Stem Cell Research & Therapy

REVIEW

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Nanoscale therapeutics for erectile dysfunction: a meta-analysis of stem cell-derived extracellular vesicles as natural nanoparticles in diabetic rat models

Kecheng Lou[1], Junjie Hu[1], Jiayue Tong[1] and Zhanshi Wang[2*]

Abstract

Background Erectile dysfunction (ED), a prevalent male sexual disorder, severely impacts quality of life. Extracellular vesicles (EVs), natural nanoparticles (30–200 nm) secreted by stem cells, represent a novel nanomedicine platform for ED treatment due to their ability to encapsulate bioactive cargo (e.g., miRNAs, proteins) and target damaged tissues. Stem cell-derived extracellular vesicles (SC-EVs) have emerged as a promising therapeutic strategy for multiple diseases. This meta-analysis evaluates the therapeutic efficacy of SC-EVs in rat ED models and explores their translational potential.

Methods We systematically searched PubMed, Embase, Cochrane Library, and Web of Science for studies published up to December 2024. Randomized controlled trials (RCTs) assessing EVs in ED treatment were included. A random-effects model was applied to account for between-study heterogeneity, with standardized mean differences (SMDs) and 95% confidence intervals (CIs) calculated for continuous outcomes.

Results Twenty studies involving 324 rats were included. EVs significantly improved erectile function (SMD = 4.19, 95% CI: 3.31–5.08, $P < 0.00001$). Subgroup analyses revealed no significant differences between EV sources (e.g., mesenchymal stem cells [MSCs] vs. adipose-derived stem cells [ADSCs], $P > 0.05$) or disease models (diabetes mellitus [DM] vs. cavernous nerve injury [CNI], $P > 0.05$). EVs upregulated the expression of nitric oxide synthase isoforms (nNOS and eNOS), increased smooth muscle content (α-SMA), and improved smooth muscle-to-collagen ratios ($P < 0.00001$ for all). Funnel plot asymmetry and Egger's test ($P < 0.05$) indicated publication bias, but trim-and-fill analysis confirmed robust results post-adjustment.

Conclusion SC-EVs demonstrate significant therapeutic potential for ED in rat models, particularly in restoring vascular and neural integrity. However, limitations include small sample sizes and short follow-up periods. Future research should prioritize clinical translation, mechanistic exploration, and standardized EV production protocols.

Keywords Stem cells, Extracellular vesicles (EVs), Erectile dysfunction (ED), Meta-analysis, Diabetic complications

Introduction

Erectile dysfunction (ED), documented since ancient times, is defined as the persistent inability to achieve or maintain an erection sufficient for sexual intercourse [1]. Reports indicate that ED is prevalent among men over 40 years of age, with its incidence increasing with

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age. By the age of 70, the prevalence of ED ranges from 50 to 100% [2]. It is projected that the global population affected by ED will rise to 322 million by 2025, making it a significant health concern in aging societies [3, 4].

Current treatment strategies for ED include lifestyle modifications, psychological therapy, and pharmacological interventions. Lifestyle improvements, such as dietary changes and exercise, can alleviate symptoms in some cases [5–10]. Psychological therapy is particularly effective for psychogenic ED, as it helps reduce anxiety and stress [11]. However, for patients with comorbid chronic conditions such as DM or cardiovascular disease, the efficacy of lifestyle interventions is limited [12–14]. Pharmacological treatments like sildenafil enhance erectile function by potentiating nitric oxide (NO) signaling, but their effectiveness depends on the integrity of neural and vascular function. These drugs are less effective in patients with organic ED and may lead to tolerance and dependence with long-term use [15–21].

Mesenchymal stem cell secretome has been shown to have great therapeutic potential in the treatment of ED [22], and SC-EVs, which are part of the secretome, have also shown great therapeutic potential. EVs exhibit anti-inflammatory, pro-angiogenic, and tissue-repair properties, making them particularly promising for neurogenic and vasculogenic ED. They promote tissue regeneration and functional recovery, addressing the limitations of current therapies [23–26]. Additionally, as natural intercellular signaling carriers, EVs avoid issues related to immune rejection and ethical concerns, offering a high safety profile [27]. Consequently, SC-EVs represent a novel therapeutic approach for ED with complex etiologies, particularly in repairing neural and vascular damage [28, 29].

Methods

Search strategy and selection criteria

A comprehensive search was conducted across multiple databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane Library (https://www.cochranelibrary.com/), and Web of Science (http://webofscience.com), for studies published up to December 2024. The search strategy employed the following key terms: *("Dysfunction"OR" erectile dysfunction"OR"impotence") AND ("stem cells") AND ("extracellular vesicles"OR"extracellular particles"OR"exosomes"OR"ectosome"OR"microvesicle")*. No language restrictions were applied to ensure the inclusivity of the search. Some studies, such as those by Song J [30] and Li M et al. [31], analyzed multiple EV groups, resulting in their inclusion more than once in certain analyses.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) Evaluated the role of SC-EVs in treating ED; (2) The objects of the study were ED rats; (3) Assessed erectile function via electrical stimulation of the cavernous nerve, with outcomes measured by intracavernosal pressure/mean arterial pressure ratio (ICP/MAP), neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS), alpha-smooth muscle actin (α-SMA), or smooth muscle-to-collagen ratios. In cases of duplicate data, only the most recent study was included. Studies were excluded if they: (1) Lacked sufficient data for further analysis; (2) Were duplicates or redundant publications; (3) Were expert opinions, conference abstracts, editorials, case reports, letters, reviews, or meta-analyses.

