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Review Article

Clinical Frontiers of Exosome Research: A Comprehensive Analysis of Human Trials in Diagnostics, Therapeutics, and Regenerative Medicine

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Abstract

Background: Exosomes, key mediators of intercellular communication, transport functional biomolecules, making them promising tools for diagnostics and therapeutics across various human diseases.

Objectives: To systematically review and analyze the clinical applications of exosomes, focusing on their sources, functions, therapeutic roles, and research trends through a bibliometric approach.

Methodology: A comprehensive PubMed search was conducted using the term "exosomes" in titles and abstracts, limited to clinical studies, including Clinical Trials, Phase I–IV studies, and Randomized Controlled Trials. Ninety clinical trials were included. Bibliometric analysis using VOSviewer identified key terms, conceptual clusters, and emerging research topics.

Results: Exosomes demonstrated diverse clinical applications in oncology, neurodegenerative diseases (e.g., Alzheimer's), cardiovascular conditions, osteoarthritis, COVID-19, spinal cord injuries, transplant rejection, and skin regeneration. Predominant exosome sources included plasma, serum, urine, saliva, tears, ascites, adipose tissue, and stem cells. Functionally, exosomes served as diagnostic biomarkers, therapeutic agents, and molecular delivery systems. Key terms included miRNA, plasma, safety, efficacy, and trial, with conceptual clusters reflecting a shift from molecular exploration to clinical implementation. Emerging themes included precision medicine, biobank integration, and regenerative therapies using mesenchymal stem cell-derived or herbal-modified exosomes.

Conclusion: Exosome-based interventions show promising safety and efficacy but face challenges in standardizing isolation methods, conducting large-scale randomized trials, and ensuring long-term follow-up. Future research should focus on integrating exosome platforms into precision medicine with robust clinical frameworks.

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Keywords
Exosomes, clinical trials, biomarkers, therapeutics, bibliometric analysis
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Introduction

Extracellular vesicles (EVs) are released by all cells, both prokaryotic and eukaryotic, both normally and during acquired disorders.[1] Ectosomes and exosomes are the two general types into which EVs fall. Ectosomes, which comprise microvesicles, microparticles, and big vesicles with a diameter of around 50 nm to 1 μm, are vesicles that pinch off the plasma membrane surface by outward budding.[2] Exosomes (Figure 1) are endosomal-derived EVs that range in size from 40 to 160 nm (average diameter of 100 nm).[3] Multivesicular bodies are eventually formed by sequential invagination of the plasma membrane. These bodies can intersect with different intracellular vesicles and organelles, adding to the diversity of exosome contents.[4–7] Many components of a cell, including DNA, RNA, lipids, metabolites, and cytosolic and cell-surface proteins, can be found in EVs, including exosomes, depending on the cell of origin.[4,8,9] There is still much to learn about the physiological function of exosome production. Exosomes are thought to play a part in preserving cellular homeostasis by removing extraneous or surplus components from cells.[2,10] Additionally, recent research examined here shows that some cellular components accumulate in exosomes in a functional, targeted, mechanism-driven manner, indicating that these exosomes may play a part in controlling intercellular communication.[11–13]

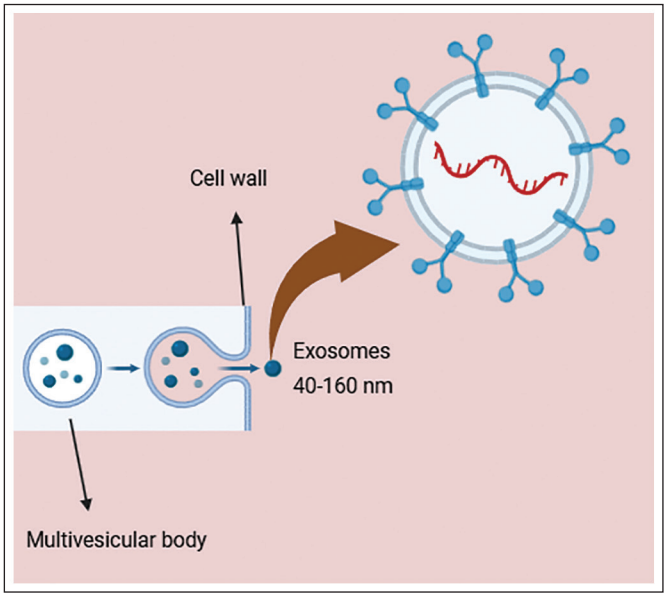


Figure 1. Biogenesis and Structure of Exosomes. Exosomes (40–160 nm in Diameter) Originate From the Inward Budding of Multivesicular Bodies (MVBs) and are Secreted Through Fusion With the Cell Membrane. These Nanosized Extracellular Vesicles Carry Functional Biomolecules Such as RNA, Proteins, and Lipids, and Play Critical Roles in Intercellular Communication.

Source: Figure created using BioRender.com.

Exosomes are increasingly recognized for their multifaceted roles in health and disease, with implications spanning cancer progression, cardiovascular diseases, central nervous system (CNS) disorders, pregnancy, immune modulation, and viral infections.[14] These nanoscale vesicles mediate intercellular communication by transferring proteins, metabolites, and nucleic acids to recipient cells, thereby modulating their biological responses.[15] Depending on context, exosome-mediated signaling may either promote or suppress disease pathogenesis.[4,16] Their unique ability to influence complex intracellular pathways has positioned exosomes as promising candidates for therapeutic interventions, particularly in cancer and neurological diseases.[17] Exosomes can be engineered to carry diverse therapeutic agents, such as chemotherapeutics, immune modulators, antisense oligonucleotides, and siRNAs, while their intrinsic lipid and protein composition enhances pharmacokinetics, bioavailability, and reduces toxicity.[6,18,19] Beyond therapeutics, exosomes offer powerful diagnostic potential. As they are present in all biological fluids, liquid biopsies allow for non-invasive access to their cargo, enabling real-time disease monitoring. For example, pediatric glioma patients are undergoing exosome-based liquid biopsies to assist with diagnosis and prognosis. Furthermore, multicomponent analyses of exosomes provide insights into disease progression and therapeutic responses.[2,20–23] The functional significance of exosomes is further illustrated in Table 1, which summarizes their key membrane markers, diverse cargo, and broad biological roles—from gene regulation and immune balance to angiogenesis and metastatic potential—underscoring their central role in intercellular communication and disease modulation. This review provides a comprehensive overview of the clinical applications of exosomes based solely on data from clinical trials to offer an accurate and up-to-date picture of their real-world translational relevance. Across diverse studies, exosomes have demonstrated significant promise as diagnostic and prognostic biomarkers. However, a clear research gap remains in the systematic clinical validation of these findings, especially across larger, multicenter trials and in standardized protocols for exosome isolation, characterization, and dosing. Additionally, there is a need for greater clarity on exosome pharmacokinetics, biodistribution, and long-term safety. This review addresses this gap by focusing strictly on clinical trial data, moving beyond preclinical and *in vitro* findings, to provide a grounded and realistic evaluation of

Table 1. Hallmarks, Cargo, and Functional Roles of Exosomes in Intercellular Communication and Disease Modulation. Exosomes are Extracellular Vesicles Generated by All Cells, and They Carry Nucleic Acids, Proteins, Lipids, and Metabolites. They are Mediators of Near and Long-distance Intercellular Communication in Health and Disease, and Affect Various Aspects of Cell Biology.

