RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2026, **16**, 30633

Therapeutic exosomes in cancer: efficacy and safety perspectives

Rajib Dhar, [a] Ling Shing Wong [cd] and Vetriselvan Subramaniyan *[ab]

Extracellular vesicles (EVs) are essential signalling mediators within biological systems, playing a vital role in cell-to-cell communication. In cancer research, exosomes (a subpopulation of EVs that originate from endosomes) have become the most highlighted area of study in the current decade. Tumor-derived exosomes (TEXs) participate in tumor development and cancer progression. They regulate tumor cell growth, immune suppression, angiogenesis, metastasis, epithelial–mesenchymal transition and organ-specific metastasis. The molecular signatures of exosomes, including DNA, RNA, proteins, and lipids, play a crucial role in cancer development and hold significantly promising biomarkers for cancer. Beyond their pathological role, EVs offer a cell-free platform for the development of therapeutic methods for cancer. This phenomenon is having a huge impact compared to cell-based therapy by overcoming several limitations, such as toxicity, high cost, and effectiveness. Multiple therapeutic exosome sources are available, including stem cell-derived exosomes, plant-derived exosomes, immune cell-derived exosomes, and modified exosomes. Compared with conventional cell-based therapies, exosome-based strategies present several advantages, including reduced toxicity, biocompatibility, improved stability, and specificity. Multiple therapeutic exosomes sources are available, including stem cell-derived exosomes, plant cell-derived exosomes, immune cell-derived exosomes, milk-derived exosomes, bacteria-derived exosomes, and modified/engineered exosomes. The therapeutic impact of these exosomes is strongly influenced by multiple factors, such as their cellular origin, heterogeneity, inner cargos, surface charge, surface composition and physicochemical properties. This review discusses the current limitations, key challenges and future perspectives related to exosome-based therapeutics with particular emphasis on the comparative and translational potential of different exosome sources.

Received 15th January 2026
Accepted 30th April 2026

DOI: 10.1039/d6ra00373g

rsc.li/rsc-advances

1. Introduction

Cancer is a complex disease that promotes uncontrolled cell growth and the development of tumors. It leads to high death rates worldwide.[1] The global scientific community is dedicated to trying to address this crisis. In traditional cancer theranostics (therapeutics and diagnostics), progress has been limited for several reasons, such as toxicity, specificity, and failure to achieve early diagnosis. Early diagnosis of cancer is very challenging,[2] but exosome-based cancer profiling can transform cancer liquid biopsies.[3,4] Drawbacks are connected with several cancer treatment approaches, such as surgery (this method promotes cancer),[5] radiotherapy (secondary malignancies, infertility),[6] chemotherapy (cardiac and nephrological complications, and neurotoxicity),[7] and immunotherapy (endocrine, pulmonary, and neuro-related issues, and CAR-T cell therapy toxicity).[8] Extracellular vesicle (EV)-based cancer research is addressing these scientific problems in more efficient ways. EVs can be classified into several subpopulations, including exosomes, microvesicles, and apoptotic bodies, with exosomes receiving the most attention in cancer studies.[9] They carry a dynamic molecular cargo like DNA, RNA, proteins, and lipids, whose composition reflects the status of the parent cell (whether healthy or suffering from any pathological complications). During cancer development, EVs play a significant role in tumor microenvironment (TME)-related cellular communication (especially exosomes, a subpopulation of EVs).[10] In 2015, a milestone invention happened when scientific research indicated that exosome integrins play a role in organ-specific metastasis (based on their surface integrin).[11] After this, exosomes were highlighted more in cancer research. Exosomes are also carriers of several cancer biomarkers (diagnostic and

[a]*Integrated Therapeutics and Drug Discovery Lab, Jeffrey Cheah Sunway Medical School, Faculty of Medical and Life Sciences, Department of Biomedical Sciences, Sunway University, Bandar Sunway, 47500 Selangor Darul Ehsan, Malaysia. E-mail: rajib.d@imail.sunway.edu.my; vetris@sunway.edu.my*

[b]*College of Health Sciences, Abu Dhabi University, United Arab Emirates*

[c]*Faculty of Health and Life Sciences, INTI International University, Nilai, 71800 Malaysia. E-mail: lingshing.wong@newinti.edu.my*

[d]*Faculty of Nursing, Shinawatra University, 99 Moo 10, Bangtoey, Samkhok, Pathum Thani 12160, Thailand*

prognostic).[12] Advanced nanotechnology-based exosomes profiling overcomes challenges related to the early detection of cancer.[13] In this review, we cover the link between cancer and exosomes, therapeutic exosome sources and their complications in cancer therapy, and the improvement of exosome-based cancer therapy.

Rajib Dhar

Mr Rajib Dhar is a PhD scholar in the Faculty of Medical and Life Sciences, Department of Biomedical Sciences, at Sunway University, Malaysia, working in the Integrated Therapeutics and Drug Discovery Lab. He specializes in exosome biology and cancer therapeutics. His research focuses on the development and mechanistic understanding of therapeutic exosomes as next-generation cell-free strategies against cancer. Rajib's work integrates molecular oncology, extracellular vesicle biology, and translational medicine to address tumor progression control and targeted therapeutic delivery. He has established a strong publication track record in the exosome field, with contributions to high-quality peer-reviewed journals. Driven by a clear research vision and a commitment to excellence, Rajib aspires to conduct advanced research in exosome-based precision cancer medicine.

2. Exosomes biogenesis

Exosomes biogenesis (Fig. 1) is the maturation process of endosomes. Several molecules together synchronously conduct this process. In this process, the early endosome to the late endosome, and the late endosome to the multivesicular body (MVB) (the inside of a MVB carries multiple intraluminal vesicles-ILVs) development was observed.[14] Endosomal sorting complex required for transport (ESCRT) complex-dependent and ESCRT complex-independent pathways are associated with exosome biogenesis. The ESCRT complex-dependent pathway is regulated *via* ESCRT-0, ESCRT-I, ESCRT-II, ESCRT-III, ALIX, TGS101, *etc.*[15] The ESCRT complex-independent pathways link with lipids, transmembrane proteins, and sphingomyelinase.[16] In cancer, exosome release depends on ESCRT complex-independent pathways.[17] In this process, sphingomyelinase-based hydrolysis reactions convert sphingomyelin into ceramide and phosphatidylserine. Ceramide supports the fusion of MBVs to the plasma membrane and releases exosomes.[17] Rab proteins are also significant molecules linked with membrane trafficking and vesicle release.[18]

Ling Shing Wong

Prof. Ts. Dr Wong Ling Shing is a Malaysian environmental scientist and multidisciplinary researcher, holding a PhD from the National University of Malaysia (UKM, 2011). His research spans biosensors, bioindicators, photosynthetic microbes, agricultural biomass, nanotechnology, health sciences, artificial intelligence, and renewable energy. Wong has led over 25 research projects and published more than 250 scientific articles. He has received numerous accolades, including awards at the Malaysia Technology Expo (MTE) and International Technology Expo (ITEX), as well as the Vice Chancellor Award and Most Promising Young Researcher recognition from INTI International University in 2016. He currently serves as Pro Vice-Chancellor for Research and Innovation at INTI International University, President of Einstein Research Academy, and Editor-in-Chief of INTI Journal, and is a certified Technologist (Ts.) under the Malaysia Board of Technologists (MBOT). Wong is a strong advocate for advancing the Sustainable Development Goals (SDGs) through multidisciplinary research.

Vetriselvan Subramaniyan

Professor Dr Vetriselvan Subramaniyan, PhD, FMSA, FIABMS, FRSB, is the Principal Investigator of the Integrated Therapeutics and Drug Discovery Lab in addition to teaching pharmacology at Sunway University's Faculty of Medical and Life Sciences in Malaysia. He has contributed to pharmacology, translational medicine, and biomedical sciences at universities in Malaysia and overseas, including Monash University Malaysia, Arba Minch University, and MAHSA University. He has over 16 years of experience in teaching, research, academic leadership, and international collaboration. His main areas of interest are drug development, molecular pharmacology, obesity, natural product treatments, translational medicine, and public health. Through research funding, patents, keynote addresses, and invited talks at important conferences, his work has garnered notice on a global scale. Stanford University and Elsevier rank him in the top 2 percent of scientists worldwide. Professor Vetriselvan is a Fellow of the Royal Society of Biology (FRSB), the Malaysian Scientific Association (FMSA), and the Indian Association of Biomedical Scientists (FIABMS). In addition to actively participating in postgraduate supervision, curriculum development, and international academic collaborations, he has held academic leadership positions as Acting Dean and Deputy Dean.

