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Exosomes: Next generation medicine

Pradeep Mahajan, Ajit Kulkarni, Shweta Waghdhare *, Sanskruti Mahajan and Swetha Subramanian

Department of Stem Cells, StemRx Bioscience Solutions Pvt. Ltd, Navi Mumbai, India.

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Abstract

Extracellular vesicles (EVs) are the substances that are conveyed by most sorts of cell, which play a critical role in cell-to-cell communication. Exosomes are among the most commonly explored EVs. Exosomes contain lipids, RNAs and proteins. Many examinations have shown that exosomes derived from cells play different biological roles in normal as well as diseased condition. Recent investigations have explored exosomes as natural drug delivery vehicles, as they have ability to deliver different cargo to nearby and targeted cells with high specificity and efficiency. In the last decade, there has been increased interest in exosomes research due to their potential role in disease diagnosis as intercellular messengers. Exosomes have potential in targeted drug/gene delivery, due to their unique properties, such as low immunogenicity, excellent tissue/cell penetration capacity and innate stability. As a result, exosomes can be used for disease detection and for various treatments. In this review, we focus on the potential use of exosomes as valuable diagnostic and prognostic biomarkers for their cell-lineage and state-specific contents, and their possible use as therapeutic vehicle for drug and gene delivery. As a drug, exosomes have a variety of applications in various diseases.

Keywords: Extracellular vesicles; Exosomes; Drug delivery; Cancer

1. Introduction

Cells communicate with each other with the help of chemical messengers. These are essentially in the form of extracellular vesicles (EVs). EVs are used as drug delivery vehicles, owing to their unique structure. EVs contain lipids, specific proteins, and genetic materials including messenger RNA (mRNA), microRNA (miRNA), genomic DNA (gDNA) and other small non-coding RNAs from their progenitor cell. EVs are classified into three subgroups relying on their size and origin, (a) exosomes (diameter in the range of 30–150 nm), (b) micro vesicles or exosomes (50 nm–1 µm), and (c) apoptotic bodies (50 nm–5 µm) [1].

Exosomes were identified in late 1980s as vesicles derived from a multivesicular body (MVBs). At the point when MVBs fuse with the cell membrane, exosomes are delivered into the extracellular environment by exocytosis [2]. Exosomes act as a communication tool to deliver chemical cargo to the recipient cell [3]. Exosomes play a major role in intercellular signaling within the human body and in cellular processes, such as signal transduction, antigen presentation, and immune response [2, 4.]

Exosomes are tiny vesicles that carry mRNA, maintain protein activity of secretory cells. They have the ability to cross blood brain barrier since they are naturally cell determined nanocarriers [5]. They can possibly enter the targeted cells and play various biological roles with stable signal transduction. Hence, they have attracted widespread attention in the field of tissue regeneration and tissue repairing. Exosomes can be applied for the treatment of several diseases including kidney, liver, brain and heart. It has a potential in healing of injured tissue or diseased organs. The range of current

*Corresponding author: Shweta Waghdhare
Department of Stem Cells, StemRx Bioscience Solutions Pvt. Ltd, Navi Mumbai, India.

scientific interest in exosomes is wide and goes from understanding their functions and pathways to involving them in diagnostics, as biomarkers, and in the improvement of therapeutics [6].

