Supplement Article

Human Placental Mesenchymal Stem Cell-Derived Exosomes in Wound Healing and Scar Therapy: A Systematic Review and Meta-analysis

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Abstract

Exosome therapy represents an emerging regenerative medicine approach for optimizing wound healing and reducing scarring. Extensive preclinical research on human placental mesenchymal stem cell-derived exosomes (hpMSC-exosomes) demonstrates significant therapeutic potential in aesthetic and reconstructive surgery applications. Despite compelling preclinical evidence supporting the efficacy of exosomes in wound healing, human clinical studies remain scarce. The author's current study includes 738 patients treated with hpMSC-exosomes over a 7-year period across multiple aesthetic and reconstructive indications, with 175 cases involving wound healing and 118 cases involving scar therapy. The objective of this systematic review and meta-analysis is to comprehensively evaluate the current evidence for hpMSC-exosomes in wound healing and scar therapy, analyzing their mechanisms of action, clinical applications, and safety profiles through a review of preclinical studies, safety data, and clinical case series in both animals and humans. Analysis of the author's series will be included. Information sources included PubMed, Cochrane Library, EMBASE, Web of Science, and ClinicalTrials.gov resulting in a meta-analysis of 21 global preclinical studies (323 animals) which demonstrated superior outcomes compared with controls across multiple parameters: wound healing rate, neovascular density, re-epithelialization rate, and collagen deposition. hpMSC-exosomes demonstrated accelerated wound healing through enhanced angiogenesis, reduced inflammation, improved collagen production, and immunomodulatory effects. Most studies utilized rodent models, with limited translation to human trials. Current human evidence is predominantly based on early-phase trials, case series, and observational studies. Large-scale, well-designed clinical trials are essential to advancing exosome therapy in wound healing and scar management. hp-MSC-exosomes represent a promising therapeutic modality for wound healing and scar therapy with demonstrated safety and efficacy. Standardization of manufacturing processes and FDA approval remain critical for widespread clinical implementation.

Level of Evidence: 3 (Therapeutic)

The evolution of cellular medicine and regenerative therapies has introduced novel approaches to optimize wound healing and achieve scarless tissue repair.[1] Exosomes, a subset of extracellular vesicles ranging from 50 to 150 nm in diameter, serve as critical mediators of intercellular communication and tissue regeneration.[2] These naturally occurring nanovesicles contain complex cargo including DNA, messenger RNA, microRNA, proteins, and lipids that facilitate therapeutic effects without the risks associated with live cell therapies.[3] The 4-phase wound healing process-hemostasis, inflammation, proliferation, and remodeling- has been extensively studied to identify interventions that optimize healing outcomes.[4] The axolotl salamander serves as the gold standard for scarless healing, demonstrating rapid hemostasis, minimal inflammation, accelerated proliferation, and efficient remodeling.[5] Research efforts focus on replicating this scarless healing model in human therapeutics. Current regenerative therapies include autologous fibroblasts, mesenchymal stem cells (MSCs), platelet-rich plasma, and, more recently, allogeneic exosomes.[6] Although tissue-cultured fibroblasts achieved FDA approval,

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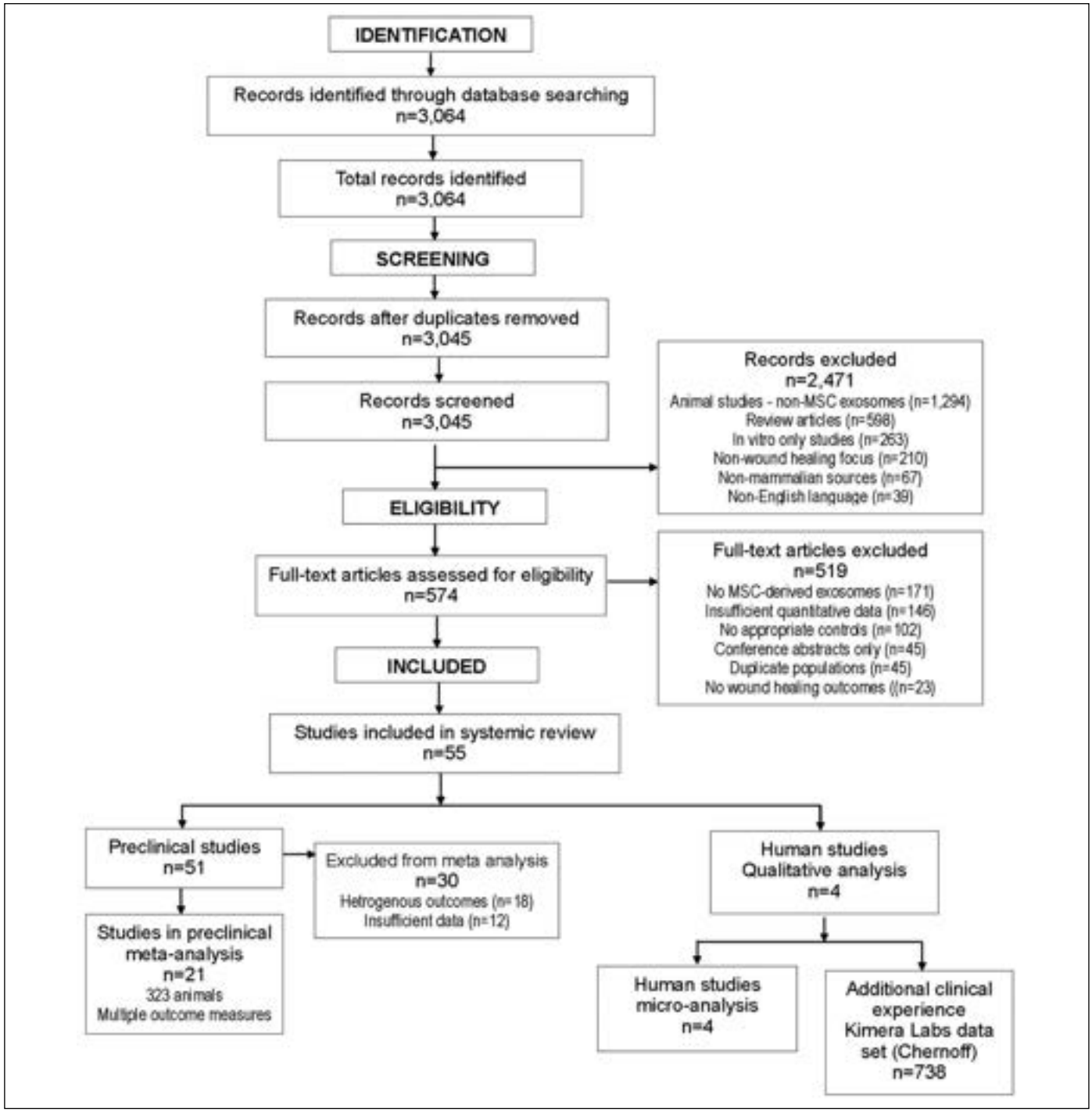