Category	Description
Key membrane markers	CD9, CD63, CD81, transmembrane proteins, flotillin-1
Exosomal cargo	Nucleic acids (DNA, RNA), TSG101, HSP70, HSP90, ALIX, amino acids, metabolites, cholesterol
Biological functions of exosomes	
Regulation of gene transcription and translation	Modulate gene expression in recipient cells
Survival and proliferation	Promote cell viability and division
Reproduction and development	Participate in reproductive and developmental processes
Angiogenesis and wound healing	Facilitate blood vessel formation and tissue repair
Waste management	Remove unwanted cellular components
Host–microbiome interaction and viral immunity	Mediate immune defense and microbiota communication
Balance of immune response	Regulate central and peripheral immunity
Receptor-ligand signaling	Facilitate intercellular communication
Apoptosis	Influence programmed cell death pathways
Cellular differentiation and neoplasia	Affect lineage specification and tumor formation
Cellular migration and metastatic disease	Support cancer cell movement and dissemination
Metabolic reprogramming and regulation	Modify metabolic activity in target cells

Note: ALIX: ALG-2 interacting protein X; CD9: Cluster of differentiation 9; CD63: Cluster of differentiation 63; CD81: Cluster of differentiation 81; HSP70: Heat shock protein 70; HSP90: Heat shock protein 90; TSG101: Tumor susceptibility gene 101.

the current and potential future roles of exosomes in clinical medicine.

Methodology

Search Strategy and Data Sources

A systematic PubMed search was conducted on March 28, 2025, using the keyword "exosomes" in the title and abstract. Filters included Clinical Trial, Protocol, Phase I–IV, and Randomized Controlled Trial, limited to human studies in English. Only interventional studies indexed in PubMed were included; observational studies and external registries (e.g., ClinicalTrials.gov) were excluded. The Boolean string used was: ("exosomes"[Title/Abstract]) AND (Clinical Trial OR Clinical Trial Protocol OR Clinical Trial Phase IOR Clinical Trial Phase IIOR Clinical Trial Phase IIIOR Clinical Trial Phase IVOR Randomized Controlled Trial) AND (humans) AND (english[lang]). A total of 90 clinical trials met the inclusion criteria and were selected for in-depth review and analysis.

Inclusion and Exclusion Criteria

Only interventional studies were included in this analysis, as defined by the applied PubMed filters (Clinical Trial, Clinical Trial Protocol, Phase I–IV trials, and Randomized Controlled Trials). Observational studies were excluded to maintain consistency in evaluating therapeutic and diagnostic interventions. No external clinical trial registries (e.g., ClinicalTrials.gov, EU Clinical Trials Register) were consulted in this study; all included records were indexed in PubMed and published in peer-reviewed journals. The selection was limited to English-language articles that reported original clinical trial data involving human participants.

Data Extraction and Categorization

Each clinical trial was reviewed to extract key data, including the disease studied, exosome source (e.g., plasma, urine, stem cells), application type (diagnostic, therapeutic, or drug delivery), intervention details, trial phase, and sample size. Clinical outcomes such as efficacy, safety, biomarkers, and therapeutic responses were also recorded to assess the role of exosomes across various conditions.

Bibliometric Analysis

To investigate research trends and thematic structures within clinical exosome research, a bibliometric analysis was performed using VOSviewer (version 1.6.20).[24] Bibliographic data were exported from PubMed in RIS format and uploaded into the software for analysis. Terms were extracted from the titles and abstracts using the full counting method, with a minimum occurrence threshold applied based on relevance criteria (e.g., appearing at least 10

times). Several visualizations were generated to support the analysis, including a Term Co-occurrence Density Map to highlight frequently used keywords, a Conceptual Mapping diagram to identify clusters of thematically related terms, and an Overlay Visualization to illustrate the emergence and evolution of recent research topics over time. This integrated approach enabled both qualitative insight and quantitative mapping of the clinical research landscape surrounding exosomes.

Results and Discussion

Trajectory

Clinical research on exosomes has progressed significantly over the past decade, as illustrated in Figure 2. The figure depicts the number of clinical exosome-related publications per year from 2008 to 2025. Initial research between 2011 and 2014 focused on biomarker discovery and exosome profiling. From 2015 onward, publications increased, reflecting the growing use of exosomes in oncology, neurology, nephrology, and infectious disease. A major surge is seen in 2018, with continued high output through 2024. The drop in 2025 may be due to incomplete data. The overall trend highlights a shift from foundational research to translational and clinical applications such as regenerative medicine, immunotherapy, and diagnostics. This finding aligns with prior reports indicating an exponential surge in research focusing on the biology and clinical properties of exosomes.[14,15]

Descriptive Summary (n = 90 Trials)

This analysis of 90 clinical trials highlights the diverse clinical applications of exosomes. Commonly sourced from plasma, serum, and urine, exosomes were mainly used as diagnostic and prognostic biomarkers, especially in cancers like breast, prostate, and liver. Non-oncology uses included nephrology, infectious diseases, and endocrine disorders. About 21% of trials explored therapeutic roles, particularly stem cell-derived exosomes for coronavirus disease 2019 (COVID-19), neurodegenerative diseases, and drug delivery. Around 7% focused on treatment monitoring, with some studying how physiological or pharmacological factors influence exosomes. Overall, the findings underscore exosomes' promise in diagnostics, therapy, and precision medicine, though standardization and larger trials are still needed.

Exosomes are released by all cells and present in all bodily fluids, making them suitable for non-invasive liquid biopsies. Their molecular cargo allows for detailed diagnostic evaluation, with surface proteins aiding immunological capture. Exosomes have shown diagnostic utility in cardiovascular diseases,[25] CNS disorders,[21] and cancer.[15,26,27] This initiative is swiftly extending to additional disorders affecting the liver,[28–31] the kidney,[32,33] and the lung.[34–37]

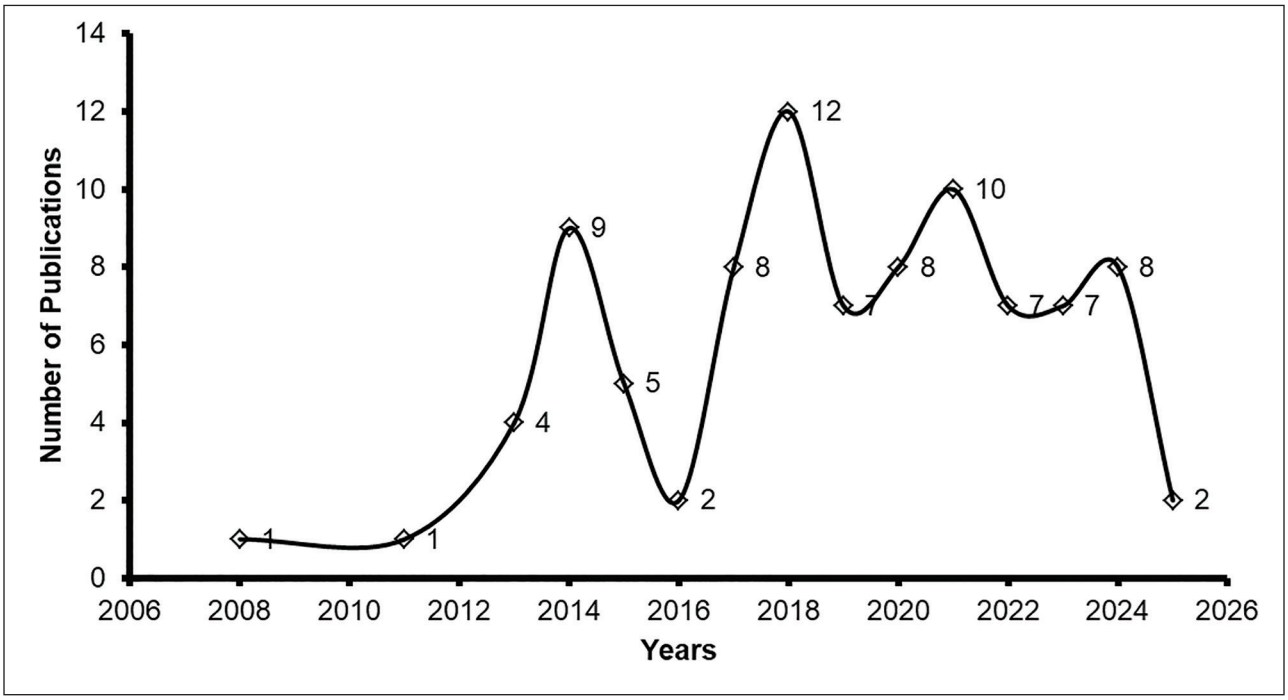


Figure 2. Trends in Clinical Research on Exosomes (2008–2025). The figure Shows the Annual Number of Clinical Studies on Exosomes From 2008 to 2025. Each Point Marks the Number of Publications per Year, With a Peak in 2018 (12 Studies) and Steady Output From 2020 to 2024. The Drop in 2025 May Reflect Incomplete Data. The Trend Highlights Rising Clinical Interest in Exosome Applications.