1.1. Composition of Exosomes

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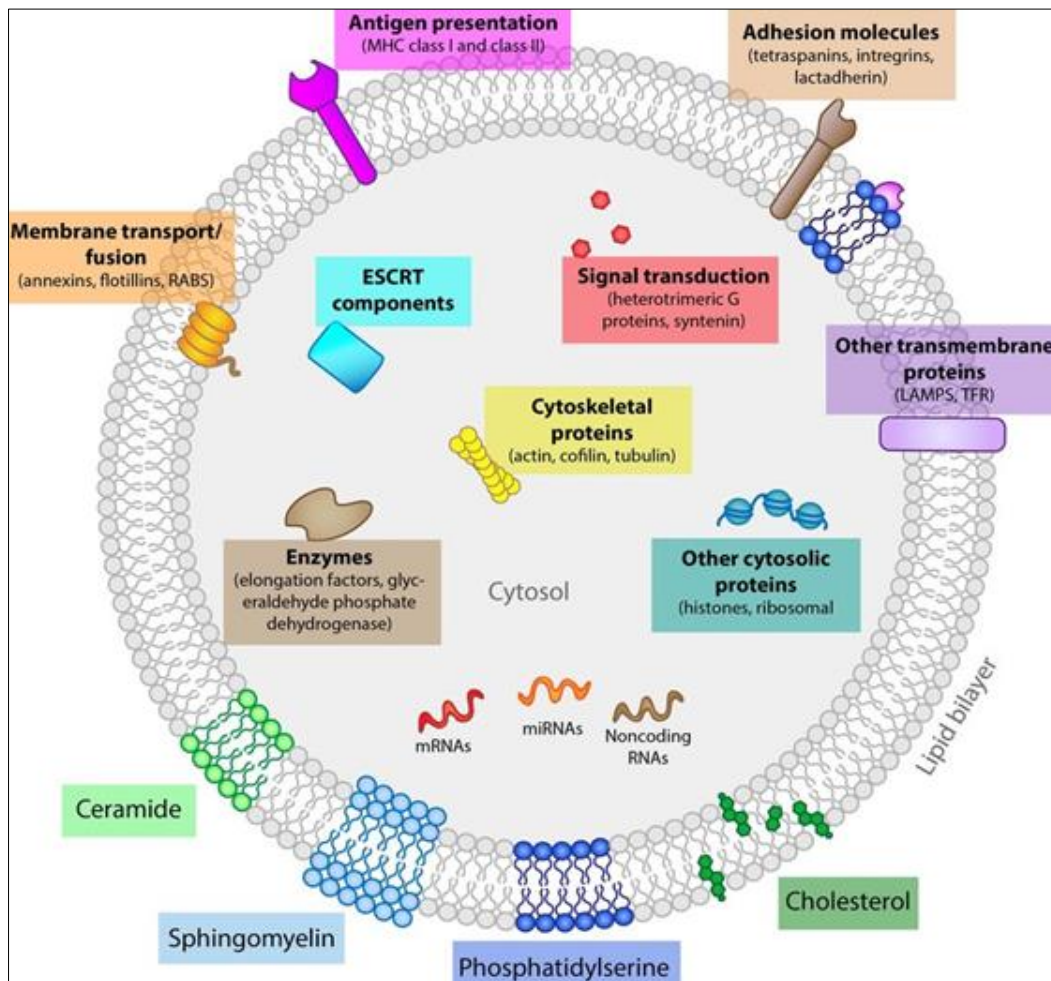


Figure 1 Composition of Exosomes

The main components of exosomes are DNA, nucleic acids, lipids and proteins. Proteins usually found in exosomes include that connected with membrane transport, for example, annexins, RAB GTPases, flotillins, MVB- producing proteins like ALIX, and tumor susceptibility gene 101 proteins (TSG101) [7]. Exosomes are packaged with a conserved set of protein, for example, tetraspanins, including CD9, CD63, and CD81 as well as heat shock proteins (HSP70). These are the basic specific exosomes markers. Different nucleic acids have been distinguished in exosomes, like mRNA and miRNA, as well as tRNA, lncRNA snRNA, circRNA and snoRNA. These RNAs function as gene expression modulators and might be helpful as potential biomarkers. The lipid parts in exosomes include phosphatidylserine (PS), sphingomyelin (SM), phosphatidic acid (PA), phosphatidylinositol (PI), ceramide, and cholesterol [8].

