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Therapeutic Application of hUC-MSC-derived Exosomes in Diabetic Wounds: A Scoping Review

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Correspondence: Viviane Fernandes de Carvalho: Nursing Postgraduate program of Guarulhos University, Guarulhos, São Paulo, Brazil. Email: dravivicarvalho@gmail.com

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Meline Rosseto Kron[1], André Oliveira Paggiaro[2], Viviane Fernandes de Carvalho Belizario[1]

[1] Nursing Postgraduate Program of Guarulhos University, Guarulhos, São Paulo, Brazil
[2] Plastic Surgery Division, Hospital das Clínicas, Faculty of Medicine, University of São Paulo (USP), São Paulo, Brazil

Abstract

Introduction. Diabetic foot ulcers (DFUs) represent a severe and debilitating complication of diabetes mellitus, often proving refractory to conventional therapies due to a persistent pro-inflammatory state that delays granulation tissue formation and re-epithelialization. While stem cell therapies offer potential, challenges regarding tumorigenicity, cell survival, and regulatory hurdles have spurred interest in cell-free approaches, specifically nanometric vesicles known as exosomes derived from human umbilical cord mesenchymal stem cells (hUC-MSCs). This scoping review aimed to map the extent and nature of evidence regarding the therapeutic application of hUC-MSC-derived exosomes in diabetic wound management across preclinical and clinical settings.

Methods. Conducted according to the Joanna Briggs Institute (JBI) methodology and PRISMA-ScR guidelines, systematic searches were performed in PubMed, Embase, CINAHL, Lilacs, and grey literature (Google Scholar and Research Square) through January 31, 2026.

Results. Nineteen studies met the inclusion criteria, primarily comprising preclinical investigations (n=15) alongside two randomized clinical trials. Preclinical evidence consistently demonstrates that hUC-MSC-derived exosomes accelerate wound closure by enhancing angiogenesis (CD31 and VEGF upregulation), modulating macrophage polarization toward the anti-inflammatory M2 phenotype, and promoting extracellular matrix restructuring. Clinical trials involving 130 participants reported favorable outcomes, including complete ulcer closure and a documented safety profile over a 24-month

follow-up period. Technological advancements include the use of biomaterial carriers, such as hydrogels and scaffolds, to ensure sustained release and localized retention within the wound bed.

Discussion. While evidence is consistent in the preclinical domain, a significant translational gap remains due to mechanistic differences between rodent contraction-based healing and human re-epithelialization. Standardizing dose-response protocols and conducting multicenter randomized trials are essential to bridge the gap toward real-world clinical implementation.

Keyword: Wound Care Innovation, hUC-MSC, Diabetic Foot, Exosomes, Healing, Scoping Review

Introduction

Wounds in individuals with diabetes, particularly diabetic foot ulcers (DFUs), are considered the most debilitating and burdensome complications of diabetes mellitus (DM). They frequently result in hard-to-heal wounds and partial or total amputation of lower limb segments, imposing significant social and economic burdens.[1,2] Although traditional wound care based on dressings and other adjuvant therapies is improving these outcomes3, a substantial proportion of DFUs remains refractory to these approaches due to a persistent inflammatory state.[4] This state is sustained by hyperglycemia, advanced glycation end-products (AGEs), and reactive oxygen species (ROS), which impair the proliferation of fibroblasts and keratinocytes, thereby delaying granulation tissue formation and re-epithelialization.[5–8]

Stem cell therapies have garnered considerable attention from researchers. However, due to challenges regarding cell survival, potential tumorigenic risks, pharmacodynamic limitations, and regulatory hurdles imposed by health authorities, alternative approaches to harness biologically active molecules are being investigated, such as the use of exosomes.[9–11] Extracellular vesicles, specifically exosomes derived from human umbilical cord mesenchymal stem cells (hUC-MSCs), have emerged as a promising tool due to their ability to transfer molecules such as microRNAs, growth factors, and cytokines. These nanometric vesicles have demonstrated the potential to modulate tissue repair processes by promoting angiogenesis, attenuating oxidative stress, favoring extracellular matrix (ECM) remodeling, and regulating macrophage polarization from pro-inflammatory to anti-inflammatory phenotypes.[12–14]

