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Unique therapeutic potentialities of exosomes based nanodrug carriers to target tumor microenvironment in cancer therapy

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ABSTRACT

Cancer is a complex syndrome with a high mortality rate worldwide due to the lack of effective treatments. The lack of effective coordination between tumor cells and immune system components may be an important reason for the failure of tumor cells to be successfully eliminated after treatment. Tumor microenvironment (TME) barriers hinder the entry and dispersion of nanotherapeutic medicines in tumors. Extracellular vesicles (EVs) are membrane-bound structures responsible for cell-to-cell coordination and carry different biomolecules responsible for physiological and pathological communication between cells. Their role has been a mystery for decades, and over the past two decades, their structure and content have revealed some amazing facts. Recent studies have shown that exosomes play a key role in intercellular communication during the pathogenesis of diseases such as cancer and are responsible for cancer proliferation and metastasis. Inspired by the structure of their endogenous lipid membranes, researchers have tried to mimic their fine structure in the laboratory and tried to load certain biological and chemical drugs. Therefore, exosomes have received particular attention in nanotechnology, and these lipid polymeric micelles have emerged as potential candidates for nanocarriers in nanotechnology to overcome various obstacles in targeted drug delivery. In view of the importance of exosomes, this review highlights the potential of exosomes for use in nanodrug-based medication delivery. The majority of the investigation in these fields has not yet moved out of the laboratory. It will take a lot of time and work to implement these experimental findings in clinical settings.

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1. Introduction

There has been a significant progress in drug delivery via nanotechnology for various diseases and cancers remained special focus throughout decades. Nanotechnology has broadened application in several form of cancer therapies, such as radiotherapy (RT), photothermal therapy (PTT), immunotherapy (IMT), chemotherapy (CTX), gene therapy, sonodynamic therapy (SDT), photodynamic therapy (PDT), chemodynamic therapy (CDT) [1,2]. The goal is to provide a treatment that is both effective and safe. These treatments can potentially improve patients' lives but also have several severe downsides. For instance, chemotherapeutic agents are notorious for their systemic toxicity and struggle to achieve therapeutic efficacy, increasing resistance, drug resistance, poor tissue penetration, poor targeting, and low bioavailability [3]. There is no doubt that the tumor microenvironment is directly responsible for these flaws due to its anatomical and physiological features (TME) [4].

TME is a multifaceted, intricate network structure that affects the distribution of anticancer medications and hinders therapeutic intervention [5]. It causes medication resistance, immunosuppression, and inefficient transport of drugs because of its abnormal physiology compared to that of healthy tissues [6,7]. These characteristics include acidic environments, elevated glutathione (GSH) levels, metabolic disorders, soluble substances, and low oxygen levels. Immune homeostasis is essential for the proper function of the immune system; however, studies have discovered that, as many stromal cells in TME have immunosuppression capabilities, TME gradually has an immunosuppressive effect [8]. Abnormal vascular network, complicated extracellular matrix (ECM), a dynamical network of carcinogenic cells (such as tumor-associated stromal cells) and non-cancerous cells (such as immune cells, inflammatory cytokines, endothelial cells). Tumor cells can avoid homeostatic immunological responses and abnormally regulate immune responses triggered by tumor invasion, leading to immune suppression [9].

TME variables and pathways contribute directly to tumor growth, tumor immune escape, the limited success rate of interventions, and the developed resistance of cancer survivors to therapeutic interventions, despite considerable breakthroughs in targeted therapy for cancer [10]. Since the tumor microenvironment (TME) is an interesting target for targeted therapy, learning about the mechanisms and elements that make up TME and creating effective targeting strategies is crucial for increasing antitumor efficacy [11].

Recent decades have seen a tremendous uptick in interest in nanoscience within the pharmaceutical business, as it has been widely

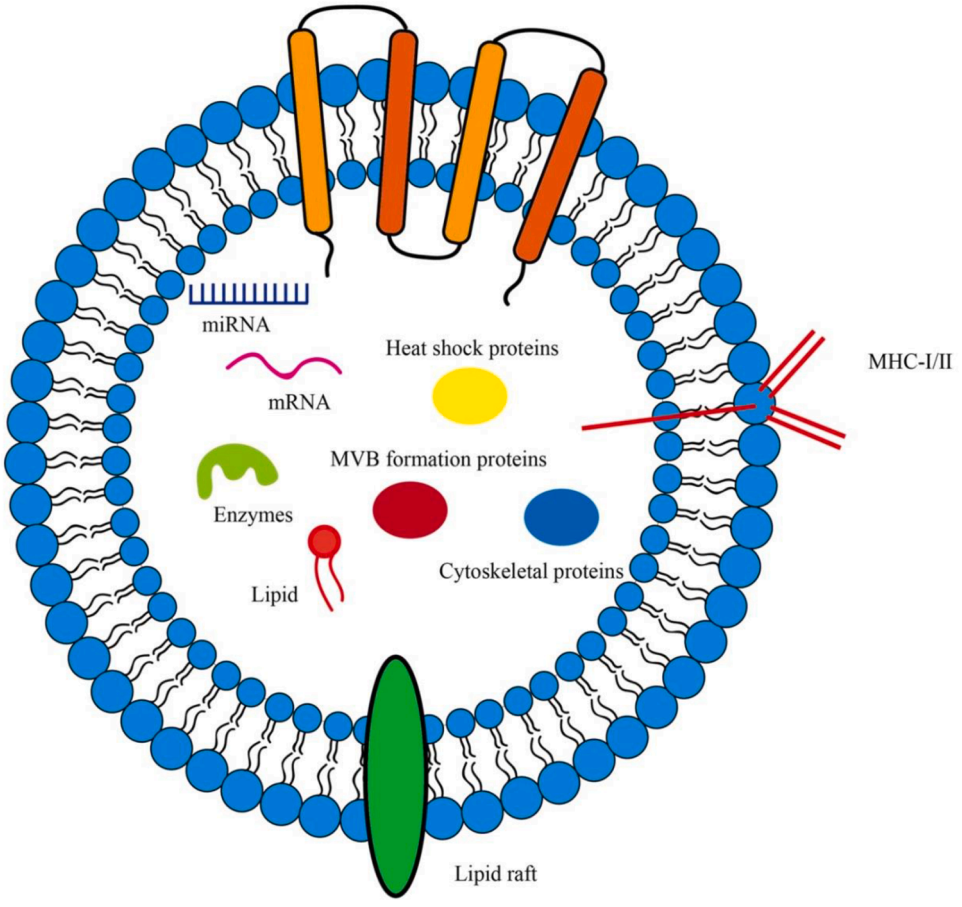

Fig. 1. The major molecular composition of exosomal constituents (Published in open access Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License [179]).

