Mesenchymal Stem Cell-Derived Extracellular Vesicles for Tissue Repair Across Multiple Body Systems: A Narrative Review

Running Title: MSC-Derived EVs: Multimodal Tissue Repair

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Abstract

Mesenchymal stem cell (MSC)-derived extracellular vesicles (EVs), operationally referred to as "exosomes" when meeting established size and biogenesis criteria, have emerged as potent cell-free therapeutic agents across diverse tissue systems. This narrative review synthesizes 40 peer-reviewed studies (2017–2026) identified through PubMed, evaluating MSC-EV efficacy across four body systems: orthopedic/musculoskeletal, neurological, cardiac, and integumentary (wound/skin). Study designs ranged from in vitro mechanistic analyses and small animal models to large animal preclinical studies and systematic meta-analyses. Across all four systems, MSC-derived EVs consistently reduced tissue inflammation, suppressed apoptosis, promoted angiogenesis, and activated regenerative signaling cascades including Wnt/β-catenin, PI3K/AKT, TGF-β/Smad, and Nrf2/HO-1 pathways. A preclinical meta-analysis of 37 randomized controlled animal MI trials demonstrated a mean ejection fraction improvement of +11.89% (95% CI: 9.44–14.34) with MSC-derived EVs versus controls. Engineered and preconditioned EV preparations consistently outperformed native exosomes. GMP-compatible manufacturing processes including anion exchange chromatography purification and lyophilization with trehalose have been validated. Umbilical cord and Wharton's Jelly-derived MSC-EVs represent particularly favorable sources given their ethical accessibility and favorable immunogenicity profile. These findings collectively support advancement of MSC-derived EVs toward formal clinical investigation.

Keywords: extracellular vesicles; mesenchymal stem cells; exosomes; tissue regeneration; cell-free therapy; wound healing; myocardial infarction

1. Introduction

Extracellular vesicles (EVs) are membrane-enclosed nanoparticles secreted by virtually all cell types that transfer proteins, nucleic acids, and lipids between cells, regulating diverse biological processes [1]. Within the EV family, "exosomes" refer operationally to small EVs (typically 30–150 nm) of endosomal origin characterized by tetraspanin markers (CD9, CD63, CD81) and endosomal sorting complex required for transport (ESCRT) machinery involvement; per International Society for Extracellular Vesicles (ISEV) guidance, the generic term "extracellular vesicles (EVs)" is preferred unless endosomal biogenesis is formally demonstrated [2]. Throughout this review, "exosome" and "MSC-EV" are used interchangeably in accordance with cited source terminology, with the understanding that the preparations described are operationally defined small EVs.

Mesenchymal stem cells (MSCs), derived from bone marrow, adipose tissue, umbilical cord (Wharton's Jelly), placenta, and other sources, have been investigated for tissue regeneration for over two decades. However, direct MSC transplantation carries risks of immune rejection, tumorigenicity, embolism, and inconsistent engraftment [3]. Emerging evidence across hundreds of preclinical studies indicates that the therapeutic benefit of MSC transplantation is mediated primarily through paracrine secretion rather than direct cell engraftment, with EVs identified as the dominant effector [4]. MSC-derived EVs replicate the anti-inflammatory, pro-angiogenic, anti-apoptotic, and immunomodulatory properties of parent cells while offering advantages including stability, storage feasibility, scalability, and elimination of viable cell administration risks [3,5].

Regulatory classification of MSC-derived EVs is an active area of global policy development. In the United States, the FDA Center for Biologics Evaluation and Research (CBER) regulates these products as biologics under Section 351(a) of the Public Health Service (PHS) Act, requiring an Investigational New Drug (IND) application before clinical use and a Biologics License Application (BLA) for marketing approval. This regulatory pathway mandates rigorous Chemistry, Manufacturing, and Controls (CMC) documentation, clinical safety and efficacy demonstration, and Good Manufacturing Practice (GMP) compliance [6]. The regulatory and operational case for Wharton's Jelly-derived MSC exosomes manufactured under this framework has been previously established by the authors of this review, who identified WJ-MSC exosomes as the most scientifically advanced and regulatory-compliant class of regenerative biologic products currently available in the United States when produced under cGMP conditions with a Drug Master File (DMF) Type II designation and third-party batch virology testing [47,48].