Preclinical evidence indicates that hUC-MSC-derived exosomes possess a potential therapeutic impact on the repair of diabetic wounds.[15–17] Experimental studies have shown that these vesicles exert multifunctional actions, including the promotion of fibroblast migration, angiogenesis, and modulation of local inflammation critical components for effective healing.[18,19] Research across various animal models has shown accelerated re-epithelialization and ECM restructuring when treated with hUC-MSC-derived exosomes, either alone or in combination with carriers such as hydrogels.[20,21]

Early-phase clinical trials have begun to translate these findings to human samples. In a phase I/II trial involving patients with DFUs non-responsive to standard care, participants received local injections of allogeneic preparations rich in hUC-MSC-derived exosomes. The result was complete ulcer closure in all participants, and no adverse events or recurrence over a 24-month follow-up period.[22] Similarly, another randomized clinical trial involving individuals with DFUs showed that the topical application of an exosome gel derived from Wharton's jelly led to complete healing in 62% of patients by the sixth week, compared to markedly longer healing times in control groups.[23] These outcomes were accompanied by a favorable safety profile, suggesting not only clinical efficacy but also viability in a real-world practice setting.

Despite this encouraging progress, the current body of literature remains fragmented. Experimental designs differ considerably between studies, including the source and characterization of exosomes, administration routes (topical vs. injectable), frequency and duration of application, and the incorporation of delivery vehicles like hydrogels. Furthermore, although some clinical studies suggest robust signs of efficacy, sample sizes are small, and the regulatory landscape governing exosome-based therapies remains immature. Considering these limitations, a scoping review is justified to map the existing evidence on the application of hUC-MSC-derived exosomes in the treatment of diabetic wounds.

Accordingly, this review addressed the following research question: What is the extent and nature of the evidence on the therapeutic application of hUC-MSC-derived exosomes in the management of diabetic wounds across clinical and preclinical settings?

Methods

Study Design

This scoping review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for evidence synthesis, which advocates for a rigorous and transparent process to map the extent, range, and characteristics of literature in complex or emerging fields.[24] The review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), and the PRISMA-ScR checklist was used to guide reporting.[25]

The protocol was developed using the Population, Concept, and Context (PCC) framework. The review addressed the following research question: What is the extent and nature of the evidence on the therapeutic application of hUC-MSC-derived exosomes in the management of diabetic wounds across clinical and preclinical settings?

Literature Selection

Eligibility criteria were defined according to the PCC framework. The population comprised: (i) individuals with diabetes mellitus presenting with cutaneous wounds, including DFUs; (ii) *in vivo* diabetic wound models; and (iii) relevant *in vitro* models reproducing diabetes-related conditions. The concept of interest was the therapeutic application of exosomes derived specifically from hUC-MSCs, used either alone or in combination with biomaterials or delivery vehicles. The context included any clinical care setting for human studies and any laboratory setting for preclinical studies, without geographic restriction.

Evidence sources considered eligible encompassed primary quantitative research such as randomized clinical trials, quasi-experimental studies, cohort analyses, and animal experiments. In addition, *in vitro* experimental studies, as well as relevant secondary studies for evidence mapping, were included. Studies evaluating mesenchymal stromal/stem cells from sources other than the human umbilical cord were excluded, as were studies on non-diabetic wounds without a clearly diabetes-related component, editorials, comments, letters, and conference abstracts without accessible full text.

Information Sources and Search Strategy

The databases PubMed (MEDLINE), Embase, CINAHL, and Lilacs were searched, along with Google Scholar and Research Square for grey literature, without a lower date limit, including studies published up to January 31, 2026. Inclusion was restricted to publications in English, Portuguese, or Spanish. The search strategy was built using controlled vocabulary and free terms related to diabetic foot ulcers and exosomes.