implemented throughout most drug delivery systems (DDSs) [12–15]. It allows for synergistic tumor therapy, which can help treat cancer more effectively than monotherapy by working together to counteract each other's side effects [16,17]. Unlike their larger-sized counterparts, nanomaterials have a wide range of interesting and useful physical, chemical, and biological features [18, 19]. It benefits from having a lot of surface area with a specified purpose, excellent stability, a long storage life, changeable activity, and inexpensive cost [20]. Improving drug bioavailability while decreasing toxicity is the goal of nano drug delivery systems (NDDSs), which include passive targeting approaches such as enhancing permeability and retention (EPR) effects and targeting the tumor microenvironment (TME) [21,22].

Additionally, they use receptor-mediated activity targeting techniques, such as folate (FA), which has a high natural affinity for the FA receptor (FR), which enhances the power on tumor cells more than on normal cells [23]. NDDSs are primarily classified into nanoparticles, nano-emulsions, liposomes, micelles, exosomes, nanocapsules, nanoenzymes, and nanoplatelets based on the dispersion form, motion state, and physical structure of the system [24]. Tumor cell-based models are used in several studies of nano drug treatment for cancer [25–27].

Exosomes were first observed in reticular cells in 1983, and the term was coined in 1987 [28]. Exosome release was previously thought to be a means of excreting waste from cells. GracaRaposo et al. found in 1996 that exosomes produced by B-lymphoblast-like cells had anticancer effects [29]. Exosomes contain proteins, nucleic acids, and other compounds. In 2007, HadiValadi et al. found that microRNA and mRNA in exosomes may be transported between cells, leading to gene exchange [30]. In the past decade, researchers have made significant advances in the field of exosomes. Many studies have used exosomes as a platform for liquid biopsy and drug delivery. Due to the difficulty of obtaining relatively pure preparation methods and properly characterizing them, the term "exosomes" has become controversial due to the overlap in size and shape between them and microcapsules (less than 200 nm in diameter). In 2018, the International Society for Extracellular Vesicles (ISEV) proposed to replace exosomes with tiny Extracellular Vesicles to replace Vesicles smaller than 200 nm in diameter [31]. Nevertheless, the term exosome has become widely used in the scientific literature over the past decade. We will continue to mention exosomes in this review so that readers of all levels of experience can more clearly understand exosomes.

The main process of exosomes formation is as follows: endocytic vesicles are formed through plasma membrane invagination first, followed by early maturation into delayed endosomes. Subsequently, multiple intracavitary vesicles (ILVs) form in the late endosomes, mainly with the entry of cargo, including cytoplasmic proteins and nucleic acids, and the endosomes are subsequently transformed into multi-vesicle bodies (MVBs) by branching inward. However, MVBs can transport and fuse with cell membranes to release ILV from *in vitro* cells [32,33]. This is the sequence of events of ILVs as exosome.

Proteins (such as transcription factors, tetraglycoproteins, enzymes, and heat shock proteins), lipids, and RNAs (such as mRNA, miRNA, lncRNA, and circRNA) are the core constituents of exosomes (Fig. 1). Multiple exosome-related databases exist, including ExoCarta, Vesiclepedia, and exoRBase. There is a lot of information about exosome proteins, fats, and RNA in these databases. Even so, some exosomal components can only be found in exosomes from specific cells, while others can be found in exosomes from all cells.

Cancer has been identified as a global health challenge due to the nonresponsive and anaplastic behavior of cancer cells [34].Itis one of the leading causes of death worldwide. According to the recent report, around 2.3 million new cases are diagnosed each year, with 685,000 deaths in 2020, which makes 15% of all cancer-related deaths worldwide in women [35]. Breast cancer is one of the most commonly diagnosed cancer globally [36]. There are four molecular subtypes of breast cancer identified based on the molecular profiling done with the use of modern molecular biology tools such as microarray: luminal (A and B), triple-negative breast cancer (TNBC), and HER2-positive breast cancer (ER+/HER2-negative) [37,38]. When looking at all of the various characteristics that determine how deadly breast cancer is, TNBC stands as one of the most aggressive because it has lost all three estrogen receptors, progesterone receptor, and human epidermal growth factor receptor expression [39,40]. The advanced mortality of the disease reflects the tumor's capacity to penetrate nearby tissues and its remote position. Early diagnosis and early detection are critical for survival. Screening tests that show either an increase of cancer diagnosis tools(such as mammography and clinical examination) have a potential increase in the probability of a false-positive result hence requiring a biopsy to catch cancer at an early stage [35,41].

In the early stages of Cancer treatment, surgery is used to remove the cancer cells, after which radiotherapy is administered. In more advanced cases, surgery is accompanied by a mixture of chemotherapy and radiotherapy [42]. Chemotherapeutic medications have demonstrated various adverse effects, including fatigue, vomiting, skin rashes, intestinal disturbances, and febrile neutropenia. The drugs revealed no significant difference in treating cancerous and normal cells [43,44].