2. Roles of Exosomes in Diseases

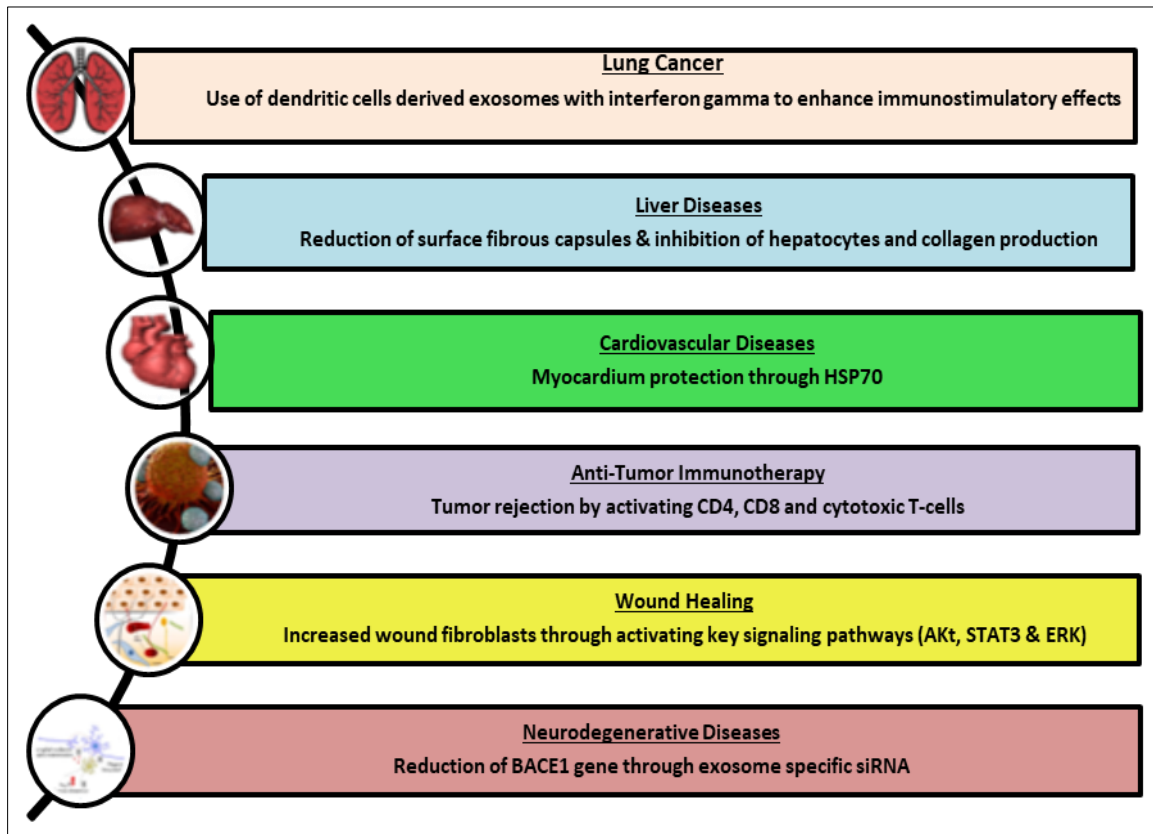


Figure 2 Roles of Exosomes in Diseases

2.1. Cancer

Cancer is one of the serious illnesses that show a higher rate of resistance toward different therapeutic strategies. Ongoing examinations present exosomes as key parts in the increased survival rate of cancerous cells after chemotherapy. Drug-resistant breast cancer cells transfer the resistive power to the adjacent sensitive cells through exosomes [9]. Several potential biomarkers were distinguished through proteomic examinations of cancer-derived exosomes from different kinds of malignant growths [10]. Different examinations in various disease subtypes showed that exosomes can be considered as potential biomarkers owing to its ubiquitous presence in various body fluids.

Ongoing exploration showed that exosomes can participate in directing the growth and affecting tumor proliferation and progression. Because of the extensive enrollment in cancer improvement, exosomes have turned into a focal point of search for another technique for malignant growth. Exosomes can be utilized for the therapeutic delivery of small molecules, proteins and RNAs to target cancer cells with a high efficiency. Exosome-conveyed proteins, lipids and nucleic acids are being tried as promising biomarkers for cancer diagnosis and prognosis, even as potential therapy focuses for malignant growth [11]. The study of exosomes in cancer has progressed at a rapid pace compared with research into their role in other diseases [12] and exosomes have been associated with several hallmark features of cancer. The role of exosomes in cancer progression is likely dynamic and specific to cancer type, genetics, and stage [13].

Tumor cells are known to secrete pathogenic exosomes to facilitate paracrine communication in the tumor microenvironment and promote tumor growth, invasion, metastasis, and drug resistance. Many clinical trials have focused on the role of exosomes as diagnostic (NCT04394572) or prognostic (NCT04288141) indicators in cancer [14]. However, exosomes may also be used as therapeutic agents in targeting cancers with known driver mutations. For example, MSC-exosomes engineered to carry siRNA specific to the oncogenic KrasG12D mutation have successfully suppressed pancreatic ductal adenocarcinoma in mice [15].

2.2. Cerebral Ischemia

Cerebral ischemia is conditions in which impaired blood stream doesn't permit adequate conveyance of oxygen and glucose to the cerebrum, prompting energy exhaustion, over-enactment of glutamate receptors, arrival of abundance glutamate, an expansion in intracellular calcium levels, loss of layer potential, cell depolarization, and, at last, cell death [16].