The final PubMed strategy included combinations of: ((“Exosomes”[Mesh] OR “Extracellular Vesicles”[Mesh] OR “exosom*”[TiAb] OR “extracellular vesicle*”[TiAb])) AND ((“Umbilical Cord”[Mesh] OR “Wharton Jelly”[Mesh] OR “umbilical cord”[TiAb] OR “Wharton*”[TiAb])) AND ((“Mesenchymal Stem Cells”[Mesh] OR “mesenchymal”[TiAb] OR “MSC”[TiAb] OR “MSCs”[TiAb])) AND ((“Diabetes Mellitus”[Mesh] OR “Diabetic Foot”[Mesh] OR “diabetic wound*”[TiAb] OR “diabetic ulcer*”[TiAb])). The PubMed strategy was developed first and then adapted to the syntax and controlled vocabulary of each database. The complete search strings for all sources are provided in Supplementary Table S1. Reference lists of included studies and relevant reviews were also manually screened to identify additional eligible records.

Study Selection

All retrieved citations were exported to Zotero reference management software (version 7.0.X, Corporation for Digital Scholarship, Virginia, USA) for duplicate removal and then transferred to the Rayyan systematic review platform (Rayyan Systems Inc., Cambridge, MA, USA) for blind screening. Titles and abstracts were reviewed independently by two reviewers (VFC and MRK), followed by full-text evaluation. Discrepancies were resolved by consensus or a third reviewer (AOP). The selection process followed PRISMA-ScR guidelines[26] and is summarized in a official PRISMA flow diagram format.

Data Extraction and Synthesis

Data were charted independently by two reviewers using a standardized extraction form developed in accordance with JBI recommendations for scoping reviews.[27] The form captured bibliographic information (author, year, country, journal), study characteristics (design, methods, population or model, wound type, intervention, comparator, and outcomes), and the principal findings relevant to the review question. The charting process was iterative, and the extraction form could be refined when necessary to ensure that all relevant information was consistently captured across heterogeneous sources of evidence.

To support structured interpretation of the mapped evidence, results were synthesized using the PAGER framework, which allowed the findings to be organized according to recurring Patterns, Advances, Gaps, Evidence for practice, and Research recommendations.[28] This approach was used to summarize major biological effects, technological approaches, methodological limitations, and priorities for future translational development.

Results

Study Selection Process

As shown in Figure 1, the search identified 1,799 records across the selected databases and sources. After duplicate removal, 924 records were screened by title and abstract. Thirty-seven reports were sought for retrieval, three of which were inaccessible. Of the 34 full-text reports assessed for eligibility, 15 were excluded because they did not meet the predefined population, context, or concept criteria. Therefore, 19 studies were included in the final evidence map.

Characteristics of Included Studies

The evidence found in the 19 studies regarding hUC-MSC-derived exosome (hUC-MSC-Exos) application in DM wounds is primarily preclinical. There is a wide variety of study designs, from animal models[20,21,29–34] and *in vitro* experiments[16,18,19,35–38] (conducted exclusively in Chinese institutions) to clinical trials and secondary research. Clinical trials originated in Jordan[22] (a randomized controlled trial (RCT) with 110 participants over 24 months) and Egypt[23] (20 patients followed for 12–16 weeks). Overall, the body of evidence indicates rapid growth in publications over the last decade, alongside increasing diversification in exosome engineering, delivery platforms, and mechanistic targets. Further characteristics of the studies are presented in Table 1.

Diabetic Wound Models and Clinical Populations

Preclinical studies employed two main diabetes induction strategies, streptozotocina (STZ) injection, sometimes combined with a high-fat diet,[21,30,32,34,36,38] and genetically diabetic models using db/db mice.[18,19] All preclinical models used full-thickness excisional wounds on rodent dorsal skin (8 mm to 2 cm).

The clinical evidence focused on chronic diabetic foot ulcers. One phase I/II trial evaluated local administration of hUC-MSC derivatives in patients with University of Texas grade II–III ulcers and reported complete closure in the treated cohort over follow-up, with favorable long-term safety observations.[22] Another randomized clinical trial assessed a Wharton's jelly MSC-derived exosome gel in chronic DFUs and reported faster healing and a higher proportion of complete recovery than the comparator group.[23]

Exosome Characterization

Isolation methods varied, with ultracentrifugation being most common, followed by commercial kits[21,32,37] or polyethylene glycol (PEG) precipitation combined with ultracentrifugation.[29]