The supply of anticancer drugs is more focused on the target delivery of the site of cancer using nano-vehicles such as synthetic nanoparticles (NPs), viral nanoparticles, and so on to overcome these side-effects or hurdles, including such bioavailability and more considerable systemic destruction of healthy cells through chemotherapy drugs in patients [45–51]. However, these nanocarriers have also had several constraints restricting their candidacy for effective and secure cancer treatment. According to the scientific literature, metallic NPs can cause systemic side effects, such as toxicities, increased oxidative stress, decreased excretion from the body, and inter-species ion-np interactions [52,53]. While the above two strategies address some of the commonly seen side effects, the overall advantages of the polymeric NPs and liposome-based nano-drug delivery system outweigh its known shortcomings, such as biocompatibility, mucositis, skin toxicity, drug modification [54,55].

Cell-secreted extracellular vehicles (EVs), specifically exosomes and other exosome-like structures, have emerged as promising therapeutic agents encapsulating a variety of active biomolecules, including nucleic acids, lipids, and proteins [56]. The unpurified exosomes are homogeneous vesicles derived from cells, also known as EVs. Exosomes, apoptotic bodies, and microvesicles are three distinct types of double-layer vesicles distinguished by their size and biogenesis [57]. An apoptotic body is 0.5- 5 micrometers in diameter and is produced and released by dying cells during the course of apoptosis. The microvesicles, which are formed by "pinching off" from the plasma membrane, have a diameter between 50 and 1000 nanometers [58]. Exosomes have a diameter of 30 to 200 nm. A

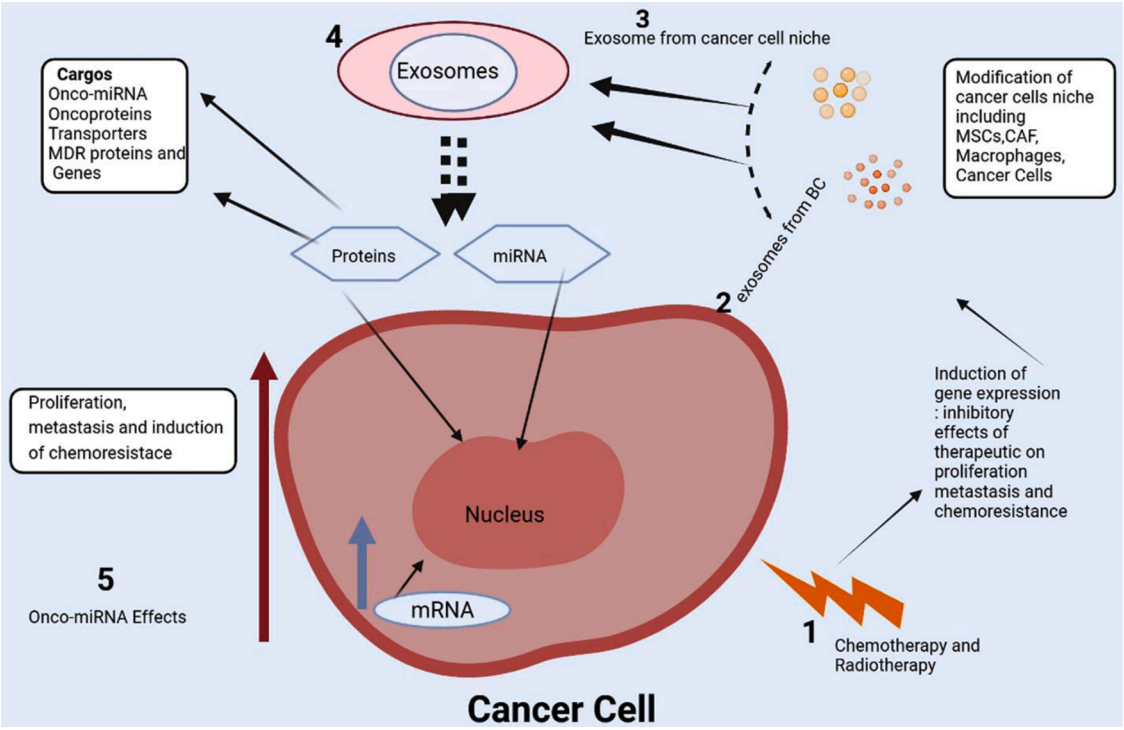

Fig. 2. Role of exosomes in Cancer. (I)Radiation therapy and chemotherapy are used in the treatment of cancer. (ii)There was a spike in mRNA production and exosomes secretion to control cancer cell development. (III)To convey regulatory cargos to Cancer cells, tumor cells secrete exosomes containing the cargos, which are then received by niche cells. (IV) Onco-miRNA and proteins are among the cargo delivered to cancer-associated cells, and their presence influences the expression of the metastases and chemoresistance-promoting genes. (This figure was created with biorender.com and extracted under premium membership).

multivesicular body (MVB) contains intraluminal vesicles (ILVs), which are organelles that are involved in the transport of biomolecules within the cell and release them via inward budding at the plasma membrane [59]. It has been shown that EVs play a role in cancer metastasis, progression of disease, diagnosis, and treatment, resulting in a rapidly expanding field of cell research [60]. These extracellular vesicles are secreted from cells through exocytosis. Researchers have successfully delivered drugs to cancer stem cells deep within tumors in mouse models by utilizing the superior targeting function and biocompatibility of cancer exosomes [61]. Exosome research remains a relatively new field, and despite significant efforts, progress has been slowed by challenges such as inefficient separation methods, difficulties in characterizing, and a lack of specific biomarkers [62].

Recently, the significance of exosomes in cell-to-cell communication has been discovered, and it has been discovered that these particles can carry and distribute macromolecules into cells. Most cells, including cancer cells capping different peptides and nuclear acid-based cargos inside the structure, release these lipid bilayers extracellular structures [63,64]. Because it is derived from the patient's own body, it will be less likely to elicit unwanted immune responses, allergic reactions, toxicity, and biodegradability issues [65]. As a result, it has a huge potential for carrying various therapeutic loads for distribution into cancer therapy methods. Therefore, more recently, scientific investigation has turned to use EVs as a cancer diagnostic marker and for the administration of nanotherapeutics. In this paper, we have highlighted the involvement of exosomes in the target drug delivery system as a suitable nanocarrier for the administration of anticancer substances.

