Review Article

Exploring the Role of Exosomes in Modern Medicine

Vedika N. Dafe*, Pooja R. Hatwar, Dr. Ravindra L. Bakal, Harshdeep V. Bindod
Department of Pharmaceutics, Shri Swami Samarth Institute of Pharmacy, At Parsodi, Dhamangaon Rly, Dist -Amravati (444709) Maharashtra, India.
***Corresponding author's E-mail:** vedikadafe27@gmail.com

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ABSTRACT

Exosomes are nano-sized membrane vesicles that transfer bioactive molecules between cells and modulate various biological processes. They are composed of lipids, proteins, and nucleic acids, and their biogenesis involves the formation of multivesicular bodies and the release of exosomes through exocytosis. Exosomes have been implicated in various physiological and pathological processes including cancer, immunotherapy, and neurodegenerative diseases. This review aims to provide an overview of the recent advances and challenges in exosomal based drug delivery systems in various diseases, including cancer, cardiovascular disease, and joint disease. This review provides an overview of the biogenesis, composition, and therapeutic applications of exosomes.

Keywords: Exosomes, drug delivery, delivery technology, exosome therapy.

INTRODUCTION

Exosomes are classified as the smallest organelles[1], spherical lipid bilayer vesicles[2], and nano-sized membrane vesicles secreted by cells ranging in diameter from 30 to 150 nm[3,4,5]. They contain complex lipids, RNAs and proteins, DNAs, messenger RNA (mRNA), microRNA (miRNA), small interfering ribonucleic acid (siRNA), and various signaling molecules [5]. Prokaryotes, eukaryotes, and various cell types can release these vesicles, and they can mediate cell-to-cell communication in both physiological and pathological conditions [4,2]. Exosome research is a rapidly growing field that offers a convergence of new potential and complicated problems in the fields of precision medicine and pharmaceutical innovation [6]. Exosomes, which are endosomal-derived nanosized extracellular vesicles (EVs) released by nearly every cell type, have received attention as possible therapeutic delivery vehicles [6]. They come from different cells [7]. Microvesicles, apoptotic bodies, and exosomes are the three main categories into which EVs belong despite significant progress in their classification. Their relative sizes range from 100 to 1000 nm, 500 to 2000 nm, and 30 to 150 nm [8]. Exosomes, a subtype of EV, were first identified as a way for cells to eliminate undesirable cell metabolites or other materials. Exosomes were initially discovered in sheep reticulocytes in 1983, and Johnstone gave them the name exosomes in 1987 [3,4]. All bodily fluids, including urine, blood, saliva, semen, breast milk, and cerebrospinal fluid, include exosomes, which are tiny vesicles that make them a great diagnostic for the identification of cancer and related conditions. Because of their inherent stability, low immunogenicity [9,10], negative zeta potential to evade immune attack, and good ability to pass through biological barriers, exosomes are unquestionably powerful drug delivery vectors in clinical settings. They are also imprinted with the ability to facilitate cell-cell communication [9]. Exosomes have been used and researched extensively as natural medication carriers. When it comes to medicine and gene delivery, it offers numerous benefits over conventional nanocarriers. First, exosome delivery can increase a drug's stability. Exosomes, for instance, can shield nucleic acids from deterioration while in transportation [11-13].

BIOGENESIS OF EXOSOME:

The biogenesis of exosomes entails their formation from the parent cell [4]. The production of exosomes is believed to include two phases of plasma membrane invagination. Initially, the cytoplasmic membrane invaginates to form an early endosome [14,15]. During this phase, cell membrane components are integrated into the endosomal membrane. Thereafter, early endosomes evolve into late endosomes, which subsequently undergo reverse outgrowth to generate multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs) [14,15]. Exosomes are believed to originate from endocytosis; microvesicles are formed by the budding and blebbing of the plasma membrane, and cells experiencing apoptosis and signaling for engulfment produce apoptotic bodies. The present discussion focuses on the biogenesis of exosomes, covering the production by parent cells and the uptake by recipient cells [4]. The endosomal system is the origin of exosomes [7,16]. Cell surface proteins and soluble proteins from outside sources are present in early endosomes, which are generated by the fusion of endocytic vesicles. Early endosomes are organelles that receive macromolecules and solutes from the extracellular environment [7,17]. The many forms of EVs are categorized based on their unique functions, size, origin of cells, morphological features, and manner of release [18]. The primary subsets are apoptotic bodies (0.8–5 cm), microvesicles (MVs) (50–10,000 nm), and small EVs or exosomes (between 30 and 150 nm), each of which has unique characteristics and roles. For example, cells participating in programmed cell death produce apoptotic bodies. Ectosomes are outward branching plasma membranes that can shed from donor cells, releasing MVs. On the other hand, when the endosomal membrane