Data extraction

Data from included studies were extracted from all available sources, including tables and figures. For data presented only graphically, WebPlotDigitizer software (AutoFEM Technologies, USA) was used to extract numerical values. Two independent researchers performed data extraction, with discrepancies resolved through third-party arbitration.

Quality assessment

The methodological quality of included studies was assessed by two authors, with disagreements resolved through consensus. Studies were evaluated based on nine criteria:(1) Blinded outcome assessment; (2) Randomization of experiments; (3) Sufficient follow-up duration ($\geq$ 2 weeks); (4) Compliance with animal welfare regulations; (5) Characterization of stem cell phenotypes; (6) Identification of SC-EVs (EVs were characterized using nanoparticle tracking analysis [NTA] for size distribution and transmission electron microscopy [TEM] for morphological validation, consistent with MISEV2023 guidelines); (7) Pre-injection assessment of erectile function; (8) Sample size calculation; (9) Detection of structural changes in the corpus cavernosum. Each criterion was scored as 1 point, and studies were categorized into three quality tiers: high quality (7–9 points), medium quality (4–6 points), and low quality (0–3 points).

Statistical analysis

Data were analyzed using Review Manager 5.3 (The Nordic Cochrane Center). Primary outcomes were expressed as standardized mean differences (SMDs) with 95% confidence intervals (CIs), representing differences in erectile function and corpus cavernosum structural changes between treatment and control groups. Each trial included one control group and one

or more treatment groups. For studies with multiple treatment groups, the control group sample size was divided equally among the treatment groups. If multiple measurements were taken over time, the last measurement was used for analysis.

Subgroup analyses were performed to compare EV types (MSCs and ADSCs) and disease models (DM or CNI). A random-effects model was applied to account for heterogeneity. Results were presented as forest plots, with studies arranged by publication year. Additionally, funnel plots were used to assess potential publication bias.

Result

Search results and characteristics of included studies

The electronic search identified a total of 232 studies, of which 20 met our inclusion criteria and were included in the meta-analysis (Fig. 1). These studies collectively involved 324 rats. The characteristics of the included studies are summarized in Table 1.

Characteristics of included studies

A total of 20 studies (324 rats) were included (Table 1). 7 studies used MSC-EVs, 7 studies used ADSC-EVs, 3 studies used BMSC, 2 studies used USC-EVs, 1 study used corpus cavernosum smooth muscle cells-derived EVs (CCSMC-EVs), 1 study used muscle stem