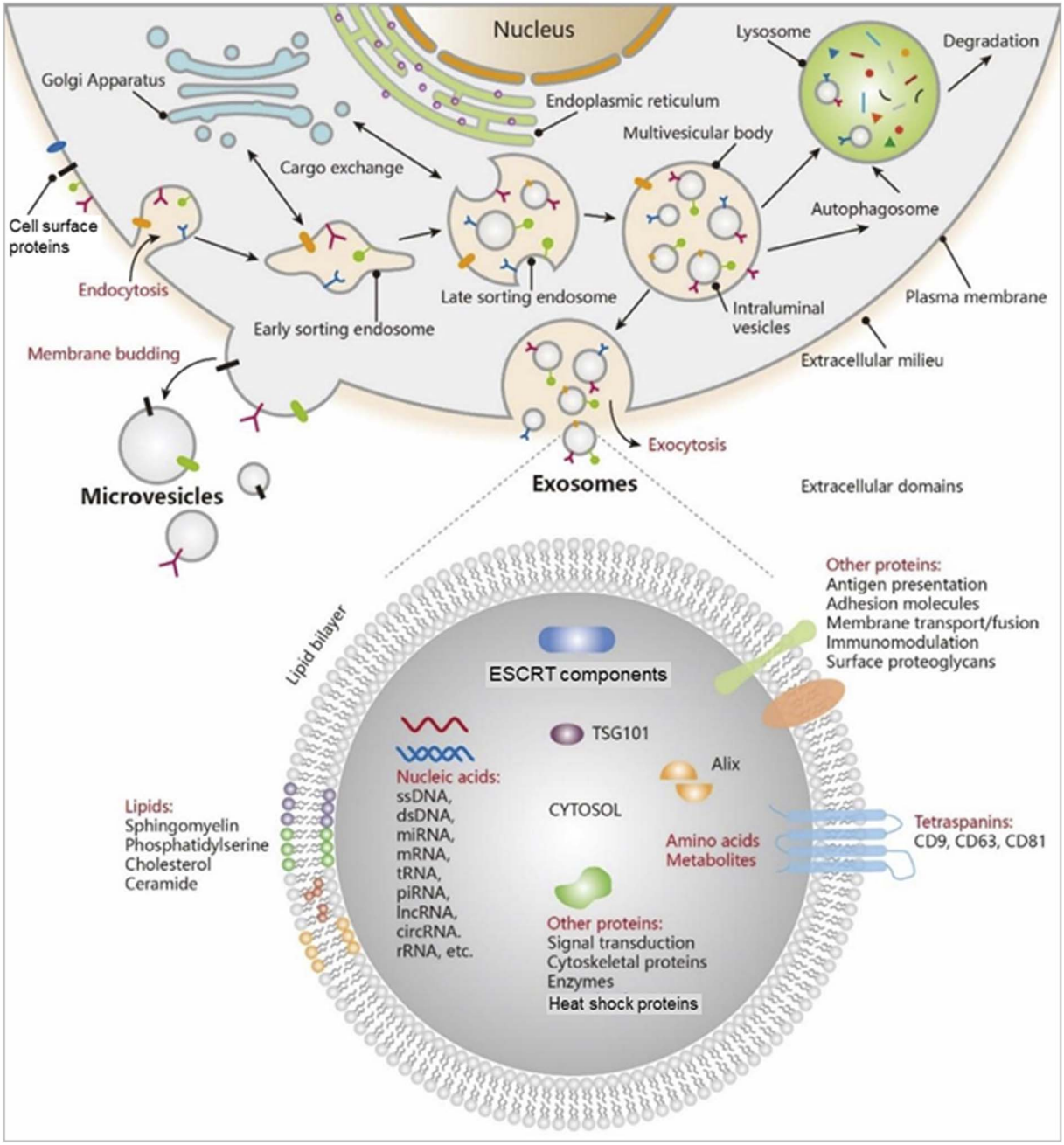

Fig. 1 Exosome biogenesis and exosome molecular cargo (reproduced with permission from ref. 19; copyright @ 2021 American Chemical Society).

3. Interrelation between exosomes and cancer

Cancer development is a complex phenomenon, during this process tumor micromovement (TME)-associated cells maintain cell-to-cell communication *via* TEXs (tumor-derived exosomes) (Fig. 2). TEX-based metabolic reprogramming promotes cancer.[20] Cancer-associated fibroblast (CAF) exosomes enhance the glycolysis process and reduce the tricarboxylic acid cycle (TCA).[20] This alternation of metabolic events enhances angiogenesis (this process develops new blood vessels and helps in the uptake of large amounts of O_2 and nutrients). The TEX's molecular cargo, such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), miRNA-21, and matrix metalloproteinases MMP2 and MMP9, activates angiogenesis.[21] Immune system suppression[22] is a key event in tumor growth.[23] In this event, tumor cells can escape immune surveillance. M2 (a subpopulation of macrophages) polarization develops an anti-inflammatory response and promotes tumor growth. Epithelial ovarian cancer-derived exosome-associated miRNA-222 promotes M2 polarization.[24] Exosome-mediated down-regulation of HKG2D (this is an NK cell receptor)

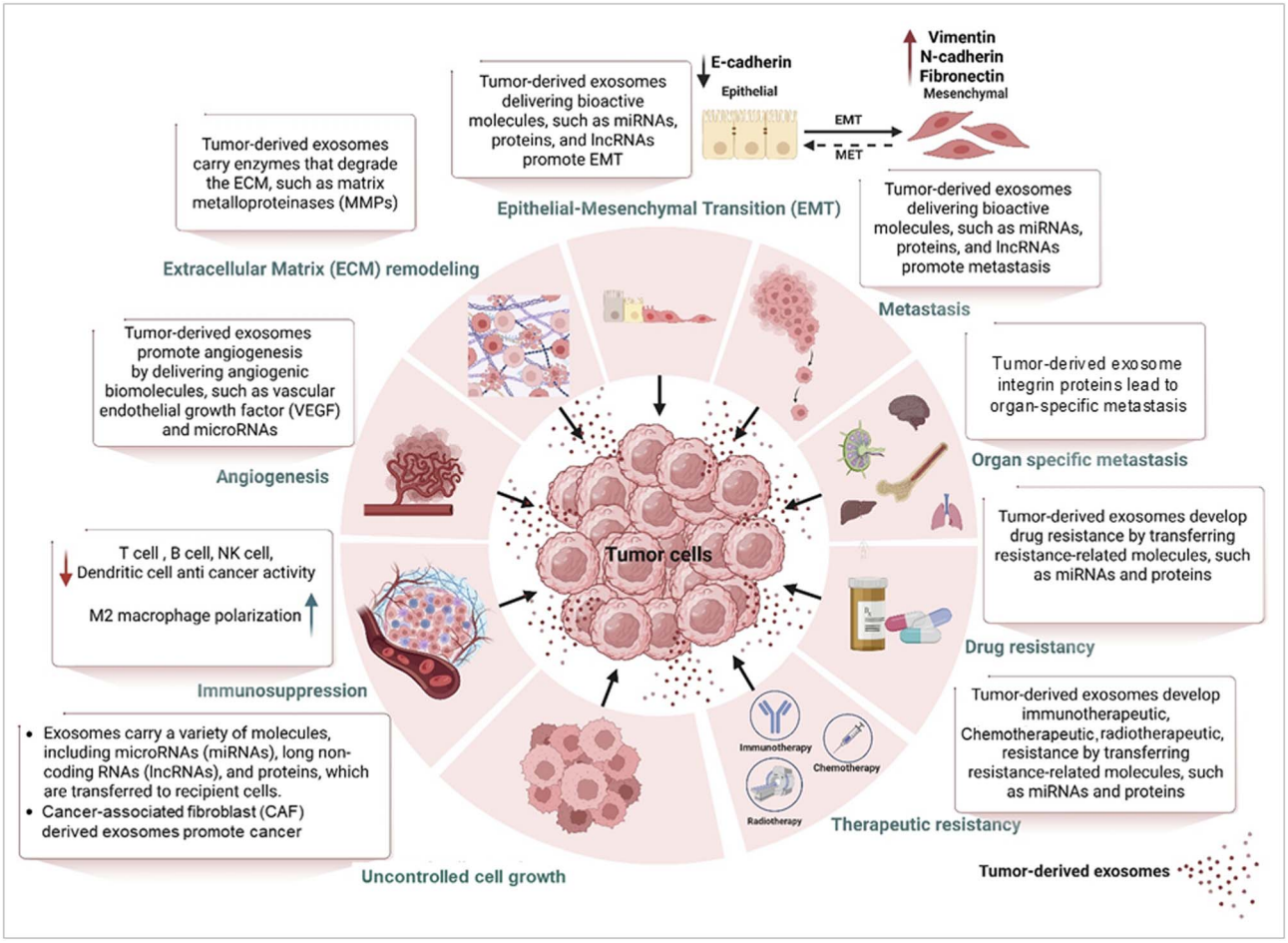

Fig. 2 The role of tumor-derived exosomes in cancer (created with biorender.com).

suppresses NK cell activity, and programmed cell death 1 (PD1), Fas ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL) expression leads to natural killer (NK) cell and T-cell apoptosis.[25] TEXs mediated downregulated dendritic cell (DC) maturation *via* galectin-9, TIM-3, and CD47, and inhibited DC differentiation by heat shock proteins HSP-70 and HSP-72 and prostaglandin E2 (PGE2).[26] In cancer, TEXs cargo TGF-β suppresses the B-cell anti-cancer activity, *via* inhibiting the proliferation of B cells.[27,28] The TEXs HMGB1 molecule reprograms the B cell's activity and promotes cancer.[29] In cancer, hypoxic tumor cell-derived exosomes suppress the myeloid-derived suppressor cell (MDSC) activity.[30] Extracellular matrix (ECM) modification promotes cancer metastasis development.[31] Significantly, TEXs relegate ECM modification (TEXs MMPs, integrins, and annexins play a vital role in the ECM) in cancer.[32] Tumor exosomes promote the epithelial–mesenchymal transition (EMT) in cancer.[33] In the advanced stage of cancer, tumor cells enter the blood circulation. These tumor cells migrate to specific organs *via* the guidance of exosome integrin proteins.[11] TEXs-mediated organ-specific metastasis happens in the brain, liver, lungs, bone, and lymph nodes.[11] In cancer treatment, the most challenging aspect is drug and therapeutic resistance. TEXs play a significant role in drug and therapeutic resistance in cancer: in breast cancer cell lines MCF-7 and MDA-MB-231, TEX-mediated miR-155 promotes resistance to doxorubicin (DOX) and paclitaxel (PTX) and drives epithelial–mesenchymal transition (EMT), while in non-small cell lung cancer (NSCLC), TEX-associated miR-100-5p contributes to cisplatin resistance.[34–36] Exosomes and cancer stem cells are interconnected and contribute to cancer progression.[34,37] Finally, exosomes have opened a new era in the understanding of cancer biology and may contribute to the advancement of precision oncology.