2. Exosomes: origin and features

Exosomes are EVs released by many cells to communicate with nearby and distant cells [66]. In 1983, Stahl discovered these vesicles while researching immature human RBC, and they were named "Exosomes" by Johnstone in 1987 [28,67]. Exosome biosynthesis starts by forwarding the engulfment of the plasma membrane through different mechanisms, in which the endosomal sorting transporters complex (ESCRT) regulates the production and sorting of macrovesicle bodies (MVBs)-ILV exosomes [68]. While the release of these exosomes to the extracellular matrix (ECM) is monitored by ALG-2-interacting protein X (ALIX) or by vacuolar protein sorting associated protein (VPS4) [69–73], these ILVs form inside of macrovesicle bodies known as MVBs, and fuse with lysosomes under lysosomal degradative pathways. These Cancer-derived exosomes are found in abundance in the human body from specific surface receptors, including TSG101,CD63, Alix,CD29, CD24, TSG101, ADAM10, CD9, and CD222, making them easily identifiable [74,75]. In a previous study, scientists reviewed and summarized the evidence that RABfamily proteins with GTPase activity contribute significantly to vesicular trafficking in breast cancer by facilitating the secretion of exosomes from the cancerous

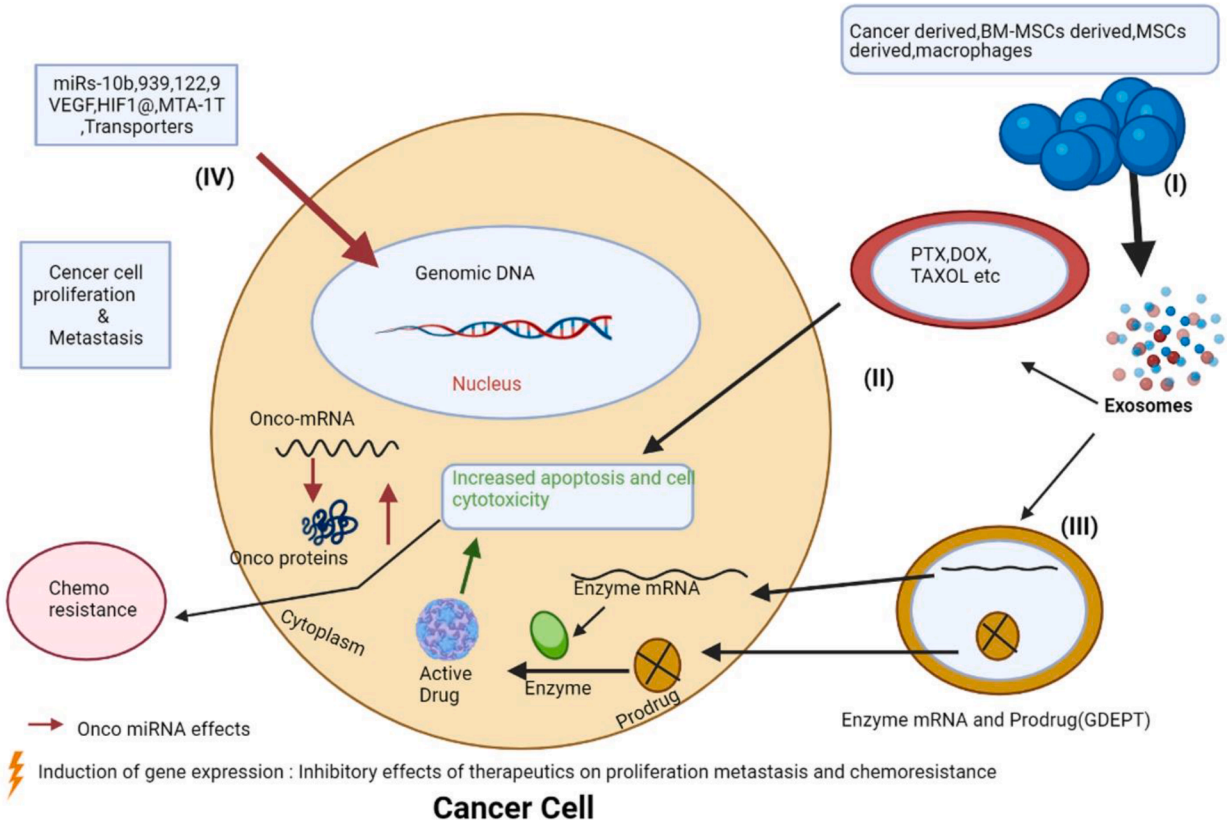

Fig. 3. In the case of cancer, exosomes have a novel potential as a drug delivery system. (I) Exosomes from the diverse model was isolated. (II) Exosomes are used to deliver the therapeutic payload. (III) Tumor suppressor gene expression and oncogene expression are regulated by nucleic acid-based therapeutic load, which may be measured by measuring the total nucleic acid load present in cancer cells. (IV)A cancer cell situated in a cancer niche secures oncogenic exosomal miRNA and protein transport, which influences the expansion of cancer cells, chemoresistance and metastases. (This figure was created with biorender.com and extracted under premium membership).

cell, and thus can be targeted to prevent breast cancer metastasis [76].

3. Role of exosomes in cancer

Cancer can develop that results from the proliferation of abnormally large numbers of cells [77]. This may be the result of genetic variation, such like gene mutations that are inherited. Carcinogens, which modify the microenvironment and increase the growth and progression of cancer, may also be to accountable for causing DNA damage [78].In general, exosomes are critical to physiological regularity in cells. Due to the small size of this class of EVs, they can readily be transferred from the host cell to the target cell during signaling for cellular homeostasis establishment [64,79]. Additionally, exosomes contribute significantly to cancer cell proliferation, angiogenesis, cell metastasis, epithelial to mesenchymal transition (EMT), and the development of chemoresistance in cancer [80]. Since synthesis of exosomes has explored membranes as a component of the mother cell membrane, a large number of discoveries have been made as they play an important role in the early diagnosis of diseases. Focusing on exosomes with specific markers has become one of the most interesting topics in science [81].The etiology of cancer has shown an increase in exosomes biogenesis in BC cells in patients, in which exosomes carry cargos into targeted cells, with integration-receptor mediated endocytosis that helps with bidirectional communication (Fig. 2(I-III)). Several functionally active cargos enrich these EVs in exosomal biogenesis, including nucleic acid, lipids, and proteins, which play a vital role in cancer (Fig. 2-IV)). In other words, growth factors, onco-miRNAs, mRNA, lipids proteins are involved in proliferation, metastasis, and chemoresistance formation in cancer cells via gene regulation. These molecules work by influencing gene expression (Fig. 2 IV, V).