Delivery strategies ranged from direct

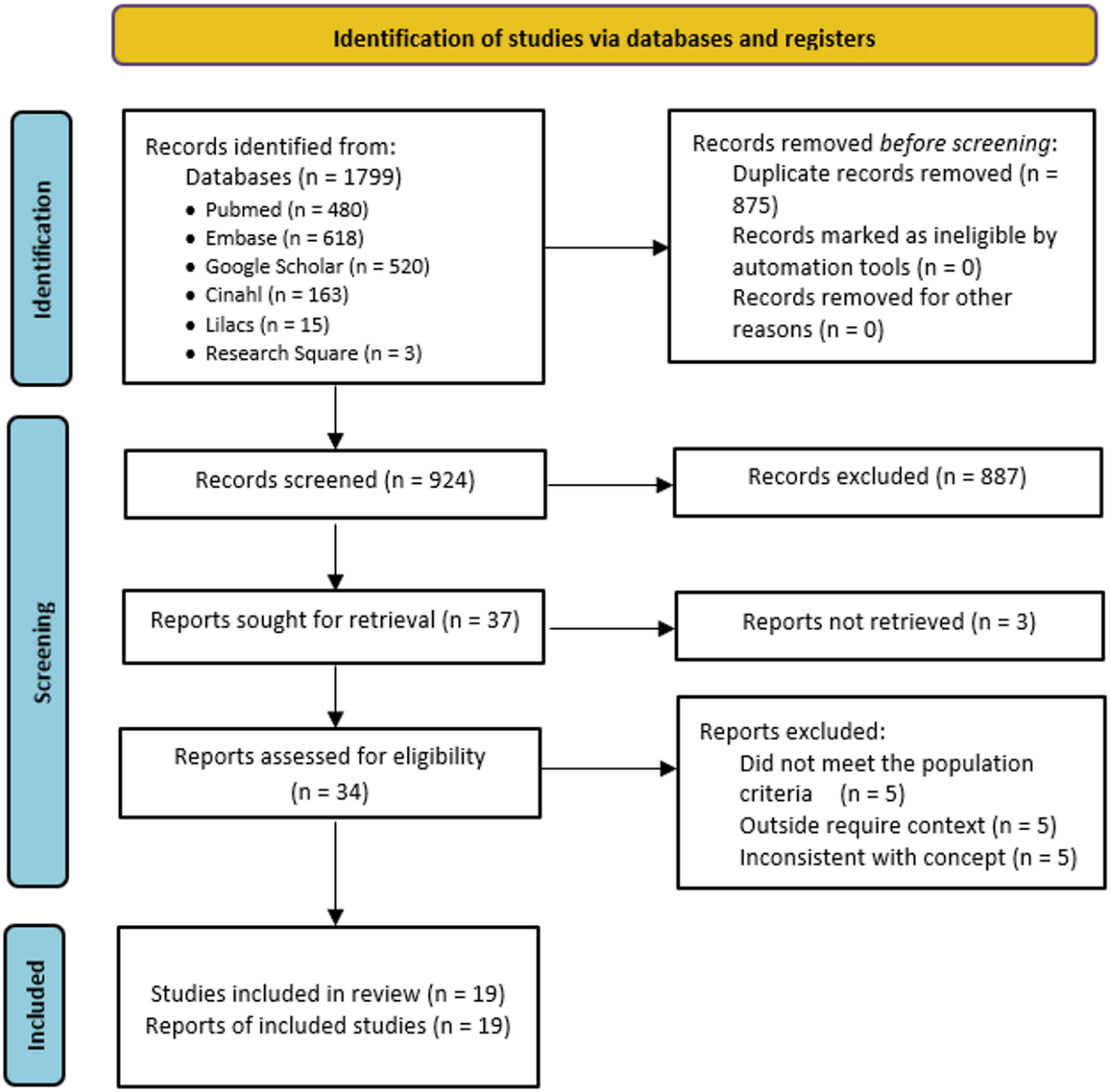

Figure 1. Search results and study selection and inclusion process.

injection[18,19,22,30,35] to biomaterial-based systems such as chitosan hydrogels29, Pluronic F-12721, decellularized porcine ECM[34], and gallium/chitosan/silk scaffolds.[23] Biomaterials address the issue of rapid exosome clearance at wound sites.

