REVIEW PAPER

Application of natural and modified exosomes a drug delivery system

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ABSTRACT

Extracellular vesicles (EVs) are small molecules produced by most cells that may aid in cell communication. They can transfer functional biomolecules from one cell to the next, and even across the body. Exosomes are some of the most studied extracellular vesicle components. Many medications may be incorporated into exosomes and then disseminated to specific organs, tissues, and cells to provide tailored medication administration. According to a new study, exosomes, which are produced by cells, have a variety of functions and aims. Several studies have proven that a broad variety of cargo may be effectively transported to the precisely specified cells. For this reason, EVs are often used to carry medicinal substances as treatment. The researchers used exosomes that had been treated with additional chemicals to boost their transportability. Exosomes offer a number of advantages over other drug delivery technologies such as nanoparticle-based systems, liposomes, and even polymeric nanoparticles. Due to their similar nature to the body's own cells, exosomes have no immunogenicity. Because of their nanoscale size, exosomes are the most promising strategy for medicine delivery to specific tissues and organs, and they have gotten the greatest attention in recent years. The ability of natural and manufactured exosomes to convey a variety of cargo to the target cell is investigated in this article.

Keywords: *Cancer, Drug delivery systems, Exosome, Nanoparticles*

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INTRODUCTION

Chemical messengers are the most common way for cells to interact; the most prevalent kind is extracellular vesicles (EVs). Many recent studies have focused on EVs for therapeutic medicine development because of their unique shape, which enables them to be changed to carry certain proteins, lipids, and genetic components like messenger RNA (mRNA), microRNA (miRNA), and other short non-coding RNAs [1].

Because of their nanoscale size, exosomes are the most promising method for delivering medications to particular organs. Exosomes are formed when a multivesicular body (MVB) contacts the plasma membrane and is released into the extracellular environment. Its job is to communicate with the receiving cell while delivering a chemical payload [2].

Exosomes are small molecules that connect to cell membranes and communicate by releasing surface proteins and cytoplasm into the receiving cell. They help cells communicate by carrying proteins and RNA between cells and even to distant organs [3]. They have a role in antigen presentation, cancer formation, and a number of physiological and pathological processes, among other things [4].

Depending on EV's origin, physiological and pathological state, and even its physiological and pathological status, the cellular release site varies.

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Exosomes include a variety of proteins, including those involved in vesicle formation and trafficking, which might signal the presence of disease pathologies like cancer or infectious illnesses [5].

Exosomes are microscopic biological entities present in almost all body fluids. These structures/contents are generally disease-specific in viral infections, neurological diseases (prions, Alzheimer's, Huntington's disease), and cancer. Exosomes have been thoroughly investigated as possible sources of novel biomarkers [6, 7].

Exosomes are self-forming nanoparticles that exist naturally in the human body and are engaged in a variety of biological and pathological processes. Due to their participation in a variety of biological and physiological processes, researchers are considering using exosomes as medicinal delivery vehicles for a variety of treatments.

Exosomes

Exosomes are classified based on their size, intracellular origin, and biophysiological characteristics. Fig. 1 depicts the interaction of microvesicles (50–1000 nm) and apoptotic bodies (500–2000 nm) in EVs with each other and the host cell [8].

Membrane budding leads to vesicle fission from the cell's surface, resulting in microvesicles, also known as ectosomes [9]. Plasma membrane proteins, cytosolic proteins, nucleic acids, and other metabolites are all found in microvesicles [10]. Apoptotic bodies are vesicles that form when apoptotic cells disintegrate during the cell death process [11].

Exosomes are the smallest extracellular vesicles, yet they have a significant effect on the cells to which they are transported.

To classify exosomes, Zhang and his colleagues [12] used an asymmetric flow field-flow fractionation approach. Exomeres, which are non-membranous nanoparticles, and two exosome subpopulations were discovered [13].

Exosomes contain the same chemical makeup as the cells that create them, and they're sorted in the same manner [14, 15]. Proteins, lipids, growth factors, transcription factors, nucleic acids, and other metabolites are among the components and structures found in exosomes [16]. The lipid composition consists of cholesterol, phosphatidylserine, sphingomyelin, and saturated fatty acids, as well as cytoplasmic, plasma, intracellular, and nucleoproteins, among other proteins. Ceramide, diacylglycerol, cholesterol, and a variety of transmembrane (surface) proteins, including tetraspanins, make up exosome membranes (CD9, CD63, CD81, and CD82) [17, 18].