4. Exosomes: a vehicle for cancer therapeutics

Although, for a long time after discovery, exosomes were intermittently studied in the disease process [82]. After exploration of their composition around two decades ago, scientists discovered that these nano-bags carry thousands of molecules. As of endogenous nature, biologically derived or synthetically prepared nanovesicles such as polymeric nanoparticles, metallic nanoparticles, micelles, and liposome with unique properties have become an important asset for nanotechnology in delivering therapeutic agents.

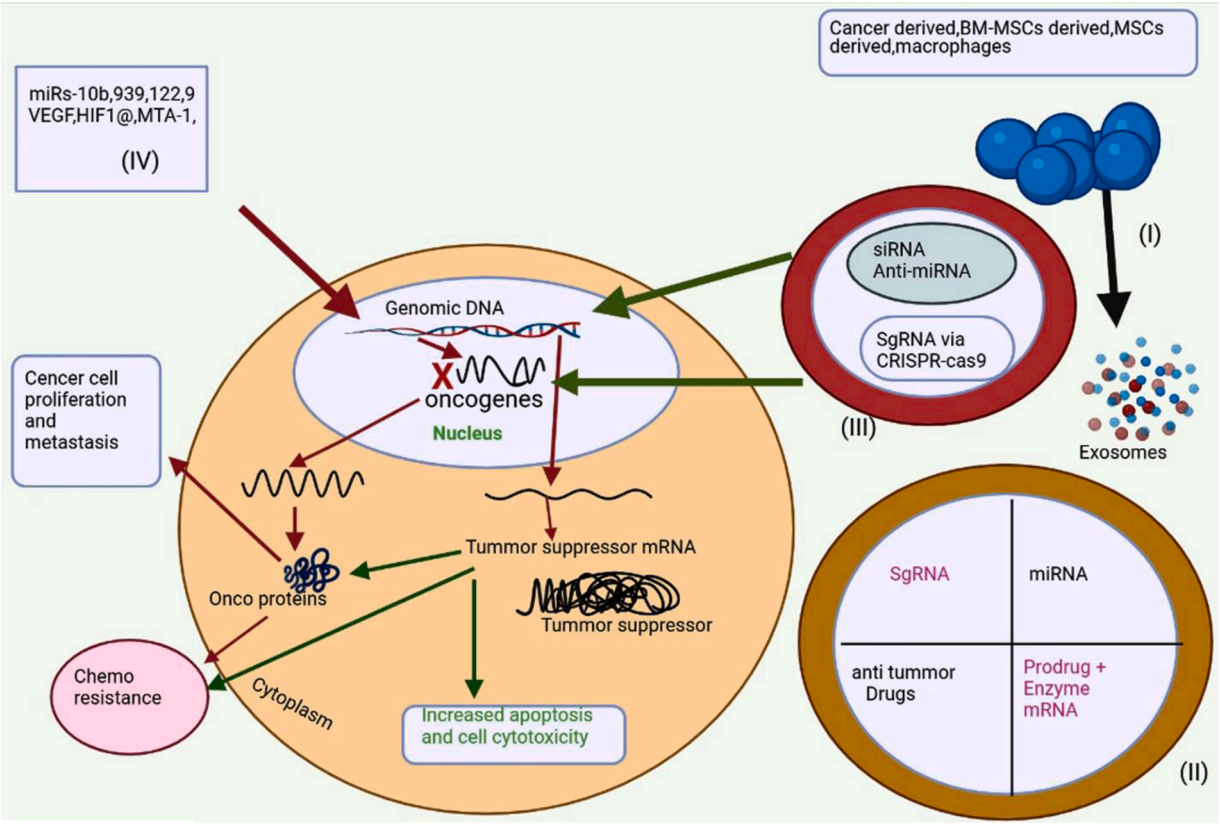

Fig. 4. (I) Extraction of exosomes from various source materials. (II) *in-vitro* studies using cancer cells have shown that anti-tumor drugs encapsulated in exosomes exhibit improved cytotoxicity and suppress the development of metastases, chemoresistance, and cancer cell proliferation. (III) When there is mRNA and a prodrug therapeutic load, cancer cells will express the enzymes and act on the prodrug, generating a net increase in cell cytotoxicity and apoptosis. (IV) The use of oncogenic miRNA and proteins extracted from exosomes transport from a cancerous cell and microenvironment, together with cellular proliferation, metastases, and chemoresistance, results in the advancement of cancer progression, metastases, and chemoresistance. (This figure was created with biorender.com and extracted under premium membership).

Nanoparticles have gained widespread usage in numerous forms, including micelles and liposomes [46,49,52]. However, the majority of these nanoparticles have some drawbacks. One of the primary issues related to the use of metallic nanocarriers is the fear and suspicion due to possible toxicity to essential organs and tissues caused by the lack of removal of metallic nanocarriers from the body [52].