4. Role of therapeutic exosomes in cancer

In cancer, therapeutic exosomes have added a new dimension.[38] There are several therapeutic exosome sources,[39] such as stem cell-derived exosomes, tumor-derived exosomes, plant-derived exosomes, chimeric exosomes, immune cell-derived exosomes, and exosomes modified at the molecular level/chemical level (chimeric antigen receptor, CAR-T cell-derived exosomes, CRISPR-Cas9 system carried exosomes) (Fig. 3).[40] Exosome-based cancer therapy is a cutting-edge approach compared to cell therapy in cancer.[41] Toxicological safety analysis is a less-

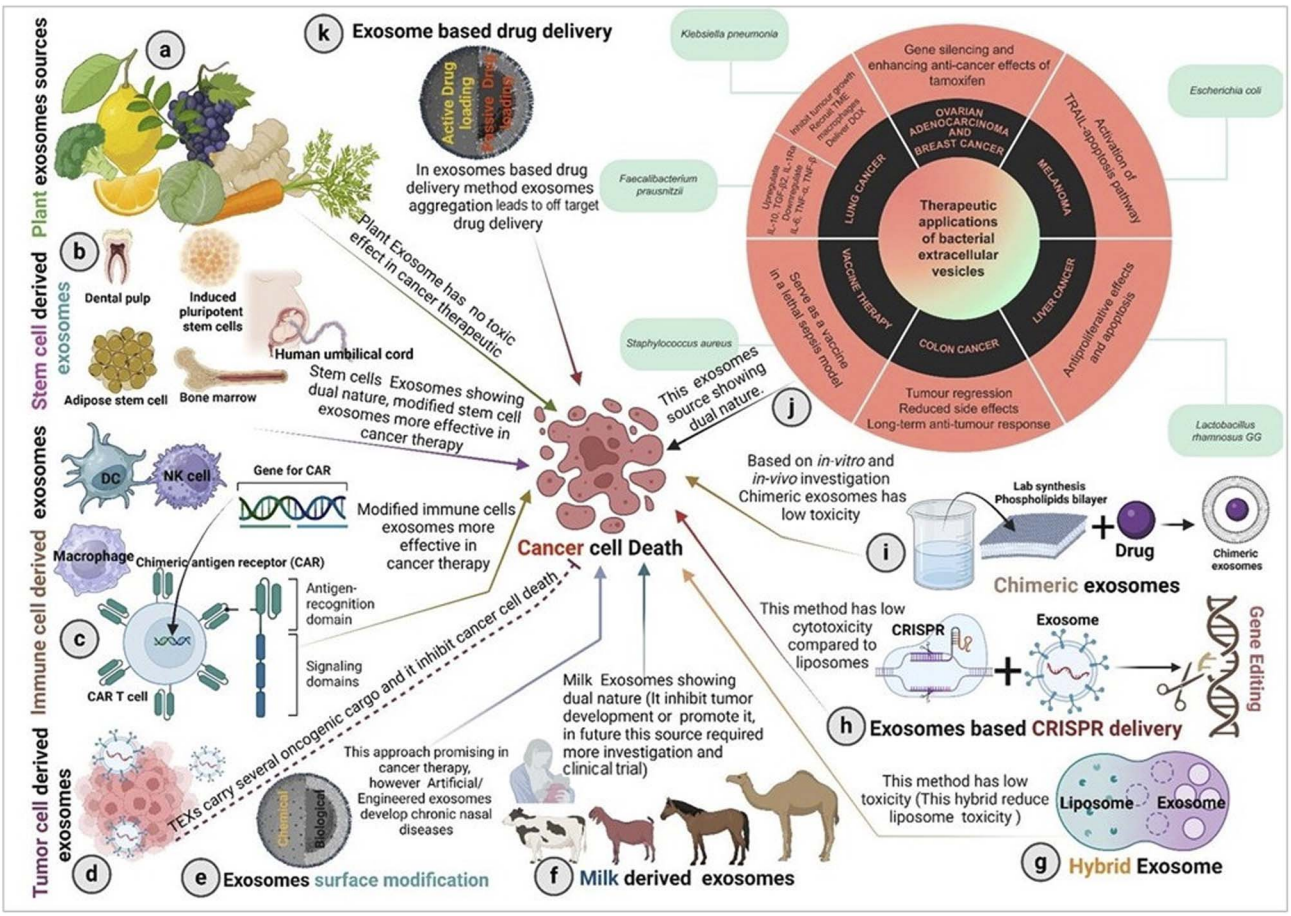

Fig. 3 The efficacy of exosome-based cancer therapeutics: (a) plant exosome sources, (b) stem cell exosome sources, (c) immune cell-derived exosome sources, (d) tumor-derived exosomes, (e) surface-modified exosomes, (f) milk-derived exosomes, (g) hybrid exosomes, (h) exosome-mediated CRISPR transport, (i) chimeric exosomes, (j) bacterial outer surface-derived EVs and their role in cancer therapy, and (k) exosome-based drug delivery ((j): reproduced with permission under Creative Commons CC BY 4.0 license ref. 67; copyright @ 2022).

exposed domain in EVs biology. During cancer development, immune cells play a vital role in cancer prevention.[42] In this phase, tumor cells derived exosomes maintain a complex cancer-promoting cell-to-cell communication *via* reprogramming immune cells.[43] On the other hand, immune cell-derived exosomes have the potential to serve as therapeutic tools in cancer therapy.[44,45] Among several immune cells-derived exosomes, the dendritic cell-derived exosome (Dex) is the most commonly used immune cell-derived exosome. During clinical trials, it has shown promising outcomes *via* developing an anti-cancer immune response.[46–48] Dendritic cell-based immune therapy has some limitations, such as a) dendritic cell (DC)-based immunotherapy stage I and II clinical trials have shown mild side-effects, b) there are storage problems relating to live DCs, and c) the presence of DC molecular activity is unknown. These limitations can be addressed *via* Dex. Dex boosts the NK cell-mediated anti-cancer activity.[48] This method can be more effective in the future *via* programmed cell death ligand 1 (PD-L1)-based surface modification, which promotes the activation of B cell- and T cell-mediated immune responses against cancer.[48,49] Cancer development and progression are regulated *via* tumor-derived exosomes (TEXs).[50] In some cases, they are used as therapeutics (TEX miRNA-124 shows anticancer activity against colorectal cancer).[51,52] This method is not recommended for therapeutic applications (because of the enrichment of oncogenic cargos).[53] In the future, it may be used after molecular-level modification, proper multi-omics and single-exosome profiling.[54] In the cancer prevention journey, stem cell-derived exosomes are the most exciting approach.[55–60] This is an efficient cell-free cancer therapeutic approach.[41] Global ongoing research activity indicates that stem cell-derived exosomes have a dual nature in cancer (they may promote or inhibit cancer).[61–65] Mesenchymal stem cell (MSC)-derived exosomes are a potential therapeutic exosome source.[55] Bone marrow mesenchymal stem cell (BMSC)-derived exosome-based miRNA transport inhibits cancer progression.[59] On the other hand, research evidence mentions that BMSC exosome miRNA-425 promotes cancer metastasis.[63] MSCs derive exosomes that regulate cancer therapeutic resistance development (in breast cancer, the MSC-derived exosome miRNA-21-5p influences DOX resistance development).[61,66] After the analysis of several research studies, it is concluded that modified exosomes are more effective compared to non-modified exosomes.[55]

Table 1 The impact of therapeutic exosomes on cancer therapy[a]

Type of exosome/exosome-based approach for cancer therapy	Challenges	Complications and impact	Future recommendations	References
Immune cell-derived exosomes	- Heterogeneity - Isolation of pure exosomes - Higher immunogenicity - Stronger resistance to immunosuppressive effects - Activate NK cells in the immune system, and Th1 activation is lower (dendritic cell-derived exosomes-DCexo)	Toxicologically, DCexo has low toxicity (validation of the toxicology of other immune cell-derived exosomes is pending)	- Single exosome profiling - Multi-omics profiling - Membrane engineering - Surface modification - Clinical trials are required (this analysis supports future immune cell-derived exosome-based immunotherapy or vaccine development)	43–49,93
Tumor-derived exosomes (TEXs)	- Heterogeneity - Enrichment of oncogenic molecules - They promote cancer	Highly toxic and not recommended as a therapeutic tool	- Single exosome profiling - Multi-omics profiling - Genetic modification - Clinical trials are required (this analysis supports us in making a decision regarding the therapeutic application of TEXs)	51–53,94
Stem cell-derived exosomes	- Heterogeneity - Large-scale production	This approach needs more time for a clear toxicological statement (results are mixed worldwide), but modified stem cell-derived exosomes are more efficient compared to unmodified exosomes	- Single exosome profiling - Multi-omics profiling - Surface modification - Clinical trials are required (this analysis supports the development of a therapeutically effective approach)	55–65,95,96
Plant-derived exosomes (PDExo)	- Heterogeneity - Isolation - Characterisation - Functional diversity of different parts of plant exosomes	Plant exosomes are a non-toxic therapeutic approach for cancer	- Single exosome profiling - Multi-omics profiling - Clarity is required about phytochemical molecule activity in plant-derived exosomes for cancer therapy - Medicinal plants will become a major source of PDExo - More clinical trials are required (this analysis supports the development of a cost-effective therapeutic approach)	68–71,97
Chimeric exosomes/artificial exosomes/engineered exosomes	- Heterogeneity - Preparation protocols - Biocompatibility concerns	- A more specific and effective cancer therapeutic approach - They lead to the development of chronic nasal diseases (artificial/engineered exosomes) – chimeric exosomes show low toxicity *in vitro* and *in vivo* models	- Standard protocol development - More toxicological investigations are required - Clinical trials are required (this analysis supports controlled, efficient, and effective exosome-based cancer therapeutic development)	75–81
Hybrid exosomes	- Heterogeneity	- Exosome–liposome hybrids have a low toxic effect compared to liposomes	- Single exosome profiling - Multi-omics profiling	85,98,99

Table 1 (*Contd.*)

Type of exosome/exosome-based approach for cancer therapy	Challenges	Complications and impact	Future recommendations	References
	- Purity	- Plant exosomes fused with engineered mesenchymal stem cell-derived exosomes have low toxicity, however, this approach does not apply to cancer therapy	- Toxicity analysis - Clinical trials are required (this shows that these exosomes need more investigation for effective cancer therapeutic development)	
Milk-derived exosomes	- Heterogeneity - Dual nature (this source also plays a role in tumor development)	- This source is also related to tumor development	- Single exosome profiling - Multi-omics profiling - Toxicity analysis - Clinical trials are required (this source is need more investigation for effective cancer therapeutic development)	100–102
Bacterial surface-derived exosomes	- Heterogeneity - Dual nature (this source also plays a role in tumor development) - Aggregation - Low antigenic expression	- This source is also associated with tumor suppression or promotion	- Single exosome profiling - Multi-omics profiling - Toxicity analysis - Clinical trials are required (engineered bacterial surface-derived exosomes may become more effective in cancer therapeutic development)	67,103,104
Genetically modified (CRISPR-Cas9 transport) exosomes	- Purity of isolated exosomes - Heterogeneity	Low cytotoxicity compared to liposomes	- Single exosome profiling - Multi-omics profiling - Toxicity analysis - Clinical trials are required, as this analysis supports the development of target-specific exosome-based gene-editing approaches	82,85–87
CAR-T cell-derived exosomes	- Systemic toxicity - Heterogeneity	- CAR-T cell therapy is effective only toward blood cancer - CAR-T cell-derived exosomes are more effective compared to CAR-T cell therapy with low toxicity	- Single exosome profiling - Multi-omics profiling - Surface modification - Clinical trials are required, as this analysis supports the development of target-specific exosome-based cell-free therapeutic approaches	88–90,105

[a] ● Single exosome profiling: this is a smart approach for exosome profiling (this method is a solution involving pure exosome isolation, inner-outer molecular profiling, exosome molecular expression analysis, and a combination of multi-omics, AI, and machine learning (ML) complete exosome analysis). This method is used for exosome-based cancer biomarker and therapeutic development. ● Multi-omics profiling: this method provides complete molecular profiling of exosomes *via* genomics, transcriptomics, proteomics, and lipidomics. ● Membrane engineering: this method modifies the exosome phospholipid membrane *via* conjugating several molecules (drugs, ligand molecules, fluorescent molecules, nanoparticles, *etc.*). ● Surface modification: this method modifies the exosome surface, like membrane engineering. ● Genetic modification: this method modifies the molecular expression of exosomes in several cases related to the inside or surface (this modification takes place in the parent cell, *i.e.* the exosome production cell). ● Clinical trials are required: clinical trials are required to measure several safety parameters, such as dose, toxicity, and side effects, and to get ethics approval for market release. ● Phytochemical molecule activity: this is applicable to plant-derived exosomes (PDExo carries several phytochemical compounds with it, we need a clear understanding of the functional mechanism of this group of molecules in relation to PDExo and to understand the contributions of these compounds to the toxicity of PDExo). ● Toxicity analysis: analysis of the toxic nature of compounds in the process.