Drugs and genes might be carried by exosomes, which could also be employed for tissue regeneration, immunomodulation, and disease detection. Coagulation, intercellular communication, and cell waste management are among the functions they play [19, 20]. Recently, there has been a great deal of interest in artificial exosomes, which are considered to be better therapeutic biomaterials than genuine exosomes. Exosomes are classified into three categories based on their origin: natural, modified, and synthetic (Fig. 2) [21].

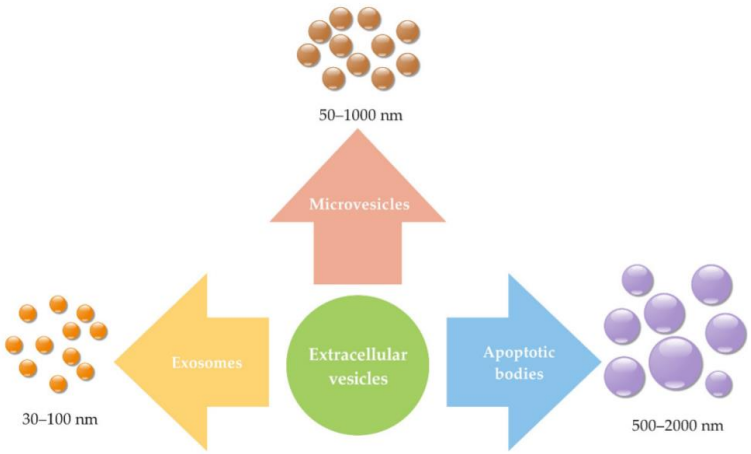

Fig. 1. Exosomes (extracellular vesicles with a diameter of 30–100 nm) are one of three kinds of extracellular vesicles that make up a cell's inner workings; they are followed by microvesicles and apoptotic bodies, which contribute to cell death [9]

Fig. 2. The three varieties of exosomes are natural exosomes (separated from a range of biological fluids), modified exosomes (naturally created and changed for certain goals), and synthetic exosomes (manufactured for specific reasons) (they mimic the properties of natural exosomes) [9]

Type of exosomes

Natural exosomes (exosomes derived from various cells)

Exosomes are nanoparticles that occur naturally [22, 23]. Cells that release chemicals into the environment include epithelial cells, endothelium, mesenchymal stem cells, macrophages, dendritic cells, tumor cells, neurons, reticulocytes, mast cells, platelets, cancer cells, B and T cells, and astrocytes [24]. Among other bodily fluids, they may be present in plasma, serum, urine, breast milk, sperm, saliva, nasal discharge, lymph, amniotic fluid, ascites, and cerebrospinal fluid. Exosomes have the potential to be employed as natural medications due to their biocompatibility [25].

Exosomes isolation techniques

Exosomes have been successfully collected from a number of sources using a variety of methods (Fig. 3). Ultracentrifugation is the most frequent method for extracting exosomes, and it produces a large number of separated exosomes. The difference in density and particle size is used in this simple and cost-effective strategy. It includes density-gradient ultracentrifugation and differential ultracentrifugation [21]. Immunocapture techniques are ways for isolating exosomes based on interactions between antibodies and surface proteins.

Ultrafiltration or size-exclusion chromatography may be used to isolate biomolecules. Polymer precipitation, a simple and straightforward process based on modifying exosome solubility, is another way to separate exosomes. Exosomes are separated and purified using microfluidic methods. These are more refined, delicate, and pure approaches [26].

Natural exosome-like nanoparticles

Immune cells produce exosomes (lymphocytes,

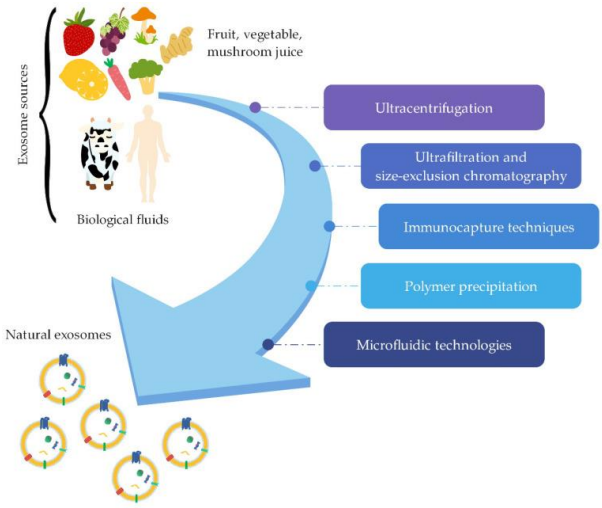

Fig. 3. Exosome isolation from various sources (ultracentrifugation, ultrafiltration, and size-exclusion chromatography, immunocapture techniques, polymer precipitation, and microfluidic technologies) (e.g., biological fluids and fruit, vegetable, and mushroom juices)[9]

