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REVIEW PAPER

Advancements in utilizing exosomes for cancer therapy through drug delivery systems: recent developments

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ABSTRACT

Researchers have successfully developed and validated diverse loading strategies, utilizing both endogenous and exogenous approaches, in laboratory and animal models, showcasing their effectiveness in advancing molecular biology research. Extracellular vesicles have advantages over synthetic carriers in disease management and therapeutics. However, their clinical application is hindered by challenges such as limited specificity, low production yield, storage stability, and targeting capability. Addressing these challenges and exploring exosome engineering techniques is crucial. Cell-derived exosomes can serve as carriers for therapeutic molecules, enabling targeted drug delivery. Understanding exosome formation and developing efficient engineering methods are essential for advancing clinical therapeutic strategies. Exosomes offer a unique approach to targeted drug delivery through intercellular communication. These natural liposomes carry endogenous biomolecules, ensuring biocompatibility and allowing for cargo loading. Genetic or chemical modifications can improve targeting and drug loading capabilities. Importantly, exosomes have weak interactions with serum proteins, extending the lifespan of the cargo. By combining the capabilities of artificial nanocarriers and intercellular signaling, exosomes provide new and reliable strategies for drug administration and medical interventions. This review examines diverse exosome types, preparation methodologies, cargo encapsulation, and their efficacy in delivering therapeutic agents across different diseases. It also highlights global companies involved in the development and testing of exosome-based therapies.

Keywords: *Exosomes, Controlled drug delivery systems, Cancer, Therapeutic biomaterials, Biomarkers*

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INTRODUCTION

Exosomes, with lipid bilayer envelopes and a size of about 100 nm, are pivotal in drug delivery, ferrying diverse molecular cargo between cells to facilitate responses to external cues [1].

Exosomes are pivotal in cancer advancement, fostering intricate communication among cellular populations, including cancer and immune cells, thus influencing tumor progression and immune responses [2, 3].

Due to their diminutive size, exosomes can overcome physiological obstacles and enhance drug stability, facilitating the transport of nucleic acids, proteins, and lipids between cells to enable responses to external stimuli [4].

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Vesicles and liposomes are nanoscale structures composed of lipid bilayers. Among these, exosomes, as organelles, have unique lipid composition, complex surface components, and membrane proteins that distinguish them from other microparticles[5]. Exosomes, surpassing synthetic microvesicles, offer enhanced biocompatibility, reduced toxicity, and prolonged bloodstream persistence. Combining exosome and liposome benefits in a hybrid nanovesicle promises a more effective drug delivery system with superior targeting [6].

Encapsulating nanovesicles in a hydrogel system allows for long-lasting drug delivery and eliminates the need for frequent injections. Hydrogels can protect the nanovesicles and create drug depots in specific areas. This method provides the controlled release of both nanovesicles and drugs for an extended period [6-10].

This analysis delves into the utilization of exosomes as conveyors for administering medications in cancer treatment. Exosomes can originate from a range of sources including cells, blood, and dietary sources. They are employed for encapsulating and transporting various therapeutic

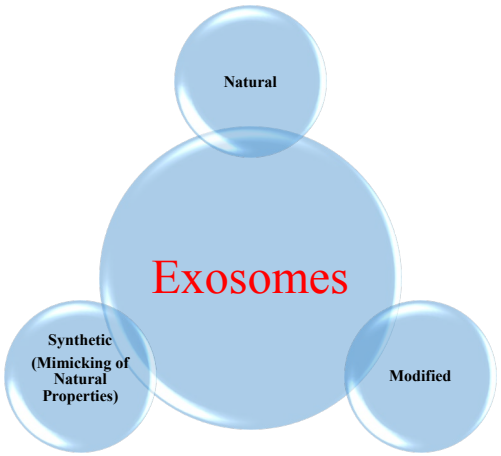

Fig. 1. Categorization of exosomes

substances like anticancer drugs, nucleic acids, and proteins. Furthermore, current investigations are centered on enhancing the drug delivery prowess of exosomes through alterations to their surface properties.

Classification of exosomes

Exosomes are divided into three groups according to their origin: natural, modified and synthetic (Fig.1) [6].

Exosomes derived from nature

Exosomes are small vesicles naturally released by cells in the body, containing essential bioactive molecules such as proteins, nucleic acids, and lipids. These substances play a crucial role in cellular signaling and communication [7]. In recent years, there has been a growing interest in utilizing exosomes from various natural sources, including plants, animals, and microorganisms, for regenerative medicine and drug delivery[8]. Plant-derived exosomes have shown promising anti-inflammatory and antioxidant effects, with potential applications in treating conditions such as arthritis and neurodegenerative diseases. Exosomes derived from animals, particularly from stem cells, have demonstrated the ability to promote tissue regeneration and wound healing. Additionally, exosomes from bacteria and other microorganisms are being investigated as delivery vehicles for drugs and vaccines [9]. In conclusion, exosomes from natural sources offer exciting opportunities for the development of innovative therapies and treatments for a wide range of diseases and health conditions. Their unique properties and efficient delivery of therapeutic substances make them a valuable tool in advancing healthcare outcomes [10].

MATERIALS AND METHODS

Methods used to extract exosomes

Various methods have been used successfully to obtain exosomes from different sources. Ultracentrifugation is considered the most effective way to obtain exosomes, as it can yield a higher quantity of exosomes. This straightforward and cost-effective method takes advantage of the differences in molecular size and density [6-8]. There are two methods that are commonly used to separate different components: density gradient ultracentrifugation and differential ultracentrifugation. Immunocapture techniques involve using antibodies and surface proteins to isolate exosomes. Biomolecules can be separated based on size using either ultrafiltration or size exclusion chromatography [9]. Polymer precipitation is a straightforward method used to isolate exosomes by modifying their solubility in a solution. Microchannels are employed in one method for isolating and purifying exosomes. These methods are more advanced, cost-effective, and yield purer results [10].

Nanoparticles similar to exosomes that occur in nature

Activated cells secrete exosomes to other cells in the body, such as leukocytes, erythrocytes, thrombocytes, the immune system, and malignant cells [5-7]. Exosomes are released from healthy cells and can be found in various bodily fluids, such as urine, saliva, and blood. Scientists are currently studying exosomes produced by mammals, which are similar to human exosomes but have unique properties due to differences in protein, fat, and RNA composition between animals and plants[8]. Plant exosomes from sources like ginger, lemon, orange, grapefruit, cauliflower, and carrot show promise in treating diseases and delivering therapeutic drugs due to their ability to reduce pain[9]. Berries with similar properties to animal exosomes have been identified and isolated. Strawberry exosomes have been found to protect against damage from harmful chemicals and are considered safe for use. In summary, mushrooms contain exosome-like nanoparticles with various beneficial components like lipids, proteins, and RNA. Scientists have used advanced techniques to isolate these exosomes from mushrooms like shiitake, which have shown promise in reducing inflammation and potentially aiding in liver failure treatment. These exosomes can also be combined with therapeutic compounds and used as carriers for drug delivery [10].