Exosome surface proteins or surface engineering can enhance anticancer activity. The most exciting fact about exosomes is that the surrounding conditions (*e.g.* pH and hypoxia) influence the exosome anti-cancer cargo packaging, which is also regulated releasing rate of exosomes.[61] In the future, stem cell-derived exosome research will need toxicological validation and single exosome profiling with omics profiling.[54,68] The limitations of stem cell-derived exosomes include a lack of

standard protocols for stem cell-derived exosome isolation, purification, storage, large-scale production, and heterogeneity.[61] Plant-derived exosomes (PDExs) (vegetables, fruits, *etc.*) are a natural source of exosomes for cancer therapy with low toxicity.[69–72] This source of exosomes requires deep molecular profiling (multi-omics based), standard protocols for high-yield isolation methods, specific PDEx marker development, and toxicological investigations (PDExs are associated with several phytochemical functional mechanisms, and it is still unknown how they work, which needs to be explored) for effective cancer solutions.[70] During clinical trials, plant exosomes show effective anti-cancer activity, and they are also a potential cancer drug delivery tool.[71] Exosomes are vehicles for cellular transport (*e.g.*, drugs and genetic material).[73,74] This method overcomes several traditional delivery system limitations (toxicity, biocompatibility, biological membrane crossing, specificity), and cancer targeting becomes more effective.[73] Exosome-based drug delivery should be non-toxic and non-immunoreactive (exosome off-target drug transport can lead to toxicity).[73,74] This method faces some limitations, such as those related to exosome heterogeneity, large-scale production, specific drug delivery, and improper drug loading.[74] All these limitations have encouraged scientific minds to develop effective and modified exosomes. These modifications were conducted based on deep chemical and biological concepts. At the current time, exosome biology is being transformed *via* the fusion of several advanced exosome synthesis approaches.[75–81] This approach has led to the development of exosomes called artificial chimeric exosomes (ACEs)[75–77]/engineered exosomes[78–80]/exosome and liposome hybrids.[81] ACEs are lab-assembled controllable cancer therapeutic tools. Large-scale exosome production is a challenging process, but this method solves these problems. Research evidence shows that ACEs are low toxicity and biocompatible as cancer therapeutics (proven and evidenced *in vitro* and *in vivo* models).[75] Engineered exosomes can be used to develop smart cancer-targeting platforms. This method reduces off-target cancer therapeutic side effects. The surface modification of exosomes enhances the efficiency and effectiveness of cancer therapy.[82] Overall, the toxicity of modified exosomes is influenced by exposure to synthetic chemicals during the modification process.[83] Engineered exosomes (exo-liposome hybrids) have reduced toxicity compared to liposomes.[81] Limitations of artificial chimeric exosomes and engineered exosomes in cancer therapy include the potential development of chronic nasal diseases.[75–81,84] Exosome-based CRISPR-Cas9 (a gene editing tool) delivery is a cell and tissue-specific, efficient cancer-targeting approach.[85] This transport shows effective anti-cancer activity in *in vitro* and *in vivo* models.[82,86,87] Chimeric antigen receptor (CAR)-T cell therapy is a remarkable cancer therapeutic approach, but it has several limitations (*e.g.* toxicity and effectiveness only against blood cancer).[88] CAR-T cell-derived exosomes show effective anti-cancer activity with low toxicity compared to CAR-T cell therapy.[88–92] Several exosome-

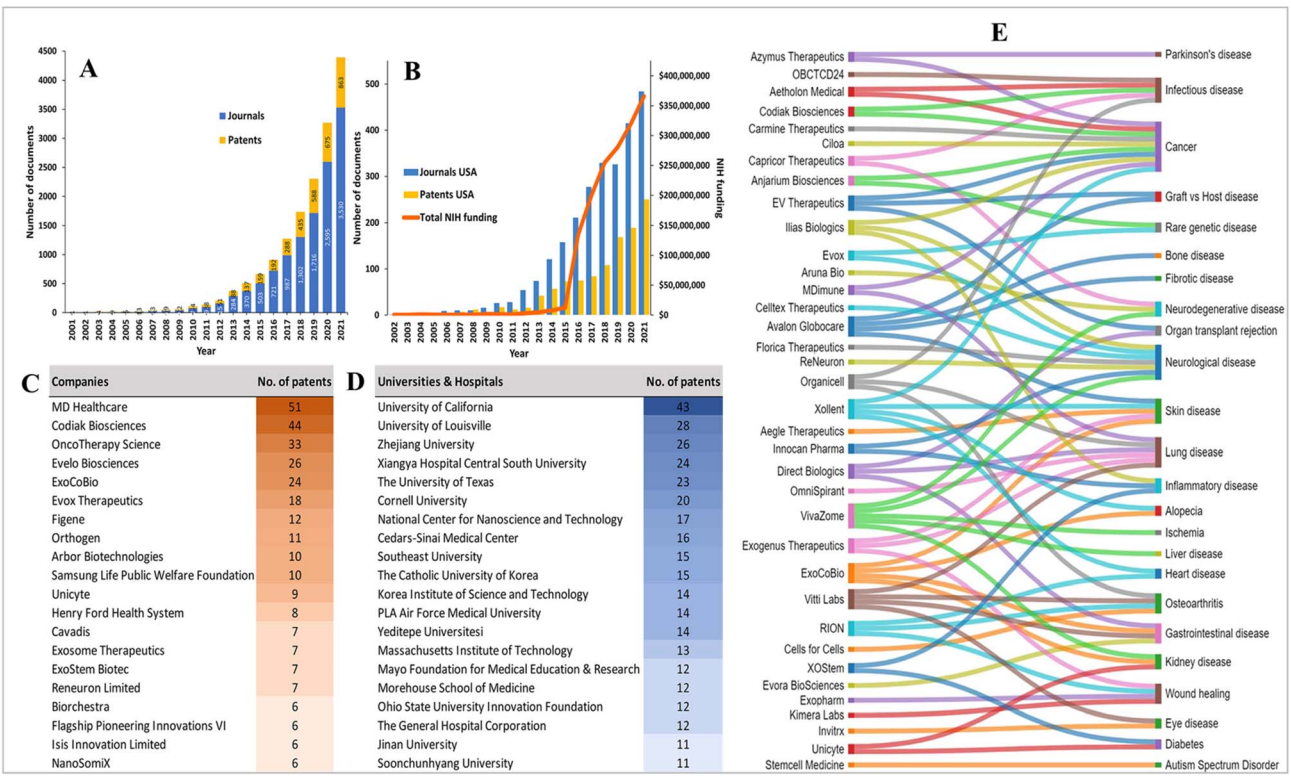

Fig. 4 The landscape of exosome research, from academic institutes to the pharmaceutical industry: (A) journal publications and patent-filing activity, (B) funding activity, (C) company-based exosome patent filings, (D) university- and hospital-based patent filings, and (E) pharma industry investment in exosome-based investigations for several diseases (reproduced with permission from ref. 84; copyright @ 2022 American Chemical Society).

Table 2 A quantitative summary of key global exosome trends

Parameter	Key quantitative trend	Evolving research focus	References
Annual publication growth	A compound annual growth in exosome-related publications over the past decade	Indicates high and rapidly accelerating interest, moving the field from niche discovery to mainstream translational science and clinical research	111,112
Dominant research fields (application)	Cancer research is the most dominant application, followed by diagnostics/biomarkers	Confirms a primary focus on exosomes as non-invasive biomarkers and targeted drug delivery vehicles for oncology, indicating the translational value of their cargo	113–116
Geographical contribution (publication and market share)	China and the USA are the most prolific countries in terms of publications. North America dominates the commercial market share	Highlights strong academic output from Asia-Pacific (especially China) and market leadership/ a commercialization focus in North America, driven by robust funding and research infrastructure	111,115,117–119
Industrial translation barriers (market focus)	Exosome diagnostics and therapeutics market CAGR is high. Reagents and kits hold the largest product segment share	This indicates that immediate industrial needs and investments are focused on enabling technologies, specifically addressing the core barriers of isolation, characterization, and standardization before the widespread rollout of therapeutics	114–116,120

