EVs on blood vessel density from all studies combined

Risk of bias assessment

The risk of bias in animal experiments was assessed using the SYRCLE's ROB tool, and the findings are summarized in Fig. 11. Overall, a majority of studies were categorized as having an 'unclear' risk of bias across most domains. Specifically, although 38 studies (45.8%) reported randomizing animals to experimental groups, only one study provided details regarding the method of randomization, which is crucial to assess adequate random sequence generation and reducing selection bias. 49 studies (59.0%) demonstrated a low risk for reporting baseline characteristics, indicating a lower risk of selection bias. However, the risk of bias remained unclear across all studies for the domains of allocation concealment (selection bias) and blinding of personnel (performance bias). Only 4 studies (4.8%) clarified that animals were randomly housed, addressing performance bias to some extent. Blinding during outcome assessment (detection bias) was reported for 23 studies (27.7%), indicating a lower risk in this aspect. In terms of selective reporting (reporting bias), all studies were categorized as having a low risk based on what was reported in the methods. However, none of these studies reported publishing an a priori protocol to verify this judgment. Finally, a high risk of attrition bias was identified in 10 studies (12.0%), while 33 studies (39.8%) demonstrated a low risk, and the remaining 40 studies (48.2%) had an uncertain risk in this domain.

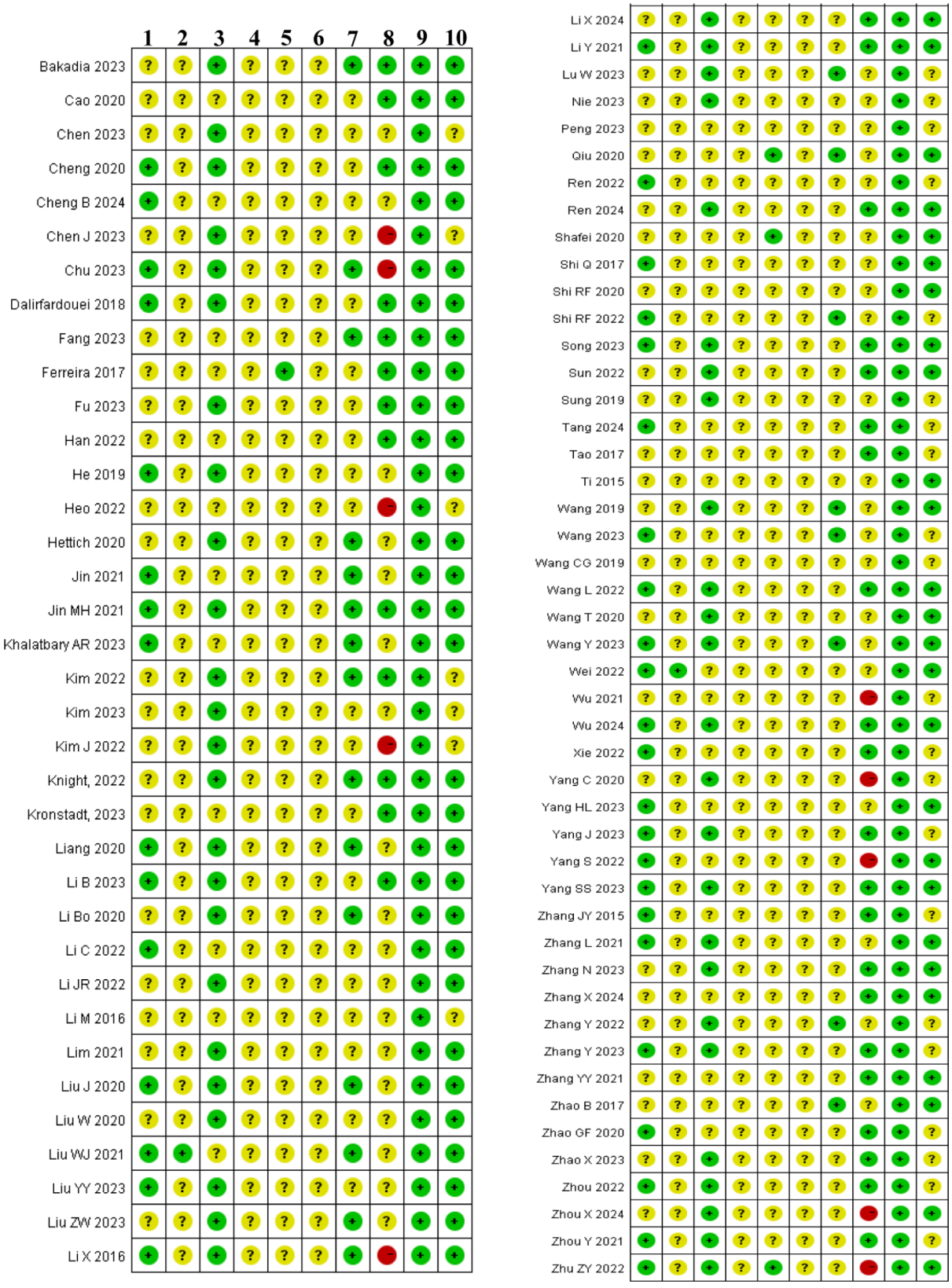

Fig. 11 (See legend on next page.)

(See figure on previous page.)