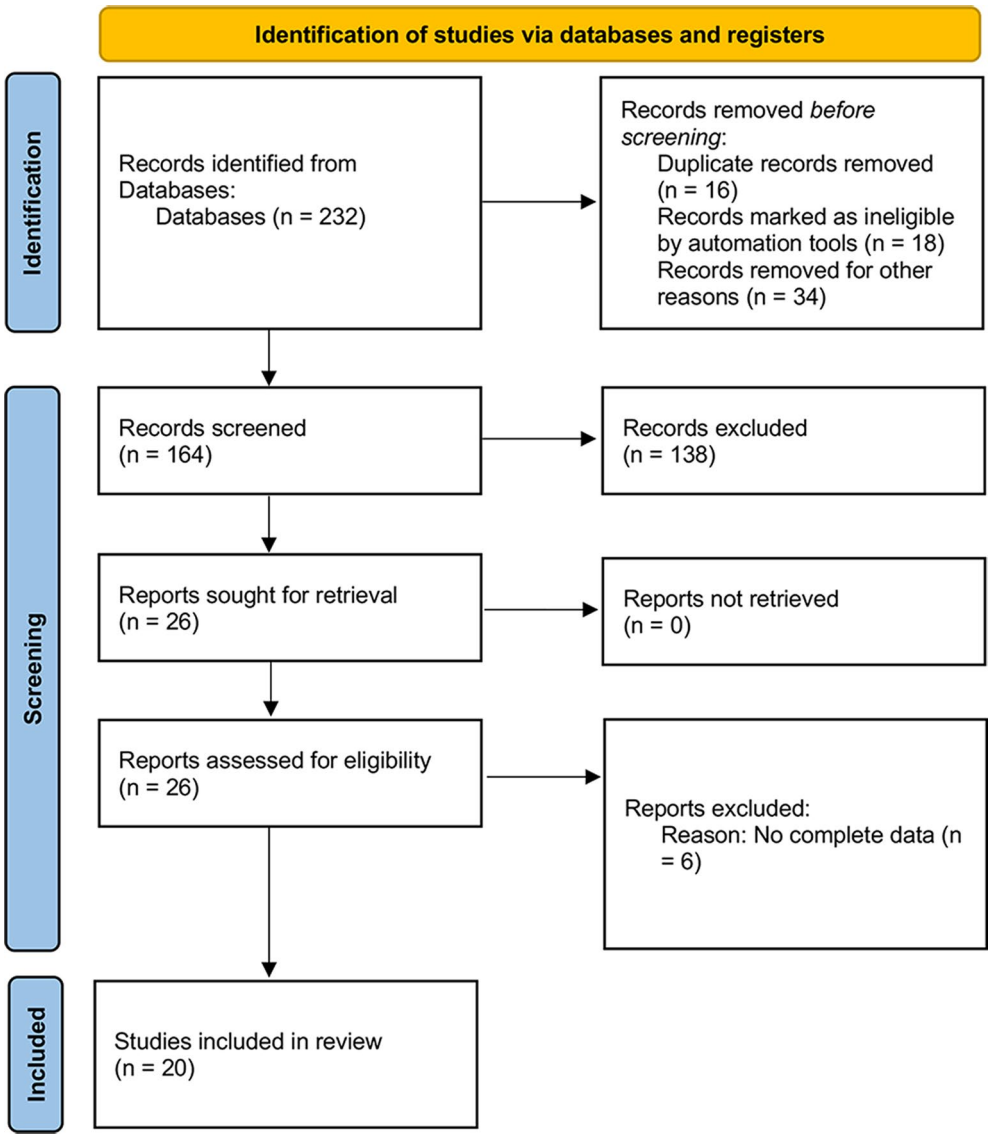

Fig. 1 Flowchart of study selection

Table 1 Characteristics of the studies included in the meta-analysis

Year	First author	Species	Age (weeks)	Sample size	Cell type	Injection dose	Disease type	Follow-up (weeks)	Ref
2018	Ouyang X	SD rats	10	16	MSC	100ug	CNI	4	[32]
2019	Liu Y	SD rats	12	12	MSC	100ug	AI	4	[33]
2020	Song J	SD rats	8	24	BMSC, ADSC and CCSMC	100ug	DM	4	[30]
2023	Li K	SD rats	96 and 10	16	MSC	100ug	Aged	4	[34]
2018	Zhu L	SD rats	10	16	ADSC	100ug	DM	4	[35]
2018	Li M	SD rats	12	36	BMSC and ADSC	100ug	CNI	3	[31]
2020	Wang J	SD rats	8	12	ADSC	200ug	DM	2	[36]
2017	Chen F	SD rats	/	16	ADSC	/	DM	4	[37]
2021	Liang L	SD rats	/	12	ADSC	400ug	CIH	8	[38]
2020	Yang Q	SD rats	/	8	USC	100ug	PD	4	[39]
2019	Ouyang B	SD rats	/	16	USC	100ug	DM	4	[40]
2020	Guo N	SD rats	12	8	PC	5ug	CNI	2	[41]
2023	Ock J	SD rats	8	8	MCP	5ug	DM	2	[42]
2023	Chen Z	SD rats	8	10	MSC	100ug	CNI	4	[43]
2019	Liu Q	SD rats	96	30	BMSC	1 × 10 6	Aged	2	[44]
2021	Kim J	SD rats	8	12	MSC	1 × 10 6	CNI	4	[45]
2024	Zhang J	SD rats	8	20	MSC	100ug	DM	4	[46]
2021	Zou Z	SD rats	/	20	MDSC	1 × 10 6	CNI	4	[47]
2020	Huo W	SD rats	8	20	MSC	100ug	DM	4	[48]
2023	Liu S	SD rats	12	12	ADSC	100ug	CNI	4	[49]

Sprague–Dawley rats

cells-derived EVs (MDSC-EVs), 1 study used pericyte-derived EVs (PC-EVs), and 1 study used mouse corpus cavernous pericyte-derived EVs (MCP-EVs). 8 studies constructed rat diabetic model, 7 studies constructed a rat CNI model, 2 studies constructed a rat aged model, 1 study constructed a rat Aterial Injury model, 1 study constructed a rat chronic intermittent hypoxia (CIH) model, and 1 study constructed a rat Peyronie's disease (PD) model. In the different studies, the follow-up time after injection ranged from 2 to 8 weeks. In all studies, erectile function was assessed by electrical stimulation of the cavernous nerve after anesthesia, and the results were presented as ICP/MAP. In addition to erectile function, 20 studies measured histologic changes and molecular changes, including smooth muscle cell content, nNOS, eNOS, α-SMA, and the ratio of smooth muscle to collagen in the corpus cavernosum.

Quality of included studies

The quality of the included studies was at a high level as shown by the quality assessment results. Thirteen of the studies were of high quality and seven were of moderate quality (Table 2).

Effects of SC-EVs on structural and molecular changes in rat corpus cavernosum.

A pooled analysis of all included studies showed that SC-EVs therapy significantly improved ED compared to controls (SMD 4.19, 95% CI = 3.31 to 5.08, P < 0.00001, I2 = 77%: Fig. 2a).

In order to elucidate the intrinsic mechanisms of stem cell therapy, we also analyzed the changes in the structure of the corpus cavernosum between the two groups. The expression of both nNOS and eNOS was higher in the stem cell group than in the control group(nNOS: SMD 4.18, 95% CI = 2.63 to 5.73, P < 0.00001, I2 = 86%; Fig. 2b; eNOS: SMD 2.83, 95% CI = 1.57 to 4.10, P < 0.0001, I2 = 79%; Fig. 2c). In addition, the smooth muscle (labeled with anti-α-SMA antibody) content was much higher in both stem cell groups than in the control group (SMD 5.33, 95% CI = 4.12 to 6.54, P < 0.00001, I2 = 74%: Fig. 3d). In addition, we performed a meta-analysis of the Smooth muscle/Collagen results, which showed an increased smooth muscle-to-collagen ratio in the stem cell-treated group compared with the control group SMD 3.40, 95% CI = 2.57 to 4.23, P < 0.00001, I2 = 74%: Fig. 3e). Despite some heterogeneity among studies (I^2 = 74–86%), the results remained stable after excluding individual studies