Biological Effects

Wound Closure and Healing Outcomes

Despite variability, studies converged on the benefits of wound closure and improved repair markers. Preclinical closure rates ranged from near-complete by day 12 to 97.4% by day 1430. Hydrogel/biomaterial carriers showed superior performance compared to free exosomes.[21,23,29,32,34] Clinically, Kishta et al.[23] reported a 62% recovery rate (mean 6 weeks vs. 20 weeks in control), and Jafar et al.[22] reported 100% closure (mean 4.2 weeks) with a favorable long-term safety profile. Chen L et al.[39] found a significant standardized mean difference (SMD) of 4.03 (95% CI: 3.29–4.76) favoring exosomes in

Table 1. Characteristics of Included Studies.

Study	Country	Evidence Category	Design	Population / Model	Target Wound Type
Zhang B et al. (2015)	China	Primary preclinical	*In vivo*	STZ-induced diabetic SD rats	Burn wounds
Yang J et al. (2020)	China	Primary preclinical	*In vivo* and *in vitro*	STZ-induced diabetic SD rats	Full-thickness excisional wounds
Wei Q et al. (2021 preprint) – miR-221-3p	China	Primary preclinical	*In vivo* and *in vitro*	db/db diabetic mice; HUVECs	Full-thickness excisional wounds
Wei Q et al. (2022) – miR-17-5p	China	Primary preclinical	*In vivo* and *in vitro*	db/db diabetic mice; HUVECs	Full-thickness excisional wounds
Yan C et al. (2022)	China	Primary preclinical	*In vivo* and *in vitro*	STZ-induced diabetic C57BL/6 mice; HUVECs	Full-thickness excisional wounds
Teng L et al. (2022)	China	Primary preclinical	*In vivo*	STZ-induced diabetic SD rats	Full-thickness excisional wounds
Yang S et al. (2023)	China	Primary preclinical	*In vivo*	STZ-induced diabetic SD rats	Full-thickness excisional wounds
Zhao X et al. (2023)	China	Primary preclinical	*In vivo* and *in vitro*	db/db diabetic mice; fibroblasts	Full-thickness excisional wounds
Ge L et al. (2023)	China	Primary preclinical	*In vivo* and *in vitro*	Diabetic mice; HUVECs	Full-thickness skin wounds
Yang J et al. (2024)	NR	Primary preclinical	*In vivo*	Diabetic mice	Full-thickness excisional wounds
Wu S et al. (2024)	China	Primary preclinical	*In vivo*	STZ-induced diabetic SD rats; fibroblasts	Full-thickness excisional wounds
Yang R et al. (2024)	China	Primary preclinical	*In vivo* and *in vitro*	db/db diabetic mice; keratinocytes	Full-thickness skin wounds
Shi X et al. (2024)	China	Primary preclinical	*In vivo* and *in vitro*	STZ-induced diabetic SD rats	Full-thickness skin wounds
Chen X et al. (2025)	China	Primary preclinical	*In vivo*	STZ-induced diabetic C57BL/6 mice	Not clearly specified in source spreadsheet
Zhang X et al. (2026)	NR	Primary preclinical	*In vivo* and *in vitro*	STZ-induced diabetic SD rats	Full-thickness skin wounds
Jafar H et al. (2025)	Jordan	Primary clinical	Phase I/II open-label clinical trial (single arm)	Adults with T2DM and chronic DFUs (n=110)	Diabetic foot ulcers
Kishta MS et al. (2025)	Egypt	Primary clinical	Randomized controlled clinical trial	Adults with T2DM and persistent DFUs (n=20)	Diabetic foot ulcers
Dehghani L et al. (2024)	NR	Secondary evidence	Narrative review	Review of diabetic wound studies	Various diabetic wound types
Chen L et al. (2025)	NR	Secondary evidence	Systematic review and meta-analysis	Meta-analysis of animal diabetic wound studies	Full-thickness excisional wounds

animal models. The variables related to wound healing outcomes and inflammatory markers are presented in Table 2A and Table 2B, for preclinical and clinical studies, respectively.