Table 2. Frequency of Exosome Sources Across Studies.

Source of Exosomes	Frequency
Plasma-derived exosomes	10
Serum exosomes	9
Urinary exosomes	9
Neuron-derived exosomes (plasma/serum)	5
Blood exosomes (circulating/peripheral)	5
Adipose tissue (stem cells/MSCs)	5
Bone marrow mesenchymal stem cells (MSCs)	3
Platelet-derived exosomes	3
Umbilical cord/Wharton's jelly MSCs	3
Circulating exosomes (general)	3
Prostate cancer cells/urine/tissue	3
MSC-derived exosomes (general)	2
KSHV-associated tumors	1
Tear exosomes	1
Saliva exosomes	1
Human milk exosomes	1
Induced sputum exosomes	1
EGFR-mutant lung cancer cells	1
Multiple myeloma cells	1
ONFH literature (osteonecrosis)	1
NF-PA patients' serum	1
Ascites fluid exosomes	1
Follicular helper T cells	1
Topical platelet-derived vesicles	1
Autologous ascites-derived exosomes	1
AML patient plasma exosomes	1
Adenoid tissue and blood exosomes	1
Placenta-derived MSCs	1
Porcine MSCs	1

Note: AML: Acute myeloid leukemia; EGFR: Epidermal growth factor receptor; KSHV: Kaposi's sarcoma-associated herpesvirus; MSC: Mesenchymal stem cell; NF-PA: Non-functioning pituitary adenoma; ONFH: Osteonecrosis of the femoral head

Therapeutic Applications

Several clinical trials (Table 2) have investigated mesenchymal stem cell (MSC)-derived exosomes in COVID-19,[1,34,38–40] showing safety and efficacy. Chu et al. used nebulized umbilical cord mesenchymal stem cell (UC-MSC) exosomes in seven patients, showing no adverse events and reduced lesion burden.[34] Zhu et al. tested aerosolized adipose MSC exosomes in a Phase 2a trial, showing immune modulation and lung repair.[40] Sengupta et al. reported improved oxygenation and reduced inflammatory markers in 24 acute respiratory distress syndrome (ARDS) patients treated with ExoFlo™, achieving 83% survival.[39] Zamanian et al. found reduced mortality (19% vs. 54%) in a randomized controlled trial using human placental mesenchymal stromal cell-derived small extracellular vesicles (hPMSC-sEVs)[1] (Table 3). Salomon-Zimri et al. applied exosomes in amyotrophic lateral sclerosis (ALS) patients to monitor biomarkers like TAR DNA-binding protein 43 (TDP-43) and microtubule-associated protein 1 light chain 3 (LC3), underscoring diagnostic and therapeutic roles.[38] MSC-derived exosomes in COVID-19 show immunomodulatory effects by reducing inflammation (C-reactive protein (CRP), ferritin, D-dimer), reversing lymphopenia (cluster of differentiation 3 positive (CD3+), cluster of differentiation 4 positive (CD4+), cluster of differentiation 8 positive (CD8+)), improving oxygenation (192% increase in partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2)), and supporting tissue repair through bioactive molecule delivery. Delivery methods include nebulization and intravenous infusion, with consistent safety.

In skin regeneration, Pak et al. used placenta-derived exosomes for perianal fistulas with significant improvement and no adverse effects. Park et al. showed improved hydration, elasticity, and pigmentation using human adipose tissue stem cell-derived exosome-containing solution (HACS) with microneedling.[29] Svolacchia et al. demonstrated dermal regeneration using filtered nanofat vesicles.[41] Wyles et al. found increased collagen and elastin from topical human platelet extract (HPE). These studies confirm exosome safety and efficacy in dermatology.[42] Exosomes in cancer therapy include immunomodulation, monitoring drug resistance, and reducing tumor progression. Exosomes reprogram cells,[43] induce cytotoxic T lymphocyte (CTL) responses,[44] suppress NK cells,[45] promote dormancy,[46] and track therapy response.[36] Guizhi Fuling Decoction (GZFL) exosomes reduce osteoclast activity in myeloma.[36] Gupta et al. explored umbilical cord Wharton's jelly (UC-WJ) exosome therapy in knee osteoarthritis (OA). A randomized trial (n = 168) compared UC-WJ to hyaluronic acid and saline. A non-randomized open-label study (n = 12) used clinical/imaging assessments. Another study used cell-free stem cell-derived cell-free stem cell-derived conditioned medium (CCM) in a 24-month follow-up. These trials show promise for minimally invasive OA therapy.[11,12,47]

Exosomes' immunomodulatory roles were shown by Müller et al., who isolated plasma exosomes that downregulated cluster of differentiation 69 (CD69) on CD4+ T cells, indicating immune suppression in cancer. Yang et al. demonstrated that follicular helper T cell (Tfh)-derived exosomes from antibody-mediated rejection (AMR) patients expanded B and plasma cells, implicating them in graft rejection.[48,49] In tissue injury, Akhlaghpasand et al. showed that intrathecal human umbilical cord mesenchymal stem cell (HUC-MSC) exosomes improved neurological function, bowel control, and autonomy in spinal cord injury.[10] Civelek et al. reported sensory and motor recovery in a patient with radial nerve injury treated with MSC exosomes. These trials support exosomes' regenerative potential.[3] Dang et al. showed that exosomal long non-coding RNA taurine upregulated gene 1

Table 3. Therapeutic Applications.