Figure 1. PRISMA flow diagram showing the systematic identification, screening eligibility assessment, and inclusion of studies for comprehensive systematic review and meta-analysis of MSC-derived exosomes in wound healing and scar therapy. MSC, mesenchymal stem cell; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses;

cost limitations led to market withdrawal.[7] Presently, no exosome products have FDA approval in the United States, creating challenges for standardized clinical implementation.[8]

METHODS

This systematic review and meta-analysis was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Figure 1 illustrates the PRISMA flow diagram for this study. Primary analysis focused on the author's clinical data from 738 patients treated with human placental MSC (hpMSC)-derived exosomes (Kimera Labs, Miramar, FL) between 2017 and 2025. IRB approval was granted through the International Cell Surgical Society (ICSS-2021-011). Initial safety and proof-of-concept studies were conducted on 100 patients, and the study is continuing across multiple indications, including aging skin, acne, wound healing, scar therapy, and pain modulation. For this study, wound healing and scar therapy will be discussed, with other indications reviewed in subsequent publications.

A comprehensive systematic search was conducted using the PubMed (National Library of Medicine, Bethesda, MD), Cochrane Library (Wiley, Hoboken, NJ), EMBASE (Elsevier, Amsterdam, the Netherlands), Web of Science (Clarivate Analytics, Philadelphia, PA), and ClinicalTrials.gov (National Library of Medicine) databases for studies published between 2010 and 2024. Search terms included: "mesenchymal stem cell exosomes," "wound healing," "placental exosomes," "MSC-derived extracellular vesicles," and "scar therapy." Human-specific searches included: "exosome therapy wound healing humans," "clinical trials," and "human participants." Studies were included if they: (1) used mammalian mesenchymal-derived exosomes, (2) evaluated wound healing or scar management, (3) involved in vivo studies, (4) reported clinical outcomes, and (5) were published in English with full text availability.

Of the 3064 initially identified studies on exosomes and wound healing, 51 preclinical studies met the systematic review criteria, with 21 studies (involving 323 animals) included in the quantitative meta-analysis. Quantitative meta-analysis was performed for preclinical studies with comparative outcome measures using RevMan 5.4 software. Standardized mean differences (SMD) with 95% CIs were calculated for continuous outcomes. Statistical heterogeneity was assessed using I^2 statistics. Only 4 studies, with a fifth including this publication, met the requirements for human participants. Given the limited number of human studies and heterogeneous methodologies, descriptive analysis with narrative synthesis of consistent patterns and outcomes will be performed for human studies, rather than formal meta-analysis with statistical pooling, as was done for the pre-clinical studies. Consistent patterns were identified across human studies. Pre-clinical studies were evaluated using modified Stroke Therapy Academic Industry Roundtable quality assessment guidelines.

The analyzed exosome product (Kimera Labs, Miramar, FL) consists of isolated and purified placental MSC-derived extracellular vesicles suspended in saline solution, manufactured at 2 concentrations: LUXIR (base) and LUXIR Plus (3× concentrated). Manufacturing adheres to cGMP guidelines and FDA regulations per 21 CFR 210, 211, and GLP HCT/P regulations per 21 CFR 1271.

Comprehensive donor screening includes testing for CMV, hepatitis 8/C, HIV, HTLV, syphilis, West Nile virus, Zika virus, JCV PCR, and COVID-19. Manufacturing utilizes ISO 7 compliant airflow standards with ISO 5 certified laminar flow units. Product characterization employs multiple analytical methods including:

- ELISA protein analysis
- Western blot analysis for surface markers (CD63, CD81)
- RNA purification and sequencing
- High-pressure liquid chromatography
- Atomic force microscopy
- Electron microscopy
- dSTORM super-resolution fluorescence microscopy

RESULTS

Quantitative meta-analysis of 21 global preclinical studies demonstrated significant therapeutic benefits of MSCderived exosomes in wound healing applications. Pooled analysis revealed superior outcomes compared with control therapies across multiple parameters:

- Wound healing rate: SMD = 5.42 (95% CI, 4.40-6.44; $P < .00001$) $I^2 = 73\%$[9]
- Neovascular density: SMD = 5.48 (95% CI, 4.31-6.64; $P < .00001$) $I^2 = 68\%$[10]
- Re-epithelialization rate: SMD = 5.06 (95% CI, 3.75-6.37; $P < .00001$) $I^2 = 71\%$)[11]
- Collagen deposition: SMD = 4.78 (95% CI, 3.58-5.98; $P < .00001$) $I^2 = 69\%$[12]
- Scar width reduction: SMD = −8.10 (95% CI, −10.31 to −5.89; $P < .00001$) $I^2 = 82\%$[13]

The meta-analysis revealed optimal therapeutic windows for exosome intervention. Peak efficacy was observed at 7 days post-administration (OR = 1.82; 95% CI, 0.69-2.95) compared with 14 days (OR = 2.29; 95% CI, 0.01-4.56).[14] This temporal pattern suggests rapid therapeutic engagement with wound healing mechanisms.