Table 1. Classify the various types of exosomes

Type	Source	Ref
Food-derived exosomes	Milk - lemon - ginger - grapes	[3-5]
Cell-secreted exosomes	Cancer cells - Human embryonic kidney - Immune cells	[8]
Blood-derived exosomes	Red blood cells	[13]

Modified exosomes

Extracellular vesicles are tiny particles that can be engineered for therapeutic purposes, such as facilitating the delivery of medications from the gastrointestinal system to the nervous system. Extracellular vesicles are made up of biomolecules that can be disassembled into different elements and utilize diverse pathways to showcase their therapeutic potential. These vesicles can be customized in two ways: internally, by modifying the drugs they carry, and externally, by changing their intended destination.

The crucial role of exosomes in delivering drugs

Exosomes are increasingly recognized for their potential in drug delivery, boasting low immunogenicity and high bioabsorption rates, with variations in pharmacokinetics depending on their source [12].

Therefore, it is important to categorize exosomes based on their different origins in order to better understand their unique biochemical features. The primary goal of this section is to classify exosomes sourced from various origins, as detailed in Table 1.

Multiple research groups isolate exosomes from diverse cell types, like tumor and immune cells, for drug delivery, each with unique properties, informing their varied roles and applications [14].

HEK293T cells are commonly employed in biopharmaceutical production due to their ease of cultivation, minimal upkeep needs, and notable transfection efficacy.

Exosomes derived from HEK293T cells share similarities with membranes found in different tissues, indicating potential for targeted drug delivery. Multiple administrations of HEK-derived exosomes did not elicit any notable immune response or toxicity in mice. These exosomes can improve drug delivery by transporting functional membrane proteins to cancer cells [15-17].

mVSVG-Exo, transgenic HEK exosomes, boost phagocytosis of xenogenic tumor cells by the immune system. Treatment with exosomes from HEK293T cells expressing membrane proteins enhances tumor penetration and activity [18].

Exosomes carrying the native PH20 hyaluronidase have been shown to effectively suppress tumor growth by promoting the degradation of hyaluronic acid within the tumor microenvironment. When PH20 and DOX are co-administered in exosomes, they enhance the antitumor effect in mouse models. Exosomes from HEK cells hold promise for drug delivery and therapy advancements. [19- 21].

Cancer cells, especially those that have high levels of Rab27a and Rab27b proteins, have a remarkable ability to produce exosomes efficiently. These exosomes have a strong attraction to the cells they come from.

For instance, exosomes from the HT1080 fibrosarcoma cell line are twice as abundant in HT1080 cells compared to those from the HeLa cervical carcinoma cell line [22-23].

HT1080 exosomes with antibodies accumulated significantly at tumor sites, outperforming HeLa exosomes in animals. However, using cancer cell-derived exosomes for therapy faces challenges despite their favorable properties. Caution is needed due to potential associations with tumor metastasis [24].

It induces immune tolerance in T cells towards tumor antigens. However, dendritic cells (DCs) have a limited lifespan once matured. To overcome this limitation, researchers have explored the use of DC-derived exosomes (DEX) as a potential solution. DEX retains the immunostimulatory capacity of DCs and offers numerous advantages [25]. Exosomes derived from cancer cells have a unique molecular makeup personalized for each individual, allowing for precise manipulation and control of biological substances. The incorporation of specific lipids in DEX membranes enables extended storage at -80 °C, resulting in enhanced stability during preparation. DEX membrane-derived ligand peptides have shown promise in activating natural killer (NK) cells and displaying a greater abundance of MHCII molecules compared to dendritic cells (DCs) [26].

This suggests that DEX membranes could offer advantages for immune modulation and potential therapeutic applications. They allow for a longer recovery time during leukapheresis. Isolating DEX from immature dendritic cells (imDCs) can decrease the expression of immunostimulatory molecules like CD86 and CD40. This decrease in expression helps to reduce the risk of activating naive T cells and potentially triggering a negative immune response [27].

This approach enables targeted immune modulation, enhancing the efficacy of DEX membranes in immunotherapy [28]. Mesenchymal

stem cells (MSCs) are the preferred source for clinical exosome production, obtained from diverse tissues and cultured in vitro [29]. Kalluri's team developed a GMP-compliant method for isolating exosomes from bone marrow-derived MSCs, exhibiting a threefold increase in production compared to BJ fibroblasts while preserving MSC-like traits [30-31].

Le's team found that exosomes from red blood cells (RBCs) are highly versatile for delivering RNA drugs, possessing various advantageous properties for therapeutic use [32]. Their effortless acquisition, be it directly from patients or from blood banks, stands out as a significant advantage [33].

This eliminates the need for complex cell culture procedures and reduces the risk of in vitro mutations. Additionally, RBCs are cells without a nucleus, meaning that exosomes isolated from them are devoid of potential risks associated with genetic material transfer. RBC-derived exosomes can also be matched with the blood types of recipients, similar to blood transfusions, to minimize the chances of inducing toxic or immunogenic responses. Finally, RBC exosomes demonstrate a higher efficiency in delivering therapeutic RNAs compared to other cell types [34].

Cow's milk-derived exosomes aid IgG transportation via Fc receptor (FcRn), showing specific binding to the upper gastrointestinal tract [35]. Agrawal et al. identified that ingesting paclitaxel-laden exosomes (ExoPAC) efficiently arrested tumor progression in mice without triggering adverse reactions or immune suppression.

Zhang et al. engineered ginger-based nanocarriers (GDNVs) with folic acid modifications, showcasing enhanced compatibility with biological systems and precise drug delivery to cancer cells compared to positively charged liposomes [36].

Characterization

In order to determine if the extract comes from exosomes, it is important to consider multiple factors. The International Society of Extracellular Vesicles (ISEV) recommends examining two types of proteins: transmembrane or GPI-anchored proteins linked to the plasma membrane and/or endosomes, along with cytoplasmic proteins commonly present in extracellular vesicles (EVs) [37].

To confirm the extract's exosomal origin, evaluate transmembrane/GPI-anchored proteins linked to membranes/endosomes and cytoplasmic proteins, as recommended by the International Society of Extracellular Vesicles (ISEV) [37].

ISEV-recommended protein analysis confirms the exosomal origin of the extract while assessing shared non-EV protein samples determines exosome purity in biological fluids. Exosome analysis in research involves transmission electron microscopy (TEM) for morphology, nanoparticle tracking analysis (NTA) for size, and western blotting for protein markers [38].

Methods for characterizing exosomes can be categorized into two main groups: external features (such as morphology and particle size detection) and physical properties (such as membrane and lipid raft analysis). Table 2 summarizes the purpose, advantages, and limitations of commonly used techniques for characterizing exosomes.