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invaginates, the outer membrane of the multivesicular bodies (MVB) merges with the plasma membrane, which causes the release of exosomes. Exosomes, also referred to as small extracellular vesicles (EVs), represent one of the most fascinating kinds of EVs. To ensure stability and structural rigidity as before, EVs generally incorporate phosphatidic acid, phosphatidylserine (PS), sphingomyelin (SM), cholesterol, and arachidonic acid [18]. Exosomes enter the extracellular matrix (ECM) through exocytosis, where exosomal surface proteins facilitate the identification of target cells for the subsequent absorption [19]. Following the import of various molecules into the cells, integrins, tetraspanins, and intercellular adhesion molecules intervene to help exosomes engage with specific receptors of the recipient cells. These molecules then internalize exosomes by the same conventional mechanisms including:

(i) Phagocytosis: Exosomes and some extracellular fluids are phagocytosed in phagocytosis, an internalization process that is nearly identical to macropinocytosis. Both phagocytic cells, such as dendritic cells (DCs) and macrophages, and non-phagocytic cells, such as T cells, employ this method [20].

(ii) Macropinocytosis: The process of macropinocytosis occurs when the plasma membrane deforms, creating protrusions that encircle the extracellular fluid and exosomes and subsequently allowing exosomes to be taken up. Numerous elements mediate this complex process, which necessitates Na+/H+ exchange and depends on Ras-related C3 botulinum toxun substrate 1 (Rac1), actin, and cholesterol [21].

(iii) Clathrin/caveolin-mediated endocytosis: For the exosomes to be internalized, the clathrin protein forms a structure resembling a basket knit. The target cell's plasma membrane folds internally, and the clathrin-coated vesicle is then squeezed out of the membrane. To carry out specific tasks, the exosome then releases all of its cargo into the endosomes of the target cell [22].

(iv) Internalization through lipid raft: Caveolin-1, whose clusters in the plasma membrane are arranged in rafts, may also mediate the endocytosis process in a manner like the clathrin-dependent method. Caveolin 1, glycolipids, and cholesterol are rich in the invagination of the plasma membrane known as caveolae [23].

(v) Direct plasma membrane fusion: The integrins or tetraspanins, as well as the Lysosomal Associated Membrane Protein 1 (LAMP-1) and glycoprotein type I transmembrane protein, are implicated in this fusion process. These proteins mainly reside across lysosomal membranes, though they can also occasionally be expressed across the cell's plasma membrane [24,25] . Other receptor-mediated endocytosis ligands and receptors have also been found, including receptor/ligand complexes; however, additional analysis is necessary to clarify their function in exosomal internalization [26].

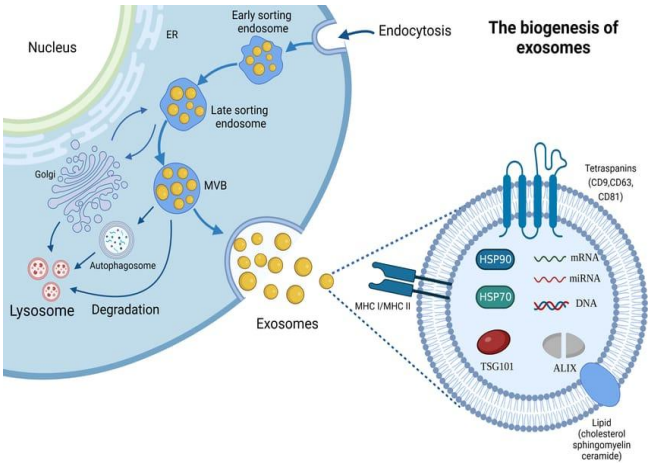

Figure 1: The biogenesis and composition of Exos. ER; Endoplasmic reticulum, MVB; Multivesicular Body [10].