Fig. 11 Risk of bias assessment of the 83 reviewed studies based on SYRCLE's ROB tool represented by RevMan 5.4. [1] Randomization (selection bias); [2] Random sequence generation (selection bias); [3] Baseline characteristics (selection bias); [4] Allocation concealment; [5] Random housing (performance bias); [6] Blinding of personnel (performance bias); [7] Blinding of outcome assessment (detection bias); [8] Incomplete outcome data (attrition bias); [9] Selective reporting (reporting bias); [10] other sources of bias (attrition bias). A domain concerning the declaration of the randomization method was added (domain 1), while the domain of "blinding of outcome assessment" was not covered in this review

Conclusions

Our review synthesized a wide range of preclinical studies focusing on the efficacy, characteristics, modification methods, study designs, and reporting quality of MSC-EVs in wound healing and skin regeneration. The findings highlight the potential of MSC-EVs as promising therapeutic agents for enhancing wound healing in both diabetic and non-diabetic animal models. This improvement was evident in primary outcomes (i.e. wound closure rates) and secondary outcomes, including blood vessel density, collagen deposition, and scar width. Subgroup analyses demonstrated that ApoSEVs exhibited superior efficacy compared to ApoBDs and sEVs in wound closure outcomes. However, subgroup analyses did not yield definitive conclusions regarding the comparative effectiveness in collagen deposition and revascularization. Among frequently used routes of administration, subcutaneous injection displayed greater improvement in wound closure, collagen deposition and revascularization compared to topical dressing or covering. Regarding accessible source of MSCs, ADSCs showed the most significant effect on wound closure rates and collagen deposition, as compared, whereas BMMSCs exhibited superior outcomes in revascularization. Lastly, the effect size of sEVs treatment varied considerably and did not appear to follow a dose-response relationship. Due to the limited number of studies administrating ApoEVs, it was difficult to characterize any clear trend regarding dose-response.

Moreover, the high heterogeneity observed in collection conditions, separation methods, storage methods, modifications, treatment dose, administration route, and frequency of MSC-EVs, as described above, underscores the urgent need for standardization in these areas. Without standardized protocols, comparability between studies is compromised, potentially impeding clinical translation [90]. These measures can also ensure consistency and reproducibility across studies, enabling more meaningful comparisons and improving the reliability of research findings. In line with MISEV 2023 recommendations, each EV preparation should be characterized by quantitative measures of the EV source (e.g., number of secreting cells, volume of biofluid, mass of tissue), and along with estimates of EV abundance (particle number, protein, and/or lipid content). Our assessment of adherence to international guidelines (e.g. ISCT criteria and MISEV 2023) [13, 14] revealed suboptimal compliance, with only 79.5% and 55.4% of studies meeting the respective recommendations. This highlights the need for greater awareness and adherence to established guidelines. Following these standards can enhance the rigor and robustness of research methodologies, ultimately improving the reliability and validity of study outcomes.

Although MSC-EVs therapy shows great potential, several unresolved issues still warrant future research. First, the use of more precise nomenclature for EVs is necessary. As defined by MISEV 2023, exosome should be characterized by their origin from the endosomal system, distinguishing them from other subtypes of sEVs (e.g., ectosome). However, none of the included studies using the term 'exosome' clarified its biogenesis origin. In addition, ApoEVs have not been accurately defined or fully embodied in MISEV 2023, despite their growing prominence in tissue regeneration research [91, 92]. Secondly, further research is critically needed to deepen our understanding of the underling mechanism driving the functional difference between ApoSEVs and ApoBDs. These differences may be linked to several key factors, including the unique bioactive molecules they encapsulate, the size, and their distinct biogenesis processes. One study [34] investigated the protein and gene expression profiles of ADSCs-derived ApoSEVs and ApoBDs. The findings revealed that proteins enriched in apoSEV were associated with cell adhesion, migration, and proliferation, while genes related to transcription and biological development were upregulated. In contrast, proteins in ApoBDs were linked to cellular metabolism and energetics, with genes associated with cellular metabolism regulation upregulated. Thirdly, the precise therapeutic cargo of EVs needs to be determined. Finally, optimal strategies for EV modifications must be identify before clinical translation, as personalized MSC-EVs-based skin therapy may become the future approach. Different skin type, condition, and defects will likely require tailored therapeutic solutions [93].

Materials and methods

Literature search strategy

The protocol of this study was developed a priori, peer-reviewed, registered, and published in the International Prospective Register of Systematic Reviews (PROPSPERO; protocol ID: CRD42024499172). It's important to note that the current review specifically focuses on the in vivo component of the intended studies. The search process began by formulating a query (i.e., keywords) based on relevant published studies. Three bibliographic

databases containing peer-reviewed journals, namely, Web of Science (Science Citation Index Expanded), PubMed, and Embase, were searched. Only publications written in English were included. All retrieved articles were consolidated in EndNote, and duplicates were subsequently removed. The search encompassed studies published until September 3rd, 2023. To update our study, an additional search was conducted on June 15th, 2024, triggered by an activated search-alert established earlier. No restrictions on publication date were imposed. Study selection processed through two stages, with two reviewers (YFZ, HY) independently conducting screening. The first stage involved reviewing titles and abstracts, while the second stage entailed assessing the full text of articles based on predefined exclusion and inclusion criteria. Disagreements between reviewers were resolved through discussion. The search strategies were tailored to each database, incorporating controlled vocabulary, MeSH terms (e.g. mesenchymal stem cells, mesenchymal stromal cells, extracellular vesicles, exosomes, microvesicles, apoptotic vesicles, apoptotic bodies), abbreviations (e.g. MSCs, EVs, MVs, ApoEVs, ApoBDs, ApoSEVs), and filters for preclinical animal models.

Eligibility criteria

In the first stage of the qualitative synthesis, we included only peer-reviewed original research articles meeting the following criteria: (1) written in English, (2) evaluating MSC-EVs therapeutic roles in wound healing and skin regeneration, and (3) conducted in mammalian animal models. Human trials were not included in this review. Studies were excluded if they: (1) were not original research (e.g., reviews, reports, commentaries, and conference proceedings), (2) were written in languages other than English, (3) were unrelated to MSC-EVs applications in skin regeneration, or (4) solely conducted in vitro studies.