Table 2. Outline the objectives, benefits, and limitations of exosome characterization techniques

Methods	Benefits	Limitations	Ref
Flow Cytometry	Flow cytometry enables high-throughput, fast analysis with low sample concentration.	slow, limited detection, cannot measure exosome size, low accuracy and resolution, restricted by polydispersity and low refraction.	[14]
WB (Western Blot)	Mature technique, analyzes marker proteins, effective for exosomes in cell culture media.	Complex and time-consuming operation, marker protein detection varies with parental cell type, not suitable for exosomal marker proteins in biological fluids.	[17]
DLS (Dynamic light scattering)	10 nm measurement limit is ideal for monodisperse systems. It accurately detects similar-sized particles or molecules. Important in materials science, chemistry, and nanotechnology where particle size affects properties.	The method has limitations in accurately measuring complex exosome samples with varying sizes, as well as determining the concentration of exosomes and distinguishing proteins from viruses.	[24]

Methods	Benefits	Limitations	Ref
NTA (Nanoparticle Tracking Analysis)	This method offers fast detection speed, real-time observation of exosomes, higher resolution than flow cytometers, and a lower measurement limit of 30-40 nm for fluorescent particles.	Furthermore, the complexity of operation and the challenge of distinguishing contaminated proteins from exosomes are additional considerations to keep in mind. Additionally, the quantification of exosomes may be impacted by factors such as camera levels and detection thresholds.	[16]
SEM or TEM	Electron microscopy allows direct observation of exosome morphology, with SEM providing surface structure information and TEM providing internal structure and particle size distribution.	Compared to SEM, TEM can be more challenging to operate, requires more extensive sample preparation, may not be suitable for high-throughput analysis of multiple samples, and typically offers lower resolution .	[32]
ELISA (Enzyme-linked immunosorbent analysis)	Furthermore, this method offers a distinct advantage with its rapid detection capability and ability to efficiently and quantitatively analyze protein transcripts. It is also well-suited for high-throughput evaluation, making it highly valuable for large-scale research projects.	However, it is worth mentioning that this method can be complex and time-consuming to perform. The repeatability of results may not be optimal, and there are various interference factors that need to be taken into account.	[39]

Recent advancements in character processing, domestically and internationally, include the introduction of a novel method by Islam et al. This technique, called nanoparticle-based, time-dependent fluorescent immunoassay, enables direct EV measurement without preprocessing [39]. Using biotinylated antibodies, it captures EVs from urine and cell supernatants, specifically aiming at transmembrane proteins and tumor-associated antigens [40].

Upon comparison of the performance of two lanthanide-based tracers, it was observed that they exhibited a 2-10-fold higher signal-to-noise ratio compared to the lectin chelate assay [41]. The step-wise separation is simple and time-saving compared to western blotting and flow cytometry. Furthermore, it holds potential for diagnosing and prognosticating tumor cells in the EV region, thus expanding its utility. In addition to protein markers, the presence of exosomes can be controlled by considering phospholipid species found in lipid bilayers. Therefore, it is essential to explore the development of diverse markers for the identification of various exosomes[42].

Anti-cancer drugs

Exosomes' unique traits facilitate drug delivery, including small molecule chemotherapeutics, therapeutic nucleic acids, and proteins, with notable strides seen in cancer therapy (Fig.2) [43].

Exosomes, small vesicles, have been observed to carry both water-soluble and fat-soluble chemotherapy medications, like Doxorubicin (Dox) and Paclitaxel (PTX). Several investigations indicate that employing exosomes as transporters for chemotherapy agents can enhance their efficacy in combating cancer.

Doxorubicin, a potent immunosuppressive agent utilized in tumor treatment, faces clinical constraints due to inadequate biocompatibility and severe adverse reactions, including myelosuppression and cardiotoxicity [44].

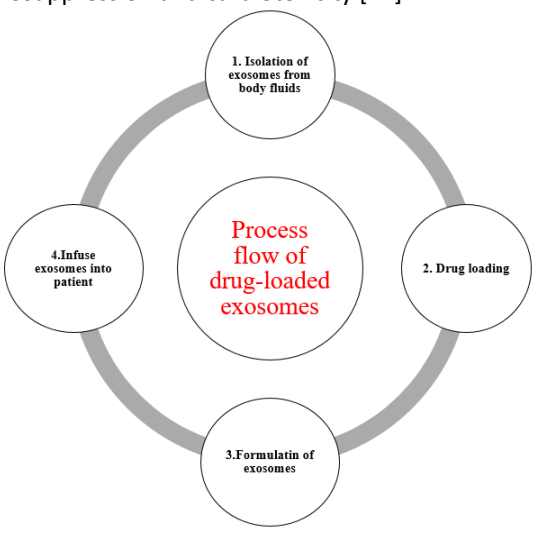

Fig. 2. Demonstrates drug loading into exosomes from body fluids, membrane modification, and the need for formulation prior to human therapy.

Researchers are investigating nanoparticle technology to improve Doxorubicin's biocompatibility and efficacy, yet obstacles concerning the immune system and oxidative stress remain [45]. Exosome-mediated delivery of Dox shows promise in cancer therapy. In a mouse model of colon adenocarcinoma, Doxorubicin-treated exosomes derived from macrophages showed enhanced immunogenicity, outperforming free Doxorubicin or Doxorubicin-loaded liposomes [46-47].

The cholesterol and phospholipid components of exosomes enable them to effectively target cancer cells and deliver Dox. Dox-loaded exosomes can help reduce cardiotoxicity, a common side effect of Dox therapy, by preventing drugs from reaching myocardial endothelial cells [46].

Recent research indicates that exosomes derived from mesenchymal stromal cells possess the capability to enhance the absorption and anticancer impact of Doxorubicin in osteosarcoma, highlighting the significance of selecting appropriate exosomes for therapeutic applications [47].

Another powerful anticancer drug, PTX, faces challenges in the medical field due to its limited bioavailability and high toxicity at high doses [48]. However, exosomes loaded with PTX from mesenchymal stromal cells or cancer cells have demonstrated anti-cancer properties and the ability to target resistant cancer cells [48].

Moreover, PTX-loaded exosomes from macrophages can conquer multidrug resistance by eluding the drug efflux transporter known as P-glycoprotein. In the case of glioblastoma multiforme, exosomes from U-87 MG cells have been effective in transporting PTX across the blood-brain barrier, leading to better clinical outcomes [49-51].

Furthermore, naturally occurring hydrophobic compounds like curcumin are being studied for their potential in exosome therapy [52]. These instances illustrate the advantages of exosomes as therapeutic tools for different cancer types. For more information, please refer to Table 3.

Table 3. Different types of cancer therapeutic cargo

Therapeutic agents	Cancer Type	Method	Ref
Nucleic acid	Brain - Hepatocellula - Lung - Leukemia	Electroporation- Transfection- Incubation- Electroporation	[20-24]
Protein	Colon – Pancreatic – Breast- any type of cancer	Transfection - Transfection - Electroporation - Aponin/Electroporation	[25-28]
Paclitaxel	Lung – Glioblastoma and astrocytoma – (Pulmonary metastasis) – Prostate - Pancreatic	Incubation- Incubation and Sonication- (Incubation , Electroporation , Sonication) - Incubation - Incubation	[29 -31]
Doxorubicin	Colon – Breast - Osteosarcoma- Ovarian	Incubation - Electroporation - Incubation - Electroporation	[32-35]

Interactions of hydrogels with exosomes as drug delivery systems

Exosomes, extracellular membrane vesicles crucial for intercellular communication, offer an effective means for drug delivery due to their biocompatibility and specificity. They outperform traditional carriers like liposomes and polymeric nanomaterials. Exosomes sourced from immune cells, tumor cells, and MSCs show promise as nano-sized vehicles for delivering biomolecules and therapeutic agents [55-57]. Figure 3 illustrates the use of exosomes in drug delivery.