Table 2 Quality assessment of studies

Year	First author	Blind assessment	Random assignment	Sufficient follow-up time	Animal welfare	Characterization of stem cell phenotypes	Identification of SC-EVs	Tests to evaluate ED before injection of SC-EVs	Sample size calculation	Structural changes	Total	Ref
2018	Ouyang X	1	0	1	1	1	1	0	1	1	7	[32]
2019	Liu Y	0	1	1	1	1	1	0	1	1	7	[33]
2020	Song J	0	0	1	1	1	1	1	1	1	7	[30]
2023	Li K	0	1	1	1	1	1	1	1	1	8	[34]
2018	Zhu L	0	1	1	1	0	1	0	1	1	6	[35]
2018	Li M	0	1	1	1	1	1	0	1	1	7	[31]
2020	Wang J	0	0	1	1	1	1	1	1	1	7	[36]
2017	Chen F	0	1	1	1	0	1	0	1	1	6	[37]
2021	Liang L	0	1	1	1	1	1	0	1	1	7	[38]
2020	Yang Q	0	1	1	1	1	1	0	1	1	7	[39]
2019	Ouyang B	0	1	1	1	0	1	1	1	1	7	[40]
2020	Guo N	0	0	1	1	0	1	0	1	1	5	[41]
2023	Ock J	0	0	1	1	0	1	0	1	1	5	[42]
2023	Chen Z	0	0	1	1	1	1	0	1	1	6	[43]
2019	Liu Q	0	1	1	1	1	1	0	1	1	7	[44]
2021	Kim J	1	0	1	1	1	1	0	1	1	7	[45]
2024	Zhang J	0	1	1	1	1	1	0	1	1	7	[46]
2021	Zou Z	0	1	1	1	0	1	0	1	1	6	[47]
2020	Huo W	0	1	1	1	0	1	1	1	1	7	[48]
2023	Liu S	0	1	1	1	0	1	0	1	1	6	[49]

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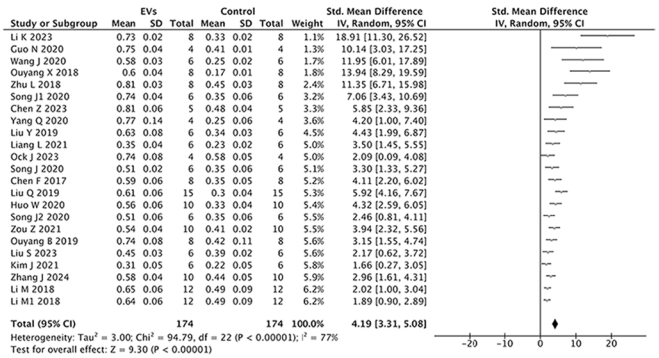

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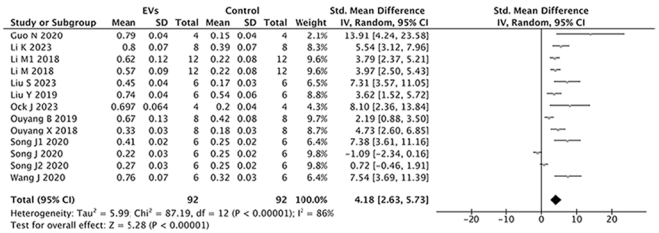

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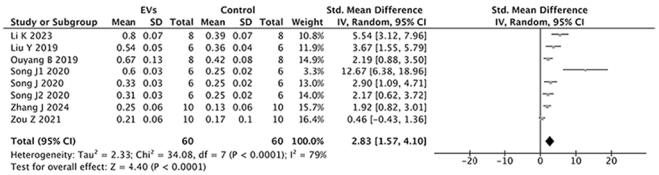

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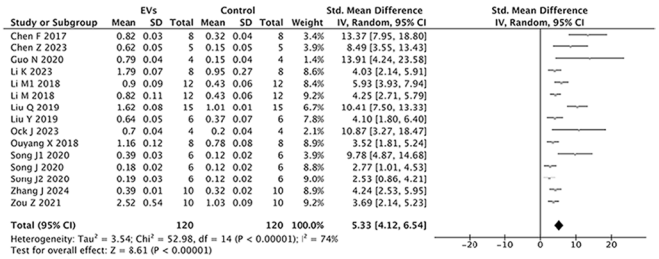

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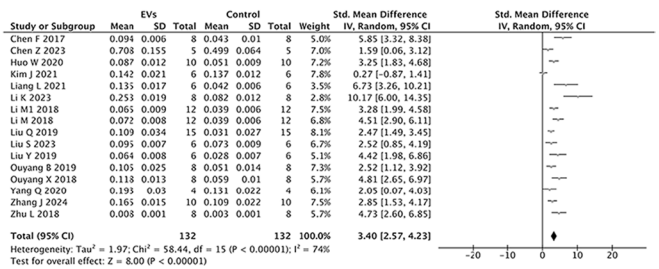

Fig. 2 **a** Effect of the SC-EVs on ICP/MAP in ED. **b** Effect of the SC-EVs on nNOS in ED. **c** Effect of the SC-EVs on eNOS in ED. **d** Effect of the SC-EVs on α-SMA in ED. **e** Effect of the SC-EVs on Smooth muscle/Collagen in ED

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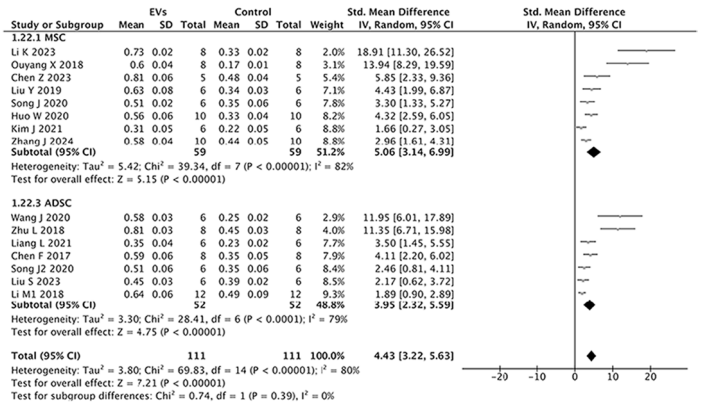