Mean quality scores across systematic review studies were 5.08 ± 0.752, comparable to other preclinical systematic reviews in regenerative medicine. Quality assessment revealed consistent methodology across studies, though heterogeneity existed in exosome sources, concentrations, and delivery methods.[15]

Human Clinical Evidence Studies

The first of 5 human evidence studies (NCT02565264) evaluated plasma-derived exosomes for chronic wound healing over 28 days. Results demonstrated that patients with chronic wounds had significantly lower baseline serum exosome levels compared with controls, with treatment showing enhanced healing parameters and an excellent safety profile.

A randomized, split-faced study of 25 patients evaluated hpMSC-exosomes combined with fractionated CO_2 laser therapy for the treatment of acne scars. All patients demonstrated superior improvement in acne scar appearance compared with laser treatment alone, with reduced post-procedural erythema and a shortened recovery time over 12 weeks.

Another study involved a clinical practice case series utilizing placental MSC-exosomes for aesthetic procedures and traumatic injury demonstrated significantly accelerated wound healing within hours to days. Patients reported marked improvements in pain, swelling, and recovery time compared with standard care.

The fourth study involved the evaluation of stem cell-conditioned medium containing exosomes for chronic ulcerative wounds and demonstrated improved healing rates compared with standard care, with conditioned medium serving as effective growth factor supplementation.

Within the author's 738 patients treated with hpMSC-exosomes, 175 cases were wound management cases, and 118 cases were scar therapy cases. The wound healing cases included 131 females and 44 males, with ages ranging from 19 to 72 years and an average age of 48 years. The scar therapy cases included 78 females and 40 males. Ages ranged from 21 to 56 years, with an average age of 32 years.

In the author's series of 21 patients with recurrent keloids, CO_2 laser excision combined with topical exosome application, followed by the application of an amniotic membrane graft as a scaffold, resulted in 18/21 patients (85.7%) remaining recurrence-free at 2-year follow-up.[16] All patients had multiple previous failed excisions. Hypertrophic scar treatment demonstrated anti-fibrotic capabilities with acoustic wave-assisted exosome delivery, utilized to enhance topical exosome absorption into the hypertrophic scar, to adhere to the FDA guidelines for topical applications.

Figure 2 illustrates a 28-year-old female with a keloid on the right ear after multiple piercings. Two previous scalpel excisions were performed, both with recurrence. She underwent CO_2 laser excision, topical exosomes, with an amniotic membrane graft (Gratitude Therapeutics, Indianapolis, IN). She is now 5 years with no recurrence.

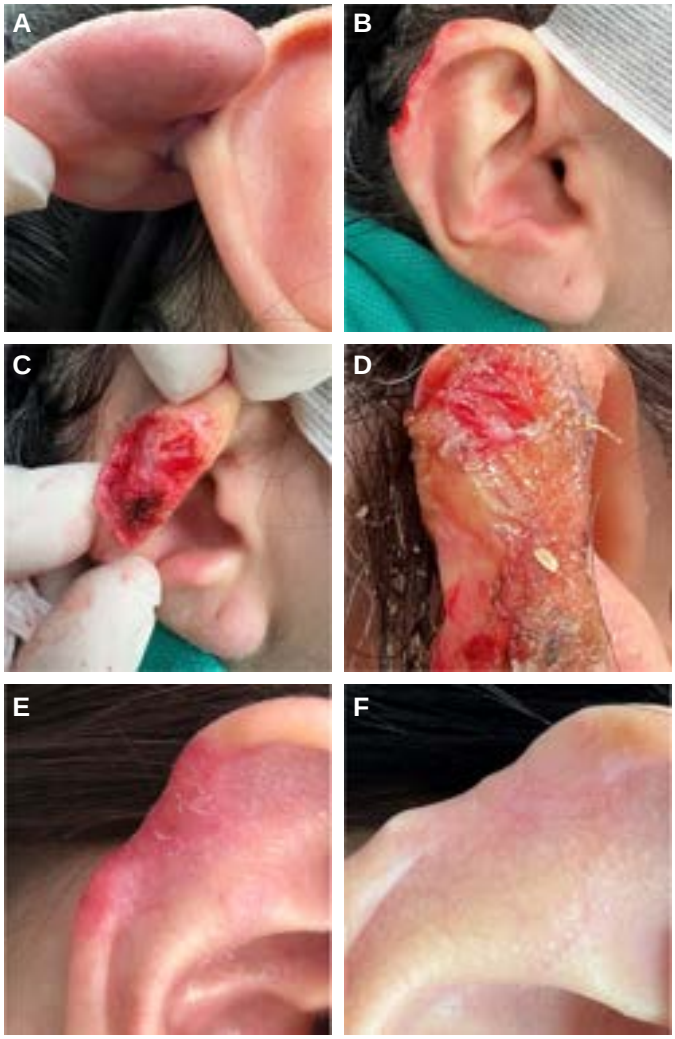

Figure 2. (A) Photo of a 28-year-old female patient who presented with a keloid on her right ear. (B, C) Patient's ear post-CO_2 laser excision. (D) Amniotic membrane graft plus topical exosomes. (E) One year postprocedure. (F) Five years postprocedure.