Despite this regulatory framework, the preclinical evidence base for MSC-derived EVs has grown substantially across multiple tissue systems. The objective of this narrative review is to synthesize 40 peer-reviewed studies across orthopedic/musculoskeletal, neurological, cardiac, and wound/skin indications, identify converging mechanisms of action, characterize delivery and manufacturing advances, and assess the collective readiness of the evidence base to support clinical translation and regulatory engagement. This review extends the authors' prior analysis

[47,48] by grounding the regulatory case for WJ-MSC exosomes in a comprehensive body-system-by-body-system synthesis of the preclinical literature.

2. Methods

2.1 Literature Search Strategy

A structured literature search was conducted in PubMed/MEDLINE through April 2026. Search terms included combinations of: "mesenchymal stem cell exosomes," "MSC extracellular vesicles," "MSC-derived EVs," paired with indication-specific terms: "intervertebral disc degeneration," "osteoarthritis," "musculoskeletal," "spinal cord injury," "neurological," "myocardial infarction," "cardiac repair," "wound healing," "skin regeneration," and "alopecia." No publication date restriction was applied, although the final corpus spans 2017–2026. Language was restricted to English.

2.2 Inclusion and Exclusion Criteria

Studies were included if they: (1) evaluated MSC-derived EVs or exosomes as the primary intervention; (2) reported quantitative outcomes in in vitro systems, animal models, or clinical participants; or (3) were systematic reviews or meta-analyses synthesizing preclinical or clinical MSC-EV data. Studies evaluating non-MSC EV sources alone, or MSC whole-cell therapy without an EV-specific comparator or arm, were excluded. Review articles were included when they provided mechanistic synthesis or regulatory/translational framing not captured by primary studies.

2.3 Data Extraction and Organization

For each included study, the following data were extracted: first author, institution, publication year, journal, PMID, DOI, study design (in vitro, in vivo model, review, meta-analysis), MSC source, EV preparation method, delivery route, primary outcome measures, key findings, and translational or regulatory significance. Studies were organized by body system for narrative synthesis.

2.4 Terminology

In accordance with ISEV Minimal Information for Studies of Extracellular Vesicles (MISEV2018) guidelines, "extracellular vesicles (EVs)" is used as the generic term throughout this review. Source-specific terminology from cited studies (e.g., "exosomes," "small EVs," "nanovesicles") is preserved in descriptions of individual studies to maintain fidelity to primary source reporting.

3. Results

3.1 Orthopedic and Musculoskeletal Applications

Ten studies addressing MSC-derived EV applications in orthopedic and musculoskeletal (MSK) conditions were identified, spanning intervertebral disc degeneration (IVDD), osteoarthritis (OA), bone repair, tendon, and cartilage regeneration (Table 1). Study designs included five original research articles employing in vitro and in vivo models and five comprehensive reviews.

Intervertebral disc degeneration was the most investigated MSK condition. Jin et al. (2024) demonstrated that hypoxia-preconditioned bone marrow MSC (BMSC)-derived exosomes delivered BNIP3-enriched cargo to nucleus pulposus cells (NPCs), activating mitophagy via the BNIP3/ANXA2/TFEB axis. This restored mitochondrial quality control and delayed NPC aging in a rat IVDD model, with treated discs showing preserved extracellular matrix (ECM) synthesis versus controls [7]. Xia et al. (2019) further established anti-inflammatory and anti-oxidant mechanisms in disc tissue, demonstrating that MSC-exosomes suppressed NLRP3 inflammasome activation in hydrogen peroxide-injured NPCs, reduced reactive oxygen species (ROS) production, and restored mitochondrial function; intradiscal exosome injection in rabbits significantly slowed degenerative progression on MRI [8]. Liao et al. (2019) reported that MSC-exosomes reduced advanced glycation end-product (AGE)-induced endoplasmic reticulum (ER) stress and NPC apoptosis via AKT and ERK signaling pathway activation in a rat tail IVDD model, representing the first demonstration of MSC-exosome modulation of ER stress in intervertebral disc disease [9]. Chen et al. (2025) extended these findings by showing that exosomal miR-223-3p from MSCs targets FBXW7, suppressing TNF-alpha-induced NPC apoptosis (17.64% vs. 26.58% in TNF-alpha group); intradiscal injection improved Pfirrmann MRI grade, disc height index, and histology in a rat caudal IDD model [10].