Author	Source of Exosomes	Clinical Application	Type of Study	Conclusion
Zamanian et al.[1]	Placental mesenchymal stromal cells	Severe COVID-19	Randomized controlled trial	hPMSC-sEVs reduce mortality in severe COVID-19.
Zhu et al.[40]	Adipose-derived MSCs	Severe COVID-19	Pilot study	Nebulized MSC-exosomes are safe and potentially effective.
Narita et al.[44]	DC-derived exosomes	CTL activation in esophageal cancer	Phase I/II clinical trial	DC-exosomes activate CTLs in esophageal cancer
Whitham et al.[51]	Circulating extracellular vesicles	Systemic effects of exercise	Proteomic and imaging study	Exercise releases EVs aiding tissue crosstalk.
Muller et al.[48]	Plasma exosomes	Biological activity and immune suppression	Methodological study	Plasma exosomes modulate immune cell activity.
Park et al.[52]	Adipose tissue stem cells	Facial aging treatment	Randomized, split-face trial	HACS plus microneedling improves skin aging.
Yu et al.[36]	EGFR-mutant lung cancer cells	Treatment resistance in lung cancer	Phase 1/2 clinical trial	Combination therapy well tolerated but ineffective
Yu et al.[53]	Multiple myeloma cells	Bone destruction in multiple myeloma	Clinical + experimental	GZFL inhibits MBD by targeting exosomal ERK1.
Ono et al.[46]	Bone marrow mesenchymal stem cells	Metastatic breast cancer	*In vitro* and patient samples	BM-MSC exosomes induce breast cancer dormancy
Yang et al.[49]	Follicular helper T cells	Antibody-mediated rejection after renal transplant	Experimental	Tfh exosomes promote B cell proliferation, differentiation.
Svolacchia et al.[41]	Adipose tissue	Anti-aging therapy	Clinical trial	Ultrafiltered nanovesicles aid skin regeneration.
Wyles et al.[42]	Topical platelet-derived vesicles	Aesthetic dermatology	Prospective clinical study	HPE improves skin collagen and elastin.
Sengupta et al.[39]	Bone marrow mesenchymal stem cells	Severe COVID-19 treatment	Open-label cohort	ExoFlo improved oxygenation, immunity, reduced inflammation.
Abd Elmageed et al.[43]	Prostate cancer cells	Prostate cancer transformation	Experimental (*in vivo*)	PC exosomes drive neoplastic stem cell conversion.
Akhlaghpasand et al.[10]	Umbilical cord MSCs	Spinal cord injury	Phase I clinical trial	Safe and improved sensory/motor function
Chu et al.[34]	MSC-derived exosomes	COVID-19 pneumonia	Pilot clinical study	Safe, effective for mild COVID-19 pneumonia
Civelek et al.[3]	MSCs	Radial nerve injury	Pilot single-patient study	Exosomes enhanced nerve regeneration and recovery.
Dai et al.[20]	Autologous ascites-derived exosomes	Colorectal cancer	Phase I clinical trial	Safe, induces tumor-specific immune response
Dang et al.[50]	Circulating exosomes post-MI	MI	RCT and cohort (human and animal)	Exosomal TUG1 affects angiogenesis post-MI
Gupta et al.[11]	WJ	Knee OA	RCT, single-blind, multi-center	Evaluates WJ safety in knee OA treatment
Gupta et al.[47]	WJ	Knee OA	Non-randomized, open-label, multi-center	WJ promising for OA symptom relief
Gupta et al.[12]	Stem cell-derived extract (CCM)	Knee OA	Non-randomized, open-label, multi-center.	Feasibility of CCM in knee OA treatment

(Table 3 continued)

(Table 3 continued)

Author	Source of Exosomes	Clinical Application	Type of Study	Conclusion
Hong et al.[45]	AML patient plasma exosomes	AML	Observational	AML exosomes impair immunotherapy efficacy
Kwon et al.[54]	Adipose-derived stem cell exosomes	Acne scars	Randomized, split-face trial	Exosomes enhance laser treatment outcomes.
Liu et al.[13]	Adenoid tissue and blood exosomes	Adenoid hypertrophy with OME	Protocol study	Study to explore exosomes in pediatric OME.
Pak et al.[29]	Placenta-derived MSCs	Non-Crohn's complex perianal fistula.	Phase I clinical trial	Safe and effective for complex perianal fistula.

Note: AML: Acute myeloid leukemia; BM-MSC: Bone marrow mesenchymal stem cell; CCM: Cell-free stem cell-derived conditioned medium; CTL: Cytotoxic T lymphocyte; DC: Dendritic cell; EGFR: Epidermal growth factor receptor; EVs: Extracellular vesicles; GZFL: Guizhi Fuling Decoction; HACS: Human adipose tissue stem cell-derived exosome-containing solution; HPE: Human platelet extract; hPMSC-sEVs: Human placental mesenchymal stromal cell-derived small extracellular vesicles; MBD: Myeloma bone disease; MSC: Mesenchymal stem cell; MI: Myocardial infarction; OA: Osteoarthritis; RCT: Randomized controlled trial; Tfh: Follicular helper T cell; TUG1: Exosomal long non-coding RNA taurine upregulated gene 1; WJ: Wharton's jelly.

(exo-LncRNA TUG1) from MI patients inhibits angiogenesis via hypoxia-inducible factor 1-alpha/vascular endothelial growth factor-alpha (HIF-1α/VEGF-α) suppression, reversible by remote ischemic conditioning (RIC). Exosomal TUG1 reduction restored endothelial function, positioning it as a target for MI recovery, especially post-percutaneous coronary intervention (PCI).[50]

Applications of Exosomes as Biomarkers

Table 4 summarizes clinical studies using exosomes as biomarkers across diverse diseases. Exosomal microRNAs (miRNAs), proteins, and other molecules are widely studied for diagnostic, prognostic, and monitoring purposes. Neurodegenerative disorders, particularly Alzheimer's disease and mild cognitive impairment (MCI), were frequently assessed using neuronal-derived plasma exosomes, examining markers like insulin signaling and synaptic proteins.[21,55–57] Parkinson's disease was evaluated using protein kinase B/mammalian target of rapamycin (Akt/mTOR) markers.[16]

Cancer applications included detecting exosomal miRNAs, proteins, and mutations in prostate, pancreatic, ovarian, hepatocellular, renal, and pituitary cancers. Pan et al. studied exosomal miRNAs in ovarian cancer; Kahlert et al. and Kanwar et al. identified KRAS and tumor protein 53 (p53) mutations in pancreatic cancer. Resistance markers such as cluster of differentiation 133 (CD133) and docetaxel-resistance proteins were studied in prostate and colorectal cancers.[6,58]

Exosomal RNA and protein markers were explored in inflammatory and infectious diseases like schistosomiasis, asthma, and maternal HIV via serum, sputum, and milk samples.[59–61] Novel uses included autoimmune profiling in Down syndrome and osteosarcoma biobanking.[62–65] Overall, Table 3 underscores exosomes' biomarker versatility and potential in personalized medicine.

The Use of Exosomes as a Vehicle

The therapeutic potential of exosomes as delivery vehicles is highlighted in two key studies. Bahadur et al. identified exosomes as effective nanocarriers for intranasal delivery of anti-Alzheimer's drugs, noting their biocompatibility, ability to cross the blood–brain barrier, and enhanced bioavailability over conventional systems.[92] Eirin et al. analyzed MSC-derived exosomes from pigs with and without metabolic syndrome, revealing that while healthy MSC exosomes support cell repair, metabolic syndrome (MetS)-derived exosomes carry pro-inflammatory proteins that may reduce regenerative efficacy. This underscores the impact of donor health on exosome function.[93] Both studies support exosomes as smart delivery platforms across neurological and metabolic diseases (Table 5).

Table 4. Applications of Exosomes as Biomarkers.