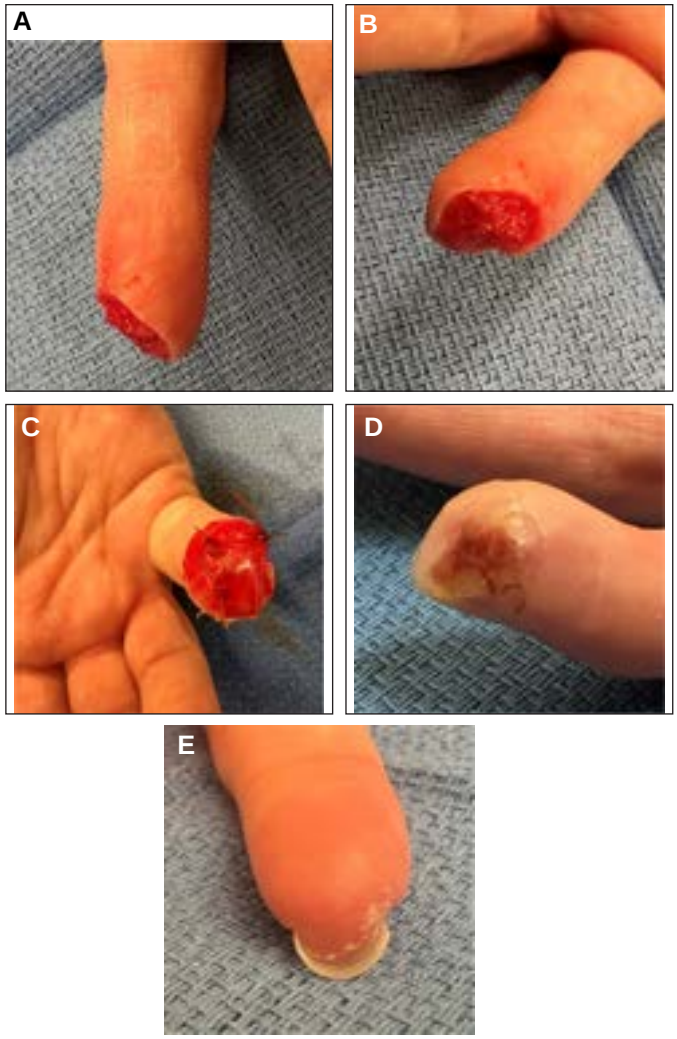

Figure 3. (A) Photo of a 35-year-old female patient with a right fifth distal digit amputation. (B) Amniotic membrane graft plus topical exosomes. (C) Three weeks posttreatment. Note neovascularization of the graft. (D) Eight weeks posttreatment. Note the near scarless healing, as well as fingerprint and nailbed regeneration.

Second and third-degree burns treated with topical exosomes demonstrated enhanced neovascularization, reduced inflammation, and accelerated healing without requiring skin grafting.[17] Traumatic wound reconstruction cases showed improved vascularity, reduced inflammation, sensory nerve restoration, and scarless healing patterns with topical exosome application.

Figure 3 illustrates a 35-year-old female, 8 hours after accidental amputation of her right distal fifth digit. She underwent placement of an amniotic membrane graft, and topical exosome application, daily for 7 days. At 3 weeks, neo-vascularization is evident in the graft. At 8 weeks, scarless healing with fingerprint, and nailbed regeneration is noted.

Post-Surgical Applications

In another study, pretreatment of planned surgical incisions 1 h before to incision, followed by daily application for 1 week posttreatment, resulted in scars approaching the "scarless healing" model at 1-month follow-up.[18] Intraoperative wound bed topical applications improved vascularity and reduced postoperative inflammation and bruising.

Chronic Wounds

Diabetic ulcers in immunocompromised patients demonstrated wound contracture, re-epithelialization, and regeneration with exosome therapy.[19] Autoimmune conditions including lichen sclerosis showed resolution of ulcerations and pain within 30 days of topical treatment.

Safety Profile and Therapeutic Patterns

Comprehensive safety analysis of over 738 patients over 6 years revealed no allergic reactions, hypersensitivity responses, or adverse events attributable to exosome therapy. Multiple administration routes were evaluated, including topical, subdermal, subcutaneous, intravenous, and intra-articular applications.[20]

Despite methodological heterogeneity in the above human studies, consistent therapeutic patterns emerged:

1. Enhanced wound healing acceleration across all study types
2. Reduced recovery time and post-procedural symptoms

3. Improved scar appearance
4. High patient satisfaction with treatment outcomes
5. Good safety profile across different patient populations and indications
6. Shortened recovery times and improved aesthetic outcomes in cosmetic procedures

ClinicalTrials.gov analysis reveals 33 registered exosome therapy trials with 20 (60.6%) utilizing MSC-derived exosomes. However, most focus on systemic diseases rather than wound healing, highlighting opportunities for expanded research in aesthetic and reconstructive fields.

Ongoing clinical development reveals multiple Phase I and II trials:

- NCT04326959: Umbilical cord stem cell conditioned medium for keloids
- NCT06319287: Topical purified exosome product for diabetic foot ulcers (Phase IIa)
- NCT05887804: Comparative umbilical cord stem cell therapies for keloids
- NCT05475418: Human adipose tissue-derived exosomes pilot study
- NCT06253975: Adipose tissue-derived extracellular vesicles randomized trial

Mechanisms of Action in Wound Healing

Hemostatic Phase

Exosomes regulate coagulation through CD9-mediated platelet activation and fibrinogen binding enhancement.[21] They contain annexin V with anticoagulant activity, creating equilibrium between pro- and anticoagulant proteins.[22] Exosomes induce both intrinsic and extrinsic coagulation pathways involving Factors XII and VII.[23]

Inflammatory Phase

hpMSC-exosomes promote anti-inflammatory processes by suppressing apoptosis and inducing macrophage phenotype transition from pro-inflammatory M1 to anti-inflammatory M2.[24] Key microRNAs (miR-34a-5p, miR-124-3p, miR-146a-5p, miR-223) facilitate macrophage polarization.[25] Exosomes contain prostaglandin E2, regulating neutrophil migration and macrophage polarization.[26]

Chemoattractant proteins (CXCL8, CXCL16, DEFA1, HERCS, IFITM2, XCL2) enhance immune response and infection protection.[27] Exosomes decrease reactive oxygen species synthesis and shift inflammatory T cells toward FOXP3+ regulatory T cells.[28] They decrease inflammatory cytokine IL-6 and chemokine receptor CCR7 whereas increasing anti-inflammatory TGF-beta 3.[29]