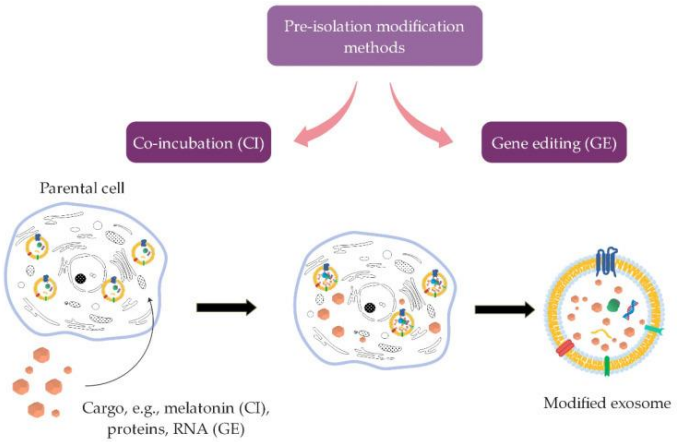

Fig. 4. Pre-isolation exosome modification methods (co-incubation and gene editing) are used to modify exosomes before they are isolated from parental cells (intended for the integration of RNA and proteins)[9]

red blood cells, platelets, dendritic cells, and tumor cells). Exosomes are produced by immune cells and may be discovered in a number of biofluids (urine, milk, and plasma). Cow milk exosomes are the most researched exosomes of animal origin; they have a protein, lipid, and RNA makeup comparable to human exosomal nanoparticles but are structurally and functionally distinct. Plants follow the same idea; they vary from animals in terms of protein, lipids, RNA composition, and lipid composition [27, 28].

Ginger, lemon, grapefruit, grape, broccoli, and carrot produce edible plant exosomes that may be used to treat inflammatory diseases. Nanoparticles resembling exosomes generated from a number of plant sources might be utilized to deliver medicinal drugs. Because of their anti-inflammatory properties, they may potentially be used as drug delivery vehicles. Perut et al. [29] identified and isolated strawberry exosomes with a morphology similar to mammalian exosomes[29]. It has been discovered that strawberry exosomes protect against oxidative stress and are non-toxic. Mushrooms may also contain exosome-like nanoparticles containing lipids, proteins, and RNA. Liu et al.[30] used successive centrifugation to extract exosomes from a variety of edible mushrooms [30]. Shiitake mushroom exosomes (L. edodes) have been demonstrated to have anti-inflammatory characteristics and may be utilized to treat fulminant hepatic failure (FHF). To separate the aforementioned exosomes, researchers used ultrafiltration, size exclusion chromatography, precipitation, and microfluidic techniques. They may be mixed with physiologically active components and used as drug delivery vehicles after being separated [31].

Modified exosomes (exosomes modified with other substances)

Exosomes are naturally occurring exosomes that may be changed for therapeutic purposes, [26], such as increasing the surface charge or facilitating the passage of medications through the digestive tract and into the neurological system [21]. Exosomes, or exosomes composed of chemicals that can be disassembled into their component components, have been used in several ways to show their therapeutic potential. Exosomes may be modified in two ways: internally, by modifying the cargo structure, and externally, by modifying the outer surface structure.

Interior alterations

Among the inside changes are methods for integrating medicinal chemicals into spontaneously formed exosomes. Various levels of freight efficiency and stability are provided by these systems [32]. Pre-separation (Fig. 4) and post-isolation (Fig. 5) approaches for cargo inclusion are divided based on whether the changes are made before or after exosome isolation.

Application of natural exosomes as drug delivery system

Exosomes exhibit a broad spectrum of functions in malignancies, according to several pieces of research. To begin, tumor cells interact with the tumor microenvironment (TME), which consists of endothelial cells, fibroblasts,