In osteoarthritis, Liu et al. (2024) demonstrated that MSC-derived EVs from infrapatellar fat pad, purified by anion exchange chromatography (AEX), suppressed OA progression in an ACL-transection mouse model. Weekly intra-articular injections improved gait metrics, reduced OARSI scores, preserved Type II collagen, decreased MMP13 and ADAMTS5, reduced osteophyte formation, and suppressed synovial M1 macrophage polarization. Importantly, AEX purification is a GMP-scalable approach [11]. Liu et al. (2022) demonstrated that exosomes from stem cells overexpressing miR-140-5p enhanced chondrocyte proliferation and migration, reduced apoptosis, and increased collagen II and aggrecan secretion by targeting VEGFA; intra-articular injection in a rat OA model enhanced cartilage regeneration and subchondral bone remodeling compared to unmodified exosomes [12].

Review evidence consolidated the breadth of MSK application and translational barriers. Teo et al. (2023) synthesized evidence for MSC-derived small EVs in cartilage, bone, tendon, and disc repair, identifying lipid, protein, and nucleic acid cargo as drivers of therapeutic effects and highlighting clinical translation challenges including scale-up, potency assays, delivery optimization, and regulatory classification [13]. Gerami et al. (2023) reviewed MSC-exosome mechanisms across OA, bone fractures, osteoporosis, tendon injury, and disc degeneration,

identifying miRNA cargo (miR-21, miR-23, miR-125b) as key mediators and confirming that MSC-EV therapy avoids cell-therapy immunogenicity concerns [14]. Malekpour et al. (2021) provided comprehensive foundational coverage confirming that exosomes replicate MSC function as cell-free agents across ECM remodeling applications [15]. Fang and Vangsness (2024) specifically addressed manufacturing and preservation, identifying lyophilization with 50 mM or 4% trehalose as optimal for EV preservation without aggregation at room temperature, with direct applicability to off-the-shelf product development under a BLA pathway [16].

3.2 Neurological Applications

Ten studies addressed MSC-derived EV applications in neurological conditions, with a primary focus on spinal cord injury (SCI) and secondary coverage of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), traumatic brain injury (TBI), and stroke.

In SCI, Bian et al. (2026) demonstrated that hypoxic preconditioning enriched miR-615-3p in BMSC exosomes, which targeted PDE4C to activate the cAMP/PKA pathway in SCI neurons, reducing calcium overload and ER stress. In a mouse SCI model, treated animals showed improved locomotor function, reduced lesion volume, attenuated edema, and decreased inflammation over 14 days [17]. This study is notable for demonstrating that hypoxic conditioning, a GMP-feasible manufacturing enhancement requiring no genetic modification, materially improves EV therapeutic potency.

Lee et al. (2020) addressed the critical limitation of poor CNS targeting with native exosomes by engineering macrophage membrane-fused MSC nanovesicles (MF-NVs). These constructs showed superior targeting to injured spinal cord versus unmodified nanovesicles after systemic injection, attenuated apoptosis and inflammation, prevented axonal loss, enhanced angiogenesis, decreased fibrosis, and improved function in SCI mice, establishing systemic IV delivery as a viable route when targeting is adequately addressed [18]. Shaikh et al. (2024) demonstrated that UC-MSC exosomes loaded with the CB2 receptor agonist AM1241 improved motor recovery in SCI mice by activating Nrf2/HO-1 signaling, boosting antioxidant defense (SOD, GSH) while reducing proinflammatory cytokines and apoptotic proteins, illustrating the potential for drug-loaded exosomes to amplify therapeutic effect beyond native preparations [19].

Kodali et al. (2019) provided direct evidence for intranasal EV delivery, demonstrating that unilateral intranasal administration of hMSC-EVs produced bilateral distribution across virtually all forebrain regions within six hours in both intact and seizure-injured rats, with EV incorporation by neurons being higher in injury areas (CA1, entorhinal cortex), suggesting injury-directed targeting [20]. This delivery route is noninvasive, repeatable, and relevant for TBI, stroke, and neurodegenerative applications.