Exosomes, released by different cell types, mediate intercellular communication by transporting bioactive molecules. They carry nucleic acids, proteins, and lipids, facilitated by surface receptors like HSP70, crucial for tissue homeostasis and bodily function [58].

Exosome isolation techniques aim to balance quantity and function preservation. These vesicles, distinct in structure and cargo, play vital roles in intercellular communication and immune regulation, transporting nucleic acids and proteins [59].

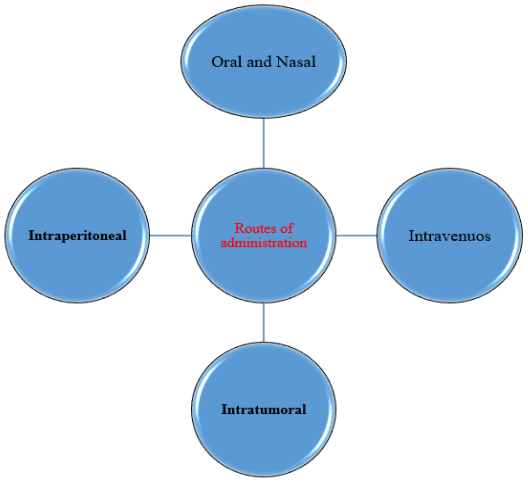

Fig. 3. Illustrates the utilization of exosomes for drug delivery.

Table 4. Composite hydrogel delivery systems with controlled release capabilities

Type of Hydrogels	Molecules Name	Release Time(Days)	Application	Ref
Chitosan	α-tocopherol	6	Cardiac tissue engineering	[24]
Alginate	-	10	Myocardial infarction treatment	[28]
GelMA	Melatonin	25	Osteoporosis treatment	[31]
GelMA	Gemcitabine	4	Osteosarcoma treatment	[32-35]
GelMA	SDF-1 α	7	Wound healing	[20-24]
GelMA	Paclitaxel - Deferoxamine Bovine serum albumin	5, 11, 35	Bone regeneration	[25-28]
Chitosan	-	-	Tissue engineering scafolds	[29 -31]
Chitosan	-	1	ischemia treatment	[32-35]
Chitosan	miR-126-3p	6	Wound healing	[27]
Chitosan	Lidocaine, rifampicin ,Carboxyfluorescein,	No Day (5.5hr)	Wound Healing	[28]
Gelatin with Hyaluronic acid	-	-	Regeneration of Cartilage	[31]
alginate with Hyaluronic acid	-	14	Regeneration of Bone	[32-35]
Hyaluronic acid - lysine (Poly-ε-L)	-	21	Skin regeneration	[20-24]
Oxidative hyaluronic				
fibroin of silk	miR(675)	36	treatment of dysfunction	[25-28]
silk with chitosan	-	-	Wound healing	[31]
Alginate	-	7	Wound healing	[32-35]
Chitosan and alginate	mRNA	14	Vaccine delivery	[54-57]
alginate with GelMA	-	-	Wound Dressing	[58]
Alginate, Collagen, gelatin	Dexamethasone, Moxifloxacin	1	Corneal wound healing	[60]

Hydrogels made from natural proteins or polysaccharides provide stability and adaptability for tissue engineering and drug administration. In drug delivery, natural hydrogels are favored over nanovesicles due to their stability and flexibility in drug release. For example, liposome-based approaches may face issues such as instability, rapid elimination from the bloodstream, infiltration of the reticuloendothelial system, and swift degradation [60].

Encapsulating nanovesicles within hydrogels enhances their membrane integrity and stability, preventing rapid clearance. Incorporating nanovesicles also improves hydrogel properties by nanofunctionalization, modifying charge, pore size, hydrophobicity, and hydrophilicity. This allows for the development of controlled-release hydrogel materials with numerous applications in various fields of biomedicine (Table 4)[60].

The low tensile strength of unmodified collagen means it has low rigidity or hardness, which can limit its applications in areas requiring greater mechanical strength, such as tissue engineering scaffolds or drug delivery systems [61]. To address these limitations, a common technique involves introducing acrylate groups or amine-containing outgroups to produce acrylated collagen (Coll-AC). Through the use of photoinitiators, Coll-AC can undergo photopolymerization to form hydrogels [62]. This modification allows the hydrogel to maintain the excellent biocompatibility and bioactivity of collagen, while also providing enhanced properties. It maintains an irregular cell-binding arginine-glycine-aspartate (RGD) motif and a matrix metalloproteinase-degradable amino acid sequence, resulting in the retention of the beneficial properties of collagen in Coll-AC hydrogels [63].

Exosomes loaded with curcumin improve solubility, bioavailability, and stability in Alzheimer's models, enhancing cognitive function and demonstrating anti-Alzheimer effects (Fig.4)[64].

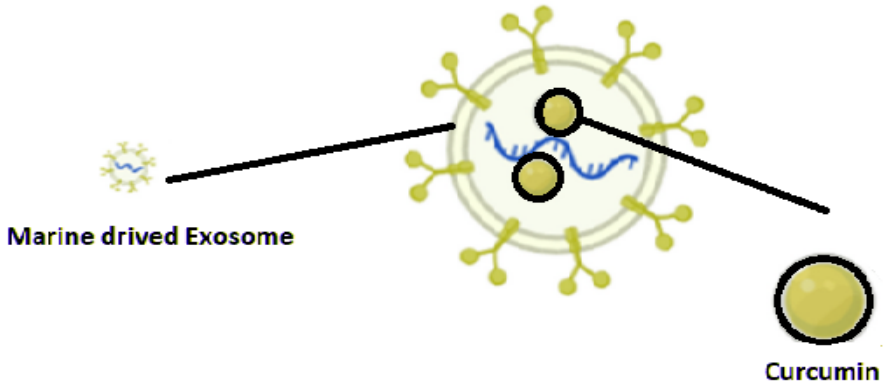

Fig. 4. Explain how curcumin integrates into exosomes in mouse tumor cells to produce exosomal curcumin

In bacterial infection treatment, exosomes containing antibiotics are more effective than free antibiotics in vivo and in vitro. For example, integrating linezolid, a synthetic antibiotic targeting methicillin-resistant Staphylococcus aureus, into exosomes from mouse RAW264.7 macrophages enhances infection reduction without affecting macrophage cytotoxicity [65].

Cheng et al. conducted a study on mechanically fortified vesicle-GelMA hydrogels to assess their resilience to elongation, torsion, and compression. The researchers also examined the release characteristics of deferoxamine, a hydrophilic compound, from the hydrogel material. The results showed that the GelMA hydrogel released about 80% of the deferoxamine within the first 4 hours, while the vesicle-GelMA hydrogel released only around 25%. Additionally, both in vitro and in vivo experiments were performed to investigate the controlled release capability of the hydrogel composition and its effects on angiogenesis and osteogenic differentiation [64].

The results showed that the hydrogel composite effectively promoted these processes. Furthermore, the hydrogel composite impacted the attachment and growth of MC3T3-E1 and HUVEC cells. This study offers valuable insights into the potential uses of mechanically reinforced vesicle-GelMA hydrogels in regenerative medicine and tissue engineering. The research discusses their mechanical properties, release behavior, and effects on cellular behavior [65].