Markers of Angiogenesis, Inflammation, and Tissue Regeneration

Secondary outcomes favored tissue repair. Angiogenesis increased across all studies

Table 2. Preclinical efficacy outcomes and biological signals.

Study	Model	Exosome Preparation / Strategy	Delivery Strategy	Main Wound-Healing Outcome	Key Biological Markers	Safety Note
Zhang B et al. (2015)	STZ-induced diabetic SD rats	Serial centrifugation; native exosomes	Subcutaneous injection	Accelerated wound closure versus control; complete closure reported	↑ Collagen deposition; ↑ re-epithelialization	Not reported
Yang J et al. (2020)	STZ-induced diabetic SD rats	ExoQuick/commercial kit; native exosomes	Pluronic F127 hydrogel; topical application	Significantly accelerated healing versus control with near-complete closure	↑ CD31; ↑ VEGF; ↑ vessel density; ↑ collagen deposition; ↑ re-epithelialization; ↑ Ki67; ↑ TGF-β	No significant adverse events reported
Wei Q et al. (2021 preprint) – miR-221-3p	db/db diabetic mice; HUVECs	Ultracentrifugation; native exosomes	Periwound injection (every other day)	Accelerated wound closure; complete healing reported by day 21	↑ VEGF; ↑ vessel density; ↑ blood perfusion; ↑ tube formation; ↑ collagen deposition; ↑ re-epithelialization	Not reported
Wei Q et al. (2022) – miR-17-5p	db/db diabetic mice; HUVECs	Serial/differential centrifugation; native exosomes	Periwound injection (every other day)	Accelerated wound closure with complete healing reported by day 12	↑ CD31; ↑ VEGF; ↑ vessel density; ↑ blood perfusion	Not reported
Yan C et al. (2022)	STZ-induced diabetic C57BL/6 mice; HUVECs	Ultracentrifugation; native exosomes	Subcutaneous injection	Significantly accelerated healing versus control	↑ CD31; ↑ blood perfusion; ↓ oxidative stress	Not reported
Teng L et al. (2022)	STZ-induced diabetic SD rats	Ultracentrifugation; native exosomes	Subcutaneous injection	~98% closure reported within 7 days; accelerated healing versus control	↑ CD31; ↑ VEGF; ↑ vessel density; ↓ TNF-α; ↑ M2 macrophages/CD206; ↑ collagen deposition; ↑ re-epithelialization	Not reported
Yang S et al. (2023)	STZ-induced diabetic SD rats	Ultracentrifugation + PEG precipitation; native extracellular vesicles	Chitosan hydrogel	Statistically significant improvement in closure versus controls	↑ Tube formation; ↑ collagen deposition	Not reported
Zhao X et al. (2023)	db/db diabetic mice; fibroblasts	Ultracentrifugation; optogenetic eNOS loading	Subcutaneous injection	Accelerated wound closure versus control	↑ CD31; ↑ vessel density; ↑ eNOS; ↓ TNF-α/IL-6/IL-1β; ↑ collagen deposition; ↑ re-epithelialization	No local irritation reported
Ge L et al. (2023)	Diabetic mice; HUVECs	Ultracentrifugation/ commercial kit; miR-132 overexpression	Subcutaneous injection	Complete closure/ improved healing reported	↑ Blood perfusion; ↓ TNF-α/IL-6; ↑ M2 macrophages; ↑ collagen deposition	Not reported
Yang J et al. (2024)	Diabetic mice	Ultracentrifugation; native exosomes	Subcutaneous injection	Accelerated wound closure versus control	↑ VEGF; ↑ N2 neutrophils	Not reported
Wu S et al. (2024)	STZ-induced diabetic SD rats; fibroblasts	Ultracentrifugation; quercetin pretreatment	Subcutaneous injection	Statistically significant improvement in closure versus control	↑ VEGF; ↑ vessel density; ↑ blood perfusion; ↑ collagen deposition; ↑ re-epithelialization	Not reported
Yang R et al. (2024)	db/db diabetic mice; keratinocytes	Serial centrifugation; coenzyme Q10 pretreatment	Not specified	Statistically significant improvement in closure versus control	↑ Collagen deposition; ↓ ferroptosis	Not reported
Shi X et al. (2024)	STZ-induced diabetic SD rats	ExoQuick kit; native exosomes	Gallium/ chitosan/silk sponge scaffold	Accelerated healing versus control with statistically significant improvement	↑ Vessel density; ↓ TNF-α/IL-6; ↑ collagen deposition; ↑ re-epithelialization	Not reported
Chen X et al. (2025)	STZ-induced diabetic C57BL/6 mice	Differential centrifugation; native exosomes	Intraperitoneal injection	Sheet reports improved healing, but wound-healing outcomes are not clearly documented	Macrophage polarization; INS/SOD1; PI3K/AKT signaling	Not reported
Zhang X et al. (2026)	STZ-induced diabetic SD rats	Ultracentrifugation; native exosomes	pADM/PF-127 thermosensitive hydrogel; topical application	~96–97% closure within 14 days; statistically superior to comparators	↑ CD31; ↑ vessel density; ↑ M2 macrophages/ CD206; ↓ CD68; ↑ collagen deposition; ↑ re-epithelialization	No cytotoxicity observed; >80% cell survival; no organ damage reported