BIOCHEMICAL COMPOSITION OF EXOSOME:

Expertise about exosome content is thoroughly researched since it influences exosome activity and, to a certain degree, its involvement in intercellular communication [7]. Lipid-bilayered extracellular vesicles with a diameter of 30 to 200 nm are known as exosomes. These vesicles, which are naturally secreted by nearly all cell types, are made by endosomal membrane budding and contain a cell's proteins, lipids, carbohydrates, and nucleic acids [9]. Additionally, these nanoscale biological vectors transport proteins, lipids, and nucleic acids produced by cells as signaling molecules to promote communication and signal transduction among nearby cells [9,27]. The parent cell's structure is reflected in the exosome's interior and exterior contents. Nevertheless, certain characteristics, such as tetraspanins (CD9, CD81, CD82, and CD63), syndecans, heat shock proteins (Hsp60, Hsp20, Hsp70, Hsp22, Hsp90, and alpha-B Crystallin), biogenesis-associated proteins (ESCRT proteins, CHMP4, TSG101, STAM1, VPS4, PLD2), membrane transport and fusion proteins (annexins, GTPases, and Rab molecules), nucleic acids (long non-coding RNAs, miRNA, mRNA, and DNA), and lipids, frequently span the membrane of exosome structure [9,28]. On the outermost surface of exosomes, a glycan canopy is affixed to the outer leaflet lipids and surface proteins [8,29]. In comparison to the parent cells, exosomes have higher levels of cholesterol, diglycerides, phospholipids, sphingolipids, glycerophospholipids, and ceramides beneath this glycosyl canopy [8]. The exosome membrane is mostly composed of lipid layers that contain ceramide, diacylglycerol, sphingolipid, and cholesterol, in contrast to the membranes of other EVs [30]. For large-scale preparations for subsequent procedures like translation and cargo loading into exosomes, the storage conditions for pure exosomes present a difficulty. These consist of buffer, storage temperature, and pH, which affect their stability [31]. A total of 332,666 gene sequences, 2838 miRNA bases, 1184 distinct lipids, and 63,100 proteins were found and made available in Exocart [30,32].

Protein: Numerous proteins that have been found in the exosome membrane or lumen are carried by exosomes.

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Exosomal proteins include: (i) cell surface proteins, including those that are affected by their endosomal pathway, including tumor-sensitive gene 101 (TSG101), heat shock proteins (HSC70), fusion proteins (flotillin and annexin)(30); tetraspanins (like CD81, CD82, CD37, CD63, and CD9), CD86 [5], MHC class II, MHC class I, lactadherin (LA), lactadherin (LA), lysosome-associated membrane protein-2b (Lamp-2b), and integrins; (ii) MVB associated proteins, including Alix and tumor susceptibility gene 101 (TSG101); and (iv) cytoskeletal proteins, including tubulin, actin, and cofilin [7,33,34]. Numerous types of membrane proteins, including lipid-anchored membrane proteins, transmembrane proteins, peripherally associated membrane proteins, and soluble proteins of the exosome lumen, are found in exosomes [8]. Proteins involved in vital physiological functions such cell adhesion, metabolism, membrane fusion, and signal transduction are also found in exosomes. Furthermore, the lumen contains DNA, mRNAs, microRNAs, and other noncoding RNAs [35].

Nucleic Acids: Nucleic acids, including messenger RNAs (mRNAs), micro-RNAs (miRNAs), and double-stranded DNA (dsDNA), are also found in exosomes. Because of the diverse variety of molecules they can transport, their biological functions may differ based on their cellular origin. The presence of conserved transmembrane proteins in exosomes, such as tetraspanins (CD81, CD63, and CD9), Alix, and Tsg101, suggests that their biological activities are similar [26,30,36] and may be used as possible exosome identifying markers. They also possess cell-type-specific proteins that reflect their biological roles and cellular origins [30,37]. According to Valadi et al., exosomes generated from human and mouse mast cells contain RNA that can be transported to other cells [7].

Lipids: Lipids, which include phosphatidylserine, glycosphingolipids, sphingomyelin, and cholesterol, are among the most important elements of exosomes [7,38,39]. The encapsulated payload is stabilized and protected by the lipid membrane, which also prevents the extracellular environment from degrading it [40]. Exosomes biophysical characteristics and interactions with recipient cells are influenced by their lipid composition, which can change based on the physiological state and type of parent cell [5].