In the second stage of the search, only studies meeting the following criteria were included: (1) controlled interventional design, (2) examination of at least one EVs protein marker, (3) characterization of the size of isolated MSC-EVs, (4) characterization of MSCs by differentiation potential or MSCs surface marker, (5) isolation of EVs from MSCs, (6) investigation of wound healing and skin regeneration either macroscopically or microscopically, qualitatively or quantitatively, and (7) availability of full text either online or after request from the authors. Studies were excluded if they: (1) did not characterize EVs by size and at least one EVs protein marker, (2) did not characterize MSCs by differentiation potential or MSCs surface marker, (3) did not isolate EVs from MSCs, (4) did not assess wound healing or skin regeneration macroscopically or microscopically, qualitatively or quantitatively, (5) were not controlled, (6) did not include the pre-specified primary outcomes or reported insufficient data on the outcomes, or (7) their full text could not be retrieved despite contacting the authors.

Data extraction and synthesis

Data were independently extracted by two groups of reviewers: YFZ and HY, as well as HJT and ZXX. Data were gathered from various sources, including texts, tables, figures, supplementary materials, and referenced methods. Information was collected on various study characteristics, encompassing general study details, animal model characteristics (e.g., species, age, model of disease or injury), techniques for MSCs and EVs isolation and characterization, modifications to MSCs or EVs, and dosage. All data collected are detailed in our registered PROSPERO protocol. We applied generally accepted size-based definitions of EV subtypes, including exosomes (< 200 nm in diameter), sEVs (< 200 nm in diameter), ApoBDs (1–5 μm in diameter) [14, 94], to assess whether authors' use of these terms aligned with MISEV recommendations. Additionally, ApoSEVs (< 1 μm in diameter), recently characterized in some research, were also defined in this study.

Since MSCs are a heterogeneous population of cells widely accessible from a variety of tissue sources, ISCT published guidelines [13] to standardize MSCs characterization. Studies were evaluated for adherence to ISCT criteria, which encompass: (1) adherence to plastic in standard culture conditions, (2) positive and negative expression of specific surface antigens, and (3) multipotent differentiation potential of MSCs. Additionally, international guidelines for investigating extracellular vesicles (EVs) were published in 2024 under the title 'Minimal Information for Studies of EVs' (MISEV 2023). Researchers are encouraged to characterize EVs by quantity, two measures of single vesicle analysis, and assess the presence of categories 1 and 2 protein content of EVs (i.e. transmembrane proteins associated with plasma membrane and/or endosomes, and cytosolic proteins in EVs). These criteria were utilized to evaluate the adherence of studies to EVs characterization guidelines.

Quality and risk of bias assessment

Risk of bias was evaluated by two independent reviewers (YFZ, HJT) using the SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) risk of bias tool. Disagreements between reviewers were resolved through discussion. The SYRCLE tool features 10 different parameters, including: (1) random sequence generation, (2) baseline characteristics, and (3) allocation concealment, to evaluate selection bias; (4) random housing and (5) researcher blinding, to evaluate performance bias; (6) random outcome assessment, and (7) blinding of outcome assessment, to evaluate detection

bias; [8] incomplete outcome data, to evaluate attrition bias; [9] selective reporting, to evaluate reporting bias; and [10] other source(s) of bias, if any. We modified the tool to include another item, declaration of the randomization method, but we excluded point [6] and thus did not check for random outcome assessment. Each of which was scored as having a low, high, or unclear risk of bias for each study. We further assessed sample size calculation, quality of reporting, adherence to MISEV20223 characterization criteria, and adherence to ISCT minimal criteria to characterize MSCs.

Meta-analysis

The studies identified through our comprehensive search were checked for eligibility for a meta-analysis. We conducted a meta-analysis for four outcomes: wound closure rate, scar reduction, angiogenesis, and collagen deposition, using Review Manager 5.4 (Cochrane) to compare MSC-EVs with placebo controls. In cases where numerical data were unavailable, we extracted data from figures using GetData Graph Digitizer. Studies were excluded from the meta-analysis if sample size and treatment dose information were not provided, or if they did not characterize EVs (except apoptotic vesicles) based on MISEV 2023 guidelines. We chose standardized mean difference (SMD) as the metric for continuous outcome measures, accompanied by 95% confidence intervals (CIs), calculated using a random-effects inverse variance meta-analysis. This choice was made to account for the expected heterogeneity in measurement techniques of outcomes. Statistical heterogeneity was assessed using the Cochrane I^2 test. Planned subgroup analyses included subgroups based on disease models (e.g. diabetes, non- diabetes) and intervention characteristics (e.g. tissue source of MSCs, subtype of EVs).

Abbreviations

ADSCs	Adipose mesenchymal stem cells
ADSC-EVs	Adipose mesenchymal stem cells-derived extracellular vesicles
AFM	Atomic force microscopy
AMS	Amniotic membrane-scaffold
ApoBDs	Apoptotic bodies
ApoEVs	Apoptotic extracellular vesicles
ApoSEVs	Apoptotic small extracellular vesicles
BCA	Bicinchoninic acid assay
BMMSC-EVs	Bone marrow mesenchymal stem cells-derived extracellular vesicles
DLS	Dynamic light scattering
EV	Extracellular vesicles
GelMA	Gelatin methacryloyl
IFN-γ	Interferon-gamma
ISCT	International Society for Cell and Gene Therapy
LPS	Lipopolysaccharide
MISEV2023	Minimal information for studies of extracellular vesicles 2023
MSCs	Mesenchymal stem cells
MSC-EVs	Mesenchymal stem cells-derived extracellular vesicles
NTA	Nanoparticle tracking analysis
SEC	Size exclusion chromatography
SEM	Scanning electron microscopy
sEV	Small extracellular vesicles
tBHQ	Tert-butylhydroquinone
TEM	Transmission electron microscopy
TFF	Tangential flow filtration
TRPS	Tunable resistive pulse sensing
ucMSC-EVs	Umbilical cord mesenchymal stem cells-derived extracellular vesicles

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-024-05744-0.