Author	Source of Exosomes	Clinical Application	Type of Study	Conclusion
Mustapic et al.[56]	Neuronal EVs from plasma	Tracking cognitive changes with insulin therapy	Placebo-controlled clinical trial	EV biomarkers track cognitive change post-insulin
Wang et al.[18]	AML cells	AML prognosis and therapy	*In vitro* and *ex vivo* study	circ_0009910 modulates AML via miR-5195-3p
Spinetti et al.[66]	Serum	Critical limb ischemia	Clinical and animal study	miR-15a/16 impair PACs; potential biomarkers
Propper et al.[6]	Circulating plasma	Metastatic colorectal cancer	Phase I/II clinical trial	HER2/3 exosomes reflect CRC treatment response
Skogberg et al.[67]	Thymus	Down syndrome autoimmunity	Comparative study	DS exosomes show broader unique TRA profiles.
Zang et al.[37]	Osteosarcoma patients' samples	Dynamic monitoring in osteosarcoma	Biobank Protocol Study	Biobank enables dynamic monitoring of osteosarcoma.
Agarwal et al.[5]	Prostate cells (urine/tissue)	Prostate cancer diagnosis	Randomized, double-blind pilot	EVs correlate with Gleason score in PCa.
Arenaza et al.[59]	Circulating exosomes	Type 2 diabetes risk	Randomized controlled trial (protocol)	Exercise alters exosomal miRNA in children.
Athauda et al.[16]	Neuronal exosomes (serum)	Parkinson's disease	Secondary analysis of RCT	Exosomes reflect neuroprotective drug effects
Chugh et al.[68]	KSHV-associated tumors	KSHV cancers (KS, PEL)	Observational	Tumor exosomes enhance migration, inflammation.
Danielson et al.[25]	Plasma-derived exosomes	Left ventricular remodeling post-MI	Observational with validation	Plasma exRNAs linked to post-MI remodeling.
Du et al.[69]	Plasma-derived exosomes	Air pollution exposure	Randomized crossover trial	TRAP exposure alters exosomal miRNA profiles.
Duan et al.[21]	Serum-derived exosomes	AD	Case-control	miR-125b, miR-451a differentiate AD patients.
Eitan et al.[22]	Plasma EVs	Prostate cancer and diet	Randomized controlled trial	Protein restriction shifts EV metabolic signals.
Ellison and Terker[70]	Urinary exosomes	Hypertension	Experimental with human validation	Potassium intake regulates renal transporters.
Estébanez et al.[23]	Blood exosomes	Obesity and training effects	Experimental, controlled	Training relates exosomal proteins to health.
Fernandez-García et al.[2]	Platelets and AAA tissue	Abdominal aortic aneurysm	Observational with patient cohort	Ficolin-3 levels predict AAA progression.
Fotuhi et al.[71]	Plasma-derived exosomes	AD	Case-control	BACE1-AS distinguishes AD stages by blood.
García-Del-Muro et al.[26]	Serum and exosomes	Renal cell carcinoma	Phase I/II clinical trial	Molecular markers linked to pazopanib response.
Goetzl et al.[55]	Neuronal exosomes (plasma)	AD	Observational	Decline of synaptic proteins mirrors AD progression.
Grigor'eva et al.[72]	Tear exosomes	Healthy characterization	Observational	Exosomes in tears carry RNA and DNA.
Gu et al.[28]	Plasma exosomes	Cholangiocarcinoma and gallbladder carcinoma	Case-control with validation	piR-10506469 elevated in CCA and GBC
Hogan et al.[62]	Urinary exosomes	Glomerular diseases	Cohort protocol paper	Urine exosomes useful for kidney biomarkers
Huang et al.[63]	Urinary exosomes	Thyroid cancer recurrence	Case series	U-Ex Tg detects recurrence post-ablation.
Isobe et al.[32]	Urinary exosomes	Kidney function	Assay development and validation	pNCC levels reflect renal transporter activity
Kahlert et al.[73]	Serum exosomes	Pancreatic cancer	Observational	Exosomes carry mutated tumor DNA markers.

(Table 4 continued)

(Table 4 continued)

Author	Source of Exosomes	Clinical Application	Type of Study	Conclusion
Kanwar et al.[74]	Serum exosomes	Pancreatic cancer	Device development and case-control	ExoChip isolates and quantifies exosomes effectively.
Khalyfa et al.[60]	Plasma exosomes	Obstructive sleep apnea	Observational with functional assays	SDB alters exosomal effects on adipocytes
Kharaziha et al.[58]	Prostate cancer exosomes	Prostate cancer	Comparative proteomics and validation	Exosomes indicate docetaxel therapy resistance.
Lea et al.[27]	Blood exosomes	Ovarian malignancies	Proof-of-concept, diagnostic assay	PS-positive exosomes predict ovarian cancer.
Li et al.[75]	Neuron-derived exosomes	Obstructive sleep apnea	Observational	Exosomes associate OSA with cognitive decline.
Liang et al.[61]	Plasma exosomes	Coronary artery disease	Case-control	SOCS2-AS1 predicts CAD diagnosis.
Liu et al.[76]	ABCA1-labeled serum exosomes	AD	Observational	miR-193b elevated in AD serum exosomes.
López de Las Hazas et al.[8]	Blood exosomes	Cardiovascular health in elderly	Randomized controlled trial	Walnut intake modulates circulating exosomal miRNAs.
Sivadasan et al.[77]	Saliva	Oral cancer detection	Proteomic profiling	Identified 139 salivary proteins linked to cancer.
Sun et al.[33]	Urine	Early diabetic nephropathy	Randomized clinical study	CD63+ exosomes show renal protection indicator.
Amosse et al.[78]	Adipose tissue	Obesity and metabolic syndrome	Observational (EV phenotyping)	MIF exosomes active in obesity inflammation
Connolly et al.[4]	Platelets	Familial hypercholesterolemia	Observational pre-/post-apheresis	Apheresis reduces prothrombotic microparticles.
Solakoglu. et al.[7]	Plasma	Bone graft outcome	Randomized controlled trial	miRNAs indicate bone metabolism post-surgery.
Wang et al.[65]	Peripheral blood exosomes	Biomarkers for DGF	High-throughput sequencing study	Identified miRNAs linked to kidney DGF
Zubiri et al.[64]	Urinary exosomes	Diagnosis of diabetic nephropathy	Proteomics + validation	Exosomal proteins distinguish diabetic nephropathy stages.
Sedlarikova et al.[79]	Serum	Monoclonal gammopathies (MM, MGUS)	Two-phase biomarker study	Exosomal PRINS may aid multiple myeloma diagnosis.
Rennings et al.[19]	Urinary exosomes	TZD-induced fluid retention in insulin resistance	Double-blind crossover trial	TZDs do not impair diuretic exosomal response.
Siva et al.[35]	Plasma	Personalized cancer therapy	Clinical observational	Radiotherapy causes systemic DNA damage responses
Zhang et al.[80]	Adipose tissue	Gestational diabetes mellitus prediction	Prospective cohort	Visceral fat regulates miRNA-148, predicts GDM.
Wang et al.[31]	Serum exosomes	Biomarker for HCC	Clinical observational study	Exosomal miR-21 is elevated in HCC patients.
Zahoor et al.[81]	Human milk	Mother-to-child transmission of HIV	Comparative analysis	HM exosomes show miRNA biomarkers for HIV
Sánchez-Vidaurre et al.[82]	Induced sputum	Asthma diagnosis	Clinical observation	Exosomal RNA detected in asthmatic patient sputum.
Yu et al.[36]	EGFR-mutant lung cancer cells	Treatment resistance in lung cancer	Phase 1/2 clinical trial	Combination therapy well tolerated but ineffective

(Table 4 continued)

(Table 4 continued)

Author	Source of Exosomes	Clinical Application	Type of Study	Conclusion
Winston et al.[57]	Neuron-derived exosomes	Early Alzheimer's detection	Randomized controlled trial	NDEs reveal early biomarkers for MCI.
Yu et al.[83]	Serum of NF-PA patients	Non-functioning pituitary adenoma	Experimental	CDK6 and RHOU are reliable invasiveness biomarkers.
Rodosthenous et al.[84]	Plasma EVs	Blood pressure regulation and PM exposure	Observational cohort study	Exosomal miRNAs mediate PM-BP association.
Sakaue et al.[85]	Ascites fluid	Pancreatic cancer prognosis	Clinical + animal model	Exosomal CD133 glycosylation predicts better prognosis.
Shi et al.[30]	Serum	HCC	Clinical + *in vitro*	Low exosomal miR-638 linked to poor survival.
McKiernan et al.[86]	Urine exosomes	High-grade prostate cancer prediction	Prospective clinical utility trial	Urine exosomes predict high-grade prostate cancer.
Macas et al.[87]	Serum exosomes	Prostate cancer immunomodulation	Observational clinical study	Exosomal cytokines reflect tumor microenvironment changes.
Prunotto et al.[88]	Human urine	Kidney disease research	Proteomic study	Podocyte exosomes valuable for kidney biomarkers
Meningher et al.[89]	Serum extracellular vesicles	Schistosomiasis detection and monitoring	Case-control study	miRNAs in EVs diagnose and monitor schistosomiasis.
Nandula et al.[90]	Urinary exosomes	Endothelial function in T2DM with CKD	Randomized placebo-controlled trial	Canagliflozin improves endothelial cell function T2DM
Nandula et al.[9]	Urine and blood exosomes	Cardio-renal risk in T2DM	Randomized clinical trial	Dapagliflozin improves cardio-renal biomarkers T2DM.
Pan et al.[91]	Plasma	Epithelial ovarian cancer	Clinical observational	Exosomal miRNAs valuable biomarkers for EOC