Review synthesis by Schepici et al. (2023) documented how MSC-exosomes maintain blood-spinal cord barrier integrity, promote angiogenesis, reduce apoptosis, suppress neuroinflammation, and stimulate axonal regeneration across animal SCI models [21]. Liao et al. (2025) reviewed

genetic engineering and chemical pretreatment strategies to optimize exosome yield and targeting for SCI, covering hypoxia preconditioning, cytokine priming, gene modification, and hydrogel-exosome combination strategies for sustained delivery [22]. Zeng (2023) provided comprehensive mechanistic context for MSC-mediated SCI repair, covering neuroprotection via growth factor secretion, neuronal differentiation, angiogenesis, immunomodulation, and glial scar reduction [23]. Herbert et al. (2022) addressed safety concerns and clinical trial considerations, supporting hydrogel-delivery formats for next-generation IND protocols [24].

Broader neurological coverage was provided by Guy and Offen (2020), who reviewed MSC-exosome outcomes across Alzheimer's, Parkinson's, ALS, MS, TBI, stroke, and SCI animal models, identifying ALS and Alzheimer's as priority next indications after SCI [25]. Giovannelli et al. (2023) critically examined GMP manufacturing challenges including scalability, batch consistency, formulation, storage, quality controls, and cost for neurodegenerative disease applications, directly addressing market access and CBER submission considerations [26].

3.3 Cardiac Applications

Ten studies addressed MSC-derived EV applications in cardiac disease, primarily myocardial infarction (MI). The cardiac body of evidence is the most quantitatively mature, with a published systematic review and meta-analysis providing pooled effect size estimates from 37 randomized controlled preclinical trials.

Khan et al. (2022) conducted a systematic review and meta-analysis of 37 preclinical randomized controlled animal MI trials, demonstrating an overall EV-treated versus control ejection fraction mean difference (MD) of +10.85% (95% CI: 8.79–12.90) and fractional shortening MD of +7.19% (95% CI: 5.43–8.96). MSC-derived EVs specifically showed the strongest improvement: EF MD = +11.89% (95% CI: 9.44–14.34) [27]. An improvement of approximately 12% in ejection fraction exceeds the threshold for clinical meaningfulness and establishes MSC-EVs as the leading EV source for cardiac indication.

Mechanistic and translational advances have been substantial. Zhao et al. (2025) demonstrated in a porcine post-MI model that autologous PBMSC exosomes combined with renal sympathetic denervation produced 11–26% higher ejection fraction versus single-treatment groups at 90 days, with improved survival and reduced fibrosis mediated through transfer of the miR-141-200-429 cluster, activating Wnt/beta-catenin signaling in ischemic cardiomyocytes via Dkk1 suppression and GSK3beta phosphorylation [28]. Large animal (porcine) data with 90-day follow-up from an autologous sourcing model represents the highest available translational evidence class. Tzng et al. (2025) from Stanford conducted a head-to-head comparison of iPSC-cardiomyocyte exosomes versus MSC exosomes in a porcine ischemia-reperfusion model, finding MSC-exosome strengths in anti-inflammatory activity, structural stabilization, and ECM remodeling, while iPSC-CM exosomes showed superiority in metabolic and cardiomyocyte-specific effects [29].

Two studies demonstrated the advantages of biomaterial-based delivery. Yan et al. (2024) showed that a conductive polypyrrole-chitosan hydrogel loaded with human endometrial MSC-derived

exosomes improved post-MI cardiac function, reduced ventricular remodeling and fibrosis, promoted angiogenesis, and inhibited apoptosis via EGF/PI3K/AKT signaling, while the conductive hydrogel resynchronized cardiac electrical transmission and reduced arrhythmia [30]. Chen et al. (2025) demonstrated that sodium alginate hydrogel co-loaded with BMSC-derived EVs and p38alpha antagonistic peptide reduced myocardial fibrosis and improved cardiac performance in a murine MI model, establishing a novel anti-fibrotic combination strategy suitable for catheter-based delivery [31]. Yuan et al. (2023) applied miR-29b-loaded UC-MSC exosomes via a gelatin microneedle patch directly to infarcted myocardium, achieving reduced inflammation, smaller infarct size, inhibited fibrosis, and improved cardiac function; the microneedle patch improved exosome retention in myocardium versus direct injection [32].