Supplementary Material 1: Distribution of (A) separation methods and (B) characterization methods of EVs across the included studies. Studies may have incorporated more than one method within each domain.

Supplementary Material 2: An overview of modification methods, including modifications to MSCs, EVs directly and co-treatments with other therapy.

Supplementary Material 3: Dosage regimen of administered MSC-EVs. Details pertaining to storage temperature, storage suspending medium, route of administration, units of dose used, and number of doses was extracted from 78 articles. Studies may have incorporated more than one dosage regimen.

Supplementary Material 4: Summary of study characteristics of all included studies

Supplementary Material 5: Subgroup analysis for collagen deposition in diabetic wound healing model. Subgroup analysis is conducted for mice wound healing studies administering MSC-EVs with similar modification, treatment dose and administration route. Each row represents pooled estimate data from studies within that subgroup. Data is presented as a forest plot with standardized mean difference and 95% confidence intervals. I2 value represents the statistical heterogeneity within each subgroup. Effect sizes $<$ 0 favours MSC-EVs treatment and $>$ 0 favours control. The 'Overall Efficacy' is a pooled estimate effect of MSC-EVs on collagen deposition from all studies combined.

Supplementary Material 6: Subgroup analysis for collagen deposition in diabetic wound healing model. Subgroup analysis is conducted for mice wound healing studies administering MSC-EVs with similar modification, treatment dose and administration route. Each row represents pooled estimate data from studies within that subgroup. Data is presented as a forest plot with standardized mean difference and 95% confidence intervals. I2 value represents the statistical heterogeneity within each subgroup. Effect sizes $>$ 0 favours MSC-EVs treatment and $<$ 0 favours control. The 'Overall Efficacy' is a pooled estimate effect of MSC-EVs on collagen deposition from all studies combined.

Acknowledgements

This work was funded by the National Natural Science Foundation of China under (No. 81971852 and No. 82202476).
Not applicable.

Author contributions

Conceptualization: YFZ, HY, ZXX, and HJT; Methodology: YFZ, and YH; Investigation: YFZ, and ZXX; Formal Analysis: YFZ, HY, and HJT; Visualization: YFZ and HY; Supervision: HJT, XHC, and YJL; Writing-Original Draft: YFZ; Writing-Review and Editing: XHC, and YJL.
Acknowledgements.

Funding

This work was funded by the National Natural Science Foundation of China under (No. 81971852 and No. 82202476).

Data availability

Raw data from the meta-analyses are provided in Supplementary files. Queries can be sent to YFZ (yuyufan75@foxmail.com).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors have reviewed and agreed on the contents of the manuscript.

Competing interests
The authors declare that there are no competing interests.

Author details
[1]Department of Plastic and Cosmetic Surgery, Nanfang Hospital, Southern Medical University, 1838 Guangzhou North Road, Guangzhou, Guangdong 510515, P. R. China