Exosomes as nanocarriers is one of the techniques for the treatment of cerebral ischemia therapy. The targeting ability of exosomes can be improved through suitable surface modification. Tian et al. proposed a straightforward, fast and productive technique to conjugate functional ligands onto exosomal surfaces utilizing bioorthogonal without copperazide-alkyne cycloaddition. The cyclo(Arg-Gly-Asp-DTyr-Lys) peptide [c(RGDyK)], which displays high affinity to integrin $\alpha\beta3$ in reactive cerebral vascular endothelial cells after ischemia explicitly, was formed on the mesenchymal stromal cell (MSC)-derived exosomes surface. Besides, curcumin, a natural polyphenol from *Curcuma longa*, was loaded onto the cRGD-Exo. The outcome shows that modified exosomes particles showed more accumulation in ischemic brain when compared with unmodified exosomes [17]. Various examinations have focused on understanding the capability of exosomes in interceding intercellular correspondence, immune system functions, advancement and separation, neuronal capability, cell signaling, recovery, and viral replication. As exosomes are naturally-formed and are engaged with numerous biological and pathological processes, they have multiple benefits when contrasted with other nanoparticles [18].

2.3. Cardiovascular Disease

Exosomes play a role in the improvement of metabolic diseases as well as in cardiovascular wellness. They have been found to transfer metabolites and work with intercellular correspondence through exosomal miRNA exchange among pancreatic β -cells, fat tissue, skeletal muscles, and the liver of mice and humans [19].

In myocardial infarction, reperfusion of the blocked coronary vessel prompts ischemia-reperfusion injury (I/R injury) and decrease of this negative impact is critical to recover on the patients. For instance, exosomes delivered via cardiac progenitor cells (CPCs) show angiogenic impacts, lessen myocyte cell death in an animal model [20]. Also improves cardiovascular function and diminish fibrosis in a rodent model of IR injury [21]. Recently, studies illustrate that the beneficial impact of stem cells on cardiovascular function are mediated by exosomes and developed invasive procedure of intramyocardial injection have shown more effective results compared to coronary injection [22].

They are closely related to the occurrence and development of cardiovascular diseases like atherosclerosis, hypertension, pulmonary hypertension, myocardial hypertrophy and myocardial localized necrosis. The cardiovascular framework is a significant site for intercellular transmission of exosomes. MicroRNA levels of exosomes connected with cardiovascular disease, including, miR-499, miR-133, miR-208, miR-194, miR-192, and miRNA-34a, are up regulated in patients with acute myocardial localized necrosis and cardiovascular breakdown [23].

2.4. Neurodegenerative Diseases

Parkinson's disease is portrayed by the development of Lewy bodies, comprise of misfolded α -synuclein. In such circumstances, exosome transmission of infectious proteins induces serial cell-to-cell infections. Exosomes function as α -synuclein transporters that host α -synuclein accumulation and empower neuron-to-neuron, neuron-to-neuroglia, and neuroglia-to-neuroglia propagation of α -synuclein. Exosomes containing α -synuclein are taken up by neuroglia (microglial cells and astrocytes), and the α -synuclein causes a neuroinflammatory reaction that is focal in the pathogenesis of Parkinson's disease. Infected neuroglia triggers neurodegeneration by discharging proinflammatory elements and additional exosomes. In this way, exosome transport of α -synuclein may contribute to a threatening inflammatory cycle in the pathogenesis of Parkinson's disease [24].

Exosomes are enhanced in Alzheimer's disease plaque totals of β -amyloid protein in the brain which cause synaptic signal blocking as proven by high concentrations of the exosomal protein marker ALIX in these plaques. Nonetheless, exosomes derived from human cerebrospinal fluid likewise prevent synaptic interruption by β -amyloid protein. Exosome detection in Parkinson's and Alzheimer's diseases is possibly beneficial for improving the early diagnosis and tracking of these diseases. The intersection between exosomal biogenesis and the regulation of secretory vesicles in neuronal cells offered new vision into the putative association among exosomes and the pathogenesis of neurodegenerative diseases. Exosomes could participate in the clearing of misfolded proteins, thereby exerting detoxifying and neuroprotective functions, or take part in the propagation and aggregation of misfolded proteins, successfully promoting the "infectivity" of protein aggregates and contributing to disease progression [25].