Pan et al. (2023) provided comprehensive mechanistic review across atherosclerosis, MI, heart failure, ischemia-reperfusion, aneurysm, and stroke, confirming apoptosis inhibition, inflammation regulation, cardiac remodeling attenuation, and angiogenesis promotion as primary MSC-EV mechanisms and documenting superior biocompatibility versus whole-cell therapy [33]. Joladarashi and Kishore (2022) reviewed bioengineering strategies to control exosome cargo by manipulating parental cells, validating engineered exosomes for MI and HF as priority commercial targets [34]. Yang et al. (2024) contextualized MSC exosome therapy within the historical progression from direct cell injection to current exosome-based approaches [35]. Suzuki et al. (2017) established the foundational mechanistic basis, demonstrating that BMMSCs exert cardioprotective effects primarily via paracrine secretion, with exosomes as the key effector [36].

3.4 Wound and Skin Applications

Ten studies addressed MSC-derived EV applications in wound healing, skin regeneration, and hair loss conditions. This body of evidence encompasses the broadest range of delivery systems and the most direct GMP manufacturing documentation of any body system reviewed.

Diabetic wound healing represents a major unmet need, with 6.5 million chronic wounds annually in the United States. Zhang et al. (2025) demonstrated 97.4% wound closure at 14 days in type II diabetic rats treated with UC-MSC exosomes loaded into a thermosensitive porcine acellular dermal matrix (dECM) hydrogel, versus significantly lower closure in controls. Transcriptomics revealed upregulation of PI3K-Akt and ECM-receptor pathways and downregulation of insulin resistance genes, with increased CD31+ vessel density, M2 macrophage polarization, and Ki67+ proliferation [37]. Jiang et al. (2020) demonstrated that hBM-MSC exosomes accelerated full-thickness wound healing in rats by shifting TGF-beta signaling from pro-fibrotic (TGF-beta1, Smad2/3/4) to pro-regenerative (TGF-beta3, Smad7), a critical mechanism for scar-free wound healing [38].

Lee et al. (2023) demonstrated that adipose-derived MSC exosomes combined with hyaluronic acid achieved superior wound closure in a porcine wound model (the most clinically relevant skin model) with increased re-epithelialization and collagen type III deposition; in a mouse dermal filler model, the combination produced thicker tissue layers, increased vascularization, and higher collagen content [39]. Li et al. (2022) confirmed that ADMSC exosomes promote fibroblast

migration and proliferation via WNT/beta-catenin signaling, with pathway dependence confirmed by WNT inhibitor (XAV939) rescue studies [40]. Jin et al. (2021) identified that peroxiredoxin II (Prx II), mediated via miR-21-5p and miR-221, protects dermal MSCs from ROS-induced apoptosis, with Prx II-expressing MSC exosomes demonstrating significantly greater wound healing than Prx II-knockout counterparts, highlighting the importance of antioxidant cargo in oxidatively stressed wound microenvironments [41].

GMP manufacturing documentation for wound-healing exosomes was provided by Lee et al. (2025), who reported the first published GMP production of umbilical cord blood MSC-released exosomes with full quality control per Korean MFDS guidelines. UCB-MSC exosomes promoted dermal fibroblast and keratinocyte proliferation and migration, suppressed pro-inflammatory mediators, and accelerated wound healing in a mouse model. The GMP documentation presented is directly applicable to FDA CMC submissions [42]. Hu et al. (2019) demonstrated that 3D spheroid-cultured human dermal fibroblast exosomes outperformed bone marrow MSC exosomes in collagen induction and photoaging reversal, with needle-free injector delivery increasing procollagen type I, decreasing MMP-1, and elevating TGF-beta [43].

In androgenetic alopecia and hair loss, Yu et al. (2025) demonstrated that HUCMSC exosomes enriched with miR-21-5p and let-7b-5p activated Wnt/beta-catenin signaling in human dermal papilla cells by targeting Cyclin D1, c-MET, and LEF1, promoting hair follicle anagen entry in a DHT-induced mouse alopecia model [44]. Li et al. (2022) showed that ADSC exosomes promoted hair regrowth via TNF-alpha pathway downregulation and Wnt/beta-catenin activation in an additive effect with minoxidil, suggesting combination product potential [45]. Narauskaite et al. (2021) synthesized the mechanistic role of EVs across all four wound healing phases (hemostasis, inflammation, proliferation, remodeling), documenting how EVs modulate macrophage polarization, fibroblast activation, keratinocyte migration, and angiogenesis across delivery systems [46].