Received: 6 July 2024 / Accepted: 7 October 2024
Published online: 24 March 2025

References

1. Caplan H, Olson SD, Kumar A, George M, Prabhakara KS, Wenzel P, et al. Mesenchymal stromal cell therapeutic delivery: Translational challenges to clinical application. Front Immunol. 2019;10:1645.
2. Nagelkerke A, Ojansivu M, van der Koog L, Whittaker TE, Cunnane EM, Silva AM, et al. Extracellular vesicles for tissue repair and regeneration: evidence, challenges and opportunities. Adv Drug Deliv Rev. 2021;175:113775.
3. Su H, Wang Z, Zhou L, Liu D, Zhang N. Regulation of the Nrf2/HO-1 axis by mesenchymal stem cells-derived extracellular vesicles: implications for disease treatment. Front Cell Dev Biol. 2024;12:1397954.
4. Manchon E, Hirt N, Bouaziz JD, Jabrane-Ferrat N, Al-Daccak R. Stem cells-derived Extracellular vesicles: potential therapeutics for Wound Healing in Chronic Inflammatory skin diseases. Int J Mol Sci. 2021;22(6).
5. Li Q, Liu J, Su R, Zhen J, Liu X, Liu G. Small extracellular vesicles-shuttled miR-23a-3p from mesenchymal stem cells alleviate renal fibrosis and inflammation by inhibiting KLF3/STAT3 axis in diabetic kidney disease. Int Immunopharmacol. 2024;139:112667.
6. Gui Q, Ding N, Yao Z, Wu M, Fu R, Wang Y, et al. Extracellular vesicles derived from mesenchymal stem cells: the wine in Hebe's hands to treat skin aging. Precis Clin Med. 2024;7(1):pbae004.
7. Tsiapalis D, O'Driscoll L. Mesenchymal stem cell derived Extracellular vesicles for tissue Engineering and Regenerative Medicine Applications. Cells. 2020;9(4).
8. Park GH, Kwon HH, Seok J, Yang SH, Lee J, Park BC, et al. Efficacy of combined treatment with human adipose tissue stem cell-derived exosome-containing solution and microneedling for facial skin aging: a 12-week prospective, randomized, split-face study. J Cosmet Dermatol. 2023;22(12):3418–26.
9. Han HS, Koh YG, Hong JK, Roh YJ, Seo SJ, Park KY. Adipose-derived stem cell exosomes for treatment of dupilumab-related facial redness in patients with atopic dermatitis. J Dermatolog Treat. 2023;34(1):2220444.
10. Song Y, You Y, Xu X, Lu J, Huang X, Zhang J, et al. Adipose-derived mesenchymal stem cell-derived exosomes Biopotentiated Extracellular Matrix Hydrogels accelerate Diabetic Wound Healing and skin regeneration. Adv Sci (Weinheim Baden-Wurttemberg Germany). 2023;10(30):e2304023.
11. Ma Q, Liang M, Wu Y, Ding N, Duan L, Yu T, et al. Mature osteoclast-derived apoptotic bodies promote osteogenic differentiation via RANKL-mediated reverse signaling. J Biol Chem. 2019;294(29):11240–7.
12. Xin L, Wei C, Tong X, Dai Y, Huang D, Chen J, et al. In situ delivery of apoptotic bodies derived from mesenchymal stem cells via a hyaluronic acid hydrogel: a therapy for intrauterine adhesions. Bioact Mater. 2022;12:107–19.
13. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315–7.
14. Welsh JA, Goberdhan DCI, O'Driscoll L, Buzas EI, Blenkiron C, Bussolati B, et al. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. J Extracell Vesicles. 2024;13(2):e12404.
15. Li B, Luan S, Chen J, Zhou Y, Wang T, Li Z, et al. The MSC-Derived Exosomal lncRNA H19 promotes Wound Healing in Diabetic Foot Ulcers by Upregulating PTEN via MicroRNA-152-3p. Mol Therapy-Nucleic Acids. 2020;19:814–26.
16. Yang S, Chen S, Zhang C, Han J, Lin C, Zhao X, et al. Enhanced therapeutic effects of mesenchymal stem cell-derived extracellular vesicles within chitosan hydrogel in the treatment of diabetic foot ulcers. J Mater Sci - Mater Med. 2023;34(9):43.
17. Tang W, Du X, Wu Z, Nie Z, Yu C, Gao Y. circ-Erbb2ip from adipose-derived mesenchymal stem cell-derived exosomes promotes wound healing in diabetic mice by inducing the miR-670-5p/Nrf1 axis. Cell Signal. 2024;121:111245.
18. Shi R, Jin Y, Hu W, Lian W, Cao C, Han S, et al. Exosomes derived from mmu_circ_0000250-modified adipose-derived mesenchymal stem cells promote wound healing in diabetic mice by inducing miR-128-3p/SIRT1-mediated autophagy. Am J Physiology-Cell Physiol. 2020;318(5):C848–56.
19. Shi R, Jin Y, Zhao S, Yuan H, Shi J, Zhao H. Hypoxic ADSC-derived exosomes enhance wound healing in diabetic mice via delivery of circ-Snhg11 and induction of M2-like macrophage polarization. Biomed Pharmacother. 2022;153.
20. Ti D, Hao H, Tong C, Liu J, Dong L, Zheng J et al. LPS-preconditioned mesenchymal stromal cells modify macrophage polarization for resolution of chronic inflammation via exosome-shuttled let-7b. J Translational Med. 2015;13.
21. Wang Z, Feng C, Liu H, Meng T, Huang W-Q, Song K-X, et al. Exosomes from circ-Astn1-modified adipose-derived mesenchymal stem cells enhance wound healing through miR-138-5p/SIRT1/FOXO1 axis regulation. World J stem Cells. 2023;15(5):476–89.
22. Jin J, Ou Q, Wang Z, Tian H, Xu J-Y, Gao F et al. BMSC-derived extracellular vesicles intervened the pathogenic changes of scleroderma in mice through miRNAs. Stem Cell Res Ther. 2021;12(1).
23. Li X, Liu L, Yang J, Yu Y, Chai J, Wang L, et al. Exosome Derived from Human umbilical cord mesenchymal stem cell mediates MiR-181c attenuating burn-induced excessive inflammation. EBioMedicine. 2016;8:72–82.
24. Liang J-X, Liao X, Li S-H, Jiang X, Li Z-H, Wu Y-D et al. Antiaging properties of exosomes from adipose-derived mesenchymal stem cells in Photoaged Rat skin. BioMed research international. 2020;2020.
25. Wu P, Zhang B, Han X, Sun Y, Sun Z, Li L, et al. HucMSC exosome-delivered 14-3-3 zeta alleviates ultraviolet radiation-induced photodamage via SIRT1 pathway modulation. Aging-Us. 2021;13(8):11542–63.
26. Wang T, Jian Z, Baskys A, Yang J, Li J, Guo H et al. MSC-derived exosomes protect against oxidative stress-induced skin injury via adaptive regulation of the NRF2 defense system. Biomaterials. 2020;257.
27. Kim SY, Yoon TH, Na J, Yi SJ, Jin Y, Kim M et al. Mesenchymal stem cells and extracellular vesicles derived from Canine Adipose tissue ameliorates inflammation, skin barrier function and Pruritus by reducing JAK/STAT signaling in atopic dermatitis. Int J Mol Sci. 2022;23(9).
28. Kim J, Lee SK, Jung M, Jeong S-Y, You H, Won J-Y et al. Extracellular vesicles from IFN-gamma-primed mesenchymal stem cells repress atopic dermatitis in mice. J Nanobiotechnol. 2022;20(1).
29. Zhang N, Yu X, Li W, Zhang K, Yu J, Liu T. Extracellular vesicles derived from adipose-derived stem cells facilitate Frostbite Wound Healing by regulating SOCS3 expression. Curr Stem Cell Res Therapy. 2023;18(4):528–39.
30. Li J, Wei C, Yang Y, Gao Z, Guo Z, Qi F. Apoptotic bodies extracted from adipose mesenchymal stem cells carry microRNA-21-5p to induce M2 polarization of macrophages and augment skin wound healing by targeting KLF6. Burns: J Int Soc Burn Injuries. 2022;48(8):1893–908.
31. Liu J, Qiu X, Lv Y, Zheng C, Dong Y, Dou G et al. Apoptotic bodies derived from mesenchymal stem cells promote cutaneous wound healing via regulating the functions of macrophages. Stem Cell Res Ther. 2020;11(1).
32. Wang Y, Jing L, Lei X, Ma Z, Li B, Shi Y, et al. Umbilical cord mesenchymal stem cell-derived apoptotic extracellular vesicles ameliorate cutaneous wound healing in type 2 diabetic mice via macrophage pyroptosis inhibition. Stem Cell Res Ther. 2023;14(1):257.
33. Yang J, Zhang X, Wang G, Ma S, Yu Y, Liao C, et al. ApoSEVs-Mediated modulation of versatile target cells promotes Diabetic Wound Healing: unveiling a Promising Strategy. Int J Nanomed. 2023;18:6955–77.
34. Zhang X, Yang J, Ma S, Gao X, Wang G, Sun Y, et al. Functional diversity of apoptotic vesicle subpopulations from bone marrow mesenchymal stem cells in tissue regeneration. J Extracell Vesicles. 2024;13(4):e12434.
35. Shafei S, Khanmohammadi M, Heidari R, Ghanbari H, Nooshabadi VT, Farzamfar S, et al. Exosome loaded alginate hydrogel promotes tissue regeneration in full-thickness skin wounds: an in vivo study. J Biomedical Mater Res Part A. 2020;108(3):545–56.
36. Bakadia BM, Ahmed AAQ, Lamboni L, Shi Z, Mukole BM, Zheng R, et al. Engineering homologous platelet-rich plasma, platelet-rich plasma-derived