Proliferative Phase

Exosomes facilitate endothelial cell proliferation, migration, and angiogenesis through microRNAs (miR-125a, miR-126, miR-130a, miR-296, miR-378) and growth factors (VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; angiopoietin-2).[30] Fibroblast migration and granulation tissue formation occur through Jagged 1 through Notch signaling pathways.[31]

LncRNAh19 inhibits miR-19b expression, upregulates transcription factor SOX9, and activates the Wnt/beta-catenin pathway (regulates cell proliferation, differentiation, and migration), promoting fibroblast proliferation and wound invasion.[32] Keratinocyte proliferation and migration are enhanced through miR-27b transfer, activating ITCH/JUNB/IRF-a signaling.[33]

Remodeling Phase

Exosomes enhance mechanical restoration, monitor scar reduction, and increase skin barrier proteins (filaggrin, loricrin, AQP3).[34] To promote scarless healing, exosomes increase Collagen III/Collagen I ratios and regulate MMP3 expression.[35] Anti-fibrotic effects are mediated through miR-192-Sp, miR-29c, miR-192, miR-215 transfer, repressing pro-fibrotic IL-17RA/Smad2 signaling.[36]

Comparative Analysis Across Exosome Sources

Source-Specific Efficacy

Systematic review of 148 studies (2018-2023) revealed significant variability across exosome sources.[37] Adipose-derived stem cell exosomes demonstrated consistent efficacy in promoting fibroblast proliferation, collagen synthesis, and angiogenesis.[27] Bone marrow-derived MSC exosomes showed superior anti-inflammatory properties and macrophage polarization.[38] Placental MSC-derived exosomes exhibited enhanced wound closure rates and appendage regeneration compared with other sources.[39]

Delivery Method Optimization

Meta-analysis in animal studies revealed subcutaneous injection as the predominant delivery method (57.8% of studies), with topical application used in 25.7% of cases.[40] Combined topical and systemic administration demonstrated synergistic effects, with enhanced re-epithelialization, angiogenesis, and collagen synthesis compared with single-route delivery.[41] To be FDA compliant, all participants in the author's study received topical application of exosomes. The author spent 2 years researching methods to optimize topical exosome absorption to achieve maximal exosome absorption without adversely affecting exosome function. The following are enhancement strategies.

Enhancement Strategies

Nitric Oxide Optimization

Nitric oxide (NO) supplementation through oral lozenges and topical serum application (Pneuma Nitric Oxide, N1o1, Austin, TX) enhances exosome absorption and efficacy.[42] NO improves tissue vascularity, mobilizes stem cells, and enhances topical absorption within 30 min of application.[43] By age 40, adults produce only 50% of endogenous NO compared with age 20, making supplementation particularly relevant for optimal outcomes.[44] All study patients were placed on oral NO lozenges 1 month before to treatment and applied NO-producing topical serum 15 min before exosome topical application.

Delivery Enhancement Devices

Dermoelectroporation (DEP Medical, Atlanta, GA) utilizes electrical current to drive macromolecules up to 800 Da through skin water channels.[45] Three-megahertz ultrasound (SaltMed, Encinitas, CA) increases intercellular spaces through cavitation, showing 30% increased absorption and twice the penetration depth compared with topical application alone.[46] Acoustic shockwave therapy (Elvation Medical, GmbH, Germany) accomplishes similar absorption enhancement with additional vascularity improvements. Dermoelectroporation, cavitating ultrasound or acoustic shockwave were used equally among all cases to aid in topical absorption in order to maximize absorption for FDA guideline adherence.

Biomaterial Scaffolds

Rapid exosome clearance (half-life 2-4 min intravenously) necessitates scaffold utilization for sustained release.[47] Hydrogel properties, including network morphology, cross-link density, and degradability control exosome release over 6 to 27 days and maintaining biological function.[48] Biomaterials under investigation include hyaluronic acid hydrogels, chitosan hydrogels, alginate hydrogels, collagen hydrogels, and decellularized amniotic membrane grafts. Amniotic grafts (Gratitude Therapeutics) were applied to all excised keloid wound beds with preivous and subsequent exosome applications.

Meta-Analysis Findings and Clinical Translation

Heterogeneity and Standardization Challenges

Systematic review analysis revealed significant methodological heterogeneity across studies, including variable exosome isolation methods, characterization protocols, and administration routes.[49] Most studies utilized rodent models, with limited translation to larger animal models or human trials. Quality scores averaged 5.08 ± 0.752 across systematic review studies, indicating moderate methodological rigor.[50]

Concentration and Dosing Analysis

Meta-analysis of preclinical studies demonstrated optimal therapeutic effects at concentrations ranging from 100 to 400 µg/mL for topical applications, with dose-dependent responses observed across multiple parameters.[51] However, standardized dosing protocols remain undefined because of variability in exosome characterization methods and cargo content assessment.

Translation Barriers

Despite promising preclinical results, translation to clinical applications faces several challenges: (1) lack of standardized manufacturing protocols, (2) regulatory approval barriers, (3) inconsistent exosome characterization methods, and (4) limited understanding of optimal delivery systems.[52] Current evidence suggests the need for larger randomized controlled trials with standardized protocols before widespread clinical implementation.

DISCUSSION

hpMSC-exosomes offer several advantages over live cell therapies, including lack of tumorigenicity risk, improved scalability, easier storage and distribution, and elimination of graft-vs-host disease potential.[53] The acellular nature maintains therapeutic efficacy while reducing safety concerns associated with live MSC administration. Unlike simple particle counting, therapeutic efficacy correlates with cargo quality, particularly RNA content, including messenger RNA and microRNA.[54] Surface markers CD63 and CD81 must both be present to validate the presence of exosomes, distinguishing therapeutic exosomes from other similarly sized biological particles.