Note: AAA: Abdominal aortic aneurysm; AD: Alzheimer's disease; AML: Acute myeloid leukemia; BACE1-AS: Beta-site amyloid precursor protein cleaving enzyme 1-antisense; CCA: Cholangiocarcinoma; CD63+: Cluster of differentiation 63 positive; CDK6: Cyclin-dependent kinase 6; DGF: Delayed graft function; EGFR: Epidermal growth factor receptor; EVs: Extracellular vesicles; ExoChip: Exosome microfluidic chip; GBC: Gallbladder carcinoma; GDM: Gestational diabetes mellitus; HCC: Hepatocellular carcinoma; HER2/3: Human epidermal growth factor receptor 2/3; KS: Kaposi's sarcoma; KSHV: Kaposi's sarcoma-associated herpesvirus; MCI: Mild cognitive impairment; MI: Myocardial infarction; MIF: Macrophage migration inhibitory factor; NF-PA: Non-functioning pituitary adenoma; PEL: Primary effusion lymphoma; piR-10506469: Piwi-interacting RNA-10506469; PM: Particulate matter; pNCC: Phosphorylated sodium-chloride cotransporter; PRINS: Psoriasis susceptibility-related RNA gene induced by stress; PS: Phosphatidylserine; RCT: Randomized controlled trial; RHOU: Ras homolog family member U; SDB: Sleep-disordered breathing; SOCS2-AS1: Suppressor of cytokine signaling 2-antisense 1; TRAP: Traffic-related air pollution; TZD: Thiazolidinedione; U-Ex Tg: Urinary exosomal thyroglobulin.

Table 5. The Use of Exosomes as a Vehicle.

Author	Vehicle for What	Source of Exosomes	Clinical Application	Type of Study	Conclusion
Bahadur et al.[92]	Anti-Alzheimer's drugs	Various nano-delivery systems, including exosomes	Alzheimer's disease	Review with clinical trial insights	Exosomes useful for nose-to-brain drug delivery
Eirin et al.[93]	Proteins for tissue repair	Porcine MSCs	Metabolic syndrome effect on EVs	Comparative experimental (animal)	MetS alters EV cargo and reparative potential.

Note: EVs: Extracellular vesicles; MetS: Metabolic syndrome; MSC: Mesenchymal stem cell.

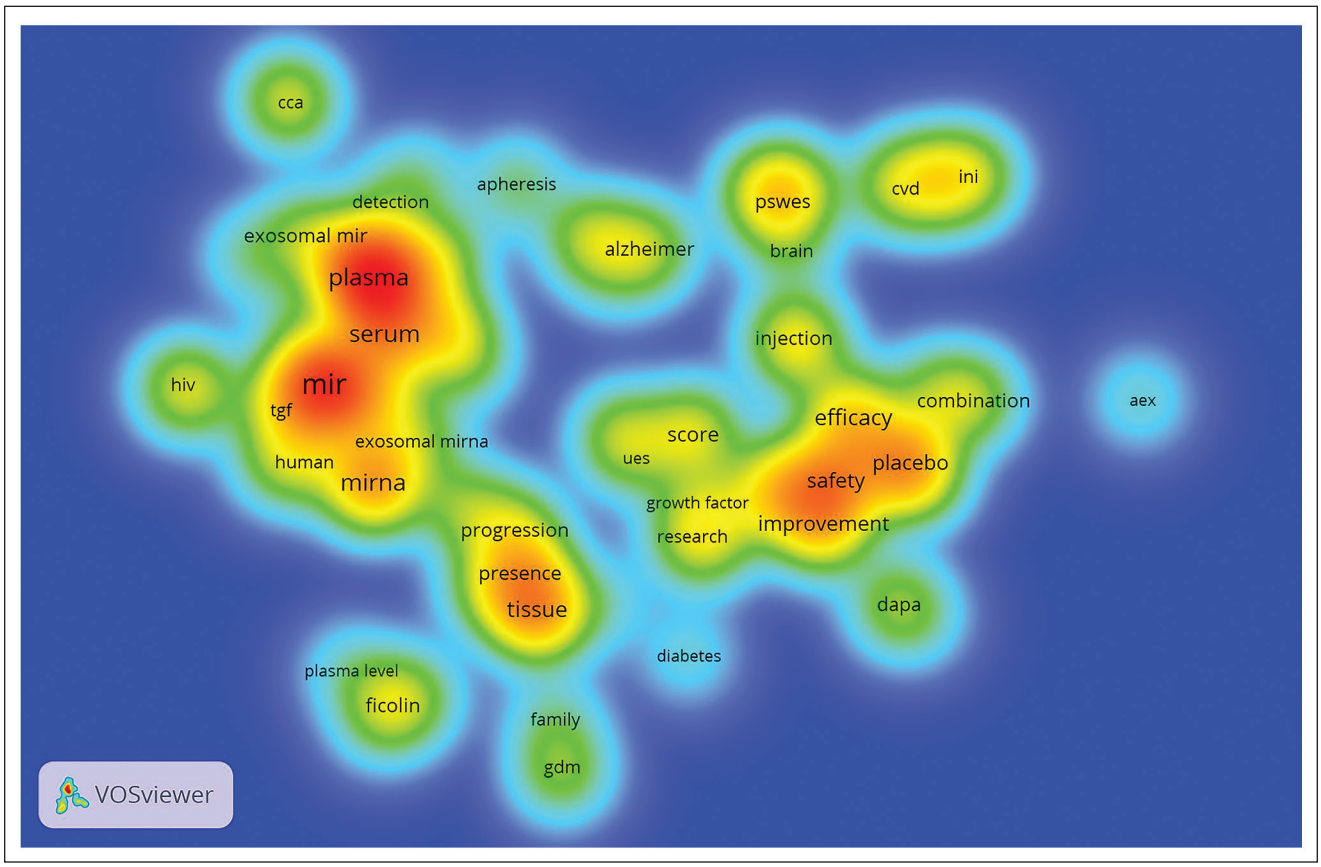


Figure 3. Term Density in Exosome Clinical Trials.

Bibliometric and Visualization Study

Most Frequent Terms

A bibliometric analysis of 3,693 terms from clinical trials on exosomes revealed key research focuses. Frequent terms like "mir," "mirna," "plasma," and "serum" reflect a strong emphasis on exosomal miRNAs as diagnostic biomarkers. Terms such as "efficacy," "placebo," and "safety" indicate a clinical focus on therapeutic evaluation. Disease-specific mentions like "Alzheimer" and "COVID" highlight growing interest in neurodegenerative and infectious conditions. Heatmaps show dense clusters around plasma/serum studies and therapeutic applications, underscoring the translational potential of exosome-based diagnostics and treatments.