Conversely, polymeric nanoparticles have several advantages for delivering therapeutic molecules, such as pH regulation and responsiveness, but they also have substantial drawbacks, such as low yield potential and lowered biodegradability [46]. While lipid-based carriers like micelles and liposomes can address yield and toxicity concerns, they can also cause drug modification and slightly increased mucositis [83]. In addition to nanoparticles, certain studies have shown the efficacy of viral particles in the delivery of targeted drugs in BC. For example, If coupled with monoclonal antibodies, the PVX plant viral particle from potato mosaic virus (PMV) can successfully target breast cancer cells [84]. The utilization of these nano vehicles overcomes biocompatibility concerns and enables mass production at a low development cost [85]. However, more research is required before using these virus nanoparticles as medication carriers can be safely assessed. A problem linked with their use is spontaneous mutation. Thus, because of all these modern NPs' deficiencies, exosomes have been widely exploited in nano-drug delivery as carriers for Cancer targeted drug delivery systems (Fig. 3).

As previously stated, the exosome is a class of EVs released by numerous types of cells, including epithelial cells, and is essential for intercellular communication using specific biomarkers present on their surface and guiding them to their target cells. Extracellular vesicles (ECVs) are nanostructures (30–150 nm) [65] with intrinsic targeting and intriguing physiological features for cancer. Polymeric nanoparticles are unique in that they originate from within the body, which enables them to avoid problems related to nanoparticle toxicity, biocompatibility, and drug modification (Fig. 3) [86].

Genomic medicine mainly focuses on the development of detection methods based on precision and personalized medicine. This has led to growing interest in liquid biopsy methods that use body fluids, mainly blood and urine, rather than tissue samples obtained through surgery [87]. The risk to the patient is very low. This process includes three important types of samples, including circulating tumor cells (CTC), free DNA (cfDNA), and exosomes (EV). Exosomes are the most attractive type of liquid biopsy because of their high

Table 1
Summary of advantages of exosomes as therapeutics in cancers.

Types	Origins	Cargo	Targeted area	Effects	Refs.
Nucleic acid	HEK293 cell	siRNA	Gene *TPD52*	Cancer progression prevention	[180]
	MCF10A cells	miR-567	ATG5	Greater sensitivity to chemotherapy	[181]
	Bio-Synthetic	siRNA	*Oncogene*	Suppression of growth	[182]
	HEK293 cell	miR1226–3p	AQP5	Reducing MDA-MB31 cell movement	[183]
	MSC	miR379, miR-19b-3p	COX2	Stop cancerous tumors from spreading.	[184]
	MSC	LNA-antimiR142–3p,	miR-150, miR142–3p	Prevent breast cancer's clonogenicity	[185]
	MDA-MB231	Let7A	c-Mycs	Suppressing of the C-Myc gene inhibits tumor development.	[186]
	HEK-293T cells	HGF siRNA	*HGF* gene	Inhibits angiogensis and tumor growth.	[196]
	HEK-293T cells	miRNA-497	Several genes	Evaluation of atitumor role and gene expression	[198]
	Glioblastoma (U87) cells	hsiRNA *HTT*	HTT mRNA	Successful silencing of HTT mRNA and protein.	[197]
	HUCMSCs	miR-148b-3p	TRIM59	Enhanced cytotoxicity	[187]
Chemical drugs	MSCs	Taxol	Cell niche for cancerous cells	Regulate the Enhancing cytotoxicity of cells	[188, 189]
	Tumor derived	DM1 and DOX		Enhanced cell toxic effects	[190]
	Macrophages	PTX and DOX		Control MDR	[191]
	Macrophages	Anti-tumor drugs	NFkB	Enhanced apoptosis due to caspase activity	[192]
	HFL-1 cells Erastins GPX4 and CDO1			TNBC cells undergo erastin-mediated ferroptosis when GPX4 activity is Suppressed and CDO1 effect is induced.	[193]
Enzyme	Neurons	Catalase	Neurons	Therapeitic purpose of Parkinson's diseases	[199]

Abbreviations: HGF: hepatocyte growth factor; HEK: human embryonic kidney.

stability and ability to be collected from body fluids such as urine or blood. Because of their regulatory role in humans, miRNAs have the potential to be diagnostic biomarkers [88]. Changes in exosomal miRNA enrichment are associated with physiological, pathological, and metabolic changes, suggesting that they may be used as diagnostic biomarkers, such as Mir-23b-3p, Mir-10B-5p, and Mir-21–5p represent good prognostic biomarkers in patients with non-small cell lung cancer (NSCLC). Several biomarkers associated with prostate and bladder cancer were identified by analyzing the complete proteome of exosomes by mass spectrometry [89]. 276 NSCLC patients were identified as exosomal protein biomarkers with overall survival, including NY-ESO-1, EGFR, PLAP, EpCAM, and Alix. Multi-marker models using exosomes from lung tissue have been successfully evaluated using the EV Array system, which contains 37 antibodies against lung cancer-associated proteins [90].

While there are numerous isolation methods for exosomes, Invitrogen offers four different techniques: classic ultracentrifugation, electroporation charge-based precipitation, cell culture techniques, and current methods like Invitrogen [91,92]. Exosomes can be isolated from MSC, malignant cells, milk-derived or created by mesenchymal stem cells(MSC) and adult embryonic kidney HEK-293T cell lines (Figs. 3& 4); Table 1) [65,93]. Exosomes employing diverse created cell lines that express certain markers or that can be marked with specific monoclonal antibodies (mAb) for targeting BC are recently developed and discovering the exosome molecular structure and biogenesis mechanisms [94].These molecular markers on exobody surface can be identified using flow cytometry. Due to different surface markers on these nanostructures, vectors from different sources tend to have specific cellular targets. So scientists use these biological vesicles to transport and deliver therapeutic payloads based on proteins, nucleic acids, and antitumor drugs to BC cells in a targeted manner [94].

Exosomes can carry therapeutic molecules/compounds such as nucleic acids and small molecule drugs. These medications can be loaded into exosomes via electroporation, saponification, and sonication (Fig. 4). It has been shown that these extracellular vesicles (exosomes) contain a DNA of about 1 kb in length, showing that they have a payload-carrying capacity [92].