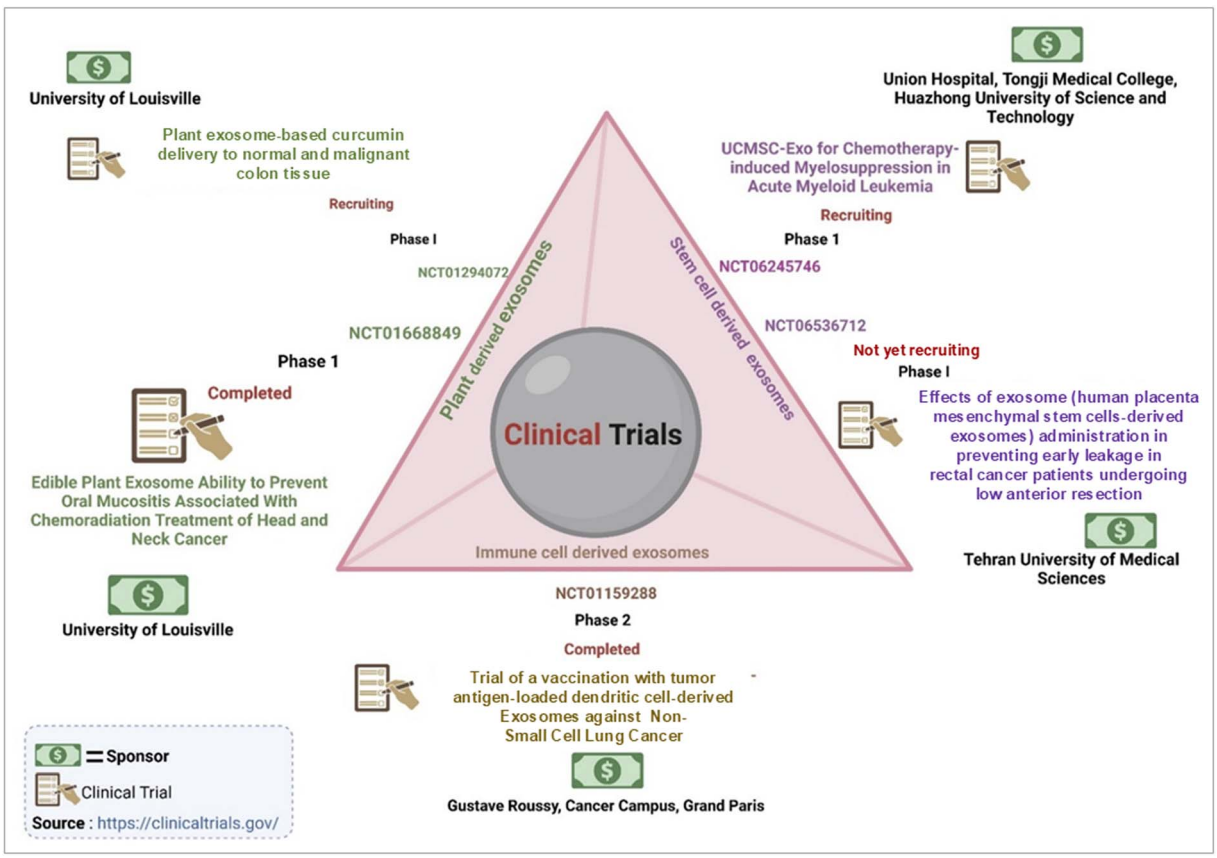

Fig. 5 Clinical trials of therapeutic exosomes (created with biorender.com).

based cancer therapeutic methods, along with complications and future improvements, are summarized in Table 1.

5. The landscape of exosome-based research and the growth of the pharmaceutical industry

Exosome-based research creates an impactful economic ecosystem. Day by day, this research area is growing, and it is developing into a big market for the pharma industry (Fig. 4). The huge number of publications[106] and patent filings and the amount of funding indicate that the exosome-based clinical industry has grown very fast. Cancer-targeting exosome therapeutic development has seen significant growth in the pharmaceutical industry compared to other diseases.[107,108] Companies based in several countries, including the United States, Canada, Italy, and China, have commercialized exosome products for research and healthcare.[109,110] Exosome research trends are summarized in Table 2. We hope that, in the future, exosomes will become a frontier of next-generation clinical research.

6. Exosome-based cancer therapeutic clinical trials

Exosome-based clinical trials[121] indicate that a large number of trials focus on developing early cancer biomarker detection.[122] This clinical research transforms cancer liquid biopsies into a more effective tool. Exosome-based clinical trials are also involved in cell signalling research and cancer therapeutic

Table 3 Exosome research-based complications with solutions

Challenge	Explanation	Solution	References
Isolation and standardization challenges	Based on the isolation process yield, the purity varies, and there is also the risk of contamination with non-exosome particles. The most challenging issue is low yields, affecting downstream analysis and applications	Single-exosome profiling and exosome barcoding	134, 135
Heterogeneity and characterization issues	This relates to exosome size, origin and molecular diversity-based variations	Single-exosome profiling and exosome barcoding	54
Low yields and sensitivity constraints	Technically challenging, with significantly lower molecular expression and low yields	Requires ultra-sensitive detection methods	136
Drug encapsulation capacity	There is no single method for drug loading—it varies for individual methods	Based on scientific evidence, select high-loading methods	137
Functional and mechanistic gaps	Exosome biogenesis, cargo selection, packaging, and uptake are less-explored domains of exosome research. Due to this reason, *in vivo* tracking and understanding physiological roles are difficult	Requires molecular-level scientific investigations	138
Storage and stability problems	Exosomes degrade or aggregate during storage, affecting experimental reproducibility	−80 °C storage alters the sample concentration, zeta value, and purity. PBS maintains the exosome concentration. Lyophilisation methods preserve particle integrity but reduce the concentration of exosomes	139, 140, 141
Clinical translation barriers	Therapeutic applications face regulatory hurdles due to undefined safety profiles, scalability issues, and batch variability	Improve exosome production and isolation, enhance cargo loading and targeting, and standardize methods for analysis and characterization	142
Reproducibility and data variability	Inconsistent methodologies lead to conflicting results, exacerbated by publication bias favouring positive findings	Utilise standardised reporting, rigorous sample preparation protocols, and advanced isolation and characterization techniques	143
Regulatory and ethical hurdles	For clinical applications, standardized manufacturing, safety, and efficacy assessments are lacking	Grow the global regulatory framework for exosome research	144, 145

(Fig. 5) research. Exosome-based cancer therapeutic research focuses on plant sources, stem cell sources and dendritic cell-derived exosomes. There are several effective modified exosomes still not involved in clinical trials. It is hoped that future exosome-based clinical trials will reveal cutting-edge cancer treatment approaches.

7. Challenges and future prospects

Exosome-based cancer therapeutic development is an innovative approach at the current time. This therapeutic development journey has led to several complications, including experimental challenges such as the use of experimental controls, low zeta potential values, specific drug delivery issues, short half-lives, determination of therapeutic doses, and a lack of standardized isolation protocols.[84] In general, exosome biology also presents a challenge known as exosome heterogeneity (it is regulated *via* exosomes origin and molecular diversity).[54,123] The analysis of the functional activity of therapeutic exosomes is associated with complex control selection; however, liposomes are now commonly used as controls. A low zeta value promotes the aggregation of exosomes, which can lead to some difficulties, such as low stability, difficulty with specific delivery, and fast immune response development. Trehalose, a natural sugar molecules prevent exosome aggregation.[124] Exosome therapy generates a lower immune response.[125] Exosome stability, storage, and the compatibility of transport related equipment remain challenging. In general, exosome storage is at 4 °C for a week, −20 °C for a month, and −80 °C for long-term use.[126] Exosome heterogeneity was solved *via* single-exosome profiling[54] and exosome barcoding.[127–129] Exosome toxicological complications require some safety steps, such as selecting less toxic therapeutic exosome sources (plants and stem cells), ensuring less toxic chemical exposure during modification (chemical and genetic), using trehalose to reduce off-target-associated exosome-based toxicity, and using single exosome profiling (a combination of exosome biology, AI, ML, and nanotechnology) for precision exosome-based cancer therapeutic development with less toxicity. Translational research in the exosome domain is challenging due to some issues, such as proper isolation methods, scalability, and a lack of regulatory agencies.[130–133] Exosome research-related challenges and solutions are summarized in Table 3.

8. Conclusions

Exosomes are a cutting-edge theranostics tool for cancer. They have some unique features, such as nanoscale size, biocompatibility, and the ability to cross the blood–brain barrier, that make them potential drug delivery vehicles. It can transport various cargo, including proteins, nucleic acids, and drugs. Their low immunogenicity contributes to efficient drug delivery. The toxicity of exosomes depends on their source and aggregation, which is associated with off-target drug delivery. Among all therapeutic exosome sources, plant-derived exosomes are safer. TEXs' oncogenic cargo limits their therapeutic applications. Stem cell-derived exosomes show a dual role in cancer therapeutics, and this source requires more investigation. Immune cell-derived exosomes cannot produce a strong anti-cancer immune response, but some research evidence suggests that modified immune cell-derived exosomes can produce a promising Th1-mediated anti-cancer immune response. Bacteria-derived and milk-derived exosomes are just in the initial phases of clinical research. These therapeutic exosome sources require further scientific investigation and validation for clinical applications. Chimeric exosomes and modified exosomes are emerging as promising therapeutic sources based on *in vitro* and *in vivo* experimental outcomes; however, clinical trial validation is required before they can be used in clinical applications. The exosome research domain faces several complications, such as heterogeneity and establishing standard isolation protocols and drug-loading methods. Advancements in technology can overcome these limitations *via* single-exosome profiling, exosome barcoding, and a nanotechnology approach. The integration of multiple disciplines, such as nanotechnology, multi-omics, artificial intelligence (AI), and machine learning (ML), is contributing to the development of an exosome-based precision oncology era. In the future, *in vitro*, *in vivo*, and *in silico* based exosome research will support the development of effective, efficient, and affordable cancer therapeutic. Exosomes may serve as a promising platform for next-generation precision cancer medicine.

Conflicts of interest

The authors of this article declare no conflicts of interest.

Data availability

No primary research results, software, or code have been included, and no new data were generated or analysed as part of this review.

Acknowledgements

There is no funding for this study.

References

1 R. L. Siegel, K. D. Miller, N. S. Wagle and A. Jemal, Cancer statistics, 2023, *Ca-Cancer J. Clin.*, 2023, **73**(1), 17–48.
2 A. Pulumati, A. Pulumati, B. S. Dwarakanath, A. Verma and R. V. L. Papineni, Technological advancements in cancer diagnostics: Improvements and limitations, *Cancer Rep.*, 2023, **6**, e1764.
3 M. Kulkarni, R. Kar, S. Ghosh, *et al.*, Clinical Impact of Multi-omics profiling of extracellular vesicles in cancer Liquid Biopsy, *J. Liq. Biopsy*, 2024, **3**, 100138.
4 D. Yu, Y. Li, M. Wang, *et al.*, Exosomes as a new frontier of cancer liquid biopsy, *Mol. Cancer*, 2022, **21**, 56.
5 S. Tohme, R. L. Simmons and A. Tsung, Surgery for Cancer: A Trigger for Metastases, *Cancer Res.*, 2017, **77**, 1548–1552.