The comprehensive meta-analysis demonstrates robust preclinical evidence supporting the efficacy of exosome therapy across multiple wound healing parameters. Effect sizes consistently favored exosome treatment over controls, with powerful evidence for enhanced angiogenesis (SMD = 5.48) and wound closure rates (SMD = 5.42).[55] However, the reliance on rodent models and methodological heterogeneity limits direct clinical extrapolation.

Manufacturing and Regulatory Challenges

Current challenges for FDA approval include GMP mass production standardization, donor cell characterization and safety, batch-to-batch consistency, prolonged viability maintenance, standardized biomarker detection, appropriate transport conditions, and storage stability.[52] Exosome companies utilize varying sources (placenta, umbilical cord, Wharton's jelly, adipose tissue, platelets), resulting in different cargo compositions and clinical capabilities. When assessing product quality, proteomic composition should be assessed, particularly the content of total protein, messenger RNA, microRNA, and the presence of exosome markers CD63 and CD81.

Comparative Efficacy

The author's clinical experience with over 750 patients suggests MSC-derived exosomes from master cell lines in sterile, cryopreserved states exhibit superior biological effects compared with other sourced products.[56] Studies demonstrate low immunogenicity and absence of tumorigenicity with MSC-derived exosomes.[57] Meta-analysis supports placental MSC-derived exosomes showing enhanced efficacy in wound closure and appendage regeneration compared with other sources.

Clinical Translation Considerations

Optimal therapeutic protocols require consideration of administration routes, dosing regimens, and enhancement strategies. Current evidence supports topical application for compliance with FDA regulations, with enhancement through NO supplementation and mechanical delivery devices.[58] Future research should focus on standardized potency assays, optimal dosing protocols, and comparative efficacy studies across different exosome sources.

Limitations

This review incorporates both single-source clinical data and comprehensive meta-analysis of preclinical literature. While safety data from 700+ patients over 6 years is encouraging, the meta-analysis reveals reliance on rodent models with limited clinical translation. Additionally, significant methodological heterogeneity across studies limits definitive conclusions regarding optimal protocols and standardization approaches.

CONCLUSIONS

hpMSC-derived exosomes demonstrate significant promise for wound healing optimization and scar therapy applications, supported by robust meta-analytic evidence from preclinical studies. The comprehensive safety profile across multiple administration routes and clinical indications, combined with strong preclinical efficacy data, supports continued investigation and development.

Meta-analysis of 21 global preclinical studies demonstrates substantial therapeutic benefits with large effect sizes across all wound healing parameters. Key clinical successes include keloid treatment with 85.7% recurrence-free rates at 2 years, enhanced burn healing without skin grafting requirements, and postsurgical scar optimization approaching scarless healing models. Enhancement strategies including NO supplementation and mechanical delivery devices maximize therapeutic potential.

However, significant methodological heterogeneity across studies and reliance on rodent models limit clinical translation. Future

research priorities include large-scale randomized controlled trials, standardized manufacturing protocols, FDA approval pathways, and optimization of delivery methods. The establishment of standardized exosome characterization methods, dosing protocols, and quality assessment measures is essential for clinical advancement.

Because the field evolves toward personalized medicine and regenerative therapeutics, exosome therapy represents a bridge between cellular medicine and precision treatment approaches. The convergence of mechanistic understanding, robust preclinical evidence, clinical safety data, and meta-analytic support positions exosome therapy as a transformative approach in aesthetic and reconstructive surgery. Continued research, regulatory advancement, and standardization efforts will be essential for realizing the full therapeutic potential of this promising technology.