4.1. Exosomes as a carrier for nucleic acids

As one of the most devastating diseases in the world, malignancy is a major concern. Other malignancies include lung cancer, stomach cancer, colon cancer and breast cancer [95].As previously stated, Cancer cells can regulate gene expression, which results in a malfunction of the cells' regular metabolic activities, resulting in chaotic and uncontrollable cell division in Cancer. In cancer, where these heterogeneous nucleic acid structures as exosomal cargos regulate cell progression, this material has a regulatory function. Normally the regulatory machinery in breast cancer inhibits the anticancer treatment by impeding oncogenic receptors, which allows the cancer cells to survive and overcome therapy [96]. Using the targeting molecules found in exosomes, researchers have explored their use in transporting regulatory chemicals to cancerous cells. Researchers isolated exosomes from blood, found small RNA molecules within them including miRNAs and anti-miRNAs, and used these to generate siRNA that helps regulate gene expression, prevents tumor growth, and enhances medication sensitivity [97] (Fig. 3(III)). By specifically targeting and suppressing the overexpression of oncogenic receptors, these small RNA molecules (called microRNAs, or miRNAs) prevent the cancer development that follows the oncogenic receptor overexpression [98].Through the use of regulatory RNA molecules, it is possible to suppress oncogenes and associated accessory regulator proteins. Delivering exosomes with siRNA targeted to the TPD52 gene reduces the production of the oncogenic receptor by limiting tumor growth [99]. This excellent targeting with exosomes resulted in considerable

suppression of cancer and enhanced apoptosis of cancer cells. miRNA acts in several ways beyond siRNA, including helping to regulate gene expression and act as a carrier of tumor suppressor miRNAs [100]. Reduced ATG5 expression and the resulting increase in the potency of anti-tumor medicines in cancer cells are results of transport of these tumor suppressor miRNAs including such as miR-567 to recipient cells via exosomes [101]. Anti-oncomirs are among the miRNAs which are known to decrease the expression of a gene encoding an oncogene. By directly targeting and knocking down oncogenes, the anti-oncomirs could prevent cancer progression. Following injection of the oncomir RNA let7 into exosomes and administration to cancer cell lines, this RNA downregulates the expression of c-Myc and inhibits metastasis in cancer cells (Table 1) [102].The oncogenic proteins' transcribed genes achieve Post-transcriptional regulation. Targeting mRNAs encoding oncogenic proteins at this stage using exosomal sgRNA along with CRISPR-cas9 boosts apoptosis and drug sensitivity in DOX-resistant ovarian cancer cells [103]. Thus, a method similar to that employed to deliver siRNA and sgRNA to block the posttranscriptional regulation of onco-miRNAs or proteins linked to cancer and drug resistance can be applied to transport these RNAs/siRNA molecules to modulate cancer and drug resistance.

Several studies have shown that the hybrid exosome delivery CRISPR/Cas9 system is capable of regulating target gene expression in MSCs [57,104]. The proposed targets provide a new method for delivering the CRISPR-Cas9 system to MSCs to allow for gene editing. Additionally, research has demonstrated that liposomes can offer additional benefits. Recently, hyperthermic intraperitoneal chemotherapy (HIPEC) has been developed to increase the therapeutic effect of exosome–liposome hybrid nanoparticles developed. GETLs are genetically engineered exosomes and thermosensitive liposomes [105]. To study its characteristics in cell-line-derived tumor xenografts (CDX) and patient-derived tumor xenografts (PDXs) for MPC treatment, the specimen was loaded with docetaxel (DTX). The results of the study indicated that DTX significantly inhibited tumor progression when gETL was loaded. Combining HIPEC with chemotherapy enhanced its anti-tumor properties [106].

The oncogenic load is actively loaded by cancer cell-derived exosomes that use an organotropism mechanism to reach and deliver it to targeted cells [107]. Cancer pathogenesis is controlled by the efficient transport of oncogenic cargo, which modulates numerous signaling pathways to promote it. The crucial role of miRNA-126 in limiting the development of metastases is due to its ability to control oncogenic gene expression and to block the downstream signaling of PTEN/PI3K/AKT [108]. Due to the organotropism impact of 231-Exo, this was dramatically amplified when miRNA-126 was supplied by exosomes [109]. As already noted, exosomes generated from cancer cells have significant advantages because they tend to focus during the development of the disease. However, given the current limited knowledge of these exosomes, they may contribute to the development of the disease in the cells they are administered.

To solve the problems connected with Cancer exosome's activities during cancer formation, the researchers employed MSCs generated exosomes [110]. Exosomes that have been extracted from mesenchymal stem cells target only the targeted cells and do not cause an immune response or adverse side effects [111]. They are utilized in administering nucleic acid-based *in-vivo* and *in-vitro* therapies, which are effective in treating various types of cancer [112]. The exosomes obtained from MSCs, which are loaded with LNA to silence the oncogenic miR-150 and miR-144–3p, can significantly suppress the production of these oncogenic miRNAs in MCF-7 stem-like cancerous cells. Tumorigenicity and clonogenicity are reduced in cancer cells when inhibited in their oncomirs. They do this by boosting the tumor suppressor genes APC gene and P2 $\times$ 7R mRNA [113]. The tumorigenicity of LNA anti-miR-144–3p *in vivo* has also been found to be reduced in a study conducted by another research group *in-vivo* [114].Research studies that have used exosomes obtained from MSCs, macrophage-derived exosomes, and B cell-derived exosomes to help overcome immunogenicity issues with treatments delivery have included those that utilized siRNA and miRNA [115].This research shows that the *in-vivo* and *in-vitro* delivery of nucleic acid-based therapies, such as reducing invasion, proliferation, and improving chemosensitivity in cancer cells, can effectively use exosomes from many sources, including cancer cells, MSCs, macrophages (Table 1) [116].