4. Discussion

4.1 Converging Mechanisms of Action Across Body Systems

A central finding of this review is the convergence of core signaling mechanisms across all four body systems examined. The Wnt/beta-catenin pathway was activated in disc NPCs [7], OA chondrocytes [12], cardiac cardiomyocytes [28], hair follicle dermal papilla cells [44], and wound fibroblasts [40]. Similarly, anti-apoptotic signaling involving Bcl-2 upregulation and Bax/Caspase-3 downregulation was reported across disc [10], neurological [19], and cardiac [30] indications. The PI3K/AKT pathway, activated in cardiac [30] and diabetic wound [37] models, represents another convergent regenerative signal. This mechanistic convergence supports the concept of a platform MSC-EV product with potential applicability across multiple therapeutic indications, which has significant implications for CMC development, potency assay design, and regulatory strategy.

Anti-inflammatory activity, uniformly present across all four systems, is mediated through multiple mechanisms including NLRP3 inflammasome suppression [8], M1-to-M2 macrophage polarization [11,37], TNF-alpha pathway downregulation [45], and Nrf2/HO-1 antioxidant activation [19,41]. This breadth of anti-inflammatory mechanism suggests that the immunomodulatory cargo of MSC-derived EVs is both potent and redundant, which is favorable from a robustness standpoint but complicates identification of a single potency-indicating assay for regulatory purposes.

4.2 Role of EV Engineering and Preconditioning

Across all four body systems, engineered and preconditioned EV preparations consistently outperformed native unmodified exosomes. Hypoxic preconditioning, which requires no genetic modification and is feasible under GMP conditions, enriched therapeutic miRNA cargo in both BMSC exosomes for IVDD [7] and SCI [17]. MiRNA loading via electroporation (miR-29b in cardiac [32]) and cargo enhancement via 3D spheroid culture [43] represent additional manufacturing strategies with GMP scalability. Macrophage membrane fusion for improved CNS targeting [18] and drug co-loading with CB2 agonists [19] or p38alpha antagonists [31] demonstrate that exosomes can serve as tunable delivery vehicles for small molecule co-therapeutics. The consistent superiority of engineered EVs over native preparations is an important regulatory consideration: potency specifications and release criteria must account for the additional complexity introduced by engineering steps.

4.3 Manufacturing and Preservation Advances

GMP-compatible manufacturing processes have been validated across several studies in this review. AEX purification has been demonstrated for MSC-EVs in an OA context [11] and is recognized as a scalable alternative to ultracentrifugation. Lyophilization with 50 mM or 4% trehalose has been identified as optimal for EV preservation without aggregation at room temperature, enabling room-temperature shipping and off-the-shelf product formats essential for commercial viability under a BLA pathway [16]. Full GMP production of UCB-MSC exosomes

with Korean MFDS-compliant quality controls has been published [42], providing a template directly applicable to FDA CMC submissions. Collectively, these manufacturing advances address a primary barrier to IND filing that has historically separated MSC-EV from clinical readiness.

4.4 Evidence Hierarchy and Translational Readiness

The cardiac body of evidence is the most mature by evidence hierarchy, anchored by a systematic review and meta-analysis of 37 randomized controlled preclinical trials demonstrating an MSC-EV EF improvement of +11.89% (95% CI: 9.44–14.34) [27] and supported by multiple porcine large animal studies [28,29]. The orthopedic and wound healing evidence bases are intermediate, with multiple well-designed in vivo original research studies across rodent and porcine models. The neurological evidence base, while robust in total study count, relies more heavily on reviews and single-injury-model in vivo studies; the intranasal delivery biodistribution data [20] and hypoxia-conditioned exosome SCI data [17] represent important mechanistic advances supporting translational readiness.