exosomes, and mesenchymal stem cell-derived exosomes-based dual-crosslinked hydrogels as bioactive diabetic wound dressings. Bioactive Mater. 2023;28:74–94.
37. Wang L, Cai Y, Zhang Q, Zhang Y. Pharmaceutical activation of Nrf2 accelerates Diabetic Wound Healing by exosomes from Bone Marrow Mesenchymal Stem cells. Int J stem Cells. 2022;15(2):164–72.
38. Wu D, Tao S, Zhu L, Zhao C, Xu N. Chitosan Hydrogel Dressing Loaded with adipose mesenchymal stem cell-derived Exosomes promotes skin full-thickness Wound Repair. ACS Appl Bio Mater. 2024;7(2):1125–34.
39. Jin MH, Yu NN, Jin YH, Mao YY, Feng L, Liu Y, et al. Peroxiredoxin II with dermal mesenchymal stem cells accelerates wound healing. Aging. 2021;13(10):13926–40.
40. Wang X, Jiao Y, Pan Y, Zhang L, Gong H, Qi Y et al. Fetal Dermal Mesenchymal Stem Cell-Derived Exosomes Accelerate Cutaneous Wound Healing by Activating Notch Signaling. Stem Cells International. 2019;2019.
41. Liu Z, Yang S, Li X, Wang S, Zhang T, Huo N, et al. Local transplantation of GMSC-derived exosomes to promote vascularized diabetic wound healing by regulating the Wnt/beta-catenin pathways. Nanoscale Adv. 2023;5(3):916–26.
42. Shi Q, Qian Z, Liu D, Sun J, Wang X, Liu H et al. GMSC-Derived exosomes combined with a Chitosan/Silk Hydrogel Sponge Accelerates Wound Healing in a Diabetic Rat skin defect model. Front Physiol. 2017;8.
43. Knight R, Board-Davies E, Brown H, Clayton A, Davis T, Karatas B, et al. Oral progenitor cell line-derived small Extracellular vesicles as a treatment for Preferential Wound Healing Outcome. Stem Cells Translational Med. 2022;11(8):861–75.
44. Xie Y, Yu L, Cheng Z, Peng Y, Cao Z, Chen B et al. SHED-derived exosomes promote LPS-induced wound healing with less itching by stimulating macrophage autophagy. J Nanobiotechnol. 2022;20(1).
45. Li M, Ke QF, Tao SC, Guo SC, Rui BY, Guo YP. Fabrication of hydroxyapatite/chitosan composite hydrogels loaded with exosomes derived from mir-126-3p overexpressed synovial mesenchymal stem cells for diabetic chronic wound healing. J Mater Chem B. 2016;4(42):6830–41.
46. Tao S-C, Guo S-C, Li M, Ke Q-F, Guo Y-P, Zhang C-Q. Chitosan Wound dressings incorporating exosomes derived from MicroRNA-126-Overexpressing synovium mesenchymal stem cells provide sustained release of exosomes and heal full-thickness skin defects in a Diabetic Rat Model. Stem Cells Translational Med. 2017;6(3):736–47.
47. Lim KM, Dayem AA, Choi Y, Lee Y, An J, Gil M et al. High therapeutic and esthetic properties of Extracellular vesicles produced from the stem cells and their spheroids cultured from ocular surgery-derived Waste Orbicularis Oculi muscle tissues. Antioxidants. 2021;10(8).
48. Yang H, Zhang Y, Du Z, Wu T, Yang C. Hair follicle mesenchymal stem cell exosomal lncRNA H19 inhibited NLRP3 pyroptosis to promote diabetic mouse skin wound healing. Aging-Us. 2023;15(3):791–809.
49. Yang S, Jiang H, Qian M, Ji G, Wei Y, He J et al. MSC-derived sEV-loaded hyaluronan hydrogel promotes scarless skin healing by immunomodulation in a large skin wound model. Biomed Mater. 2022;17(3).
50. Zhao B, Zhang Y, Han S, Zhang W, Zhou Q, Guan H, et al. Exosomes derived from human amniotic epithelial cells accelerate wound healing and inhibit scar formation. J Mol Histol. 2017;48(2):121–32.
51. Fu S, Zhang H, Li X, Zhang Q, Guo C, Qiu K, et al. Exosomes Derived from Human amniotic mesenchymal stem cells facilitate Diabetic Wound Healing by Angiogenesis and enrich multiple lncRNAs. Tissue Eng Regenerative Med. 2023;20(2):295–308.
52. Dalirfardouei R, Jamialahmadi K, Jafarian AH, Mahdipour E. Promising effects of exosomes isolated from menstrual blood-derived mesenchymal stem cell on wound-healing process in diabetic mouse model. J Tissue Eng Regen Med. 2019;13(4):555–68.
53. Zhang J, Guan J, Niu X, Hu G, Guo S, Li Q et al. Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis. J Translational Med. 2015;13.
54. Li C, An Y, Sun Y, Yang F, Xu Q, Wang Z. Adipose mesenchymal stem cell-derived Exosomes Promote Wound Healing through the WNT/β-catenin signaling pathway in dermal fibroblasts. Stem cell Reviews Rep. 2022;18(6):2059–73.
55. Zhu Z, Zhang X, Hao H, Xu H, Shu J, Hou Q et al. Exosomes Derived from umbilical cord mesenchymal stem cells treat cutaneous nerve damage and promote Wound Healing. Front Cell Neurosci. 2022;16.
56. Wang C, Wang M, Xu T, Zhang X, Lin C, Gao W, et al. Engineering Bioactive Self-Healing Antibacterial exosomes Hydrogel for promoting Chronic Diabetic Wound Healing and Complete skin regeneration. Theranostics. 2019;9(1):65–76.