The role of exosomes in the pathophysiology of neurodegenerative disorders and autism spectrum disorder (ASD) requires more review, however but this has not hindered efforts to involve them in therapy development. Such effort is largely encouraged by the intrinsic properties of exosomes to efficiently pass through the blood-brain barrier, a vascular network functioning as a particular channel to hold medications or toxins from reaching the brain [26].

2.5. Diabetes

Diabetes is a group of metabolic diseases characterized by hyperglycemia. There are two main types of diabetes, namely, type 1 and type 2 diabetes mellitus. In Type 1 diabetes mellitus (T1DM), there is an absence of insulin because of the destruction of islet β cells, and in type 2 diabetes mellitus (T2DM), insulin resistance occurs due to insulin deficiency or impaired insulin secretion [27].

Persistent hyperglycemia may induce diabetic complications by regulating the epigenetics of target cells [28]. Exosomes play significant parts in the pathology of T1DM and T2DM, including the destruction of pancreatic tissue by mediating immune reactions and inducing adipocytes to reduce insulin resistance [29]. In recent years, studies have shown that exosomes carrying miRNAs and long noncoding RNAs have important roles in the development of diabetes by controlling metabolic signs, insulin signaling and the interaction between inflammatory pancreatic cells. In addition, miRNAs carried by exosomes may be used as biomarkers in diabetes and diabetic complications, which may be helpful in identifying diabetic complications at a beginning stage, consequently permitting patients to receive effective and convenient treatment [30]. The etiology, pathogenesis and complexity of diabetes still need to be explored [31].

2.6. Skin Regeneration

The skin is the biggest organ of the human body and constitutes a protective barrier against harmful agents and wounds. Aside from its defensive ability against physical, chemical, and biological compound, the skin additionally contributes to controlling the temperature of the body, homeostasis participates in the mechanisms of sensorial perception, as well as in regenerative process [32].

Several studies have shown that some exosomes are involved in the physiological and pathological processes of the skin [33]. Contrasted with different treatment, MSCs derived exosomes have the following benefits, for example, firstly, MSC derived exosomes exert intense biological effects in view of their direct combination with target cells. Furthermore, these exosomes can be stored and transported at -70°C for long periods of time since their effective components are protected by their membrane, which is not easily destroyed. Thirdly, the concentration, dose, course and time of use are easy to control. Therefore, there is no risk of the immune rejection and tumorigenesis caused by the transplantation [34].

Exosomes have gained attention as a new potential cell free approach due to their immune-modulatory and regenerative properties. MSC derived exosomes not only help in wound healing and skin recovery but also in reducing oxidative pressure, rejuvenation, further developing hair growth, treating melanoma and autoimmune disorders like (GVHD) Graft versus host disease, psoriasis [35].

2.7. Fibrosis Condition

Renal calculi (“nephrolithiasis” or “urolithiasis”) are a common but under-estimated disease of the world involving 1–20% of the population, depending upon geographical regions [36]. Calcium oxalate (CaOx) is the most well-known constituent of the matrix accounting for approximately 80% of all renal calculi examined. The contribution of exosome-like vesicles in renal calculi was initially discovered in rat models [37].

Exosomes not only play a role in the pathogenic mechanisms of kidney diseases yet additionally act as a significant source of potential non-invasive biomarkers for diagnostics and prognostics. Contrasted with the conventional urinary and circulating biomarkers, exosomes are enriched with specific sets of biomarker molecules, particularly receptors, proteins, genetic materials. Therefore, exosomal markers have a role in biomarker discovery in specific diseases that include abnormalities of such molecules.

The protective structure of the exosomes saves its cargo from degradation; accordingly, the molecular cargo of exosomes can play essential roles in the early diagnosis and treatment of kidney disease. However, there are insufficient examinations and clinical trials in this field to ensure the efficacy of MSC-derived exosomes in the treatment of kidney diseases. Although numerous efforts have been made to broadly examine the roles for exosomes in several other kidney diseases, the contributions of exosomes in kidney stone disease remain under-investigated [38].

Fibrosis is a common feature of many chronic organ diseases wherein it causes impairment of cell-cell communication, aberrant tissue remodeling, alterations in blood stream, diminished tissue or organ function, and expand the growth of more severe life-threatening conditions such as end-stage organ illness or tumor [39].