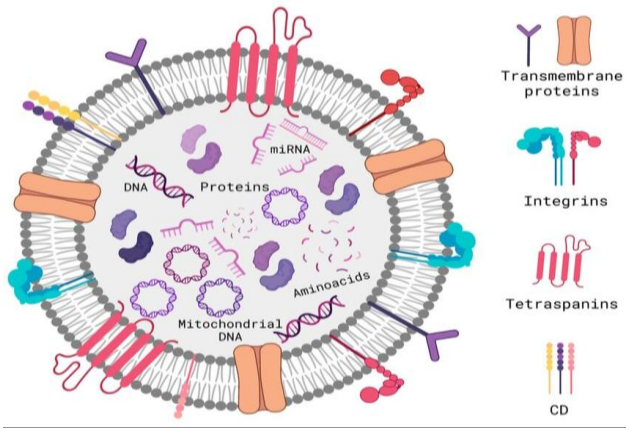

Figure 2: Schematic diagram of a general structure of an exosome [41].

SOURCES OF EXOSOME:

It is widely known that mesenchymal stem cells (MSCs) release soluble factors that have been mechanistically connected to exosomes in several preclinical and clinical investigations. These factors help MSCs achieve their regenerative and therapeutic goals. It's interesting to note that exosomes released by MSCs from various origins, such as bone marrow and the umbilical cord, exhibit distinct physiological, pathologic, or regenerative roles as cell-cell communication mediators [42,43]. For instance, exosomes derived from menstrual fluid MSCs function as blockers, whereas exosomes obtained from bone-marrow MSCs encourage tumor-induced angiogenesis in breast and prostate cancer [44]. Exosomes are produced by the majority of cells and tissues; therefore, it is not surprising that they use bodily fluids as means of transportation in physiological processes such immunological responses [45], cell-to-cell signaling [46], and some pathological activities.

Exosomes released into bodily fluids have the potential to be used as biomarkers for diagnosis, prognosis, and monitoring the effectiveness of treatment in diseases including cancer, vascular and autoimmune diseases, and others since they contain a cell-specific cargo signature [44]. Animal cells and plant cells differ structurally, particularly in the outer membrane, which is a crucial component for exosome release. Plant cells are also surrounded by a polysaccharide-based cell wall, in which paramural bodies—exosome-like vesicles—are released from the cell membrane. In contrast, animal cells have a phospholipid bilayer that permits exosome release into the extracellular area. In addition to proteins, lipids, and metabolites, it has been found that plant exosomes in the model organism Arabidopsis thaliana transport miRNAs, sRNAs (small RNAs, 18–24 nt), and tyRNAs (10–17 nt). Different appearance patterns were seen when comparing the cargo to the existence of the mi/s/tyRNAs in the apoplast. This suggests a particular loading pattern and a potential utility for long-distance delivery [44,47].

Studies that provide information on the function of parasitic EVs in parasite-parasite communication and parasite-host interaction have grown in popularity over the past few decades. Like bacterial and fungal vesicles, parasite exosomes contain virulence factors that are absorbed by host cells and contribute to the spread of the infection. A possible approach to vaccine development may be suggested by Li et al.'s observation that Toxoplasma gondii, an obligatory intracellular apicomplexan parasite, can influence macrophage activation in vitro and elicit humoral and cellular immune responses [44,48].

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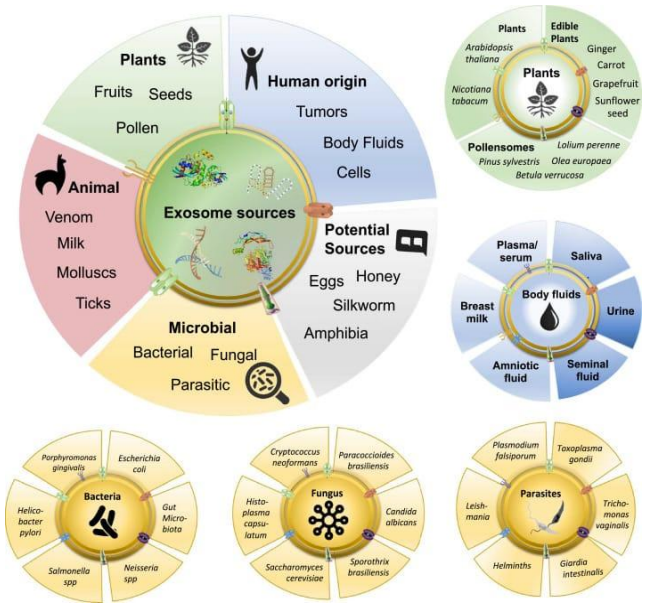

Figure 3: Illustration of the different sources for the production of exosomes, covering human, plant, animal and microbial origins [44].