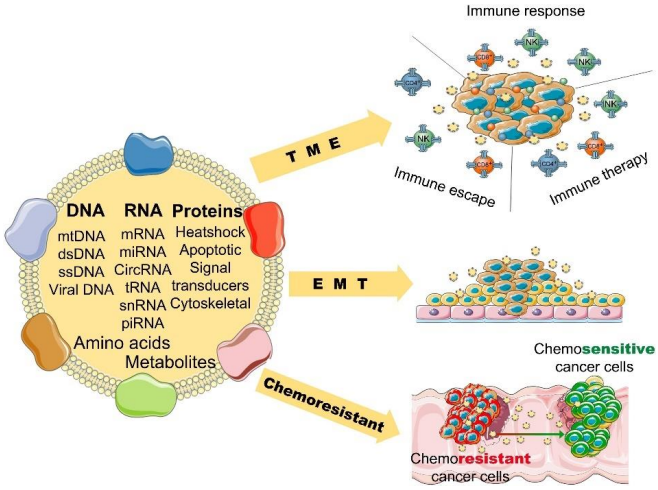

Fig. 5. Exosomes generated by tumors may have a role in cancer progression and etiology (TME, tumor microenvironment; EMT, epithelial-mesenchymal transition) [39]

and invading immune cells, and the contents of exosomes impact these interactions [33]. Exosomes affect the TME and extracellular matrix by activating extracellular receptor signals and preventing cell adhesion [34, 35]. For instance, exosomal integrins have a function in cancer cell colonization and formation of a pre-metastatic milieu [36]. According to research published in Cell Metabolism, the medication Exosomal miR-105 increases metastasis and vascular leakage in distant organs by downregulating ZO-1 and weakening the barrier function of endothelial monolayers. [37]. The most frequent cell type in the TME in most tumors is cancer-associated fibroblasts (CAFs), and exosomes from cancer cells may trigger TME cells to develop into CAFs [38] (Fig. 5).

Secondly, by activating angiogenesis, exosomes may increase tumor cell movement and dispersion [39] and EMT (epithelial to mesenchymal transition) [40]. Exosomes (brain-derived growth factors) are transported by fibroblast cells and play a crucial role in angiogenesis, or the creation of blood vessels. Growth factors found in exosomes include VEGF (vascular endothelial growth factor), PDGF (platelet-derived growth factor), TGF (transforming growth hormone), and bFGF (basal fibroblast growth factor) [41]. Exosomes drive endothelial cell reprogramming and control in order to promote angiogenesis [42]. Exosomes have a role in every aspect of EMT, from the invasive phenotype to distant metastases [43]. By inducing EMT, exosomes carrying matrix metalloproteinase (MMP) 13 increase nasopharyngeal cancer cell metastasis [44]. Exosomes produced by bladder cancer cells were shown to induce EMT in urothelial cells by upregulating mesenchymal biomarkers like SMA, S100A4, and snail while downregulating epithelial biomarkers like E-cadherin and catenin [45].

Cancer chemoresistance is also influenced by exosomes. Chemotherapeutic medications might be transported out of tumor cells via exosomes [46]. Exosome content has been associated with tumor therapy resistance [47]. EMT-delivered miR-155, for example, may increase EMT markers and cause chemoresistance in breast cancer cells [48]. Exosome-delivered miR-32-5p stimulates angiogenesis and EMT, which can result in multi-drug resistance [49]. Tumor-derived exosomes may alter the TME by suppressing immune effector cells and activating immune suppressor cells, resulting in cancer chemoresistance. Cancer cells may potentially use exosomes as a decoy to avoid being recognized by immune effector cells [50].

Benefits of natural exosomes in cancer therapy drug delivery

Exosomes have the potential to induce cancer development, yet their excellent biodistribution, biocompatibility, and low immunogenicity make them useful in medicine delivery. Because of their comparable form and content to the cell membrane, exosomes are well tolerated [51]. Exosomes are capable of evading the immune system [52]. Adriamycin-containing exosomes, for example, have relatively little immunogenicity

and toxicity. Exosomes are more effective than liposomes in penetrating tumor cells [33]. Researchers have shown that due to their tiny size, exosomes may pass across physiological barriers. Exosomes generated by dendritic cells were utilized to transmit siRNA over the BBB for the first time in 2011, demonstrating for the first time that exosomes may be used to transfer medicines across the BBB. Exosomes may potentially help anti-cancer drugs target more effectively by allowing for easy manipulation [53].

Exosomes have the potential to be an efficient carrier for chemotherapeutic drugs due to their stable lipid bilayer structure. Exosomes have recently been discovered to have a lot of potential for cancer treatment. Exosomes carrying paclitaxel, for example, might be used to treat prostate, lung, and pancreatic cancers [54]. Exosomes from diverse donor cells may transport tumor-specific antigens, proteins, and miRNAs, but they may also kill T cells and promote inflammation and cell death [55]. Although exosomes from stem cells may help with tissue repair and immunology, they can also promote tumor development by activating tumor angiogenesis-related proteins. Milk exosomes do not cause immunological exclusion or inflammation, and they may help increase medicine oral bioavailability. Exosomes from immune cells may hinder immune system clearance and prolong the time spent in the peripheral circulation [56].