Figure 3 shows a VOSviewer density map of terms from clinical trial abstracts on exosomes. Warmer colors (red/yellow) indicate more frequent terms, such as *mir*, *plasma*, *serum*, and *mirna*, highlighting biomarker-related research. Medium-frequency terms like *efficacy*, *safety*, and *placebo* cluster in yellow-green areas, reflecting clinical focus. Blue areas show emerging or less frequent topics. This map reveals

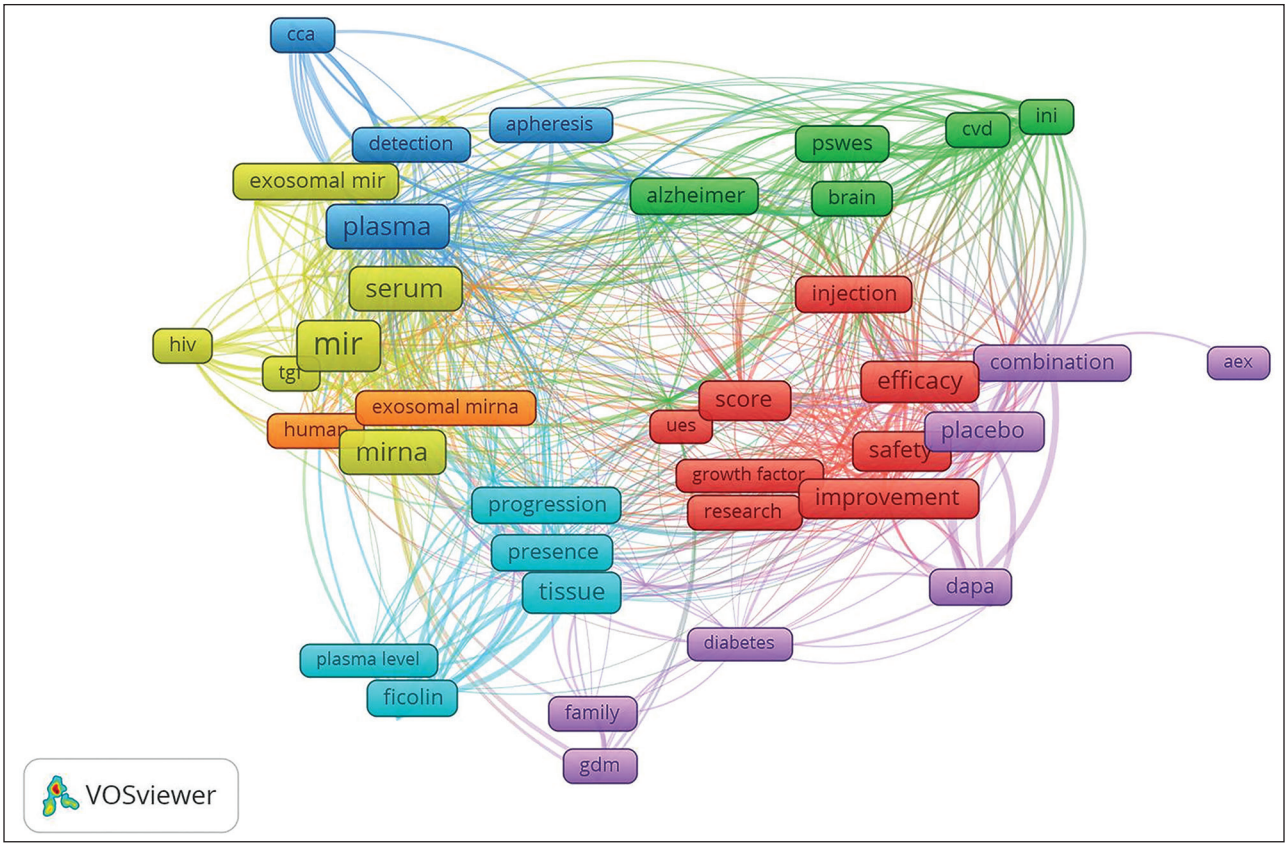


Figure 4. Conceptual Mapping. The Figure Shows the Conceptual Mapping of Exosome-based Clinical Trials Clustered into Seven Thematic Groups. The Red Cluster Focuses on Clinical Outcomes like Efficacy, Safety, and Placebo. The Green Cluster Highlights Disease-specific Terms Such as Alzheimer and Cardiovascular Disease (CVD). The Blue Cluster Represents Sample Sources and Methods like plasma, serum, and detection. The Yellow Cluster Centers on Molecular Markers such as miR and miRNA. The Orange Cluster Relates to Exosomal miRNA and Human Studies. The Purple Cluster Involves Metabolic Conditions like Diabetes and Gestational Diabetes Mellitus (GDM), While the Cyan Cluster Includes Terms like Progression and Ficolin, Reflecting Immune and Monitoring Studies.

key research themes and evolving trends in exosome-related clinical trials.

Conceptual Mapping

Figure 4 illustrates seven research clusters in exosome clinical trials. The yellow and orange clusters focus on biomarkers and RNA-based cargo. The red cluster centers on therapeutic outcomes (efficacy, safety, placebo). Green highlights neurological studies (e.g., Alzheimer's), while blue relates to biofluid sources and isolation methods. Light blue addresses disease monitoring, and purple explores emerging therapies like diabetes and drug combinations. These clusters reflect the diverse and evolving clinical applications of exosomes.

Emerging Topics

Figure 5 presents the overlay visualization of term occurrences over time, highlighting emerging topics in yellow. These recent and trending terms include efficacy, placebo, safety, improvement, combination, injection, dapa, and score, suggesting a strong recent research focus on evaluating clinical outcomes, therapeutic strategies, and treatment validation in exosome-based interventions. In contrast, earlier studies, represented in dark blue, concentrated on terms such as plasma, serum, mir, and mirna, reflecting an earlier emphasis on biomarker discovery and molecular profiling. The transition toward yellow nodes indicates a shift from foundational research to applied clinical investigations and therapeutic evaluations in the field of exosome-based clinical trials.