According to Wu et al., incorporating liposomes into GelMA hydrogels enhances their mechanical properties by creating interconnected matrices [66-68]. This improved hydrogel formulation allows for sustained release of the anti-inflammatory drug gemcitabine for up to 4 days, compared to only 6 hours with pure GelMA hydrogels. In vitro experiments demonstrated that the liposome-GelMA hydrogel effectively destroyed MG63 cells, while in vivo studies showed its ability to inhibit osteosarcoma growth, highlighting its therapeutic potential for osteosarcoma treatment [69]. In a clinical study, Kadri et al. observed that adding rapeseed liposomes improved the properties of IPN GelMA-alginate hydrogels. Additionally, this nanofunctionalization approach promoted the proliferation of keratinocytes, suggesting its potential for promoting wound healing [70].

Employing a liposome-GelMA hydrogel system, Yu et al. demonstrated controlled release of SDF-1, promising for wound healing [71]. This strategy offers potential to enhance mechanical properties, facilitate targeted drug delivery, and foster tissue regeneration in diverse therapeutic areas, including cancer therapy, blood healing, and wound healing [72].

Scientists have extensively investigated liposome-chitosan hydrogels for their potential to deliver water-soluble fluorescent dyes (carboxyfluorescein), antibiotics (rifampicin), and local anesthetics (lidocaine)[73]. In their study, water-soluble compounds were initially encapsulated within DPPC liposomes and then incorporated into a chitosan-based gel matrix. Importantly, this combination does not alter the rheological properties of the hydrogel. The sustained release of encapsulated substances from small unilamellar vesicles embedded in chitosan hydrogels was observed to be longer compared to hydrogels with multi-lamellar vesicles or chitosan gels without liposomes [74]. These findings indicate that liposome-chitosan hydrogels hold promise as effective delivery systems for water-soluble antibacterial agents and local anesthetics. Such systems could have significant applications in the field of biomedicine, particularly in the development of advanced therapeutics [75].

Study conducted by Lee et al. explored the creation of liposomal hydrogels for potential use in breast cancer treatment. These hydrogels were

made by encapsulating curcumin in liposomes and coating them with thiolated chitosan [76]. One notable feature of these hydrogels is their ability to change from a liquid to a gel state when exposed to body temperature. The encapsulation of curcuminoids within the liposomal hydrogels delays the release of bioactive compounds, resulting in improved solubility and enhanced therapeutic efficacy [77].

The biocompatibility of hydrogels was assessed, revealing the promising effects of incorporating curcumin into liposome-chitosan hydrogels on MCF-7 breast cancer cell apoptosis, suggesting their potential for breast cancer treatment [78]. These hydrogels could function as platforms for delivering curcuminoids or other anti-inflammatory drugs post-tumor removal, potentially improving therapeutic outcomes. Lee et al.'s injectable, heat-sensitive liposome-chitosan hydrogels present an innovative method for delivering curcuminoids in breast cancer treatment, offering exciting prospects [79].

In a pioneering investigation by Zhang et al., a novel approach was devised for gathering extracellular vesicles (EVs) at the injury site by incorporating EVs from mesenchymal stem cells (MSCs) into a chitosan hydrogel matrix [80]. The results of their research revealed that the hydrogel matrix (EV-chitosan) substantially improved the therapeutic effectiveness of EVs, leading to increased survival of endothelial cells, improved angiogenesis, and overall improvement in ischemic hind limbs [81].

The EV-chitosan system presents a promising cell-free therapy for ischemic conditions, aiding tissue repair without cell transplantation. Han et al.'s study showed effective transfer of microRNA-675 to EVs in silk fibroin hydrogels, addressing age-related vascular dysfunction [82]. These findings highlight EVs and hydrogel matrices' therapeutic potential for ischemia and age-related vascular issues, suggesting improved outcomes in regenerative medicine [83].

The study conducted by Lu et al. investigates the impact of integrating exosomes into alginate hydrogels for cardiovascular tissue regeneration [84]. The researchers aimed to determine how adding exosomes to the hydrogel matrix could improve the regeneration process of cardiovascular tissues [85]. They found that incorporating exosomes into the alginate hydrogel scaffold not only promoted angiogenesis but also blocked apoptosis and fibrosis in cardiac cells. Importantly, this combination approach led to better healing of scar tissue compared to using exosomes solely from MSCs in a heart tissue study [86]. These results suggest that the exosome-alginate hydrogel composite has the potential to enhance therapeutic outcomes by enabling the controlled release and targeted delivery of exosomes. This innovative strategy shows promise for advancing tissue regeneration and repair in the field of cardiac biology [87].

Shafei et al. studied the attachment of adipose-derived stem cell exosomes to alginate hydrogels, aiming to explore the benefits of incorporating exosomes into these matrices [88]. Their findings showed that this bioactive scaffold significantly influenced collagen synthesis in injured tissue, wound closure, and tube formation. The combination of exosomes and alginate-based hydrogels holds great potential for promoting tissue regeneration and wound healing, providing a new and exciting approach for various dressing applications [89].

Tao et al. linked synovial MSC-derived exosomes with chitosan, enhancing fibroblast proliferation [90]. This method significantly improved wound healing in diabetic mice, promoting re-epithelialization and collagen production [91]. Similarly, Shi et al. found that combining gingival MSC-derived exosomes with chitosan/silk hydrogel effectively healed diabetic rat skin [92]. These findings highlight the potential of exosome-chitosan combinations in diabetic wound healing.

Selective encapsulation in exosome

In the field of biology, researchers are exploring ways to overcome the limitations of current methods to achieve optimal levels of therapeutic drugs within recipient cells. One approach they are investigating is the encapsulation of drugs. Small drugs can easily enter the lumen of exosomes, but larger biomolecules like proteins and nucleic acids face challenges in this process [90]. However, by targeting specific proteins involved in exosome biosynthesis and packaging, such as those associated with the ESCRT mechanism, it is possible to selectively transport therapeutic molecules into exosomes. The interplay of exosomal proteins with therapeutic compounds enables their targeted encapsulation within exosomes, potentially improving drug delivery to recipient cells [91-92].

Di Bonito's research has discovered a fusion protein called E7/Nef, which selectively targets blood vessels when processed by Nef. When administered, E7/Nef loaded exosomes trigger

immune responses against E7. Another method involves fusing ovalbumin (OVA) to lactadherin's C1C2 domain for precise vesicle targeting [93]. De Gasal et al. developed CD8-BLVeCDTM, a protein that utilizes ESCRT recognition to package into vesicles. Yim et al. introduced the EXPLOR technology, using CRY2-CIBN-CD9 interaction for cargo transport into the bloodstream. These studies demonstrate selective drug delivery to vesicles using various targeting methods [94].

Furthermore, researchers have focused on vesicle-enriched RNA (eRNA) and its distinct sequence for specific packaging of nucleic acids into vesicles. These eRNAs possess unique motifs, including ACCAGCCU, CAGUGAGC, and UAAUCCCCA, which act in cis to target vesicles. These findings contribute to our understanding of selectively choosing target RNAs for therapeutic applications. Moreover, this study delved into tumor-derived vesicles and their content of tumor suppressor miRNAs[95].