Exosomes are now isolated from bodily fluids or conditioned cell culture medium via filtration and centrifugation, immunoaffinity chromatography, size exclusion chromatography, polymer-based precipitation, differential centrifugation, and microfluidic technologies [57]. Currently, two of the "gold standard" processes are differential ultracentrifugation coupled with density gradient centrifugation [58]. Each technique has benefits and drawbacks, and the user's application chooses which way is chosen. A combination of approaches may maximize advantages while minimizing negatives when compared to a single technique [59]. Exosomes are tiny molecules that may be broken down by the body into their constituent components to increase the bioavailability of natural products in cancer treatment. More researchers are investigating employing them as drug delivery vehicles for cancer therapies because of their better biodistribution, biocompatibility, and low immunogenicity (Fig. 6).

Breast cancer

Breast cancer is the main cause of cancer death among women, with 15% of patients dying from the disease, according to Globocan data, 30% of women in the United States will have breast cancer at some point throughout their lives, with BC being the most common [60]. According to a worldwide cancer estimate [61], breast cancer (BC) has a global morbidity incidence of 27.8% and a death rate of 15% in women. Based on expression of steroid hormone receptor genes, BC is categorized into four molecular categories. There are major differences in therapeutic options as a consequence of this heterogeneity [62].

Due to their susceptibility to chemotherapy, endocrine therapy, anti-HER2-targeted therapy, and radiation, the therapeutic value of BC cells is presently constrained. For development of more effective cancer medicines, it is essential to understand the factors that lead to resistance.

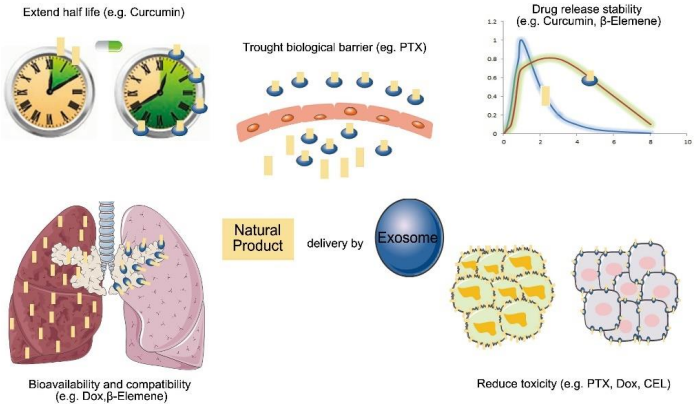

Fig. 6. Exosomes offer many benefits as a natural medication carrier in cancer treatment (PTX, paclitaxel; Dox, doxorubicin; CEL, celastrol) [39]

Exosomes play a role in intercellular communication by transporting cargo to both local and distant recipient cells and organs [63]. Researchers can enhance cancer therapy and, as a result, patient outcomes by better understanding the sources of resistance. This section explains how resistance may manifest itself in various ways. Exosomes, according to a recent study, play a significant role not only in drug resistance management but also in propagating resistance to drug-sensitive BC cells. Furthermore, resistance may be inherent in tumor cells or developed during anticancer pharmacological treatment (acquired resistance), and it has a detrimental influence on the prognosis of cancer patients [64]. The importance of exosome transmission in development of BC drug resistance has been shown by molecular insights into exosome contents. Individual reasons for chemoresistance may aid in identification of more suitable medication for each patient, perhaps leading to more successful treatment for BC patients.

Lung cancer

Extensive research has led to discovery of critical molecular targets that may influence lung cancer cell growth by changing related signaling cascades. Drugs and chemicals to treat lung cancer have also been developed, isolated, and synthesized by researchers [65]. In the realm of medication delivery, preclinical research has yielded promising outcomes, but the majority of these discoveries are still years away from human use. Due to biological barriers, poor cell absorption, and digestion by hydrolyzing enzymes or nucleases, many drugs cannot be delivered in their unmodified form; instead, they should be assigned to a vehicle capable of protecting them from these obstacles.

The structural and physiological properties of exosomes provide several opportunities for their application in lung cancer treatment and detection [66]. Due to their extensive dispersion throughout the body and capacity to reflect their cell of origin, exosomes have been investigated for diagnostic applications. They might be utilized to encapsulate and transport medicinal compounds. Exosomes are superior to all-natural and synthetic drug carriers in terms of their capacity to transport their payload to almost every cell in the body. Different imaging moieties are also being used in malignancies, particularly lung cancer, to give sensitive and safe imaging approaches when regular tissue sampling is impractical. Because of their abundance in physiological fluids, exosomes have emerged as promising candidates for creating noninvasive or less invasive diagnostic techniques.