Description: Human tissues consist of cells, bodily fluids, and malignancies. The diagrams show non-exhaustive examples of bacteria, fungi, parasites, plants, and bodily fluids. The graphic also highlights new possible sources of interest for exosome identification, such as honey, silkworms, eggs, and amphibia [44].

ROLE OF EXOSOME IN TREATMENT AND MITIGATION OF VARIOUS DISEASES:

1. **Exosome in Treatment and Mitigation of Various Complications Exosomes as a promising delivery system for anti-cancer drugs:** Exosomes are natural vesicles secreted by various cells in the body and serve as essential carriers of information between cells. Exosomes are innate carriers of functional genetic information that show off low toxin and wide tissue distribution in vivo. They also retain more than 30 times less cellular uptake than alternative delivery systems similar as nanoparticles or liposomes [49]. Furthermore, exosomes exhibit resistance to harsh environmental conditions, such as low blood pH, making them promising biocarriers for medicines, nucleic acids, and imaging agents in cancer remedy. The potential of exosomes as delivery systems for anticancer medicines, particularly compounds with low solubility and limited off- target delivery, is of significant interest.

   Manipulating exosomes by inhibiting their biogenesis or modifying their surface membranes and loading them with cargo, similar to proteins, nucleic acids, or drugs, has demonstrated remarkable potentiality in reducing tumor progression and metastasis. Specially, exosomes are at the forefront of clinical trials for diverse remedial operations; there are 118 ongoing trials as of 2022 [50].

2. **Exosomes in Immunotherapy of Primary Brain Tumor:** In 2016 the brain tumor was the upmost tumor-related death in ages 0–14 and the third most common cancer in teenager groups [51]. Cancer immunotherapy harnesses the body's own immune system to fight cancer. Unlike radiation, chemotherapy, and surgery, the immune system can potentially target tumor cells collectively while sparing non-tumor cells, which makes it captivating for the treatment of largely invasive brain tumors. Growing documentation indicates that a small cohort of largely tumorigenic, chemo- and radio- resistant stem like tumor cells called cancer stem cells (CSCs) account for the high rates of tumor outbreak after treatment, as in glioblastoma, and immunotherapy carries the additional promise of being suitable to target CSCs specifically [52]. Specially, tumor cells have been shown to produce and secrete exosomes in greater numbers than normal cells [53]. Exosomes have been extensively proved to play an important part in the arrangement of tumor microenvironment, tumor invasion and metastasis, angiogenesis and tumor immunity [54].

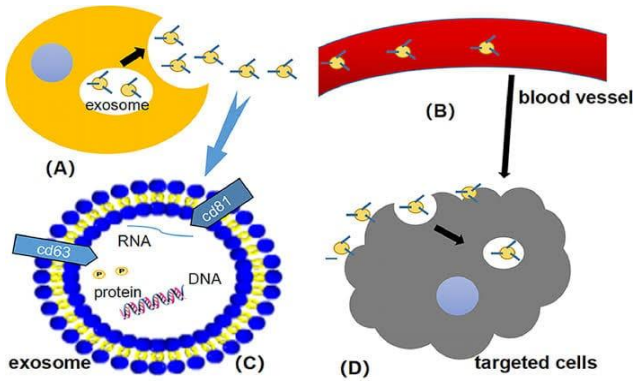

Figure 4: Mechanisms of exosome generation. (A) Biogenesis of exosomes: exosomes are membranous vesicles that germinate in cells. They are stored in MVBs. After the fusion of MVBs and cell membranes, exosomes are released into the extracellular space. (B) Exosomes are delivered via blood vessels. (C) Microstructure of exosomes: exosomes have a lipid bilayer structure, containing DNA, RNA and proteins. (D) Exosomes fuse with the plasma membrane of targeted cells and interact with them [55].