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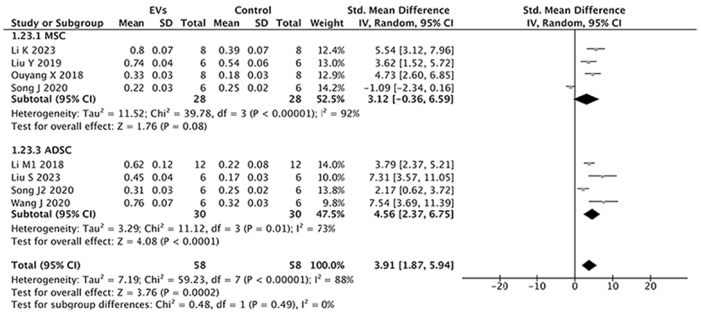

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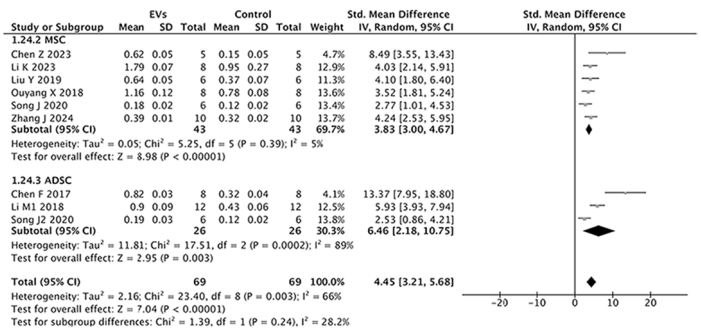

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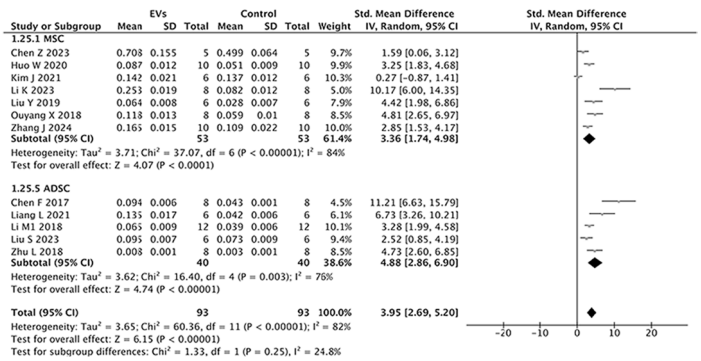

Fig. 3 **a** Effects of MSC-EVs and ADSC-EVs on ICP/MAP in the ED. **b** Effects of MSC-EVs and ADSC-EVs on nNOS in the ED. **c** Effects of MSC-EVs and ADSC-EVs on α-SMA in the ED. **d** Effects of MSC-EVs and ADSC-EVs on Smooth muscle/Collagen in the ED

one by one, as confirmed by sensitivity analysis, which fully validated the reliability of our findings. Together, these findings confirm the restorative effect of stem cell therapy on ED at the molecular level and at the tissue structure level.

The impact of different subgroups on the structural and molecular changes in the rat corpus cavernosum.

The influence of different EVs on the structural and molecular changes in the corpus cavernosum of ED rats.

Subgroup analysis results indicate that for ICP/MAP, there is no significant difference between MSC-EVs and ADSC-EVs in improving erectile function (P =0.39, Fig. 3a). For nNOS, there is no significant difference between MSC-EVs and ADSC-EVs in improving erectile function (P =0.49, Fig. 3b). For a-SMA, there is no significant difference between MSC-EVs and ADSC-EVs in improving erectile function (P =0.24, Fig. 3c). For Smooth muscle/Collagen, there is no significant difference between MSC-EVs and ADSC-EVs in improving erectile function (P= 0.25, Fig. 3d).

The influence of SC-EVs on the structural and molecular changes in the corpus cavernosum of ED rats caused by different diseases.

Subgroup analysis results indicate that for ICP/MAP, there is no significant difference in the improvement of erectile function by SC-EVs between DM and CNI (P= 0.74, Fig. 4a). For nNOS, there is no significant difference in the improvement of erectile function by SC-EVs between DM and CNI (P =0.46, Fig. 4b). For a-SMA, there is no significant difference in the improvement of erectile function by SC-EVs between DM and CNI (P =0.34, Fig. 4c). For Smooth muscle/Collagen, there is no significant difference in the improvement of erectile function by SC-EVs between DM and CNI (P =0.28, Fig. 4d).

Publication bias

The funnel plot (Fig S1) exhibited noticeable asymmetry, suggesting the potential presence of publication bias. Disappointingly, the Egger's test also indicated a certain degree of publication bias (all p< 0.05). Therefore, we employed the trim-and-fill method to examine the asymmetry of the funnel plot by hypothesizing unpublished studies. The recalculated results demonstrated that SC-EVs play a significant role in ED, with a post-trim-and-fill P-value <0.05, indicating statistical significance. Furthermore, the combined results before and after trimming and filling showed P-values <0.05, confirming the stability of the findings (Fig S2).

Discussion

ED is a common male health issue associated with various factors, including age, chronic diseases, and psychological conditions. It not only affects the quality of sexual life but may also have negative impacts on mental health, social relationships, and overall quality of life.

Stem cells are undifferentiated cells with self-renewal capabilities and the potential to differentiate into various cell types under specific conditions. They hold broad application potential in tissue repair, regenerative medicine, and clinical therapy. SC-EVs are small membrane vesicles secreted by stem cells, containing a variety of biomolecules such as proteins, lipids, and RNAs. These EVs play important roles in intercellular communication, immune regulation, and cellular repair. Figure 5.