57. Ren H, Su P, Zhao F, Zhang Q, Huang X, He C, et al. Adipose mesenchymal stem cell-derived exosomes promote skin wound healing in diabetic mice by regulating epidermal autophagy. Burns Trauma. 2024;12:tkae001.
58. He X, Dong Z, Cao Y, Wang H, Liu S, Liao L et al. MSC-Derived Exosome Promotes M2 Polarization and Enhances Cutaneous Wound Healing. Stem Cells International. 2019;2019.
59. Heo JS. Selenium-stimulated exosomes enhance Wound Healing by modulating inflammation and angiogenesis. Int J Mol Sci. 2022;23(19).
60. Zhou X, Ye C, Jiang L, Zhu X, Zhou F, Xia M, et al. The bone mesenchymal stem cell-derived exosomal miR-146a-5p promotes diabetic wound healing in mice via macrophage M1/M2 polarization. Mol Cell Endocrinol. 2024;579:112089.
61. Li X, Qu S, Ouyang Q, Qin F, Guo J, Qin M, et al. A multifunctional composite nanoparticle with antibacterial activities, anti-inflammatory, and angiogenesis for diabetic wound healing. Int J Biol Macromol. 2024;260(Pt 2):129531.
62. Hettich BF, Ben-Yehuda Greenwald M, Werner S, Leroux JC. Exosomes for Wound Healing: purification optimization and identification of Bioactive Components. Adv Sci (Weinheim Baden-Wurttemberg Germany). 2020;7(23):2002596.
63. Chen J, Yu W, Xiao C, Su N, Han Y, Zhai L, et al. Exosome from adipose-derived mesenchymal stem cells attenuates scar formation through microRNA-181a/SIRT1 axis. Arch Biochem Biophys. 2023;746:109733.
64. Sung DK, Chang YS, Sung SI, Ahn SY, Park WS. Thrombin preconditioning of Extracellular vesicles derived from mesenchymal stem cells accelerates cutaneous Wound Healing by boosting their Biogenesis and enriching Cargo Content. J Clin Med. 2019;8(4).
65. Kronstadt SM, Patel DB, Born LJ, Levy D, Lerman MJ, Mahadik B, et al. Mesenchymal stem cell culture within perfusion bioreactors incorporating 3D-Printed Scaffolds enables Improved Extracellular Vesicle yield with preserved Bioactivity. Adv Healthc Mater. 2023;12(20):e2300584.
66. Ferreira AF, Cunha PS, Carregal VM, da Silva PdC MC, Kuranth-Lima M et al. Extracellular Vesicles from Adipose-Derived Mesenchymal Stem/Stromal Cells Accelerate Migration and Activate AKT Pathway in Human Keratinocytes and Fibroblasts Independently of miR-205 Activity. Stem Cells International. 2017;2017.
67. Liu W, Yuan Y, Liu D. Extracellular vesicles from adipose-derived stem cells promote Diabetic Wound Healing via the PI3K-AKT-mTOR-HIF-1 alpha signaling pathway. Tissue Eng Regenerative Med. 2021;18(6):1035–44.
68. Wei Q, Wang Y, Ma K, Li Q, Li B, Hu W, et al. Extracellular vesicles from human umbilical cord mesenchymal stem cells facilitate Diabetic Wound Healing through MiR-17-5p-mediated enhancement of Angiogenesis. Stem cell Reviews Rep. 2022;18(3):1025–40.
69. Zhang Y, Bai X, Shen K, Luo L, Zhao M, Xu C et al. Exosomes derived from adipose mesenchymal stem cells promote Diabetic Chronic Wound Healing through SIRT3/SOD2. Cells. 2022;11(16).
70. Zhang Y, Li M, Wang Y, Han F, Shen K, Luo L, et al. Exosome/metformin-loaded self-healing conductive hydrogel rescues microvascular dysfunction and promotes chronic diabetic wound healing by inhibiting mitochondrial fission. Bioactive Mater. 2023;26:323–36.
71. Zhou Y, Zhao B, Zhang XL, Lu YJ, Lu ST, Cheng J, et al. Combined topical and systemic administration with human adipose-derived mesenchymal stem cells (hADSC) and hADSC-derived exosomes markedly promoted cutaneous wound healing and regeneration. Stem Cell Res Ther. 2021;12(1):257.
72. Nie W, Huang X, Zhao L, Wang T, Zhang D, Xu T et al. Exosomal mir-17-92 derived from human mesenchymal stem cells promotes wound healing by enhancing angiogenesis and inhibiting endothelial cell ferroptosis. Tissue Cell. 2023;83.
73. Chu Z, Huang Q, Ma K, Liu X, Zhang W, Cui S, et al. Novel neutrophil extracellular trap-related mechanisms in diabetic wounds inspire a promising treatment strategy with hypoxia-challenged small extracellular vesicles. Bioactive Mater. 2023;27:257–70.
74. Qiu X, Liu J, Zheng C, Su Y, Bao L, Zhu B et al. Exosomes released from educated mesenchymal stem cells accelerate cutaneous wound healing via promoting angiogenesis. Cell Prolif. 2020;53(8).
75. Lu W, Du X, Zou S, Fang Q, Wu M, Li H et al. IFN-gamma enhances the therapeutic efficacy of MSCs-derived exosome via mir-126-3p in diabetic wound healing by targeting SPRED1. J Diabetes. 2023.
76. Liu W, Yu M, Xie D, Wang L, Ye C, Zhu Q et al. Melatonin-stimulated MSC-derived exosomes improve diabetic wound healing through regulating