3. **HIV and exosomes:** Exosomes can be separated from HIV-1-infected cell cultures and the blood serum of infected patients. While exosomes from latent HIV-1-infected Jurkat cells (J 1.1) contain some viral proteins, similar as the precursor form of Env protein (p160) and Gag protein, they don't contain intact HIV-1 viral molecules. Still, the precursor of various HIV-encrypted mRNAs, known as HIV-TAR RNA, can be found in exosomes from infected individuals and may support the attachment of the viral Tat protein, leading to increased HIV replication and transcription. When exosomes loaded with TAR- RNA are introduced to primary macrophages, they can induce the production of tumor necrosis factor-b (TNF-b) and interleukin- 6 (IL-6) cytokines. Lately, the use of exosomes along with

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other EVs is an emerging tool to diagnose and treat HIV-1 disorder [56].

4. **Exosome as Diagnostic of COVID- 19**: Exosomes and extracellular RNAs (exRNAs) are involved in several pathological processes. Utmost exRNAs are protected from degradation inbio-fluids via incorporation into exosomes or into complexes with lipids and proteins. Different types of exRNA (eg, mRNAs, miRNAs, small nuclear RNAs, transfer RNAs, lncRNAs) are produced and released during antiviral responses, playing fundamental functions in modulating the host innate immune system. These exRNAs are involved in a complex network of interactions between the virus and infected host cells. Lately, clinical studies have revealed that the employment of human umbilical cord- derived MSCs (HUMSCs) showed a positive response in COVID-19 patients [57].

   Exosomes act as vehicles that transfer specific cargo similar as mRNA, non-coding RNAs, proteins, and DNA from parental cells to neighboring cells, and reprogram recipient cells due to their active molecular cargo; thus, exosomes are regarded as "signalosomes" for controlling fundamental cellular functions [57,58].

5. **Role of Exosomes in the CNS:** Interestingly, it has been discovered that exosomemediated interactions between neurons and glia induce neurite outgrowth and neuronal survival [59]. Concordantly, Xin et al. showed how exosomes secreted by mesenchymal stem cells (MSCs) are suitable for transferring microRNA-133b into neurons, resulting in the induction of neurite outgrowth [60]. Morel et al. showed that neurons secrete microRNA-124a through exosomes the vesicles are subsequently transported into astrocytes, thereby laterally increasing GLT1 protein expression [61]. Taken together, these observations support the hypothesis that exosomes mediate cell-cell communication within the CNS. Given this scenario, it isn't surprising that exosomes play an important part in the pathophysiology of neurodegenerative conditions [62].

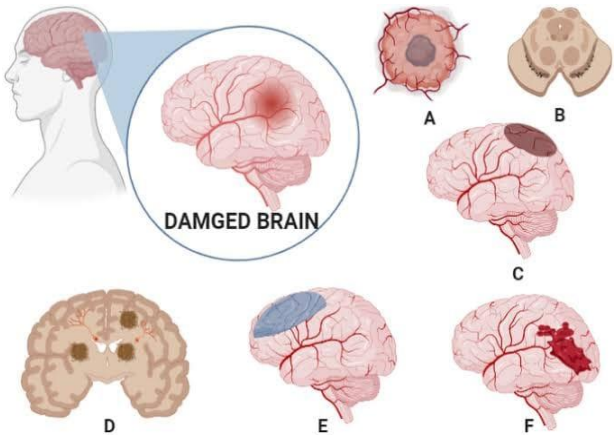

Figure 5: Various brain diseases treated using exosomes. A) Glioma, B) Parkinson's, C) Brain stroke, D) Alzheimer's diseases, E) Brain ischemia, F) Brain haemorrhage [63].