SC-EVs (including MSC-EVs, ADSC-EVs, USC-EVs, PC-EVs, and MCP-EVs) exert therapeutic effects on ED through their bioactive cargo of miRNAs and proteins. Regarding vascular endothelium, MSC-EVs improve endothelial function by delivering miR-21-5p and miR-296-5p [48], with the latter enhancing eNOS/NO signaling via PTEN-PI3 K-Akt regulation [34]. In smooth muscle modulation, miR-301a-3p and circPIP5 K1 C in ADSC-EVs suppress fibrosis by targeting TGF-β/Smad and glycolytic pathways [38], while MSC-EVs upregulate Bcl-2 to inhibit apoptosis [37]. In nerve regeneration, ESC-NVs and PC-NVs promote axonal growth by delivering neurotrophic factors such as NGF and NT-3, while activating the PI3 K-Akt and HGF/c-Met pathways, as well as the GDNF pathway, which collectively stimulate neuronal sprouting and Schwann cell migration [41]. Additionally, SC-EVs contribute to functional recovery by mitigating oxidative stress through antioxidant enzymes (SOD/CAT) and miR-337-3p-mediated NOX4 inhibition, thereby restoring erectile function via multiple mechanisms [34].

Furthermore, specific small molecules in SC-EVs demonstrate therapeutic efficacy by regulating key pathways. In endothelial repair, miRNAs including the miR-10 family and let-7 enhance NO bioavailability [40], while corin and eNOS proteins improve vascular function [36]. Fibrosis is counteracted by USC-Exos through MMP/TIMP balance restoration and CCSMC-Exos via NO-cGMP signaling [39], shows a trend of reduced collagen deposition. These findings highlight the ability of SC-EVs to simultaneously target endothelial dysfunction, fibrosis, and nerve damage, addressing the multifactorial nature of ED.

Notably, SC-EVs exhibit distinct therapeutic effects depending on ED etiology. In diabetic ED, MSC-EVs and ADSC-EVs primarily improve endothelial dysfunction and exert antifibrotic effects, restoring smooth muscle/collagen ratios and NO signaling, with CCSMC-EVs

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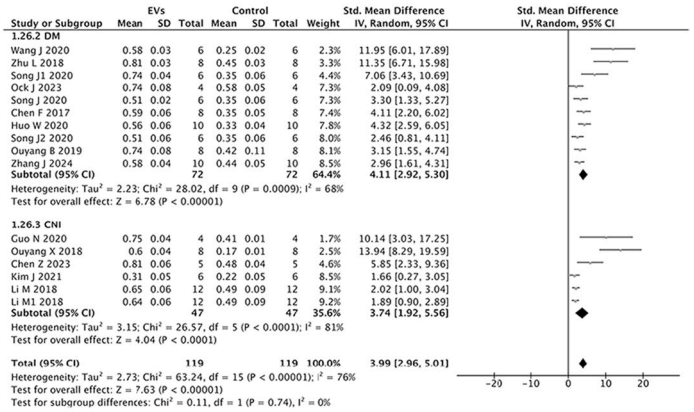

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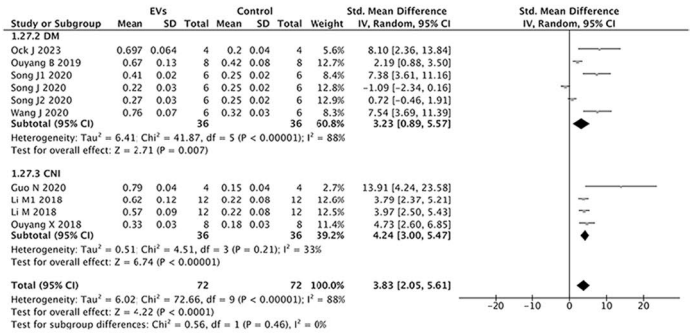

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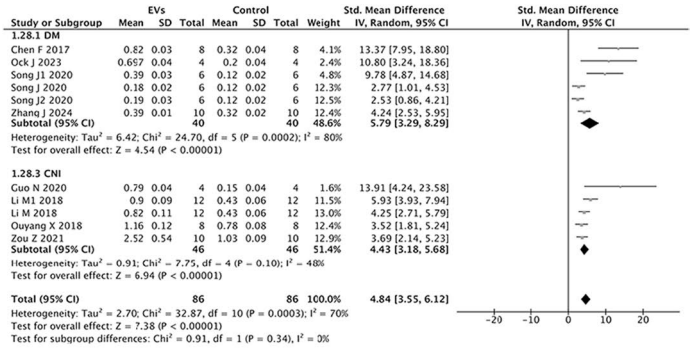

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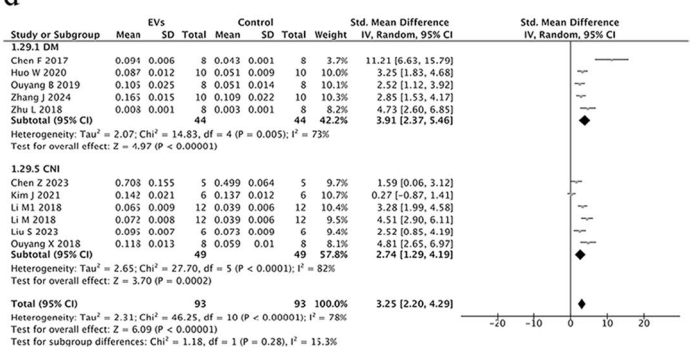

Fig. 4 **a** Effect of SC-EVs on ICP/MAP in DM and CNI-induced EDs. **b** Effect of SC-EVs on nNOS in DM and CNI-induced EDs. **c** Effect of SC-EVs on α-SMA in DM and CNI-induced EDs. **d** Effect of SC-EVs on Smooth muscle/Collagen in DM and CNI-induced EDs