Table 2B. Clinical studies: efficacy and safety.

Study	Design / population	Intervention	Comparator	Main efficacy outcome	Safety findings
Jafar H et al. (2025)	Phase I/II open-label clinical trial (single arm); Adults with T2DM and chronic DFUs (n=10)	Perilesional injection once weekly, up to 10 sessions	None reported	All participants achieved complete ulcer closure; mean healing time 4.2 weeks; no recurrence during 24-month follow-up	No significant adverse events; mild transient local reactions only
Kishta MS et al. (2025)	Randomized controlled clinical trial; Adults with T2DM and persistent DFUs (sample size reported as 20 in study-design field)	Weekly topical exosome gel for 4 weeks + standard care	Standard care / control group	62% complete recovery; mean time to full recovery 6 weeks versus 20 weeks in control	Adverse-event frequency did not differ significantly between groups; events included fever, wound infection, osteomyelitis, and blisters

(higher CD31+ density and VEGF expression). Meta-analysis confirmed significant neovascular density increase (SMD = 3.66).[39] Collagen deposition increased 1.6-fold by day 7 in Zhang et al.[20] , supported by Chen et al.[39] (SMD = 3.72). Re-epithelialization increased (SMD = 5.05) and scar width decreased (SMD = −5.75). Anti-inflammatory effects involved M2 macrophage polarization (increased CD206, decreased TNF-α) and N2 neutrophil polarization (increasing from <10% to 80.37% post-treatment). Significant reductions in IL-6 and TNF-α were reported by Zhang et al.[34], Yang et al.[29], and Teng et al.[30]

Safety Profile

Safety data remain scarce. Preclinical studies reported no adverse events and favorable biocompatibility. Clinical studies provided the most robust data, Kishta et al.[23] found no significant difference in adverse events between groups, and Jafar et al.[22] documented only mild, transient reactions (local pain, erythema, mild fever) over 24 months.

Study Limitations

Methodological limitations include small samples, lack of explicit animal counts, and poor reporting of randomization or blinding.[39] Technical heterogeneity in isolation methods and incomplete characterization of functional molecules persist. Jafar et al.[22] acknowledged their open, uncontrolled design as a limitation, while Kishta et al.[23] emphasized the need for large-scale validation.