6 G. Mohan, A. H. TP, J. AJ, *et al.*, Recent advances in radiotherapy and its associated side effects in cancer—a review, *J. Basic Appl. Zool.*, 2019, **80**, 1.
7 K. Nurgali, R. T. Jagoe and R. Abalo, Editorial: Adverse Effects of Cancer Chemotherapy: Anything New to Improve Tolerance and Reduce Sequelae?, *Front. Pharmacol*, 2018, **9**, 245.
8 A. Kichloo, M. Albosta, D. Dahiya, *et al.*, Systemic adverse effects and toxicities associated with immunotherapy: A review, *World J. Clin. Oncol.*, 2021, **12**, 150–163.
9 R. Xu, A. Rai, M. Chen, *et al.*, Extracellular vesicles in cancer - implications for future improvements in cancer care, *Nat. Rev. Clin. Oncol.*, 2018, **15**, 617–638.
10 Y. L. Tai, K. C. Chen, J. T. Hsieh and T. L. Shen, Exosomes in cancer development and clinical applications, *Cancer Sci.*, 2018, **109**, 2364–2374.
11 A. Hoshino, B. Costa-Silva, T. L. Shen, *et al.*, Tumour exosome integrins determine organotropic metastasis, *Nature*, 2015, **527**, 329–335.
12 S. Halvaei, S. Daryani, S. Z. Eslami, *et al.*, Exosomes in Cancer Liquid Biopsy: A Focus on Breast Cancer, *Mol. Ther. Nucleic Acids*, 2018, **10**, 131–141.
13 H. Shao, H. Im, C. M. Castro, X. Breakefield, R. Weissleder and H. Lee, New Technologies for Analysis of Extracellular Vesicles, *Chem. Rev.*, 2018, **118**, 1917–1950.
14 S. Gurung, D. Perocheau, L. Touramanidou and J. Baruteau, The exosome journey: from biogenesis to uptake and intracellular signalling, *Cell Commun. Signal.*, 2021, **19**, 47.
15 J. Dai, Y. Su, S. Zhong, *et al.*, Exosomes: key players in cancer and potential therapeutic strategy, *Signal Transduct. Targeted Ther.*, 2020, **5**, 145.
16 Y. Zhang, Y. Liu, H. Liu and W. H. Tang, Exosomes: biogenesis, biologic function and clinical potential, *Cell Biosci.*, 2019, **9**, 19.
17 M. Tschuschke, I. Kocherova, A. Bryja, *et al.*, Inclusion Biogenesis, Methods of Isolation and Clinical Application of Human Cellular Exosomes, *J. Clin. Med.*, 2020, **9**, 436.
18 N. P. Hessvik and A. Llorente, Current knowledge on exosome biogenesis and release, *Cell. Mol. Life Sci.*, 2018, **75**, 193–208.
19 H. Yan, Y. Li, S. Cheng and Y. Zeng, Advances in Analytical Technologies for Extracellular Vesicles, *Anal. Chem.*, 2021, **93**, 4739–4774.
20 H. Zhao, L. Yang, J. Baddour, *et al.*, Tumor microenvironment derived exosomes pleiotropically modulate cancer cell metabolism, *Elife*, 2016, **5**, e10250.
21 M. Ahmadi and J. Rezaie, Tumor cells derived-exosomes as angiogenenic agents: possible therapeutic implications, *J. Transl. Med.*, 2020, **18**, 249.
22 Y. Wu, W. Han, H. Dong, X. Liu and X. Su, The rising roles of exosomes in the tumor microenvironment reprogramming and cancer immunotherapy, *MedComm*, 2024, **5**(4), e541.
23 Y. Tie, F. Tang, Y. Q. Wei and X. W. Wei, Immunosuppressive cells in cancer: mechanisms and potential therapeutic targets, *J. Hematol. Oncol.*, 2022, **15**, 61.
24 X. Ying, Q. Wu, X. Wu, *et al.*, Epithelial ovarian cancer-secreted exosomal miR-222-3p induces polarization of tumor-associated macrophages, *Oncotarget*, 2016, **7**, 43076–43087.
25 E. I. Buzas, The roles of extracellular vesicles in the immune system, *Nat. Rev. Immunol.*, 2023, **23**, 236–250.
26 R. Hosseini, L. Asef-Kabiri, H. Yousefi, *et al.*, The roles of tumor-derived exosomes in altered differentiation, maturation and function of dendritic cells, *Mol. Cancer*, 2021, **20**, 83.
27 F. M. Karami, J. Azami, N. Jaafari, *et al.*, Exosome application in treatment and diagnosis of B-cell disorders: leukemias, multiple sclerosis, and arthritis rheumatoid, *Cell. Mol. Biol. Lett.*, 2022, **27**, 74.
28 V. W. Xue, J. Y. Chung, C. A. G. Córdoba, A. H. Cheung, W. Kang, E. W. Lam, K. T. Leung, K. F. To, H. Y. Lan and P. M. Tang, Transforming Growth Factor-β: A Multifunctional Regulator of Cancer Immunity, *Cancers*, 2020, **12**(11), 3099.
29 L. Ye, Q. Zhang, Y. Cheng, *et al.*, Tumor-derived exosomal HMGB1 fosters hepatocellular carcinoma immune evasion by promoting TIM-1^{+} regulatory B cell expansion, *J. Immunother. Cancer*, 2018, **6**, 145.
30 X. Tian, H. Shen, Z. Li, T. Wang and S. Wang, Tumor-derived exosomes, myeloid-derived suppressor cells, and tumor microenvironment, *J. Hematol. Oncol.*, 2019, **12**, 84.
31 J. Winkler, A. Abisoye-Ogunniyan, K. J. Metcalf and Z. Werb, Concepts of extracellular matrix remodelling in tumour progression and metastasis, *Nat. Commun.*, 2020, **11**, 5120.
32 E. Yang, X. Wang, Z. Gong, *et al.*, Exosome-mediated metabolic reprogramming: the emerging role in tumor microenvironment remodeling and its influence on cancer progression, *Signal Transduct. Targeted Ther.*, 2020, **5**, 242.
33 J. Jiang, J. Li, X. Zhou, *et al.*, Exosomes Regulate the Epithelial-Mesenchymal Transition in Cancer, *Front. Oncol.*, 2022, **12**, 864980.
34 S. Li, M. Yi, B. Dong, *et al.*, The roles of exosomes in cancer drug resistance and its therapeutic application, *Clin. Transl. Med.*, 2020, **10**, e257.
35 T. B. Steinbichler, J. Dudás, S. Skvortsov, *et al.*, Therapy resistance mediated by exosomes, *Mol. Cancer*, 2019, **18**, 58.
36 X. Dong, X. Bai, J. Ni, H. Zhang, W. Duan, P. Graham and Y. Li, Exosomes and breast cancer drug resistance, *Cell Death Dis.*, 2020, **11**(11), 987.
37 C. Su, J. Zhang, Y. Yarden and L. Fu, The key roles of cancer stem cell-derived extracellular vesicles, *Signal Transduct. Targeted Ther.*, 2021, **6**, 109.
38 M. Yang and S. Y. Wu, The Advances and Challenges in Utilizing Exosomes for Delivering Cancer Therapeutics, *Front. Pharmacol*, 2018, **9**, 735.
39 M. H. Yoo, A. R. Lee and K. S. Moon, Characteristics of Extracellular Vesicles and Preclinical Testing Considerations Prior to Clinical Applications, *Biomedicines*, 2022, **10**, 869.
40 D. J. Beetler, D. N. Di Florio, K. A. Bruno, T. Ikezu, K. L. March, L. T. Cooper Jr, J. Wolfram and

