

Extracellular vesicles: Revolutionizing pharmacoscience and biomedical applications.

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Introduction

Extracellular vesicles (EVs) are lipid bilayer-enclosed nanoparticles secreted by virtually all cell types, carrying proteins, nucleic acids, lipids, and metabolites that reflect their cell of origin. Over the past decade, EVs have garnered intense interest in pharmacoscience and biomedical research due to their inherent ability to mediate intercellular communication and modulate physiological processes. As natural carriers of bioactive molecules, they present unique opportunities for drug delivery, biomarker discovery, and therapeutic intervention. This article explores the biology of EVs, their applications in pharmacoscience, and emerging roles in diverse biomedical fields [1].

EVs can be broadly categorized into three main subtypes based on their biogenesis and size. Exosomes (30–150 nm): Formed within endosomal compartments (multivesicular bodies) and released via exocytosis. Exosomes carry tetraspanins (e.g., CD9, CD63, CD81), heat-shock proteins, and various RNAs, reflecting specialized sorting mechanisms. Microvesicles (100–1,000 nm): Shed directly from the plasma membrane through outward budding. These vesicles often contain cytoskeletal proteins (actin, tubulin), integrins, and signaling lipids that facilitate communication with recipient cells. Apoptotic Bodies (>1,000 nm): Generated during programmed cell death, harboring nuclear fragments, organelles, and larger protein aggregates. Although less studied in drug delivery contexts, apoptotic bodies can influence immune responses and tissue remodeling [2].

EV biogenesis involves intricate intracellular pathways: the endosomal sorting complexes required for transport (ESCRT) machinery orchestrates exosome formation, while alterations in plasma membrane lipid composition (e.g., ceramide generation) promote microvesicle shedding. Once released, EVs traverse biological fluids—blood, cerebrospinal fluid, urine—protected from enzymatic degradation by their lipid membrane [3].

Biocompatibility and Low Immunogenicity: Since they derive from endogenous cells, EVs are generally well tolerated and evade rapid clearance, in contrast to synthetic nanoparticles. **Intrinsic Targeting Ability:** Surface proteins on EVs can preferentially bind specific receptors on recipient cells. For example, tumor-derived exosomes often home to metastatic niches, making them suitable for targeted oncology therapeutics [4].

Cargo Versatility: EVs can be loaded with small-molecule drugs, siRNA/miRNA, proteins, or CRISPR–Cas components. Passive loading (incubation) or active methods (electroporation, sonication) enable incorporation of hydrophilic and hydrophobic agents [5].

Recent pharmacoscience studies have demonstrated the successful loading of doxorubicin into mesenchymal-stem-cell-derived exosomes, achieving enhanced cytotoxicity against breast cancer cells with reduced off-target effects. Similarly, exosomes engineered to carry anti-inflammatory cytokines or small interfering RNAs (siRNAs) show promise for treating rheumatoid arthritis and other autoimmune diseases [6].

Circulation Half-Life: Native exosomes typically exhibit circulation times ranging from minutes to several hours, depending on surface markers and clearance pathways (e.g., uptake by hepatic Kupffer cells). **Biodistribution:** EVs administered intravenously tend to accumulate in the liver, spleen, and lungs, which can be advantageous—or limiting—depending on the therapeutic target. **Surface modification** (e.g., PEGylation, peptide ligands) can redirect EVs to specific tissues, such as the brain or myocardium. **Dose–Response Relationships:** Preclinical models show dose-dependent uptake of EVs by target cells, with higher doses occasionally triggering undesired immunomodulation. Precise quantification methods (nanoparticle tracking analysis, tunable resistive pulse sensing) are employed to standardize dosing and ensure reproducibility [7].

EVs encapsulate a wealth of diagnostic information: their cargo can reveal disease-specific signatures—mutant mRNA sequences, oncogenic proteins, or dysregulated miRNA profiles. For instance: **Oncology:** Tumor-derived exosomes in patient plasma can contain mutant KRAS mRNA, enabling early detection of pancreatic cancer with higher sensitivity than conventional biomarkers. **Neurodegenerative Diseases:** Neuron-derived EVs in cerebrospinal fluid carry tau protein and α -synuclein aggregates, correlating with Alzheimer's and Parkinson's disease progression, respectively. **Cardiovascular Disorders:** Circulating EVs enriched in cardiac-specific microRNAs (miR-1, miR-133a) can serve as early indicators of myocardial infarction, often preceding rises in troponin levels.

EVs from stem cells or immune cells can orchestrate tissue repair and modulate immune responses: Regenerative

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Received: 01-May-2025, Manuscript No. AABPS-25-166488; Editor assigned: 03-May-2025, Pre QC No. AABPS-25-166488(PQ); Reviewed: 17-May-2025, QC No. AABPS-24-166488; Revised: 21-May-2025, Manuscript No. AABPS-25-166488(R); Published: 28-May-2025, DOI: 10.35841/aabps-15.111.292

Medicine: Mesenchymal-stem-cell (MSC)-derived EVs promote angiogenesis and reduce fibrosis during myocardial infarction recovery. These vesicles deliver pro-angiogenic miRNAs (e.g., miR-126) and growth factors (VEGF), enhancing cardiac function in preclinical models [8].

Immunotherapy: Dendritic-cell-derived exosomes loaded with tumor antigens have been tested as cell-free cancer vaccines, stimulating cytotoxic T-cell responses with minimal systemic toxicity. Similarly, EVs from regulatory T cells can attenuate inflammatory cytokine production in autoimmune disease models.

Despite rapid progress, several challenges hinder the full integration of EVs into pharmacoscience and biomedical practice:

Scalable Manufacturing: Current isolation techniques (ultracentrifugation, size-exclusion chromatography) are laborious and often yield heterogeneous populations. Development of scalable, good-manufacturing-practice (GMP)-compliant methods—such as tangential flow filtration and microfluidic-based sorting—is essential.

Cargo Heterogeneity and Standardization: Even EVs derived from the same cell type can exhibit batch-to-batch variability in cargo composition. Standardized characterization protocols (proteomics, lipidomics, RNA sequencing) are needed to ensure reproducible therapeutic effects [9].

Safety and Immunogenicity Concerns: Although generally well tolerated, EVs loaded with exogenous materials may elicit immune responses or off-target effects. Rigorous preclinical toxicity assessments—focusing on chronic administration and long-term biodistribution—are necessary to establish safety profiles.

Regulatory Frameworks: Regulatory agencies are still formulating guidelines specifically for EV-based therapeutics. Clear criteria for potency assays, release specifications, and clinical endpoints will be critical for successful translation.

Looking ahead, innovative strategies—such as engineering EV-mimetic nanovesicles, designing synthetic lipid nanoparticles with EV-like surface proteins, or integrating artificial intelligence to predict EV targeting profiles—are poised to overcome current limitations. Collaborative efforts among academia, industry, and regulatory bodies will drive the establishment of robust manufacturing pipelines and facilitate multicenter clinical trials [10].

Conclusion

Extracellular vesicles have opened new horizons in pharmacoscience and biomedical research by serving as

versatile, naturally derived platforms for drug delivery, biomarker discovery, and regenerative therapies. Their inherent biocompatibility, coupled with the ability to traverse biological barriers and deliver complex cargo, positions EVs as frontrunners in next-generation therapeutics. While challenges in large-scale production, standardization, and regulatory approval remain, ongoing advancements in bioengineering and translational science will accelerate the integration of EV-based approaches into routine clinical practice paving the way for more precise, effective, and personalized medical interventions.

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