macrophage M1 and M2 polarization by targeting the PTEN/AKT pathway. Stem Cell Research & Therapy. 2020;11(1).
77. Kim S, Shin Y, Choi Y, Lim K-M, Jeong Y, Dayem AA et al. Improved Wound Healing and Skin Regeneration Ability of 3,2 '-Dihydroxyflavone-Treated Mesenchymal Stem Cell-Derived Extracellular Vesicles. Int J Mol Sci. 2023;24(8).
78. Khalatbary AR, Omraninava M, Nasiry D, Akbari M, Taghiloo S, Poorhassan M, et al. Exosomes derived from human adipose mesenchymal stem cells loaded bioengineered three-dimensional amniotic membrane-scaffold-accelerated diabetic wound healing. Archives of dermatological research; 2023.
79. Zhou Y, Zhang X-L, Lu S-T, Zhang N-Y, Zhang H-J, Zhang J et al. Human adipose-derived mesenchymal stem cells-derived exosomes encapsulated in pluronic F127 hydrogel promote wound healing and regeneration. Stem Cell Res Ther. 2022;13(1).
80. Peng H, Li HC, Zhang X, Tang JZ, Liang YP, Qiao LP et al. 3D-exosomes laden multifunctional hydrogel enhances diabetic wound healing via accelerated angiogenesis. Chem Eng J. 2023;475.
81. Fang Z, Lv Y, Zhang H, He Y, Gao H, Chen C, et al. A multifunctional hydrogel loaded with two nanoagents improves the pathological microenvironment associated with radiation combined with skin wounds. Acta Biomater. 2023;159:111–27.
82. Zhang Y, Zhang P, Gao X, Chang L, Chen Z, Mei X. Preparation of exosomes encapsulated nanohydrogel for accelerating wound healing of diabetic rats by promoting angiogenesis. Volume 120. Materials Science & Engineering C-Materials for Biological Applications; 2021.
83. Yang C, Luo L, Bai X, Shen K, Liu K, Wang J et al. Highly-expressed micoRNA-21 in adipose derived stem cell exosomes can enhance the migration and proliferation of the HaCaT cells by increasing the MMP-9 expression through the PI3K/AKT pathway. Arch Biochem Biophys. 2020;681.
84. Li B, Qian L, Pi L, Meng X. A therapeutic role of exosomal lncRNA H19 from adipose mesenchymal stem cells in cutaneous wound healing by triggering macrophage M2 polarization. Cytokine. 2023;165.
85. Cheng S, Xi Z, Chen G, Liu K, Ma R, Zhou C. Extracellular vesicle-carried microRNA-27b derived from mesenchymal stem cells accelerates cutaneous wound healing via E3 ubiquitin ligase ITCH. J Cell Mol Med. 2020;24(19):11254–71.
86. Zhang L, Ouyang P, He G, Wang X, Song D, Yang Y, et al. Exosomes from microRNA-126 overexpressing mesenchymal stem cells promote angiogenesis by targeting the PIK3R2-mediated PI3K/Akt signalling pathway. J Cell Mol Med. 2021;25(4):2148–62.
87. Sun Y, Ju Y, Fang B. Exosomes from human adipose-derived mesenchymal stromal/stem cells accelerate angiogenesis in wound healing: implication of the EGR-1/lncRNA-SENCR/DKC1/VEGF-A axis. Hum Cell. 2022;35(5):1375–90.
88. Han Z-F, Cao J-H, Liu Z-Y, Yang Z, Qi R-X, Xu H-L. Exosomal lncRNA KLF3-AS1 derived from bone marrow mesenchymal stem cells stimulates angiogenesis to promote diabetic cutaneous wound healing. Diabetes research and clinical practice. 2022;183.
89. Cheng B, Song X, Yin L, Lin J, Liu Z, Zhu Y, et al. HMOX1-overexpressing mesenchymal stem cell-derived exosomes facilitate diabetic wound healing by promoting angiogenesis and fibroblast function. Biochem Biophys Res Commun. 2024;690:149271.
90. Reiner AT, Witwer KW, van Balkom BWM, de Beer J, Brodie C, Corteling RL, et al. Concise Review: developing best-practice models for the therapeutic use of Extracellular vesicles. Stem Cells Transl Med. 2017;6(8):1730–9.
91. Caruso S, Poon IKH. Apoptotic cell-derived extracellular vesicles: more than just debris. Front Immunol. 2018;9:1486.
92. Kholodenko IV, Kholodenko RV, Majouga AG, Yarygin KN. Apoptotic MSCs and MSC-Derived apoptotic bodies as New Therapeutic Tools. Curr Issues Mol Biol. 2022;44(11):5153–72.
93. Al-Masawa ME, Alshawsh MA, Ng CY, Ng AMH, Foo JB, Vijakumaran U, et al. Efficacy and safety of small extracellular vesicle interventions in wound healing and skin regeneration: a systematic review and meta-analysis of animal studies. Theranostics. 2022;12(15):6455–508.
94. Tieu A, Lalu MM, Slobodian M, Gnyra C, Fergusson DA, Montroy J, et al. An analysis of mesenchymal stem cell-derived extracellular vesicles for preclinical use. ACS Nano. 2020;14(8):9728–43.

Publisher's note