D. Fairweather, Extracellular vesicles as personalized medicine, *Mol. Aspects Med.*, 2023, **91**, 101155.
41 K. Zhang and K. Cheng, Stem cell-derived exosome *versus* stem cell therapy, *Nat. Rev. Bioeng.*, 2023, 1–2.
42 H. Raskov, A. Orhan, J. P. Christensen and I. Gögenur, Cytotoxic $CD8^+$ T cells in cancer and cancer immunotherapy, *Br. J. Cancer*, 2021, **124**, 359–367.
43 W. Yan and S. Jiang, Immune Cell-Derived Exosomes in the Cancer-Immunity Cycle, *Trends Cancer*, 2020, **6**, 506–517.
44 Y. Zhao, T. Liu and M. Zhou, Immune-Cell-Derived Exosomes for Cancer Therapy, *Mol. Pharm.*, 2022, **19**, 3042–3056.
45 Z. Xu, S. Zeng, Z. Gong and Y. Yan, Exosome-based immunotherapy: a promising approach for cancer treatment, *Mol. Cancer*, 2020, **19**, 160.
46 J. Xia, Y. Miao, X. Wang, X. Huang and J. Dai, Recent progress of dendritic cell-derived exosomes (Dex) as an anti-cancer nanovaccine, *Biomed. Pharmacother.*, 2022, **152**, 113250.
47 B. T. Harvey, X. Fu, L. Li, *et al.*, Dendritic Cell Membrane-Derived Nanovesicles for Targeted T Cell Activation, *ACS Omega*, 2022, **7**, 46222–46233.
48 H. Tian and W. Li, Dendritic cell-derived exosomes for cancer immunotherapy: hope and challenges, *Ann. Transl. Med.*, 2017, **5**, 221.
49 B. Escudier, T. Dorval, N. Chaput, *et al.*, Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: results of thefirst phase I clinical trial, *J. Transl. Med.*, 2005, **3**, 10.
50 J. Jiang, J. Li, X. Zhou, X. Zhao, B. Huang and Y. Qin, Exosomes Regulate the Epithelial-Mesenchymal Transition in Cancer, *Front. Oncol.*, 2022, **12**, 864980.
51 J. Hong, M. Jung, C. Kim, *et al.*, Senescent cancer cell-derived nanovesicle as a personalized therapeutic cancer vaccine, *Exp. Mol. Med.*, 2023, **55**, 541–554.
52 R. Rezaei, K. Baghaei, S. M. Hashemi, *et al.*, Tumor-Derived Exosomes Enriched by miRNA-124 Promote Anti-tumor Immune Response in CT-26 Tumor-Bearing Mice, *Front. Med.*, 2021, **8**, 619939.
53 W. Sun, J. D. Luo, H. Jiang and D. D. Duan, Tumor exosomes: a double-edged sword in cancer therapy, *Acta Pharmacol. Sin.*, 2018, **39**, 534–541.
54 R. T. Morales and J. Ko, Future of Digital Assays to Resolve Clinical Heterogeneity of Single Extracellular Vesicles, *ACS Nano*, 2022, **16**(8), 11619–11645.
55 D. H. Ha, S. D. Kim, J. Lee, *et al.*, Toxicological evaluation of exosomes derived from human adipose tissue-derived mesenchymal stem/stromal cells, *Regul. Toxicol. Pharmacol.*, 2020, **115**, 104686.
56 A. Tieu, M. M. Lalu, M. Slobodian, *et al.*, An Analysis of Mesenchymal Stem Cell-Derived Extracellular Vesicles for Preclinical Use, *ACS Nano*, 2020, **14**, 9728–9743.
57 J. Phan, P. Kumar, D. Hao, *et al.*, Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy, *J. Extracell. Vesicles*, 2018, **7**, 1522236.
58 S. Han, G. Li, M. Jia, *et al.*, Delivery of Anti-miRNA-221 for Colorectal Carcinoma Therapy Using Modified Cord Blood Mesenchymal Stem Cells-Derived Exosomes, *Front. Mol. Biosci.*, 2021, **8**, 743013.
59 Z. Xunian and R. Kalluri, Biology and therapeutic potential of mesenchymal stem cell-derived exosomes, *Cancer Sci.*, 2020, **111**, 3100–3110.
60 B. Sohrabi, B. Dayeri, E. Zahedi, *et al.*, Mesenchymal stem cell (MSC)-derived exosomes as novel vehicles for delivery of miRNAs in cancer therapy, *Cancer Gene Ther.*, 2022, **29**, 1105–1116.
61 Z. Lin, Y. Wu, Y. Xu, *et al.*, Mesenchymal stem cell-derived exosomes in cancer therapy resistance: recent advances and therapeutic potential, *Mol. Cancer*, 2022, **21**, 179.
62 G. Wang, X. Ji, P. Li and W. Wang, Human bone marrow mesenchymal stem cell-derived exosomes containing microRNA-425 promote migration, invasion and lung metastasis by down-regulating CPEB1, *Regen. Ther.*, 2022, **20**, 107–116.
63 H. Wu, X. Mu, L. Liu, *et al.*, Bone marrow mesenchymal stem cells-derived exosomal microRNA-193a reduces cisplatin resistance of non-small cell lung cancer cells *via* targeting LRRC1, *Cell Death Dis.*, 2020, **11**, 801.
64 K. C. Vallabhaneni, P. Penfornis, S. Dhule, *et al.*, Extracellular vesicles from bone marrow mesenchymal stem/stromal cells transport tumor regulatory microRNA, proteins, and metabolites, *Oncotarget*, 2015, **6**, 4953–4967.
65 A. Sharma, Role of stem cell derived exosomes in tumor biology, *Int. J. Cancer*, 2018, **142**, 1086–1092.
66 T. Luo, Q. Liu, A. Tan, L. Duan, Y. Jia, L. Nong, J. Tang, W. Zhou, W. Xie, Y. Lu, Q. Yu and Y. Liu, Mesenchymal Stem Cell-Secreted Exosome Promotes Chemoresistance in Breast Cancer *via* Enhancing miR-21-5p-Mediated S100A6 Expression, *Mol. Ther. Oncolytics*, 2020, **19**, 283–293.
67 N. Hosseini-Giv, A. Basas, C. Hicks, *et al.*, Bacterial extracellular vesicles and their novel therapeutic applications in health and cancer, *Front. Cell. Infect. Microbiol.*, 2022, **12**, 962216.
68 S. Varderidou-Minasian and M. J. Lorenowicz, Mesenchymal stromal/stem cell-derived extracellular vesicles in tissue repair: challenges and opportunities, *Theranostics*, 2020, **10**, 5979–5997.
69 H. A. Dad, T. W. Gu, A. Q. Zhu, L. Q. Huang and L. H. Peng, Plant Exosome-like Nanovesicles: Emerging Therapeutics and Drug Delivery Nanoplatforms, *Mol. Ther.*, 2021, **29**, 13–31.
70 Z. Jin, J. Na, X. Lin, R. Jiao, X. Liu and Y. Huang, Plant-derived exosome-like nanovesicles: A novel nanotool for disease therapy, *Heliyon*, 2024, **10**(9), e30630.
71 M. Q. Lian, W. H. Chng, J. Liang, *et al.*, Plant-derived extracellular vesicles: Recent advancements and current challenges on their use for biomedical applications, *J. Extracell. Vesicles*, 2022, **11**, e12283.
72 N. Mu, J. Li, L. Zeng, *et al.*, Plant-Derived Exosome-Like Nanovesicles: Current Progress and Prospects, *Int. J. Nanomed.*, 2023, **18**, 4987–5009.
73 I. K. Herrmann, M. J. A. Wood and G. Fuhrmann, Extracellular vesicles as a next-generation drug delivery platform, *Nat. Nanotechnol.*, 2021, **16**, 748–759.

74 B. M. Hussen, G. S. H. Faraj, M. F. Rasul, *et al.*, Strategies to overcome the main challenges of the use of exosomes as drug carrier for cancer therapy, *Cancer Cell Int.*, 2022, **22**(1), 323.
75 Y. Zhang, Q. Liu, X. Zhang, *et al.*, Recent advances in exosome-mediated nucleic acid delivery for cancer therapy, *J. Nanobiotechnol.*, 2022, **20**, 279.
76 K. L. Zhang, Y. J. Wang, J. Sun, *et al.*, Artificial chimeric exosomes for anti-phagocytosis and targeted cancer therapy, *Chem. Sci.*, 2018, **10**, 1555–1561.
77 Y. J. Li, J. Y. Wu, J. Liu, *et al.*, Artificial exosomes for translational nanomedicine, *J. Nanobiotechnol.*, 2021, **19**, 242.
78 J. Zhao, J. Yang, J. Jiao, *et al.*, Biomedical applications of artificial exosomes for intranasal drug delivery, *Front. Bioeng. Biotechnol.*, 2023, **11**, 1271489.
79 M. Zhang, S. Hu, L. Liu, *et al.*, Engineered exosomes from different sources for cancer-targeted therapy, *Signal Transduct. Targeted Ther.*, 2023, **8**, 124.
80 S. Sadeghi, F. R. Tehrani, S. Tahmasebi, A. Shafiee and S. M. Hashemi, Exosome engineering in cell therapy and drug delivery, *Inflammopharmacology*, 2023, **31**, 145–169.
81 H. Cheng, J. H. Fan, L. P. Zhao, *et al.*, Chimeric peptide engineered exosomes for dual-stage light guided plasma membrane and nucleus targeted photodynamic therapy, *Biomaterials*, 2019, **211**, 14–24.
82 S. E. Ahmadi, M. Soleymani, F. Shahriyary, *et al.*, Viral vectors and extracellular vesicles: innate delivery systems utilized in CRISPR/Cas-mediated cancer therapy, *Cancer Gene Ther.*, 2023, **30**, 936–954.
83 M. N. Huda, M. Nafiujjaman, I. G. Deaguero, *et al.*, Potential Use of Exosomes as Diagnostic Biomarkers and in Targeted Drug Delivery: Progress in Clinical and Preclinical Applications, *ACS Biomater. Sci. Eng.*, 2021, **7**, 2106–2149.
84 R. Tenchov, J. M. Sasso, X. Wang, W. S. Liaw, C. A. Chen, *et al.*, Exosomes—Nature's Lipid Nanoparticles, a Rising Star in Drug Delivery and Diagnostics, *ACS Nano*, 2022, **16**, 17802–17846.
85 Y. Lin, J. Wu, W. Gu, *et al.*, Exosome-Liposome Hybrid Nanoparticles Deliver CRISPR/Cas9 System in MSCs, *Adv. Sci.*, 2018, **5**, 1700611.
86 A. H. Berggreen, J. L. Petersen, L. Lin, K. Benabdellah and Y. Luo, CRISPR delivery with extracellular vesicles: Promises and challenges, *J. Extracell. Biol.*, 2023, **2**, e111.
87 J. Zhuang, J. Tan, C. Wu, *et al.*, Extracellular vesicles engineered with valency-controlled DNA nanostructures deliver CRISPR/Cas9 system for gene therapy, *Nucleic Acids Res.*, 2020, **48**, 8870–8882.
88 R. C. Sterner and R. M. Sterner, CAR-T cell therapy: current limitations and potential strategies, *Blood Cancer J.*, 2021, **11**, 69.
89 W. Fu, C. Lei, S. Liu, *et al.*, CAR exosomes derived from effector CAR-T cells have potent antitumour effects and low toxicity, *Nat. Commun.*, 2019, **10**, 4355.
90 P. Yang, X. Cao, H. Cai, *et al.*, The exosomes derived from CAR-T cell efficiently target mesothelin and reduce triple-negative breast cancer growth, *Cell. Immunol.*, 2021, **360**, 104262.
91 K. Zhang and K. Cheng, Stem cell-derived exosome *versus* stem cell therapy, *Nat. Rev. Bioeng.*, 2023, 1–2.
92 H. B. Koh, H. J. Kim, S. W. Kang and T. H. Yoo, Exosome-Based Drug Delivery: Translation from Bench to Clinic, *Pharmaceutics*, 2023, **15**, 2042.
93 I. Jung, S. Shin, M. C. Baek and K. Yea, Modification of immune cell-derived exosomes for enhanced cancer immunotherapy: current advances and therapeutic applications, *Exp. Mol. Med.*, 2024, **56**, 19–31.
94 H. Chen, V. Chengalvala, H. Hu and D. Sun, Tumor-derived exosomes: Nanovesicles made by cancer cells to promote cancer metastasis, *Acta Pharm. Sin. B*, 2021, **11**, 2136–2149.
95 K. Cheng and R. Kalluri, Guidelines for clinical translation and commercialization of extracellular vesicles and exosomes based therapeutics, *J. Extracell. Vesicles*, 2023, **2**, 100029.
96 A. Rezabakhsh, E. Sokullu and R. Rahbarghazi, Applications, challenges and prospects of mesenchymal stem cell exosomes in regenerative medicine, *Stem Cell Res. Ther.*, 2021, **12**, 521.
97 L. Garaeva, R. Kamyshinsky, Y. Kil, *et al.*, Delivery of functional exogenous proteins by plant-derived vesicles to human cells in vitro, *Sci. Rep.*, 2021, **11**, 6489.
98 R. Huang, B. Jia, D. Su, *et al.*, Plant exosomes fused with engineered mesenchymal stem cell-derived nanovesicles for synergistic therapy of autoimmune skin disorders, *J. Extracell. Vesicles*, 2023, **12**, e12361.
99 X. Wang, D. Li, G. Li, *et al.*, Enhanced Therapeutic Potential of Hybrid Exosomes Loaded with Paclitaxel for Cancer Therapy, *Int. J. Mol. Sci.*, 2024, **25**, 3645.
100 M. Samuel, P. Fonseka, R. Sanwlani, *et al.*, Oral administration of bovine milk-derived extracellular vesicles induces senescence in the primary tumor but accelerates cancer metastasis, *Nat. Commun.*, 2021, **12**, 3950.
101 A. M. Timofeeva, A. P. Paramonik, S. S. Sedykh and G. A. Nevinsky, Milk Exosomes: Next-Generation Agents for Delivery of Anticancer Drugs and Therapeutic Nucleic Acids, *Int. J. Mol. Sci.*, 2023, **24**, 10194.
102 A. Das, S. Sonar and S. V. KaleleK, Milk exosomes: Harnessingnature's duality for cancer therapy, *Clin. Transl. Discovery*, 2024, **4**, e349.
103 A. Das, S. Sonar and S. V. KaleleK, Bacterial surface derived extracellular vesicles: A ground-breaking approach in cancer therapy, *Clin. Transl. Discovery*, 2024, e351.
104 Y. Li, R. Zhao, K. Cheng, *et al.*, Bacterial Outer Membrane Vesicles Presenting Programmed Death 1 for Improved Cancer Immunotherapy *via* Immune Activation and Checkpoint Inhibition, *ACS Nano*, 2020, **14**, 16698–16711.
105 K. M. McAndrews, F. Xiao, A. Chronopoulos, *et al.*, Exosome-mediated delivery of CRISPR/Cas9 for targeting of oncogenic $Kras^{G12D}$ in pancreatic cancer, *Life Sci. Alliance*, 2021, **4**, e202000875.