Teng et al. found MVP recruits tumor suppressor miRNA miR-193a into vesicles, impacting cancer cells when MVP is absent [96]. Components like GW182 and AGO2, associated with multivesicular bodies, may influence miRNA distribution to vesicles. Depleting myotransferrin in cancer cell-derived vesicles reduces their ability to transfer nucleic acids to human endothelial cells [97]. Proteins like Myoferlin, MVP, GW182, and AGO2 play key roles in selectively transporting specific nucleic acids into exosomes, highlighting the importance of thorough bioinformatics analyses [94-97].

These analyses will assist in identifying and uncovering new targets contained within exosomes. Such detailed analyses will greatly contribute to the discovery of more proteins or systems that are involved in selectively packaging nucleic acids into exosomes. Ultimately, this improved understanding will enable us to utilize the potential of exosomes for therapeutic purposes [98].

In biology, clinical exosome therapy faces challenges like limited yield and lacking standardized isolation protocols [99-100]. Researchers are developing biomimetic exosomes derived from diverse cell types to overcome these hurdles [101]. These engineered exosomes mimic natural ones, offering a promising therapeutic alternative [102].

By creating these biomimetic exosomes, scientists aim to address the limitations associated with low yield and non-standard isolation methods, providing a promising avenue for future therapeutic applications [103]. Table 5 presents a compilation of current research and advancements in the realm of biomimetic exosomes, showcasing their potential in overcoming challenges related to exosome therapy [104].

Extracellular vesicles originating from tumors

Tumor cell-derived exosomes (TEXs) possess favorable traits, rendering them appealing for cancer treatment.

They aid in the transport of therapeutic drugs to tumor cells through surface proteins (as shown in Table 6).

For instance, utilizing doxorubicin-loaded tumor cell-derived exosomes (DOX-loaded TEX) has demonstrated effective tumor growth inhibition and cardioprotective benefits by minimizing uptake by myocardial endothelial cells, facilitated by electroporation [103].

Table 5. Summarizes various studies focused on loading therapeutic molecules into exosomes.

Method	Drug loaded	References
Click Chemistry	Drugs - nucleic acids	[88]
Sonication	Doxorubicin -Paclitaxel -Small RNAs	[90]
Mimetic Nanovesicles	doxorubicin -paclitaxel	[25]
Antibody binding	CD9 antibody with Alexa-647	[44]
Incubation with Drugs	Curcumin -Doxorubicin	[66]
Extrusion	Porphyrin	[94]
Electroporation	Doxorubicin – P aclitaxel	[99]
Freeze - Thaw Cycles	Proteins - peptides	[102]

Table 6. Exosomes: Promising cancer therapy approach.

Tumor cell-derived exosome	Type of Cancer	Goal	Ref
glioblastoma (A172)	Glioblastoma	Providing biomarkers for cancer diagnosis	[87]
Breast cancer cell lines include MDA-MB-231 and BT-474	Breast	Providing biomarkers for diagnosis of tumor	[12]
Non-small cell lung cancer (NSCLC) refers to a common type of lung cancer.	Lung	Providing biomarkers for diagnosis of tumor	[25-30]
breast cancer (MB-231- MDA)	Breast	Enhancing doxorubicin cytotoxicity for tumor inhibition	[101]

Tumor-derived extracellular vesicles (TEXs) also have potential in cancer immunotherapy by presenting tumor antigens and stimulating cytotoxic T lymphocytes (CTLs). Modified TEXs loaded into dendritic cells (DCs) have demonstrated higher tumor suppression effects compared to tumor lysate-loaded DCs [104]. Additionally, TEXs can act as immune suppressors by modulating signaling pathways and carrying immunosuppressive factors like transforming growth factor-β. Reprogramming tumor metabolism is another area where TEXs show promise. By loading circular RNA acting as a miR-122 sponge targeting pyruvate kinase M2 (PKM2) onto TEXs, glycolysis inhibition, weakened drug resistance, and anticancer effects have been observed in drug-resistant colorectal cancer cells [105].

TEXs act as cancer biomarkers and monitor atherosclerosis progression; however, specifically targeting them might delay cancer onset. They hold promise in drug delivery, immunotherapy, and tumor metabolism modulation, with diagnostic applications in cancer therapy, suggesting potential for innovative treatments [106].

The inclusion of cargo in healing biomaterials

Exosomes, with their lipophilic lipid membrane bilayer, can be customized to target specific cells, allowing the inclusion of lipophilic drugs like paclitaxel and curcumin, potentially enhancing drug safety and efficacy [107]. Hydrophilic therapeutic cargoes such as drugs, RNA, DNA, and proteins can be integrated into the hydrophilic core through techniques like pore creation, while simpler methods facilitate the incorporation of small hydrophobic molecules, requiring additional modification for lipophilic ones[108-109].

Different methods integrate proteins like catalase into exosomes without compromising their structure [110]. These modified exosomes alleviate oxidative stress, offer neuroprotection, and reduce lung inflammation, hinting at potential treatments for conditions like obstructive pulmonary disease [111].

Exosomes serve as effective carriers for lipophilic substances, including hydrophobic anticancer drugs, augmenting their potency against cancer cells, offering a promising avenue in cancer therapy [112].

In conclusion, multiple techniques have been developed to incorporate both hydrophilic and hydrophobic components into exosomes, providing opportunities for efficient drug release and therapy.

Recent research demonstrates the feasibility of integrating diverse components into exosomes, as outlined in Table 7.

Plant-derived extracellular vesicles (EVs) have characteristics similar to mammalian exosomes, enabling them to enclose therapeutic agents including small molecule drugs, siRNAs, DNA expression vectors, and proteins. Recent studies, documented in Table 8, highlight the effective encapsulation of therapeutic agents within plant extracellular vesicles (EVs) [114].

Table 7. Various modification techniques enable the integration of different types of cargo into exosomes

Source of Exosome	Drug	Goals	Ref
Human plasma	Imperialine	Increased antitumor effects	[104]
Breast–colorectal cancer cells	Aspirin	Improved cytotoxicity, anti-tumor effects, Enhanced cellular uptake	[95]
macrophage of Murine (RAW264.7 cells)	Curcumin	Exosomes demonstrate antioxidant characteristics, exhibit excellent stability, and possess inflammation-specific targeting abilities.	[67]
HEK293 cell line	Doxorubicin	Exosomes have been found to possess increased potency and exhibit rapid uptake into recipient cells	[24]
MSCs	Melatonin	Enhanced kidney recovery and improved functionality.	[34]
Breast cancer cells, normal human MRC-5 fibroblasts, normal Vero epithelial cells and bovine milk were included in the exosomes.	siRNA	Exosomes help fight cancer in triple negative breast cancer.	[68]
BM-MSCs from mice	Peptide -curcumin	Exosomes induce apoptosis and suppress inflammation.	[99]
Murine melanoma cells	Hollow gold nanoparticles	High encapsulation yield	[11]

Source of Exosome	Drug	Goals	Ref
RAW264.7 cells	Vancomycin - lysostaphin	Antimicrobial efficiency	[29]
Mouse RAW264.7 cells	Linezolid	Efficacious intracellular antibiotic delivery	[101]
BM-MSCs	Doxorubicin hydrochloride	Cytotoxicity in osteosarcoma cells	[104]
M1-macrophages- U-87 cell	Paclitaxel	Exosomes show strong antitumor effects and toxicity against glioblastoma multiforme cells.	[17]
Pancreatic cancer cells	Gemcitabine	Exosomes have demonstrated impressive achievements in improving cellular uptake, enhancing the effectiveness of therapies against pancreatic cancer, and reducing harm to healthy tissues.	[113]