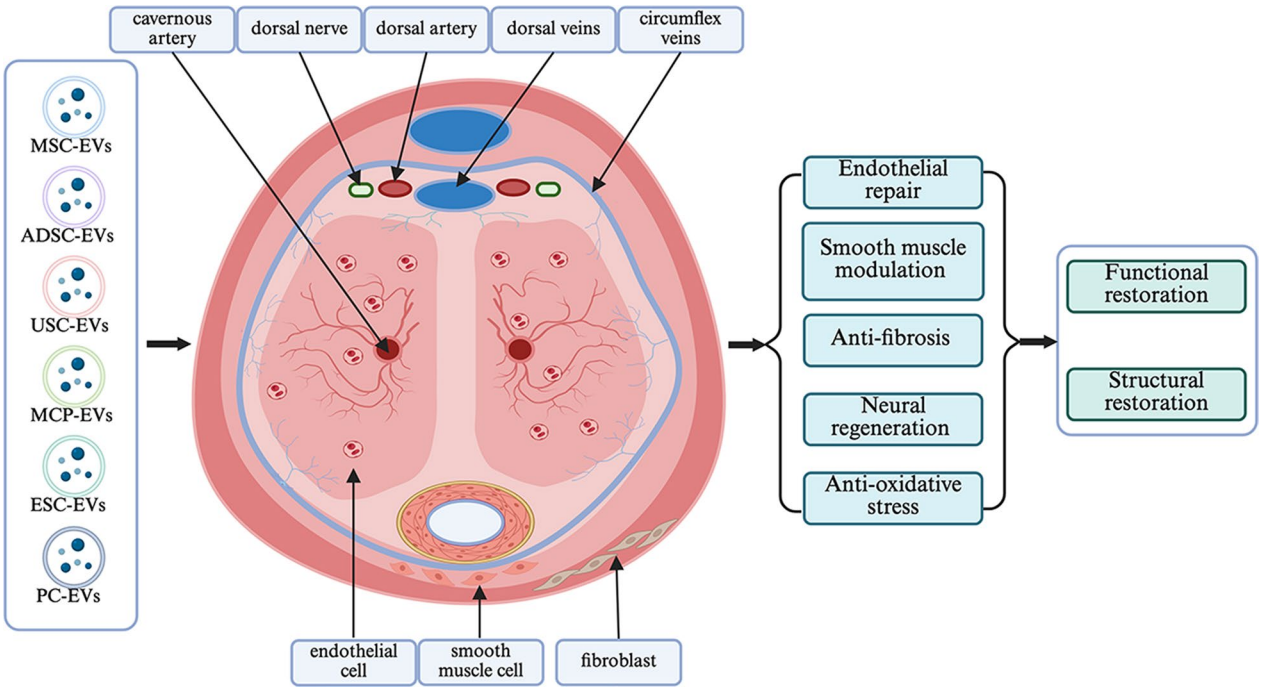

Fig. 5 SC-EVs ameliorate ED through multi-target mechanisms. In endothelial repair, MSC-EVs enhance NO production by upregulating eNOS/nNOS expression and activating the PTEN-PI3 K-AKT pathway via miR-296-5p. Concurrently, USC-EVs promote CD31 +/eNOS + endothelial proliferation and significantly improve the ICP/MAP ratio through miR-21-5p and the let-7 family. For smooth muscle modulation, MSC-EVs increase α-SMA expression and inhibit caspase-3-dependent apoptosis, while ADSC-EVs suppress fibrosis and glycolysis via the miR-301a-3p-mediated targeting of PTEN-TLR4 and the circPIP5 K1 C-miR-153-3p-SMURF1 axis, respectively. In antifibrotic processes, USC-EVs reduce collagen deposition by regulating the MMP/TIMP balance, whereas ADSC-EVs improve endothelial function through corin gene activity. Neural regeneration is primarily driven by ESC/PC-EVs, which facilitate neuronal sprouting via neurotrophin-3 and enhance Schwann cell migration through Akt/eNOS signaling. Additionally, MSC-EVs alleviate oxidative stress by suppressing NOX4 via miR-337-3p, and ADSC-EVs inhibit apoptosis by elevating Bcl-2 levels and reducing caspase-3 activity

demonstrating superior cellular uptake and prolonged efficacy. In contrast, neurogenic ED benefits more from ESC-EVs and MSC-EVs, which promote neural repair through neurotrophic factor delivery and vascular-neural crosstalk. These differential effects underscore the importance of selecting EV subtypes based on underlying pathology—employing antifibrotic EVs for diabetic ED and proneurogenic EVs for nerve injury-related ED—to optimize therapeutic outcomes. This tailored approach highlights the potential of SC-EVs as precision medicine for ED subtypes.

In ED research, stem cells and SC-EVs are considered to play significant roles. Stem cells can directly repair tissue damage related to ED by differentiating into vascular endothelial cells, smooth muscle cells, and others. SC-EVs, on the other hand, indirectly improve ED symptoms by carrying biomolecules that facilitate cell repair, anti-inflammatory responses, and angiogenesis. Unlike synthetic nanoparticles, SC-EVs inherently possess targeting moieties (e.g., tetraspanins) that enhance homing to ischemic or inflamed cavernous tissues, minimizing off-target effects—a critical advantage in nanomedicine design [50]. In addition, due to their low immunogenicity, ease of acquisition, and tunable biological functions, SC-EVs demonstrate promising clinical applications, particularly in tissue repair and disease treatment. This stem cell- and EV-based therapeutic strategy provides new insights for the clinical treatment of ED, especially for patients who respond poorly to or experience side effects from traditional treatments.