106 W. Zheng, T. Zhu, L. Tang, *et al.*, Inhalable CAR-T cell-derived exosomes as paclitaxel carriers for treating lung cancer, *J. Transl. Med.*, 2023, **21**, 383.
107 S. Roy, F. H. Hochberg and P. S. Jones, Extracellular vesicles: the growth as diagnostics and therapeutics; a survey, *J. Extracell. Vesicles*, 2018, **7**, 1438720.
108 https://www.fnfresearch.com/news/global-exosome-research-market[site visiting date 27-2-24].
109 L. Huang, E. Wu, J. Liao, *et al.*, Research Advances of Engineered Exosomes as Drug Delivery Carrier, *ACS Omega*, 2023, **8**, 43374–43387.
110 F. Tan, X. Li, Z. Wang, J. Li, K. Shahzad and J. Zheng, Clinical applications of stem cell-derived exosomes, *Signal Transduct. Targeted Ther.*, 2024, **9**(1), 17.
111 N. Verma and S. Arora, Navigating the Global Regulatory Landscape for Exosome-Based Therapeutics: Challenges, Strategies, and Future Directions, *Pharmaceutics*, 2025, **17**(8), 990.
112 Techniques Supporting Exosome Research and Applications|Thermo Fisher Scientific - IN [Internet]. [cited 2025 Sep 27]. Available from: https://www.thermofisher.com/in/en/home/brands/thermo-scientific/molecular-biology/molecular-biology-learning-center/molecular-biology-resource-library/spotlight-articles/exosome-research-applications-techniques.html.
113 Exosomes Market Size And Share | Industry Report, 2030 [Internet]. [cited 2025 Sep 27]. Available from: https://www.grandviewresearch.com/industry-analysis/exosomes-market.
114 Exosome Research Market Expand at 17.45% CAGR till 2034 [Internet]. [cited 2025 Sep 27]. Available from: https://www.towardshealthcare.com/insights/exosome-research-market-sizing.
115 D. Xia, R. Wu, S. Wang, G. Chen, Y. Lu and L. Zhao, Global Trends and Prospects Regarding Exosomes in Cancer Immunology Research Over the Past 10 Years, *Technol. Cancer Res. Treat.*, 2023, **22**, 15330338231199892.
116 W. Zhong, X. Zhao, X. Zhang, Y. Xu, M. Liu, X. Yang, Y. Jiang and X. Shen, Advancements and trends in exosome research in lung cancer from a bibliometric analysis (2004-2023), *Front. Oncol.*, 2024, **14**, 1358101.
117 China Exosome Research Products Market is Poised to Reach [Internet]. [cited 2025 Sep 27]. Available from: https://www.globenewswire.com/news-release/2024/11/12/2979489/0/en/China-Exosome-Research-Products-Market-is-Poised-to-Reach-Valuation-of-Over-US-148-93-Million-By-2032-Astute-Analytica.html.
118 China Exosome Research Products Market Size | Trends [2032] [Internet]. [cited 2025 Sep 27]. Available from: https://www.astuteanalytica.com/industry-report/china-exosome-research-products-market.
119 Exosome Diagnostics and Therapeutics Market Growth, Drivers, and Opportunities [Internet]. [cited 2025 Sep 27]. Available from: https://www.marketsandmarkets.com/Market-Reports/exosome-diagnostics-therapeutics-market-198025144.html.
120 Global Exosome Diagnostics and Therapeutics Market Trends [Internet]. [cited 2025 Sep 27]. Available from: https://www.bccresearch.com/market-research/biotechnology/exosome-diagnostics-and-therapeutics-global-markets-report.html.
121 R. Dhar and V. Subramaniyan, Exosomes: A next-generation cancer theranostics, *Nano TransMed*, 2025, 100096.
122 S. Sonar, Clinical trial status of exosomes based cancer theranostics, *Clin. Transl. Discovery*, 2024, **4**, e327.
123 E. Tzng, N. Bayardo and P. C. Yang, Current challenges surrounding exosome treatments, *J. Extracell. Vesicles*, 2023, **2**, 100023.
124 X. Li, A. L. Corbett, E. Taatizadeh, *et al.*, Challenges and opportunities in exosome research-Perspectives from biology, engineering, and cancer therapy, *APL Bioeng.*, 2019, **3**, 011503.
125 S. Bosch, L. de Beaurepaire, M. Allard, *et al.*, Trehalose prevents aggregation of exosomes and cryodamage, *Sci. Rep.*, 2016, 6, pp. 523–551.
126 N. Palomar-Alonso, M. Lee and M. Kim, Exosomes: Membrane-associated proteins, challenges and perspectives, *Biochem. Biophys. Rep.*, 2023, **37**, 101599.
127 F. Yuan, Y. M. Li and Z. Wang, Preserving extracellular vesicles for biomedical applications: consideration of storage stability before and after isolation, *Drug Deliv.*, 2021, **28**, 1501–1509.
128 D. Wu, J. Yan, X. Shen, Y. Sun, M. Thulin, Y. Cai, L. Wik, Q. Shen, J. Oelrich, X. Qian, K. L. Dubois, K. G. Ronquist, M. Nilsson, U. Landegren and M. Kamali-Moghaddam, Profiling surface proteins on individual exosomes using a proximity barcoding assay, *Nat. Commun.*, 2019, **10**(1), 3854.
129 A. Ghodasara, A. Raza, J. Wolfram, C. Salomon and A. Popat, Clinical Translation of Extracellular Vesicles, *Adv. Healthcare Mater.*, 2023, **12**, e2301010.
130 R. Dhar, V. Kumarasamy and V. Subramaniyan, Signature of exosomes in cancer translational medicine, *Int. J. Surg.*, 2025, **111**(6), 4138–4139.
131 Y. Ma, S. Dong, A. J. Grippin, L. Teng, A. S. Lee, B. Y. S. Kim and W. Jiang, Engineering therapeutical extracellular vesicles for clinical translation, *Trends Biotechnol.*, 2025, **43**(1), 61–82.
132 A. Ghodasara, A. Raza, J. Wolfram, C. Salomon and A. Popat, Clinical Translation of Extracellular Vesicles, *Adv. Healthcare Mater.*, 2023, **12**(28), e2301010.
133 A. Ghodasara, A. Raza, J. Wolfram, C. Salomon and A. Popat, Clinical translation of extracellular vesicles, *Adv. Healthcare Mater.*, 2023, **12**(28), 2301010.
134 J. Kowal, G. Arras, M. Colombo, M. Jouve, J. P. Morath, B. Primdal-Bengtson, F. Dingli, D. Loew, M. Tkach and C. Théry, Proteomic comparison defines novel markers to characterize heterogeneous populations of extracellular vesicle subtypes, *Proc. Natl. Acad. Sci. U. S. A.*, 2016, **113**(8), E968–E977.
135 K. Kunitake, T. Mizuno, K. Hattori, C. Oneyama, M. Kamiya, S. Ota, Y. Urano and R. Kojima, Barcoding of

small extracellular vesicles with CRISPR-gRNA enables comprehensive, subpopulation-specific analysis of their biogenesis and release regulators, *Nat. Commun.*, 2024, **15**(1), 9777.

136 Q. Qu, B. Fu, Y. Long, Z. Y. Liu and X. H. Tian, Current Strategies for Promoting the Large-scale Production of Exosomes, *Curr. Neuropharmacol.*, 2023, **21**(9), 1964–1979.

137 S. S. Palakurthi, B. Shah, S. Kapre, N. Charbe, S. Immanuel, S. Pasham, M. Thalla, A. Jain and S. Palakurthi, A comprehensive review of challenges and advances in exosome-based drug delivery systems, *Nanoscale Adv.*, 2024, **6**(23), 5803–5826.

138 A. Sharma, A. Yadav, A. Nandy and S. Ghatak, Insight into the Functional Dynamics and Challenges of Exosomes in Pharmaceutical Innovation and Precision Medicine, *Pharmaceutics*, 2024, **16**(6), 709.

139 M. Lee, J. J. Ban, W. Im, *et al.*, Influence of storage condition on exosome recovery, *Biotechnol. Bioprocess Eng.*, 2016, **21**, 299–304.

140 S. Gelibter, G. Marostica, A. Mandelli, S. Siciliani, P. Podini, A. Finardi and R. Furlan, The impact of storage on extracellular vesicles: A systematic study, *J. Extracell. Vesicles*, 2022, **11**(2), e12162.

141 J. Shen, Y. He, J. Deng, W. Zeng, F. Deng, X. Yu and Z. Zhang, Storage stability of exosomes in different buffers with/without lyophilization, *J. Drug Delivery Sci. Technol.*, 2025, 107278.

142 S. M. Jay, Addressing barriers to clinical translation of extracellular vesicle therapeutics, *Mol. Ther.*, 2025, **33**(5), 1879–1880.

143 S. Gandham, X. Su, J. Wood, A. L. Nocera, S. C. Alli, L. Milane, A. Zimmerman, M. Amiji and A. R. Ivanov, Technologies and Standardization in Research on Extracellular Vesicles, *Trends Biotechnol.*, 2020, **38**(10), 1066–1098.

144 C. K. Wang, T. H. Tsai and C. H. Lee, Regulation of exosomes as biologic medicines: Regulatory challenges faced in exosome development and manufacturing processes, *Clin. Transl. Sci.*, 2024, **17**(8), e13904.

145 A. Sharma, D. Khatri and D. Gugulothu, Regulatory and ethical considerations in exosome- based therapeutics, *Exosome Communication*, 2025, pp. 523–551, DOI: 10.1016/B978-0-443-29052-7.00020-9.