Disclosures

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REFERENCES

1. Guo S, Dipietro LA. Factors affecting wound healing. *J Dent Res*. 2010;89:219-229. doi: 10.1177/0022034509359125
2. Thery C, Witwer KW, Aikawa E, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the international society for extracellular vesicles. *J Extracell Vesicles*. 2018;7:1535750. doi: 10.1080/20013078.2018.1535750
3. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367:eaau6977. doi: 10.1126/science.aau6977
4. Schultz GS, Davidson JM, Kirsner RS, Bornstein P, Herman IM. Dynamic reciprocity in the wound microenvironment. *Wound Repair Regen*. 2011;19:134-148. doi: 10.1111/j.1524-475X.2011.00673.x
5. Seifert AW, Muneoka K. The blastema and epimorphic regeneration in mammals. *Dev Biol*. 2018;433:190-199. doi: 10.1016/j.ydbio.2017.08.007
6. Maxson S, Lopez EA, Yoo D, Danilkovitch-Miagkova A, Leroux MA. Concise review: role of mesenchymal stem cells in wound repair. *Stem Cells Transl Med*. 2012;1:142-149. doi: 10.5966/sctm.2011-0018
7. Boyce ST, Lalley AL. Tissue engineering of skin and regenerative medicine for wound care. *Burns Trauma*. 2018;6:4. doi: 10.1186/s41038-017-0103-y
8. FDA Center for Biologics Evaluation and Research. Regulatory considerations for human cells, tissues, and cellular and tissue-based products: minimal manipulation and homologous use. 2017. Accessed January 15, 2025. https://www.fda.gov/regulatory-information/search-fda-guidance-documents
9. Li H, Xu Y, Wan T, et al. The effectiveness of cell-derived exosome therapy for diabetic wound: a systematic review and meta-analysis. *Life Sci*. 2023;316:121391. doi: 10.1016/j.lfs.2023.121391
10. Prasai A, Jay JW, Jupiter D, Wolf SE, El Ayadi A. Role of exosomes in dermal wound healing: a systematic review. *J Invest Dermatol*. 2022;142:662-678.e8. doi: 10.1016/j.jid.2021.07.167
11. Bailey AJM, Li H, Kirkham AM, et al. MSC-derived extracellular vesicles to heal diabetic wounds: a systematic review and meta-analysis of preclinical animal studies. *Stem Cell Rev Rep*. 2022;18:968-979. doi: 10.1007/s12015-021-10164-4
12. Wei JT, He T, Shen K, et al. Adipose stem cell-derived exosomes in the treatment of wound healing in preclinical animal models: a meta-analysis. *Burns Trauma*. 2024;12:tkae025. doi: 10.1093/burnst/tkae025
13. Al-Masawa ME, Alshawsh MA, Ng CY, 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;12:6455–6508. doi: 10.7150/thno.73436
14. Sousa P, Lopes B, Sousa AC, et al. Advancements and insights in exosome-based therapies for wound healing: a comprehensive systematic review (2018-June 2023). *Biomedicines*. 2023;11:2099. doi: 10.3390/biomedicines11082099
15. Rahman E, Webb WR, Rao P, et al. Exosomes exposed: overview systematic review on evidence versus expectation in aesthetic and regenerative medicine. *Aesthetic Plast Surg*. 2025;49:557-568. doi: 10.1007/s00266-024-04276-8
16. Chernoff G. Clinical outcomes with human placental mesenchymal stem cell derived exosomes in keloid scar therapy. *Aesthet Surg J*. 2021;41:NP1150-NP1162. doi: 10.1093/asj/sjab123
17. Chen B, Sun Y, Zhang J, et al. Human embryonic stem cell-derived exosomes promote pressure ulcer healing in aged mice by rejuvenating senescent endothelial cells. *Stem Cell Res Ther*. 2019;10:142. doi: 10.1186/s13287-019-1253-6
18. Fang S, Xu C, Zhang Y, et al. Umbilical cord-derived mesenchymal stem cell-derived exosomal microRNAs suppress myofibroblast differentiation by inhibiting the transforming growth factorβ/SMAD2 pathway during wound healing. *Stem Cells Transl Med*. 2016;5:1425-1439. doi: 10.5966/sctm.2015-0367
19. Li X, Liu L, Yang J, et al. Exosome derived from human umbilical cord mesenchymal stem cell mediates MiR-181c attenuating burn-induced excessive inflammation. *EBioMedicine*. 2018;37:373-385. doi: 10.1016/j.ebiom.2018.10.044
20. Chernoff G. Safety profile of human placental mesenchymal stem cell derived exosomes: comprehensive analysis of 700 patients. *Plast Reconstr Surg Glob Open*. 2020;8:e3098. doi: 10.1097/GOX.0000000000003098
21. Siljander PR, Carpen O, Lassila R. Platelet-derived microparticles associate with fibrin during thrombosis. *Blood*. 1996;87:4651-4663. doi: 10.1182/blood.V87.11.4651.bloodjournal87114651
22. Dasgupta SK, Abdel-Monem H, Niravath P, et al. Lactadherin and clearance of platelet-derived microvesicles. *Blood*. 2009;113:1332-1339. doi: 10.1182/blood-2008-07-167148
23. Mallat Z, Benamer H, Hugel B, et al. Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes. *Circulation*. 2000;101:841-843. doi: 10.1161/01.cir.101.8.841
24. Zhao B, Zhang Y, Han S, et al. Exosomes derived from human amniotic epithelial cells accelerate wound healing and inhibit scar formation. *J Mol Histol*. 2017;48:121-132. doi: 10.1007/s10735-017-9711-x
25. Ti D, Hao H, Tong C, et al. LPS-preconditioned mesenchymal stromal cells modify macrophage polarization for resolution of chronic inflammation via exosome-shuttled let-7b. *J Transl Med*. 2015;13:308. doi: 10.1186/s12967-015-0642-6
26. Zhang J, Guan J, Niu X, et al. Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis. *J Transl Med*. 2015;13:49. doi: 10.1186/s12967-015-0417-0
27. Hu L, Wang J, Zhou X, et al. Exosomes derived from human adipose mensenchymal stem cells accelerates cutaneous wound healing via optimizing the characteristics of fibroblasts. *Sci Rep*. 2016;6:32993. doi: 10.1038/srep32993
28. Wang M, Wang C, Chen M, et al. Efficient angiogenesis-based diabetic wound healing/skin reconstruction through bioactive antibacterial adhesive ultraviolet shielding nanodressing with exosome release. *ACS Nano*. 2019;13:10279-10293. doi: 10.1021/acsnano.9b03656
29. Shabbir A, Cox A, Rodriguez-Menocal L, Salgado M, Van Badiavas E. Mesenchymal stem cell exosomes induce proliferation and migration of normal and chronic wound fibroblasts, and enhance angiogenesis in vitro. *Stem Cells Dev*. 2015;24:1635-1647. doi: 10.1089/scd.2014.0316
30. Zhang B, Wang M, Gong A, et al. HucMSC-exosome mediated-Wnt4 signaling is required for cutaneous wound healing. *Stem Cells*. 2015;33:2158-2168. doi: 10.1002/stem.1771
31. Zhang K, Zhao X, Chen X, et al. Enhanced therapeutic effects of mesenchymal stem cell-derived exosomes with an injectable hydrogel for hindlimb ischemia treatment. *ACS Appl Mater Interfaces*. 2018;10:30081-30091. doi: 10.1021/acsami.8b08449
32. Cooper DR, Wang C, Patel R, et al. Human adipose-derived stem cell conditioned media and exosomes containing MALAT1 promote human dermal fibroblast migration and ischemic wound healing. *Adv Wound Care (New Rochelle)*. 2018;7:299-308. doi: 10.1089/wound.2017.0775
33. Hoang DH, Nguyen TD, Nguyen HP, et al. Differential wound healing capacity of mesenchymal stem cell-derived exosomes originated from bone marrow, adipose tissue and umbilical cord under serum and xeno-free condition. *Front Mol Biosci*. 2020;7:119. doi: 10.3389/fmolb.2020.00119
34. Irons RF, Cahill KW, Rattigan DA, et al. Acceleration of diabetic wound healing with adipose-derived stem cells, endothelial-differentiated stem cells, and topical conditioned medium therapy in a swine model. *J Vasc Surg*. 2018;68:115S–125S. doi: 10.1016/j.jvs.2018.01.065