Table 8. Investigating the Capability of Plant Exosomes for Drug Delivery

Type of Exosome	Embedded cargo	Goals	Ref
Apple	MicroRNA(Naturally occurring)	The expression of OATP2B1 was reduced in Caco-2 cells at the mRNA, protein, and transport levels.	[66]
Ginger	Components like lipids, proteins, mRNA, 6-gingerol, and 6-shogaol offer diverse benefits due to their natural origin	Natural ingredients: pain relief, improved digestion, disease prevention	[110]
	---	Natural compounds: pain relief, anti-inflammatory effects	[104]
	Doxorubicin	Natural sources, including lipids, proteins, mRNA, 6-gingerol, and 6-shogaol, inhibit tumor growth through various mechanisms.	[65]
Grapefruit	Doxorubicin- curcumin(Inflammatory chemokine receptor)	Natural compounds inhibit tumor growth, reduce inflammation in colitis	[25-30]
Turnip	---	MCF-7 cell growth completely inhibited.	[34]
Strawberry			[87]
Lemon	---	MCF-7 cell growth effectively inhibited.	[25]
Broccoli	Sulforaphane	DSS-induced colitis was effectively prevented in B6 mice.	[15]

Commercial therapeutic biomaterials

Extensive research has shown that exosomes have enduring properties even after repeated administration, making them exceptional nanocarriers for advancing new therapeutic approaches in drug delivery and other treatments [115]. As a result, several companies have made significant progress in developing various exosome platforms. These companies are actively engaged in producing therapeutic exosomes and are currently conducting preclinical studies, with some projects already in the early stages. Table 9 presents a detailed list of these pioneering companies [116-120].

Table 9. Commercial companies utilize exosomes.

Comercial Name	Company Name	Application	Ref
ExoPr0	ReNeuron	Companies use exosomes for neurodegenerative diseases, cancer, and vaccine development	[66]
Inhaled exosome technology platform	OmniSpirant	Exosomes are studied for treating respiratory diseases like cystic fibrosis.	[110]
miRNA-loaded exosomes	TAVEC Pharmaceuticals	Gene therapy targets cancer genes to treat the disease.	[104]
Exosome Technology Platform	Paracrine Therapeutics	Regenerative medicine	[65]
Exo-101	Exogenus Therapeutics	Regenerative medicine treats inflammatory skin conditions, lung disorders, and chronic wounds.	[25-30]
EXOVEX	Exocel Bio	Regenerative medicine	[34]
AB126: Neuronal exosome platform component	Aruna Bio	Neurological diseases: Nervous system disorders	[87]

Comercial Name	Company Name	Application	Ref
AGLE-102	Aegle Therapeutics	Serious dermatologic disorders	[25]
TauSome biomarker	Exosome Sciences	Diagnose and monitor neurological disorders effectively	[15]
XoGlo	Kimera Labs	Promote healing, rejuvenate skin, regenerate wounds	[46]
ASCE products encompass therapeutic and cosmetic applications	ExoCoBio	Induce regeneration or modulate the activity of different tissues or cells	[10]
ExoFloTM	Direct Biologics	Providing signaling proteins that modulate inflammation	[4]
Inflammation modulation through signaling proteins	Ciloa	Antibodies, vaccines, therapeutic vectors	[34]
Hybridosome platform	Anjarium Biosciences	Serious dermatologic disorders	[12]
ExoSCRT	ExoCoBio	Exosome isolation and purification technology	[14]
ExoDx Prostate test	Exosome Diagnostics	Detect and evaluate prostate cancer risk effectively.	[89]
Exosome-based liquid biopsy	Exosomics Siena SpA	Utilize exosomes for cancer screening and diagnosis.	[35]
DeliverEX platform	Evox Therapeutics	Severe rare genetic disorders	[75]
Natural exosomes	Exopharm Pty Ltd	Wound healing, osteoarthritis	[46]
EXPLOR platform technology	Ilias Biologics Inc.	Precisely load specific proteins into exosomes as desired	[10]
ExoDx Prostate test for cancer detection	Exosome Diagnostics	Diagnosing and assessing prostate cancer risk	[4]
ExoRelease	Clara Biotech	Antibodies, vaccines, therapeutic vectors	[69]
Hemopurifier	Aethlon Medical, Inc.	Infection, Malignancy, Co-occurrence	[11]
Exopharm's LEAP Technology	Exopharm Pty Ltd.	Adult stem cell exosome isolation	[59]
Exo-Target	Ilias Biologics Inc.	Regenerative therapies for hair, skin	[77]
XO-Cutis	XOStem Inc.	Hair regeneration, skin rejuvenation, and wound healing treatments	[35]
REGENT	Carmine Therapeutics	Gene therapy	[25]
XO-Regen	XOStem Inc.	Articular damage, respiratory failure, neuroinflammation	[106]

Surface modification

Exosome surface engineering involves modifying the surface proteins of exosomes to change them into transporters or markers, and to convert desired protein or peptide components into products (Table 10). This modification allows for the targeted delivery of specific protein or peptide components to meet specific needs. Natural exosomes may encounter challenges such as poor stability and rapid clearance, which limits their effectiveness in delivering drugs or targeting specific sites [122].

Table 10. Surface Modification Application Examples

Type of Surface Modification	Drug	Applications	Ref
Genetic Engineering	DOX, let-7a mi RNA	Exosome surface engineering targets EGFR-expressing breast cancer tissues.	[88]
Magnetic nanoparticle technology	Co-incubation of DOX	The objective is to specifically target mouse subcutaneous H22 cells in order to suppress tumor growth	[94]
Chemical reaction	PTX (paclitaxel) and TPZ (tirapazamine) loaded on liposomes.	Targeting tumors for treatment purposes.	[44]
Genetic Engineering	siRNA	Targeting CNS for treating Alzheimer's (neurons, microglia, oligodendrocytes).	[66]
Electrostatic interaction	Saponin and Dextran	Enhancing exosome uptake by targeting cell membrane receptors. .	[98]
Chemical reaction combined with post-insertion	PTX	Targeting CNS for Alzheimer's treatment (neurons, microglia, oligodendrocytes)	[111]

Surface modification is employed to address these limitations and improve the functionality of exosomes. One benefit of exosomes is their natural origin, aiding in mitigating side effects associated with anti-inflammatory drugs.

However, the efficiency of exosome delivery may be affected by both the donor cells generating the exosomes and the cells receiving them [123].

Furthermore, exosomes originating from various sources may present different effects and intrinsic limitations when aiming for specific sites. Altering the exosomes' surface allows for customization to enhance their attributes. For instance, attaching targeting ligands onto the surface facilitates precise delivery to specific targets, thus improving their capacity to transport therapeutic cargo to desired locations within the body [124].

In summary, surface modification of exosomes offers a valuable strategy to address the constraints of native exosomes and elevate their clinical utility. Recent techniques for analyzing targets for disease treatment include attaching target peptides to drugs, genetically modifying exosome membranes or precursor cells, utilizing magnetic nanoparticles, electrostatic interactions, and incorporating molecules or proteins into exosomes after formation [125].