Liver fibrosis is a tissue damage repair response described by abnormal development of intra hepatic connective tissue, which is a common pathological cycle in the initial phase of different chronic liver illnesses, like viral hepatitis, alcoholic fatty liver, and hepatocellular carcinoma [40]. In chronic liver diseases, exosomes discharge various bioactive components into the extracellular spaces, and intercede intercellular signal transduction and materials transport. Past examinations have found that MSC-derived exosomes could mitigate acute and chronic liver injury and have the benefits of high biocompatibility and low immunogenicity [41].

The hepatocytes, Kupffer cells, hepatic stellate cells, and hepatic sinusoidal endothelial cells that constitute the liver could all secrete or act as target cells of exosomes, and the progressions of the number and composition of these vesicles reflect the physiological and pathological condition of the liver [42]. The quality and amount of these exosomes vary depending upon the phases of the disease. During the occurrence and development of liver diseases, exosomes can likewise be utilized as novel molecular biomarkers for observing the therapeutic effect of diseases [43].

Exosomes participate in an assortment of pathophysiological progressions, for example, cytokine production, macrophage activation, extracellular network remodeling, and cell activation. Most of the present studies on exosomes for the therapy of chronic liver diseases depend on cellular and animal experiments, and the clinical period of the investigation stills needs to be remained to be investigated [44].

3. Drug Delivery

Exosomes as drug delivery systems have numerous advantages, for example, they can possibly target explicit tissues, ability to cross different obstructions, including the blood–brain barrier, and their resistance inside body fluids. These properties permit them to convey drugs to where they are required as well as avoid unnecessary side effects during distribution of drug throughout the body. Exosomes additionally carry several components including proteins and nucleic acids and even anti-inflammatory and anticancer agents. Exosome have gained much attention as drug delivery vehicles, firstly due to their nanometric size because of which they can easily move between cells with low immunogenicity, innate stability, and high delivery proficiency. Furthermore, the lipid bilayer-membrane structure of exosomes confers a protected environment for bioactive molecules from degradation in the extracellular milieu [45]. Thirdly, exosomes show lower toxicity and immunogenicity than any other drug-delivery techniques [46]. Lastly, exosomes bearing explicit surface proteins, for example, integrins, can guide themselves to explicit organs. Consequently, these properties make exosomes a productive drug-delivery vehicle, anticancer agents, siRNAs, or proteins [47].

Use of exosomes as nanocarriers is effectively investigated. For instance, Alcaez et al showed the utilization of exosomes for targeted delivery of siRNA after systemic administration, which demonstrates their potential use as vehicle for gene therapies [48]. Tian et al reported that exosomes modified by targeting on ligands can be utilized for delivery of doxorubicin to tumor cells [49]. Kim et al reported good efficacy of an exosome-based framework as a conveyance vehicle for PTX to multi-drug resistant cancer cells [50].

However, the therapeutic capability of exosomal delivery system is largely confined by their uncertain loading efficiency, rapid clearance from systemic circulation, and in some cases weak targeting capacity. For cargo delivery, numerous methodologies have been investigated for exosomal loading of different drugs and other bioactive accumulates of interest. Moreover, different modifications have been applied to exosomes for prolonged blood circulation and higher tissue selectivity.

4. Exosomes in Clinical Trials

The roles and function of exosomes in various disease states have become clear, exosomes have been progressively developed and become ideal method for the treatment of disease and analysis. Many preclinical experiments have confirmed the advantages of exosomes from the field of regenerative medicine to cancers. A survey on ClinicalTrials.gov (<https://clinicaltrials.gov/>) shows the major applications of exosomes as biomarkers, exosomes-therapy, drug delivery systems, and cancer. Though there is no FDA-approved clinical product based on exosomes, the number of ongoing clinical trials including exosomes-based therapeutics and diagnostics is increasing [51, 52].

5. Conclusion

The study of exosomes is an active area of research. Progressing innovative and trails are going to yield significant data with respect to their heterogeneity and biological functions, as well as improve our capacity to harness their therapeutic and diagnostic potential. Exosomes have drawn tremendous attention considering their promising clinical applications. They act as diagnostics tools since they are transporters of molecular markers of numerous diseases and as a prospective delivery system for different therapeutic agents. Exosomes are developing as promising biomarkers and important therapeutic targets closely aligned with the improvement of precision medicine. Also, they can work as potential drug-delivery vehicles or cell-free antibodies, providing alternative strategies for exosomes- based anticancer treatment. Together, comprehensive studies clarifying the roles of exosomes in different cancers and health states can revolutionize current diagnostic and therapeutic tools in medicine.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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