Discussion

This scoping review addressed the proposed research question by mapping the extent and nature of the evidence on the therapeutic application of hUC-MSC-derived exosomes in diabetic wounds across preclinical and clinical settings. Overall, the evidence base is expanding rapidly but remains predominantly preclinical. Across animal and cell-based models, the findings consistently suggest that hUC-MSC-derived exosomes can enhance wound closure, stimulate angiogenesis, modulate inflammation, and improve extracellular matrix remodeling. Clinical translation has begun, but the current human evidence remains limited to a small number of early studies.[18–23,29–32,34–39]

These findings are clinically relevant because DFUs remain among the most severe complications of diabetes mellitus. They are associated with recurrent ulceration, infection, hospitalization, amputation, and excess mortality, even after apparent healing.[40–44] In Brazil, diabetic foot disease also represents a substantial burden for the health system and requires structured prevention, timely diagnosis, and multidisciplinary management.[45,46] The biological rationale for exosome-based therapy is therefore compelling, particularly in cases that remain refractory to standard care because of persistent inflammatory dysregulation, impaired angiogenesis, oxidative stress, and defective tissue regeneration.[3,5–8]

The mapped evidence presents a coherent mechanistic pattern. hUC-MSC-Exos tend to accelerate diabetic wound closure and restore repair parameters like angiogenesis, collagen deposition, and inflammatory reduction,

showing consistency across animal models and converging mechanisms[18,30,36], meta-analysis reinforces this direction.[39] However, the translation gap between rodent dorsal wounds and human DFUs remains a crucial concern. Rodents heal primarily by contraction rather than re-epithelialization, and animal models may not fully replicate the chronic inflammatory microenvironment and comorbidities present in humans. Thus, positive results must be interpreted with caution.

Evidence is mechanistic, with studies exploring exosomes as intercellular signaling vectors capable of reprogramming the diabetic wound microenvironment. In DFUs, local retention is critical; thus, biomaterial systems functioning as sustained-release reservoirs are preferable to repeated manipulations.[21,23,34]

The evidence base has notable gaps. The lack of dose-response data hinders therapeutic optimization. Dependence on short-term rodent models and small clinical samples leaves long-term efficacy and safety uncertain. Furthermore, the geographic concentration of preclinical work in China raises questions about generalizability.

Using the PAGER framework, the mapping indicates an urgent need to standardize dose-response protocols and molecular characterization. Without this, reproducibility remains a challenge for large-scale clinical practice. Transitioning from direct injections to biomaterial carriers like hydrogels is a viable path.[21,34]

The primary gap is the biological distance between models and humans (contraction vs. re-epithelialization), requiring models that better mimic chronic inflammation and metabolic complexity.[47] While preclinical evidence is consistent[39], future priority must be given to multicenter RCTs with larger samples and prolonged follow-up to ensure that accelerated healing translates into safe, durable tissue repair.[22,23]

This review has several strengths. It used a broad multi-database search strategy, including grey literature sources, and mapped both preclinical and clinical evidence in an emerging translational field. The review was structured using the PCC framework, conducted according to JBI methodology, and synthesized through the PAGER framework, which supported a coherent interpretation of patterns, advances, gaps, and research priorities.[28]

However, some limitations of this review should be acknowledged. The available evidence is heavily weighted toward preclinical studies, and the included studies were highly heterogeneous in design, exosome preparation, dosing, delivery strategy, and outcome reporting. The review also depended on the quality and completeness of reporting in the primary studies, which was variable. In addition, because the evidence base remains small and methodologically diverse, the mapped findings should not be interpreted as equivalent to a definitive assessment of clinical effectiveness. Finally, before resubmission, the final corpus should be rechecked to eliminate any potential duplicate study records across preprint and peer-reviewed versions.

Conclusions

The current evidence on the therapeutic application of hUC-MSC-derived exosomes in diabetic wound management is characterized by a burgeoning, yet predominantly preclinical, landscape. Regarding the extent of the evidence, this scoping review mapped 19 pivotal studies, reflecting an exponential growth in publications over the last decade, with a significant geographical concentration of experimental work in China and emerging clinical trials in Egypt and Jordan.

The nature of this evidence is multifaceted: preclinical findings consistently demonstrate that these exosomes act as potent intercellular signaling vectors that reprogram the diabetic microenvironment by enhancing angiogenesis, modulating macrophage polarization toward an anti-inflammatory M2 phenotype, and accelerating extracellular matrix remodeling. Clinically, the evidence has recently transitioned from mechanistic theory to human application, with randomized controlled trials, reporting favorable clinical outcomes in chronic DFU closure and a favorable safety profile over a 24-month period. Despite encouraging results, current research highlights the need for standardized dose-response protocols and validation across multiple centers.

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