Modified exosomes are being used as a medicine delivery method

Nanoscale drug delivery technologies have gained popularity in recent years. It has been revealed that nano-sized exosomes operate as intercellular communication channels that transport cargo to destination cells. Several nano-based pharmaceutical formulations have been created to enhance the therapeutic efficacy of chemical and biomolecular drugs. Since it was recognized that exosomes are crucial for transporting substances from one cell to another, there has been considerable interest in their research [25].

The ultimate drug delivery system would be able to distribute integrated medications to specified places while evading detection and breakdown by the body's immune system. It should also be able to respond to particular stimuli by releasing cargo molecules in a controlled manner. Exosomes are capable of transporting short RNAs, messenger RNAs, and proteins between cells.

Exosomes have shown substantial benefits over other DDSs in terms of biocompatibility and reduced clearance rates. In addition, they exhibit no long-term accumulation in any organ or tissue, reduced systemic toxicity, and enhanced cellular absorption [67].

Exosomes with surface modifications for the treatment of cerebral ischemia

Insufficient blood flow to the brain limits normal oxygen and glucose delivery, leading to energy depletion, glutamate receptor overactivation, and glutamate release. Increased intracellular calcium, loss of membrane potential, cell depolarization, and, finally, cell death cause cell death [68].

Utilizing exosomes as nanocarriers is one of several methods of treating cerebral ischemia. Alteration of the exosome's surface may improve its targeting capabilities. Utilizing bioorthogonal copper-free azide-alkyne cycloaddition, Tian et al. proposed a straightforward, efficient technique for conjugating functional ligands to exosomal surfaces. After ischemia, the cyclo (Arg-Gly-Asp-D-Tyr-Lys) peptide [c (RGDyK)] was coupled to the surface of exosomes produced by mesenchymal stromal cells (MSCs), which exhibited a high

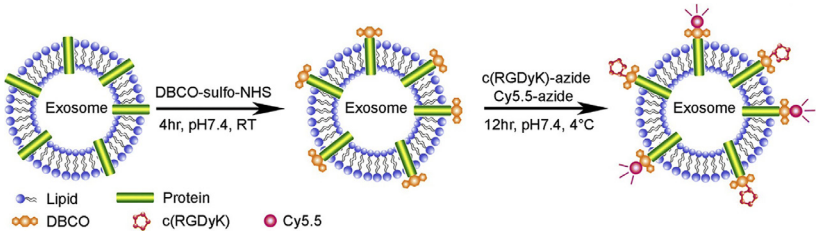

Fig. 7. DBCO-modified exosomes, c(RGDyK), Cy5,5 [69]

affinity for integrin v3 in reactive cerebral vascular endothelial cells. Curcumin, a polyphenol produced from the Curcuma longa plant, was also loaded onto the cRGD-Exo (Fig. 7). According to the results, modified exosome molecules aggregate more than unmodified exosome molecules in cerebral ischemia [69].

Breast cancer

Non-coding RNAs have not been shown to be non-functional "junk" throughout the last two decades [70]. Despite not being involved in protein-encoding, these RNAs seem to have a crucial role in a variety of human diseases, including cancer. They may be both oncogenic drivers and tumor suppressors, having various impacts on the genesis of cancer [71]. Long noncoding RNAs (lncRNAs), which include pseudogenes and circRNAs, are required for construction of a molecular scaffold that can support cellular activity. The length of lncRNAs is used to categorize the various forms of RNA. iRNAs may regulate mRNAs by binding to complementary regions, however, the formation of biological structures needs lengthy lncRNA [72]. It has been shown that a tRNA fragment called 5′-tiRNAVal inhibits the development of BC by interfering with the FZD3/Wnt/-Catenin signaling pathway, suggesting that it might be used as a diagnostic biomarker. Meanwhile, research into the effects of tRNA and its fragments has enhanced our knowledge of malignant progression of BC [73]. There is not enough evidence to suggest a link between tRNA and BC in exosomes, but advances in high-throughput sequencing technologies may help researchers better grasp their roles and processes in cancer.