35. Shi R, Jin Y, Hu W, 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 Physiol Cell Physiol*. 2020;318:C848-C856. doi: 10.1152/ajpcell.00041.2020
36. Ding J, Wang X, Chen B, Zhang J, Xu J. Exosomes derived from human bone marrow mesenchymal stem cells stimulated by deferoxamine accelerate cutaneous wound healing by promoting angiogenesis. *Biomed Res Int*. 2019;2019:9742765. doi: 10.1155/2019/9742765
37. Narauskaite D, Vydmantaite G, Rusteikaite J, et al. Extracellular vesicles in skin wound healing. *Pharmaceuticals (Basel)*. 2021;14:811. doi: 10.3390/ph14080811
38. Jiang T, Wang Z, Sun J. Human bone marrow mesenchymal stem cell-derived exosomes stimulate cutaneous wound healing mediates through TGF-β/Smad signaling pathway. *Stem Cell Res Ther*. 2020;11:198. doi: 10.1186/s13287-020-01723-6
39. Wang X, Jiao Y, Pan Y, et al. Fetal dermal mesenchymal stem cell-derived exosomes accelerate cutaneous wound healing by activating notch signaling. *Stem Cells Int*. 2019;2019:2402916. doi: 10.1155/2019/2402916
40. Zhou Y, Zhao B, Zhang XL, et al. Combined topical and systemic administration with human adiposederived mesenchymal stem cells (hADSC) and hADSC-derived exosomes markedly promoted cutaneous wound healing and regeneration. *Stem Cell Res Ther*. 2021;12:257. doi: 10.1186/s13287-021-02287-9
41. An Y, Lin S, Tan X, et al. Exosomes from adipose-derived stem cells and application to skin wound healing. *Cell Prolif*. 2021;54:e12993. doi: 10.1111/cpr.12993
42. Bryan NS, Grisham MB. Methods to detect nitric oxide and its metabolites in biological samples. *Free Radic Biol Med*. 2007;43:645-657. doi: 10.1016/j.freeradbiomed.2007.04.026
43. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. *Nat Rev Drug Discov*. 2008;7:156-167. doi: 10.1038/nrd2466
44. Taddei S, Virdis A, Ghiadoni L, et al. Age-related reduction of NO availability and oxidative stress in humans. *Hypertension*. 2001;38:274-279. doi: 10.1161/01.hyp.38.2.274
45. Banga AK, Bose S, Ghosh TK. Iontophoresis and electroporation: comparisons and contrasts. *Int J Pharm*. 1999;179:1-19. doi: 10.1016/s0378-5173(98)00360-3
46. Mitragotri S, Kost J. Low-frequency sonophoresis: a review. *Adv Drug Deliv Rev*. 2004;56:589-601. doi: 10.1016/j.addr.2003.10.02
47. Wiklander OP, Nordin JZ, O'Loughlin A, et al. Extracellular vesicle in vivo biodistribution is determined by cell source, route of administration and targeting. *J Extracell Vesicles*. 2015;4:26316. doi: 10.3402/jev.v4.26316
48. Swanson WB, Gong T, Zhang Z, Eberle M, Niemann D, Dong R. Controlled release of odontogenic exosomes from a biodegradable vehicle mediates tooth repair in rats. *J Control Release*. 2020;324:679-694. doi: 10.1016/j.jconrel.2020.06.006
49. Born LJ, Chang KH, Shoureshi P, et al. HOTAIR-loaded mesenchymal stem/stromal cell extracellular vesicles enhance angiogenesis and wound healing. *Adv Healthc Mater*. 2022;11:2002070. doi: 10.1002/adhm.202002070
50. Moghadasi S, Elveny M, Rahman HS, et al. A paradigm shift in cell-free approach: the emerging role of MSCs-derived exosomes in regenerative medicine. *J Transl Med*. 2021;19:302. doi: 10.1186/s12967-021-02980-6
51. Tao SC, Guo SC, Li M, et al. 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 Transl Med*. 2017;6:736-747. doi: 10.5966/sctm.2016-0275
52. Lener T, Gimona M, Aigner L, et al. Applying extracellular vesicles based therapeutics in clinical trials—an ISEV position paper. *J Extracell Vesicles*. 2015;4:30087. doi: 10.3402/jev.v4.30087
53. Lou G, Chen Z, Zheng M, Liu Y. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. *Exp Mol Med*. 2017;49:e346. doi: 10.1038/emm.2017.63
54. Witwer KW, Van Balkom BWM, Bruno S, et al. Defining mesenchymal stromal cell (MSC)-derived small extracellular vesicles for therapeutic applications. *J Extracell Vesicles*. 2019;8:1609206. doi: 10.1080/20013078.2019.1609206
55. Hassanzadeh A, Rahman HS, Markov A, et al. Mesenchymal stem/stromal cell-derived exosomes in regenerative medicine and cancer; overview of development, challenges, and opportunities. *Stem Cell Res Ther*. 2021;12:297. doi: 10.1186/s13287-021-02378-7
56. Chernoff G. The utilization of human placental, fetal mesenchymal stem cell derived-exosomes in treating keloid scars. *J Surg*. 2022;7:1482. doi: 10.29011/2575-9760.001482
57. Bruno S, Grange C, Deregibus MC, et al. Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. *J Am Soc Nephrol*. 2009;20:1053-1067. doi: 10.1681/ASN.2008070798
58. Antimisiaris SG, Mourtas S, Marazioti A. Exosomes and exosome-inspired vesicles for targeted drug delivery. *Pharmaceutics*. 2018;10:218. doi: 10.3390/pharmaceutics10040218