6. **Role of endothelial exosomes in cardiovascular diseases:** Exosomes were originally shown to participate in selective removal of many plasma membrane proteins. For instance, in the reticulocytes, portions of the plasma membrane are regularly internalized as endosomes, with 50 to 180% of the plasma membrane being recycled every hour. The amount of fluid internalized by macrophages corresponds to some 30% of cell volume per hour of which about two-thirds are returned to the extracellular space within about 10–15 min [64]. Despite their potential applications in eliciting a "positive" immune response, exosomes might induce some "unwanted" immune responses, such as immune tolerance and immune evasion [65]. These exosome cargoes also play an important physiological role in intercellular communication [66]. The concept of the exosome as a non-plasma-membrane-derived vesicle emerged with the description of the process of 'shedding' of the transferrin receptor (TfR) during reticulocyte maturation [67], immune signaling regulation [68,69], tumor biology [70,71], stress responses [72,73], and angiogenesis [74]. A common exosome feature is the expression of adhesion molecules, which include the integrin family [69]. To this point, one study showed that endothelial derived microparticles promoted cell survival, counteract coagulation processes, exerted anti-inflammatory effects, and induced endothelial regeneration [75]. Exosomes contain various molecular constituents, including proteins, mRNA and miRNA, which can be transferred from one cell to another via membrane vesicle trafficking, thereby influencing the dendritic cells, B cells and related adaptive immune responses [76]. Although EC-derived exosomes are lower under physiological conditions, elevated EC exosomes and their cargoes have been found in angiogenesis, vascular smooth muscle cell (VSMC) phenotypic changes, atherosclerosis and heart disease [76].

7. **Exosome as Vectors of Stem Cell Therapy:** In recent years, mesenchymal stem cells (MSCs) have attracted much attention as potential cell-based therapeutic tools due to their ability to migrate and mediate damage repair. MSCs facilitate neurological recovery and neo-angiogenesis through the secretion of neurotrophins and angiogenesis regulatory factors [77]. Stem cell therapies exhibit great potential for the treatment of various diseases. The therapeutic effects of adult stem cells remain to be fully elucidated. However, exosomes carrying a cargo of packaged signals in the form of RNA, miRNA, or protein, among others, may be a key mechanism and the vehicle of their action to reduce inflammation, alter cellular signaling, and result in tissue repair. MSC therapy, for example, is being tested in animal models and in multiple clinical trials for the treatment of disorders including acute lung injury, myocardial infarction, diabetes, sepsis, graft-versus-host disease, and hepatic and acute renal failure [78]. The therapeutic effect has

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been recapitulated in several preclinical models with administration of cell-free media from MSC cultures that, among other moieties, contain exosomes. Exosomes are also being recognized as critical mediators of health and disease and may be biomarkers of specific conditions [79].

8. **Potential of Exosomes for Diagnosis and Treatment of Joint Disease:** The potential for exosomes and their derivatives to be delivered through intra-articular injection opens up new possibilities for the treatment of joint diseases such as OAK (osteoarthritis of the knee). Exosomes contain specific information about the cells from which they are released and may have the ability to deliver molecules to specific organs or tissues at a distance [80]. In recent years, mesenchymal stem cells (MSCs) and their secreted exosomes have become a focus of research into cartilage regeneration [81]. Allogeneic MSCs even have advantages over autologous bone marrow-derived MSCs (BM-MSCs) in clinical outcomes in elderly patients with reduced cartilage degeneration [82]. Studies have shown that exosomal miRNAs play an important role in joint homeostasis. Furthermore, the imbalances in exosomes created during joint disease can be utilized as diagnostic biomarkers. Studies have also shown the potential for exosomes to be utilized as a drug delivery system (DDS) to deliver specific cargo to localized areas. In combination with tissue engineering, studies have utilized exosomes in a sustained release drug delivery system (SRDDS) to further improve efficacy [83].

9. **Impact of Exosomes from Immune Cells on Immune Responses in T2DM:** Exosomes play an essential role in modulating immune responses in T2DM by regulating immune cell function and cytokine production in several ways. Exosomes derived from immune cells can induce proinflammatory and antiinflammatory responses depending on the context, such as proteins, lipids, and nucleic acids. Exosomes secreted by inflammatory M1 macrophages impaired β-cell insulin secretion in an exosome-dependent manner. miR-212-5p was notably upregulated in M1-Exos and HFD-Exos, which impaired β-cell insulin secretion by targeting the sirtuin 2 gene and regulating the Akt/GSK-3β/β-catenin pathway in recipient β-cell. Researchers indicated that exosomal miR-144-5p derived from diabetic bone marrowderived macrophages (BMDM) can be transferred to bone mesenchymal stem cells, leading to suppressed Smad1 expression and reduced bone repair and regeneration in vitro and in vivo. One study revealed a crosstalk pathway between β-cells and macrophages mediated by the miRNA-29-TNF-receptor-associated factor 3 (TRAF3) axis. Mechanistically, miR-29 promotes the recruitment and activation of monocytes and macrophages, leading to inflammation and impaired glucose homeostasis via miR-29 exosomes in a TRAF3-dependent manner. These findings demonstrate the ability of β-cells to modulate systemic inflammatory tone and glucose metabolism through miR-29 in response to nutrient overload [84].