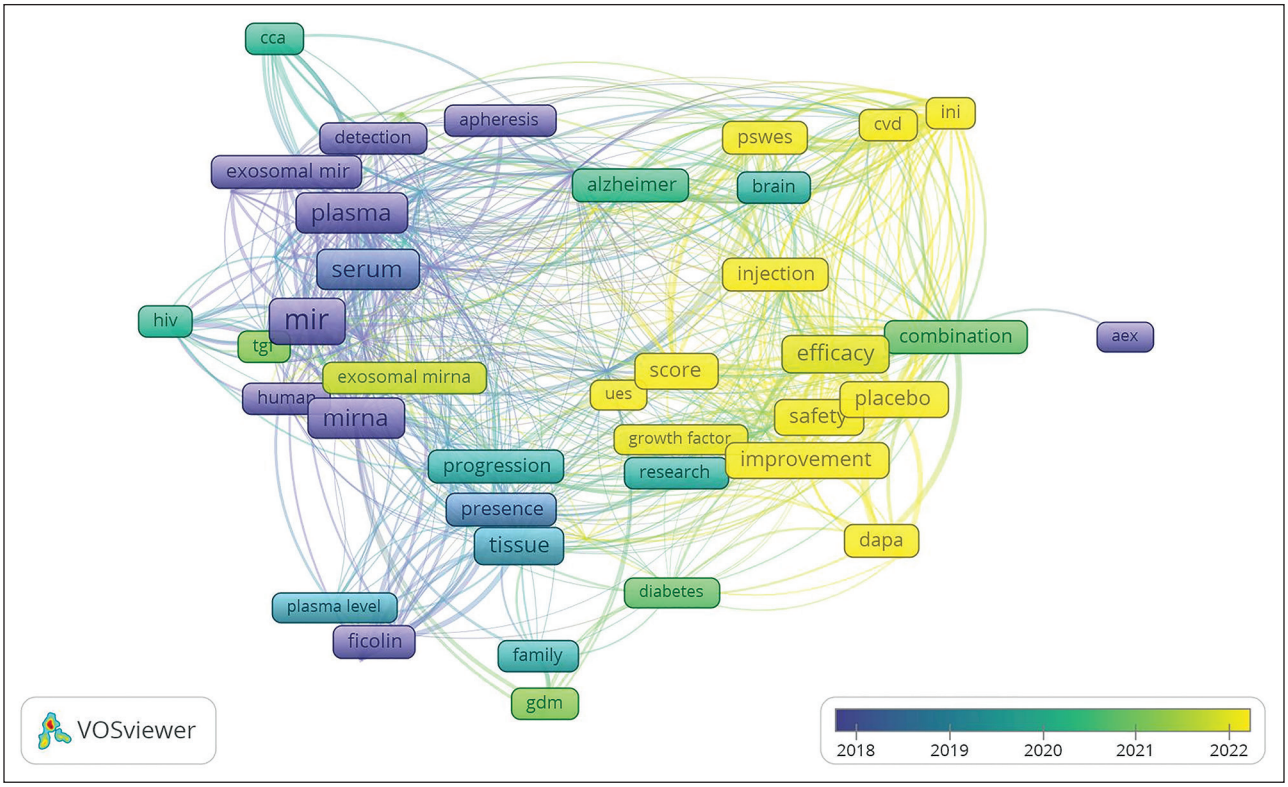


Figure 5. Overlay Visualization of Terms Extracted From Exosome-related Clinical Trial Abstracts and Titles. Terms are Color-coded Based on Their Average Publication Year, Ranging From Earlier Studies in Dark Blue (2018) to More Recent Topics in Yellow (2022). Emerging Areas Include Efficacy, Safety, Placebo, Combination, and Injection, Indicating a Growing Focus on Clinical Translation and Therapeutic Evaluation. In Contrast, Earlier Research Emphasized miR, Plasma, Serum, and miRNA, Reflecting Foundational Biomarker and Sample Analysis. This Shift Highlights the Evolution From Basic Molecular Investigations to Clinical Outcome-driven Research.

Conclusion

This systematic review, encompassing 90 clinical trials, underscores the growing clinical relevance of exosomes in diagnostics, therapeutics, and drug delivery across diverse diseases. Most studies focused on exosomal miRNAs, long non-coding RNAs (lncRNAs), and proteins as potent biomarkers for conditions such as Alzheimer's disease, acute myeloid leukemia (AML), hepatocellular carcinoma (HCC), pancreatic cancer, and prostate cancer. Exosomes were primarily derived from plasma and serum, but also from urine, ascites, sputum, tears, breast milk, saliva, and adipose- or placenta-derived stem cells. They served as biomarkers, treatment agents, and delivery vehicles, especially in trials targeting neurodegenerative diseases, COVID-19, cancer, knee OA, spinal cord and nerve injuries, and transplant rejection. Stem cell-derived exosomes and exosome-based formulations (e.g., nebulized or injected) demonstrated promising regenerative, immunomodulatory, and anti-inflammatory effects with strong safety profiles. Notably, Alzheimer's, COVID-19, and skin rejuvenation emerged as hot application areas, while miRNAs, placebo-controlled trials, and efficacy assessments dominated recent keywords (Figure 2). Conceptual and temporal mapping revealed evolving research from molecular profiling toward clinical efficacy, treatment combinations, and precision delivery systems (Figures 2–4). However, significant gaps remain—standardization in exosome isolation, characterization, and dosage, as well as the lack of large-scale randomized controlled trials (RCTs) and long-term outcome data, continue to limit clinical adoption. Future directions should focus on harmonized protocols, multicenter validation studies, and integration of artificial intelligence (AI) and omics tools to advance exosome-based strategies from promising research to clinical application.

Abbreviations

AAA: Abdominal aortic aneurysm; **Akt/mTOR:** Protein kinase B/mammalian target of rapamycin; **ALIX:** ALG-2 interacting protein X; **AML:** Acute myeloid leukemia; **AMR:** Antibody-mediated rejection; **ARDS:** Acute respiratory distress syndrome; **BACE1-AS:** Beta-site amyloid precursor protein cleaving enzyme 1-antisense; **BM-MSC:** Bone marrow mesenchymal stem cell; **CCA:** Cholangiocarcinoma; **CCM:** Cell-free stem cell-derived conditioned medium; **CD133:** Cluster of differentiation 133; **CD4+:**

Cluster of differentiation 4 positive; **CD69:** Cluster of differentiation 69; **CDK6:** Cyclin-dependent kinase 6; **COVID-19:** Coronavirus disease 2019; **CRP:** C-reactive protein; **CTL:** Cytotoxic T lymphocyte; **CVD:** Cardiovascular disease; **DC:** Dendritic cell; **DGF:** Delayed graft function; **EVs:** Extracellular vesicles; **exo-LncRNA TUG1:** Exosomal long non-coding RNA taurine upregulated gene 1; **ExoChip:** Exosome microfluidic chip; **GBC:** Gallbladder carcinoma; **GDM:** Gestational diabetes mellitus; **GZFL:** Guizhi Fuling Decoction; **HACS:** Human adipose tissue stem cell-derived exosome-containing solution; **HCC:** Hepatocellular carcinoma; **HER2/3:** Human epidermal growth factor receptor 2/3; **HIF-1α:** Hypoxia-inducible factor 1-alpha; **hPMSC-sEVs:** Human placental mesenchymal stromal cell-derived small extracellular vesicles; **HPE:** Human platelet extract; **HSP70:** Heat shock protein 70; **HSP90:** Heat shock protein 90; **HUC-MSC:** Human umbilical cord mesenchymal stem cell; **KS:** Kaposi's sarcoma; **KSHV:** Kaposi's sarcoma-associated herpesvirus; **LC3:** Microtubule-associated protein 1 light chain 3; **lncRNA:** Long non-coding RNA; **MBD:** Myeloma bone disease; **MCI:** Mild cognitive impairment; **MetS:** Metabolic syndrome; **MIF:** Macrophage migration inhibitory factor; **miRNA:** MicroRNA; **MSC:** Mesenchymal stem cell; **MVBs:** Multivesicular bodies; **NF-PA:** Non-functioning pituitary adenoma; **ONFH:** Osteonecrosis of the femoral head; **p53:** Tumor protein 53; **PaO_2/FiO_2:** Partial pressure of oxygen/fraction of inspired oxygen; **PCI:** Percutaneous coronary intervention; **PEL:** Primary effusion lymphoma; **piR-10506469:** Piwi-interacting RNA-10506469; **PM:** Particulate matter; **pNCC:** Phosphorylated sodium-chloride cotransporter; **PRINS:** Psoriasis susceptibility-related RNA gene induced by stress; **PS:** Phosphatidylserine; **RCT:** Randomized controlled trial; **RHOU:** Ras homolog family member U; **RIC:** Remote ischemic conditioning; **SDB:** Sleep-disordered breathing; **SOCS2-AS1:** Suppressor of cytokine signaling 2-antisense 1; **TDP-43:** TAR DNA-binding protein 43; **Tfh:** Follicular helper T cell; **TRAP:** Traffic-related air pollution; **TSG101:** Tumor susceptibility gene 101; **TZD:** Thiazolidinedione; **U-Ex Tg:** Urinary exosomal thyroglobulin; **UC-WJ:** Umbilical cord Wharton's jelly; **VEGF-α:** Vascular endothelial growth factor-alpha.

Authors' Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Ethical Approval

This study does not require any ethical approval.

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