Surface engineering of microRNAs involves modifying their surface proteins to transform them into carriers or signaling molecules, facilitating the targeted delivery of protein or peptide components [126]. This approach helps to address the limitations of natural microRNAs in delivering drugs or specific targets. By altering the surface properties of microRNAs, surface engineering enhances their effectiveness [127]. MicroRNAs possess inherent properties that help alleviate the adverse effects associated with anti-inflammatory medications.

Surface engineering offers a solution by allowing for the modification of microRNA surfaces to optimize their performance. For example, attaching targeting ligands to their surfaces can enable the selective delivery of microRNAs to specific locations, improving their ability to transport therapeutic cargo to desired areas within the body [128-130].

Surface engineering of microRNAs overcomes the limitations of native microRNAs, making it easier to use them in clinical applications [131]. Techniques for analyzing targets for disease treatment include binding target peptides to drugs, genetic engineering of microRNA membranes or progenitor cells, magnetic microRNA technology, electrostatic interactions, and post-incorporation of molecules or proteins into microRNAs. In genetic engineering, modified exosomes show promise for targeted gene therapy [132-135]. Cationized pullulan modification of exosomes allows for targeting of hepatocytes through interaction with asialoglycoprotein receptors, improving the precision and clinical effectiveness of exosome-based therapies [136-138].

Optimized methods for synthesizing and targeting peptides enable the customization of exosomes for different applications. Adding fluorescent labels for surface modification does not disrupt important membrane functions of genetic vehicles.

However, engineered exosomes may have limitations in certain drug delivery applications.

Comparative studies indicate that anionic fusogenic liposomes may be more effective in delivering small RNAs and causing target gene knockdown through siRNA-mediated mechanisms [139-143].

Careful consideration of specific conditions and a thorough understanding of molecular exchange mechanisms and specificity are necessary when using engineered exosomes. Blind application without informed decision-making should be avoided [144].

Additional investigation is required to elucidate how exosome diversity influences drug delivery and to refine methods for maximizing exosome loading capacity and enhancing targeting [145-147].

A comprehensive, multidisciplinary approach is necessary to understand exosome production and advance investigations in pharmacokinetics, toxicology, and clinical trials.

The progress in genetic engineering will enhance comprehension of the human body, ultimately advancing disease diagnosis and treatment.

While engineered exosomes offer advantages in drug delivery, their efficacy is not guaranteed for all applications. Informed decision-making and careful consideration of specific conditions are crucial [148].

Creating Hybrid Exosome-Liposome Structures

Recent research has investigated exosomes for drug delivery through surface modifications or hybrid nanoparticle development, showing promise for improved cancer treatment [149].

Modifying exosomes via non-genetic or genetic means can enhance therapeutic drug efficacy by

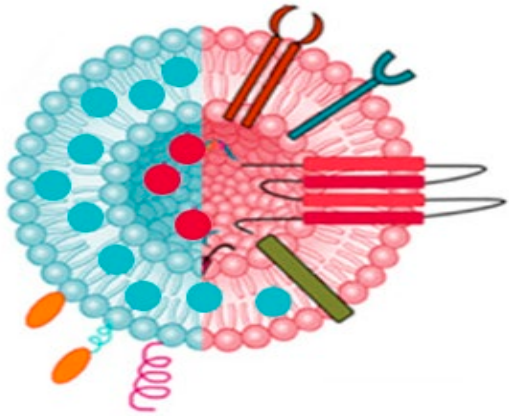

Fig.5. Illustrates the formation of hybrid exosome-liposome

improving their cytotoxicity and targeting potential [150].

As mentioned before, exosomes can carry signals containing miRNA, mRNA, proteins, and lipids. Their small size allows them to evade phagocytosis and efficiently transport cargo in the bloodstream.

Exosomes have been shown to traverse biological barriers such as the blood-brain barrier and the placental barrier [127-134]. With their high drug delivery capacity, current research is focusing on modifying exosomes through surface changes and hybridization with engineered nanocarriers such as liposomes (Fig.5).

Sato et al. aimed to enhance exosome delivery by creating a hybrid fusion with liposomes. This method modifies exosome surfaces, reducing immunogenicity and improving colloidal stability, facilitating targeted delivery of hydrophobic and hydrophilic payloads [138].

Recent studies highlight challenges in encapsulating bioactive molecules of various sizes within exosomes, especially for microRNAs, siRNAs, or particles smaller than cas9-expressing plasmids. Strategies like hybrid exosomes, formed through incubation with liposomes, show promise in delivering CRISPR-Cas9 into MSCs [139-140]. While lipidomic and proteomic tools enable exosome composition analysis, their potential in developing effective targeting liposomes in vivo requires further exploration [141]. Despite demonstrating targeting abilities for specific cell types, exosomes often fail to achieve expected therapeutic outcomes when administered systemically, revealing challenges in their use as targeted drug delivery nanovesicles. Key requirements for nanovesicle drug delivery include efficient drug loading, bloodstream stability, avoidance of macrophage uptake, endurance to reach targets, and biocompatibility. Hybrid exosomes, combining exosome and liposome features, offer the potential for enhancing targeted drug delivery capabilities. Leveraging exosomes' biocompatible properties through strategic modifications holds promise for precise drug delivery systems [142-143].

Challenges and future prospective

Exosomes have gained significant attention in recent years due to their effectiveness as carriers for diverse therapeutic substances [144-146]. These tiny carriers, synthesized by various cell types in the body, play a vital role in preventing and treating a range of diseases, spanning immunological, dermatological, cardiovascular, and neurological conditions. Surface alterations utilizing different methodologies enhance the therapeutic potential, cell-adhesion properties, and capacity of exosomes to transport bioactive components to specific cells [147]. Despite their manifold benefits, there are ongoing challenges in fully comprehending the roles of exosomes in therapeutic settings. Pharmaceutical and biotechnological companies have developed exosome-based solutions and platforms for efficient drug delivery and disease management, with several undergoing clinical trials [148-150].

CONCLUSION

Nanovesicles are critical in molecular biology, advancing cancer therapy and serving as potential liquid biopsy biomarkers for improved theranosticity in individuals with cancer. Furthermore, engineered nanovesicles provide a groundbreaking system for drug delivery, effectively navigating biological pathways while addressing safety concerns such as immunosuppression, toxicity, and biodistribution. The encapsulation of therapeutics, including pharmaceuticals, proteins, and nucleic acids, within nanovesicles can overcome challenges related to stability and exchange during circulation. Researchers have successfully developed and validated diverse loading strategies, utilizing both endogenous and exogenous approaches, in both laboratory and animal models. As a result, nanovesicle-based therapies have exhibited enhanced therapeutic effects. Researchers have successfully developed and validated diverse loading strategies, utilizing both endogenous and exogenous approaches, in laboratory and animal models. However, further research is crucial to refine nanovesicle purification and characterization methods for their application as drug delivery systems in clinical trials. Researchers have

successfully developed and validated diverse loading strategies, utilizing both endogenous and exogenous approaches, in laboratory and animal models, showcasing their efficacy in advancing molecular biology research.

CONFLICTS OF INTEREST

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