CLINICAL APPLICATIONS OF EXOSOMES:

- Since exosomes are biologically derived, they exhibit superior physicochemical stability, low immunostimulatory activity, low toxicity, biocompatibility, and biobarrier permeability when compared to conventional vectors such liposomes, nanospheres, micelles, microemulsions, and conjugates. Exosomes are fascinating vehicles for tailored medication delivery because of these characteristics [85].
- Because in vivo circulating exosomes carry biological elements (e.g., proteins and nucleic acid) indicating current physiological conditions, exosomes are being exploited as diagnostic biomarkers from bodily fluids including blood and urine [86].
- One non-invasive technique for diagnosing cancer is miRNA profiling of circulating exosomes [86].
- Exosomes can be exploited as cell-free treatments with similar effectiveness but a superior safety profile than original cell therapy because it is widely known that they inherit many physiological traits of the cells from which they originate [86].
- Exosome-based therapies provide exceptional potential for targeting and influencing particular tissues. Certain cargos, such miRNAs, can be packaged and distributed to different OAK-affected tissues, including cartilage, synovium, and subchondral bone, with the right management. Exosomes are less immunogenic and cannot directly generate tumors, in contrast to cell-based therapies [83].
- Exosomes are implicated in modulating immunological responses, according to a substantial body of scientific research. Exosomes are known to commonly target immunological cells, such as B cells, dendritic cells (DCs), and macrophages, all of which are efficient antigen-presenting cells (APCs) [87].
- Exosomes are crucial for intra-organ and intercellular communication networks because they facilitate intercellular communication by transporting signaling molecules between cells, including proteins, DNA, mRNA, and miRNA [85].
- The utilization of exosomes as anticancer vaccines is another beneficial usage for them. M1 macrophage-secreted exosomes have the ability to stimulate inflammation. Tyrosinase-related protein 2 vaccines are more effective and produce a more potent antigen-specific cytotoxic T-cell response when they are encapsulated in lipid calcium phosphate nanoparticles[88].

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CHALLENGES OF DEVELOPING TREATMENTS UTILIZING EXOSOMES:

A more complex mechanism of action, such as the synthesis of humoral components that may be impacted by regional circumstances, is the foundation of cell-based therapies[89,90]. Exosomes can carry and distribute a consistent set of cargos at appropriate concentrations with adequate manufacture, though local factors may also have an impact [83]. However, there are still a lot of obstacles to overcome, like the need for a lot of cells to produce exosomes, the time and effort needed for collection, and the unknown dangers in guaranteeing safety and effectiveness [83]. The isolation and purification of exosomes themselves present the biggest obstacle. None of the several protocols and techniques that have been devised for exosome isolation are ideal enough to be used to all types of materials [84,91]. Their therapeutic application is hampered by the need for a deeper comprehension of the mechanisms underpinning exosome-mediated intercellular communication. Notwithstanding these obstacles, more study and advancement in this area could lead to the development of innovative therapeutic uses [84].

CONCLUSIONS

Exosomes potential as prescription drug delivery vehicles has drawn more attention from researchers in recent decades. Exosomes are promising delivery systems and instruments for oncological treatments, according to a growing body of research. Exosomes have shown remarkable promise as drug carriers for targeted tumor therapy in recent years, but their clinical use is currently constrained by several issues. In the pharmaceutical industry, exosome-based drug delivery technology shows promise and has several benefits. Nevertheless, MVs, apoptotic bodies, and non-vesicular pollutants are among the other EVs that may be present in exosomes made from cell supernatants. The widely used automated, low-cost method of ultracentrifugation has drawbacks, including unpredictability in yield efficiency and trouble differentiating exosomes from other EVs in the same size range. As an alternative, immunoaffinity capture can be used to separate particular exosomes that contain antigens; however, exosomes do not have a unique identifier and therefore are not appropriate for clinical mass production.

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