4.5 MSC Source Considerations

Multiple MSC sources are represented across this review: bone marrow (BMSC), adipose (ADSC), umbilical cord (UC-MSC/HUCMSC), umbilical cord blood (UCB-MSC), endometrial (hEMSC), peripheral blood (PBMSC), and human urine-derived stem cells. Wharton's Jelly-derived and umbilical cord-derived MSCs emerged as particularly favorable sources given birth tissue accessibility, ethical sourcing without invasive procurement, large yield, and established immune privilege of neonatal-origin cells [47,48]. The HUCMSC source used in androgenetic alopecia [44] and the UC-MSC source used in wound healing [37] and SCI [19] are directly aligned with Wharton's Jelly MSC platforms under active cGMP development under a 351(a) framework. The superior immunological safety profile, neonatal-origin immune naivety, and favorable scalability of Wharton's Jelly-derived MSC exosomes have been characterized in detail by Hillman and Janani [47,48], who further established the regulatory compliance architecture — Drug Master File designation, cryogenic storage, glass-container shipping, and third-party virology testing — required for commercial BLA-track manufacturing. The autologous PBMSC approach [28] eliminates allogeneic concerns but requires same-day procurement, which limits scalability relative to allogeneic Wharton's Jelly platforms.

4.6 Limitations

This review has several limitations. First, as a narrative rather than systematic review, study selection, while curated through PubMed, was not exhaustive and was informed by clinical and translational relevance criteria. Second, the 40 studies reviewed are predominantly from non-US institutions, which is a function of publication landscape in this field rather than exclusionary intent. Third, the evidence base remains entirely preclinical for most indications; no clinical trial results are included, as no Phase I/II/III trials of MSC-derived EVs were identified with published outcomes meeting inclusion criteria at the time of compilation. Fourth, significant heterogeneity exists in EV preparation methods, dosing regimens, administration routes, and outcome measures

across studies, precluding quantitative pooling outside the cardiac meta-analysis. Fifth, publication bias toward positive results is explicitly noted by the cardiac meta-analysis authors [27] and likely applies across all body systems. Finally, regulatory guidance on potency assays and release criteria for MSC-derived EV biologics is still evolving, and the CMC implications discussed herein reflect current guidance as of April 2026.

5. Conclusion

This narrative review of 40 peer-reviewed studies demonstrates that MSC-derived extracellular vesicles exert consistent, reproducible, and mechanistically coherent therapeutic effects across orthopedic/musculoskeletal, neurological, cardiac, and wound/skin indications. The evidence base is strongest in the cardiac domain, where a meta-analysis of 37 preclinical trials demonstrates a clinically meaningful mean ejection fraction improvement of nearly 12% with MSC-derived EVs. Converging pathway activation including Wnt/beta-catenin, PI3K/AKT, TGF-beta/Smad, and Nrf2/HO-1 signaling across diverse tissue types supports the concept of a platform MSC-EV product. Engineering and preconditioning consistently enhances EV potency above native preparations. GMP-compatible manufacturing, including AEX purification and trehalose lyophilization, has been validated, and full GMP production documentation has been published for wound-healing applications.

Taken together, this body of evidence supports formal pre-IND engagement with CBER, submission of a Phase I IND for a lead indication with the strongest translational evidence package, and parallel CMC development for an allogeneic Wharton's Jelly-derived MSC-EV product. The regulatory and manufacturing infrastructure required for this pathway — including cGMP production, DMF Type II filing, cryogenic formulation, and third-party virology testing — has been characterized in prior work by the authors of this review [47,48]. The consistency of safety signals across preclinical studies and the absence of serious adverse events attributable to MSC-derived EV administration in the reviewed literature support the risk-benefit case for first-in-human investigation. Cardiac or wound healing applications represent lead indications based on evidence maturity, with orthopedic applications as near-term secondary indications given existing clinical delivery infrastructure.

Declarations

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Author Contributions

Andrew Jonathan Hillman: Conceptualization, methodology, investigation, data curation, writing – original draft, writing – review and editing.

Keyon Janani, Ph.D.: Supervision, validation, writing – review and editing.

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[Authors declare no competing interests. OR: Author [Name] discloses the following: [relationship, entity, nature of interest]. All other authors declare no competing interests.]

Ethics Statement

This manuscript is a narrative review of published literature. No original animal or human participant data were generated or analyzed by the authors. Ethics approval was not required for this study type.

Data Availability Statement

No new data were generated or analyzed in support of this research. All data discussed in this review are from publicly available published studies accessible via PubMed/MEDLINE. Full citation information including DOI and PMID is provided in the References section.

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