MiRNAs, lncRNAs, and mRNAs are among the nucleic acids found in exosome cargo. According to the results, exosomes are expected to play a substantial role in the development of BC medication resistance via transferring RNA. One discovery was that drug-resistant BC cells may have endowed drug-sensitive BC cells with resistance in part by releasing specific exosomal miRNAs, which enhanced MCF-7/overall S's resistance following co-culture [74]. Exosomal miR-100, miR-222, and miR-30a from resistant BC cell lines MCF-7/Adr and MCF-7/Doc were transferred to MCF-7/S recipient susceptible cells to establish drug resistance. However, the mechanisms behind these impacts are yet unclear. BC cells secrete a unique exosomal microRNA-221/222 that suppresses expression of P27 and ER in tamoxifen-sensitive BC cells, resulting in the transfer of drug resistance [75]. EVs from HCC1806 TNBC cells have also been shown to increase proliferation and treatment resistance in non-tumorigenic MCF10A breast cells, possibly by altering the expression of genes and microRNAs involved in cell proliferation, invasion, and migration [76].

Exosomal miR-221-3p, which targets PIK3R1, has been found to be important in the development of Adriamycin resistance in BC cells [77]. Exosomes are associated with cancer stem cells and the epithelial-to-mesenchymal transition, and they may alter the resistance and migration potential of chemoresistant BC cells into those of vulnerable cells [48]. Several components or routes have been altered in recent studies in order to diminish the effectiveness of chemotherapeutic medications and cause drug resistance. Through cell type differentiation, the growth of the cancer stem-like cell phenotype, for instance, is associated with tumor chemoresistance [78].

Chemotherapy induces BC cells to produce EVs containing miRNAs, resulting in the adaptability of cancer stem-like cells while concurrently targeting the transcription factor. One Cut Homeobox 2 is overexpressed in BC cells treated with chemotherapy, although this transcription factor was not overexpressed in individuals treated with radiation [79]. In trastuzumab-resistant BC cells, lncRNA AFAP1-AS1 was shown to be highly expressed. While lncRNAs may play a role in BC

cell malignancy, the mechanisms of drug resistance in exosomes are unknown. Trastuzumab resistance was transferred to more BC cells through exosomes, where it was linked to AUF1 and boosted ERBB2 translation while having minimal effect on mRNA expression [80].

Another abnormally expressed lncRNA has been discovered. Doxorubicin is a common first-line treatment for breast cancer [81]. Overexpression of drug resistance was detected in doxorubicin-resistant BC cells, and it was encapsulated into exosomes to transmit drug resistance to drug-sensitive BC cells [82]. It was previously established that lncRNA AGAP2-AS1 has a malignant impact on gastric cancer [83]. AGAP2-AS1 significantly contributes to the enhancement of trastuzumab resistance by packaging into exosomes and reducing cytotoxicity in an hnRNPA2B1-dependent way. On the other hand, its fundamental roles in BC are unclear, however, it is believed to play a crucial role in making BC cells more sensitive to drug-induced cell death [84].

It was also observed that the lncRNA short nucleolar RNA host gene 14 and the trastuzumab response in BC cells are related. According to functional investigations and analysis, this modified the apoptosis-related signaling pathway, and it might be employed as a diagnostic biomarker [85]. According to researchers from the University of British Columbia (BC) in Canada, exosomal lncRNA urothelial carcinoma-associated 1 loading variations may play a crucial role in the development of acquired tamoxifen resistance in BC cells [86]. In addition to the previously recognized microRNAs and lncRNAs, CircRNAs have been found in exosomes. Although exosomal circRNA and its implications for BC treatment resistance have gotten minimal attention, exosomal circRNA has been revealed to have a role in other malignancies, according to many studies. The medicine, exosomal circRNA-100338, altered the function of human umbilical vein endothelial cells, which line the blood arteries of the human body [87]. Similarly, exosomes have been shown to transport circPTGR1 and its three isoforms, which have been linked to the capacity of hepatocellular carcinoma cells to spread [82]. Given that the liver is the most common site of metastasis in BC, it is predicted that future studies will focus on exosomal circRNAs and their involvement in disease development.

Lung cancer

Experimental treatments have shown a lot of interest in liposome-based medicine delivery. Doxil® is a liposome-based doxorubicin delivery vehicle that has been effectively utilized to treat breast cancer. In the encapsulated liposomal form of doxorubicin, adverse effects such as cardiotoxicity are significantly decreased (DOx) [88]. On mice, a nanotechnology-based liposome formulation showed promise for overcoming the obstacles associated with drug delivery to lung cancer sites. Liposomes are synthetic vesicles having a bilayer phospholipid covering that may be used to transport medication. Due to the similarity between their membrane structure and that of cells, they are biocompatible and can transport both hydrophilic (in the aqueous lumen) and hydrophobic (on the phospholipid membrane) drugs [89].