This study evaluated the therapeutic effects of SC-EVs on rat ED through meta-analysis. Our findings were highly consistent with previous findings [51], which showed that SC-EVs significantly improved erectile function in rats, demonstrating their potential in ED treatment. This further supports the importance of SC-EVs in the treatment of ED. This finding not only provides experimental evidence for stem cell-based ED therapy but also offers theoretical support for future clinical applications.

Mechanistically, SC-EVs improve ED through multiple mechanisms, including specific cellular and tissue responses (e.g., tissue regeneration, anti-inflammation, anti-apoptosis, immune modulation, and antioxidant

stress) and specific molecular signaling pathways (e.g., NO-cGMP, miR-10a-3p-PKIA-RhoA-ROCK, and Akt pathways)[30, 41, 43]. These mechanisms ultimately promote vascular endothelial cell repair, improve neural function, and inhibit inflammatory responses. For example, EVs enhance erectile responses via smooth muscle cell proliferation and repair, improving penile vascular function. Additionally, EVs may carry anti-inflammatory molecules to suppress local inflammation, further facilitating tissue repair and regeneration.

Moreover, compared to traditional single-target drugs (e.g., sildenafil), SC-EVs demonstrate significant advantages in vascular and neural repair through multi-target mechanisms. EVs carry bioactive molecules (e.g., miRNAs, growth factors) that simultaneously promote angiogenesis, endothelial repair, anti-inflammatory responses, neural regeneration, and oxidative stress reduction, thereby fundamentally restoring vascular and neural function. In contrast, drugs like sildenafil improve blood flow through a single mechanism (e.g., PDE5 inhibition) without repairing damaged tissues. The multi-target effects of EVs make them particularly suitable for ED caused by complex etiologies (e.g., diabetes mellitus, neural injury, vascular diseases), offering not only symptom relief but also long-term efficacy through tissue repair and regeneration. Furthermore, as natural intercellular communication carriers, EVs exhibit low immunogenicity and high biocompatibility, reducing the risk of side effects. Future research should further clarify the key mechanisms of EVs, optimize delivery protocols, and validate their long-term efficacy and safety through large-scale clinical trials, providing new breakthroughs in ED treatment.

Limitations of the study

Although this study demonstrates the positive therapeutic effects of SC-EVs on rat ED, several limitations remain. First, most included studies were small-scale, short-term experiments lacking long-term follow-up data, necessitating further validation of the long-term efficacy and safety of EVs. Second, the specific mechanisms of EVs in ED treatment are not fully understood, and many details require further exploration through basic research. Finally, despite the therapeutic potential of EVs, While SC-EVs show promise, nanomedicine-specific challenges include batch-to-batch variability in EVs size/composition and the lack of standardized protocols for large-scale EV production under Good Manufacturing Practice (GMP) conditions. Future work should integrate microfluidic-based EV isolation and lyophilization techniques to enhance clinical feasibility.

Clinical application prospects

SC-EVs represent a novel therapeutic approach with broad application prospects. Future clinical studies should further explore optimal delivery protocols, including administration routes, frequency, and dosage. Additionally, larger-scale clinical trials are needed to evaluate the efficacy and safety of EVs in ED treatment. With a deeper understanding of EV mechanisms and continuous technological advancements, SC-EVs are expected to become a new generation of biological therapies for ED.

Conclusion

This study underscores the potential of SC-EVs as a next-generation nanomedicine for ED. Their natural nanoarchitecture enables multifunctional therapeutic effects, bridging the gap between cellular therapies and synthetic nanoparticle systems. Future research should focus on engineering EVs for enhanced targeting (e.g., surface modification with ligands) and combinatorial cargo loading (e.g., miRNAs + small molecules), advancing personalized nanomedicine for sexual health.

In summary, the results of this study indicate that SC-EVs significantly improve ED in rats, demonstrating substantial clinical potential. Future research should further investigate their mechanisms, optimize treatment protocols, and conduct large-scale clinical trials to validate their feasibility and efficacy in clinical therapy.

Supplementary Information

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Supplementary material 1. Figure S1. (a) Funnel plot of SC-EVs effect on ICP/MAP in the ED. (b) Funnel plot of SC-EVs effect on nNOS in the ED. (c) Funnel plot of SC-EVs effect on eNOS in the ED. (d) Funnel plot of SC-EVs effect on α-SMA in the ED. (e) Funnel plot of SC-EVs effect on Smooth muscle/Collagen in the ED.

Supplementary material 2. Figure S2. (a) Funnel plot of SC-EVs effect on ICP/MAP in the ED adjusted with trim-and-fill method. (b) Funnel plot of SC-EVs effect on nNOS in the ED adjusted with trim-and-fill method. (c) Funnel plot of SC-EVs effect on eNOS in the ED adjusted with trim-and-fill method. (d) Funnel plot of SC-EVs effect on α-SMA in the ED adjusted with trim-and-fill method. (e) Funnel plot of SC-EVs effect on Smooth muscle/Collagen in the ED adjusted with trim-and-fill method.

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The authors declare that they have not use AI-generated work in this manuscript.

Author contributions

KCL conceived the manuscript and performed data acquisition, data analysis and statistical analysis. JJH assisted with data acquisition, data analysis and manuscript preparation. JYT reviewed the manuscript and polished the grammar. ZSW confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

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Availability of data and materials
All data analyzed in this meta-analysis were extracted from previously published studies, which are publicly available in PubMed, Embase, and Cochrane Library. The search strategy and list of included studies are provided in the supplementary materials. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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