Dipalmitoylphosphatidylcholine is being studied for intratracheal delivery in cystic fibrosis patients to treat lung infections. In trials, this chemical was shown to boost medication absorption in pulmonary cells. The first result has spurred researchers to investigate potential applications in lung cancer [90]. These nanoparticles may be manufactured in a variety of sizes and shapes to generate combinatorial effects by combining several drugs, treatment regimens, or agents. The surfaces of these metal-based nanoparticles are readily modifiable to target ligand functionalization in order to improve their drug delivery efficiency. Their biocompatibility has yet to be determined, but they might be used to deliver drugs [91].

Clinical studies have failed because of poor bioavailability, nontargeted cytotoxicity, and immunogenicity, despite development of a range of nanoparticles for drug delivery [92]. Due to their lack of immunogenicity and capacity to cross biological barriers, natural cellular vesicles, such as exosomes, are increasingly being explored as drug carriers [93]. Aglycones and anthocyanidins, derived from berries and possessing antioxidant, antiproliferative, apoptotic, and anti-inflammatory effects, may be effective in cancer treatment. These chemicals, however, cannot be employed successfully due to their low bioavailability and retention. Munagala et al. observed that encapsulating medications in exosomes had a better therapeutic impact on cancer cells and lung cancer xenografts in mice than injecting them directly into the body, suggesting that exosomes might be beneficial as drug delivery vehicles for cancer therapy [94].

Exosomes produced by brain endothelial cells have been shown to readily cross the blood-brain barrier, suggesting that they may be used to carry anticancer medicines to the brain. The difficulty of current pharmaceutical delivery technologies to cross the blood-brain barrier is one of its primary limitations [95]. The kind of cargo and the loading of medications are the two most important factors to consider when using exosomes as drug transporters.

Loading exosomes with molecules of interest from the outside world improves their potential to deliver therapeutic medicines or genes. To be employed as therapeutic carriers, exosomes must have a high encapsulation efficiency of loading molecules, as well as biomolecule stability and exosomal structure [93]. Exosomes that have been primed with the relevant molecules are isolated after donor cells have been modified to incorporate therapeutic chemicals. This method has proven successful in loading substances into exosomes that are difficult to add physically, such as hydrophobic chemicals that cannot pass through the lipid bilayer membrane. Long noncoding RNAs, miRNAs, and siRNAs, for example, maybe delivered to exosomes by donor cell genome engineering, which facilitates the production and insertion of these molecules from scratch [96].

DISCUSSION

In the realm of molecular technology, exosome research is becoming more popular. Exosomes generated by a number of cells have not yet been identified, and more study is required [97]. Researchers at the University of Bristol have investigated exosomes produced by macrophages, rhabdomyosarcoma (RMS) cells, metastatic cancer cells, osteoclasts, pancreatic cancer cells, and bronchial fibroblasts extensively.

RMS exosomes have been shown to transport miRNA to human fibroblasts, producing migration, invasion, and angiogenesis. Exosomes produced by bronchial fibroblast cells operate as a messenger in severe asthma, encouraging proliferation and remodeling of the airway epithelium. Exosomes from pancreatic stellate cells increase proliferation and migration while also triggering profbrogenesis and activating the RhoA/Rock pathway. Exosomes from MSCs have a role in maintaining homeostasis, reacting to external stimuli, and preventing cardiac damage.

Exosomes generated from macrophages have the highest delivery quality. They have more ability to cross the BBB than other nanomaterials and are well suited for brain drug delivery. Exosomes produced by metastatic cancer cells offer therapeutic potential, since they play a crucial role in cancer cell maintenance, hence promoting cancer development.

Exosomes have been widely investigated for their involvement in cargo transport to and from cells, as well as for their usage in cargo transfer to particular target cells. Nakase and Futaki coupled exosomes with GALA peptides and cationic lipids in 2014 in order to enhance cellular absorption and transport efficiency. The combination of these two particles was used by Sato et al. to boost colloidal stability while decreasing immunogenicity. Illes and Kim have revealed improvements that improve the effectiveness of cargo conveyance and therapeutics. Kim and Illes fused exosomes with PEG and AA ligand to enhance circulation time and target pulmonary metastases.

CONCLUSION

Due to their involvement in cell-cell communication, exosomes are significant as delivery vehicles. Regardless of modifications, these nanocarriers for drug delivery are efficient and cost-effective. Exosomes with modifications have a possible future in medication delivery research. To enhance characterization techniques and standardize manufacturing, further research is required.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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