4.2. The chemo drugs delivery

Due to its particular features, exosomes may be useful therapeutic carriers in a variety of diseases and malignancies, including Alzheimer's disease and Parkinson's disease [117,118]. There is a disadvantage to exosomal delivery in that exosomes released by the body can easily migrate throughout the extracellular environment and biofluids and are absorbed by accepter cells at random [119]. The ability of Cancer cells to demonstrate invasive and metastasized conditions depends on their capacity for rapid division and multiplication that helps them escape natural immune response by producing tumor-cell clumps. Exosome's excellent targeting mechanism, which permeates different biological membranes, is crucial to delivering medications to the tumor cell. Conventional chemotherapeutics have a systemic adverse effect that is avoided by using an efficient delivery mechanism. Anti-tumorigenic drugs can be incorporated into exosomes and encapsulated within their hydrophobic core by using the exosomes' hydrophobic core [120]. When the hydrophobic core of the tumor penetrates and delivers medications to selected target cells, these chemicals stay shielded from the hydrophilic ECM microenvironment [121]. Treatments for cancer that utilize effective mitotic inhibitors, such as the substances involved in cancer cell division, are among the most popular ways of checking the cell cycle and stopping cellular division in cancerous cells. *In-vitro* and *in-vivo* studies performed by Kalimuthu et al. indicated that PTX (paclitaxel), a hydrophobic mitotic inhibitor packed inside MSC-derived exosomes, reduced breast cancer tumor growth [121].Additional research by Gomari et al. showed that Doxorubicin DOX-dispersed exosomes have higher target efficacy and lower tumor development in HER2/neu breast cancer [122]. Alternatively, higher concentrations of chemotherapeutic agents cause cancer cells to produce more exosomes, which leads to more autophagy and less apoptosis [123]. The increase in sensitivity and efficacy obtained using exosomes as a carrier has aided in developing a much lower concentration of the medicine, which is necessary to elicit a more significant response in cancer [124]. This means that when tagged with specific antibodies, the exosomes have the potential to be a drug-antibody conjugate, resulting in greater therapeutic specificity and efficacy. DM1 administration to cancer cells has been found to boost the cell toxicity (or cytotoxicity) of trastuzumab-tagged exosomes (T-DM1) [125]. Inhibiting the receptor HER2ß cells with these specific antibodies targeted delivery of

DM1 causes an increase in cell death by apoptosis via caspase activation in cancer cells. As previously stated, one of the essential steps in the development of cancer is the ability of cancer cells to evade the immune system, which is vital for the process of metastasis. A subset of the immune system and MSC has exosomes to modify the immune system and help reduce cancer [126]. One application of the exosome extract from macrophages containing immune cell-derived exosomes exhibited a statistically significant increase in the effectiveness of the chemotherapy medication paclitaxel in murine 4T1 cancerous cells [127]. In addition to this increased responsibility, we have identified a unique interaction between endosome-mediated immunological regulation and NFkB-mediated induction of apoptosis in the targeted cancer cell. Melzer et al. found that MSCs secreting exosomes delivered Taxol increased cell cytotoxicity by 90% [124]. While exosomes act as a paracrine signaling molecule, this causes cell cytotoxicity because of the cancerous cells niche. The alteration of the microenvironment and the addition of niche cells cause an increase in the level of inflammation and the mobilization of additional immune cells to the niche.

Much worry is concerned over cancer treatment because it has been shown to generate Multidrug resistance (MDR). The MDR is a transport protein that is overexpressed and exosomal delivered in response to a chemical substance, including ABC, multiple medication resistance (MDR), BRCP (Fig. 2-I) [128]. This transport protein enhances the excretion of the chemical medicine outside the cancer cell, limiting the availability of anti-tumor medicine within the cell. Based on exosomes carrying therapeutic compounds, there is the potential to reduce the production of these transporters in cancer cells, which will make it harder for cancer cells to export drugs. Researchers show that macrophage-derived exosomes PTX and DOX can successfully combat drug-resistant against MDR in cancer cells. Kim et al. report on the results from their investigation, which indicated that exosomes might be examined as a vehicle for a wide range of transporters, inhibitors, and other chemical-specific molecules used to lower the number of medications leaving cancer cells [129].

4.3. Proteins delivery

It is possible to reprogram cancer cells by engineering exosomes to carry small chemicals, genes or proteins directly into the nucleus [130]. Genetic and chemical changes are used for exosomal surface engineering with the obvious goal of improving the accuracy of targeting. Different cancer like Lung cancer, Prostate cancer, Breast cancer, colorectal cancer. Kidney (renal) cancer and Bladder cancer [131].Cancer treatment has relied on small proteins and peptides to treat the disease for more than two decades. The introduction of the exosome delivery method also makes use of these proteins and peptides [132]. The use of these peptides that can reduce the growth of tumor cells, reduce the number of new blood vessels growing, and activate the body's immune system in cancer treatment can be examined as a treatment for cancer [133]. For example, exosomes from antigen-presenting cells can convey cancer-specific antigens to cancer cells, enhancing the host immune response [134]. Once the tumor-specific antigen has recruited and activated the cytotoxic cells of the immune system, the exosomes with various antigen-specific ligand and anti-tumor antibodies on their surface will directly bind to the cancer cell. For this research, the peptides that activate cell cytotoxicity in cancer cells were encapsulated within exosomes and administered to cancer patients. Saporin and RNase-A peptides, being hydrophobic, can be delivered inside BC cells using the exosome [135,136]. Thus, exosome delivery system approaches that use peptide-based medicinal substances may represent a novel "biogenic" method for treating cancer.

5. Hybridization and bioengineering of exosomes

The use of exosomes as therapeutic vectors is important because these exosomes and their cargoes play a crucial role in the pathology of cancer [137]. Now that this new understanding of the chemical structure of exosomes has emerged, researchers are applying it to new cell designs that will allow them to bioengineer new types of exosomes. The required miRNA and protein receptors are located on these exosomes, making them ideal for targeting breast cancer cells [138]. Exosome biotechnology begins with a transduction system, such as viral vectors, plasmid vectors expressing therapeutic genes, and targeted peptides in exosomes. The therapeutic gene vector with the additional lead sequence has the therapeutic gene sequence pointing to the secretion pathway [139]. Thus, these transformed cell lines release exosomes containing therapeutic proteins and targeted compounds that can be isolated from the medium used. Co-culture of transformed cell lines with cancer cells had little effect, while isolation of exosomes from cancer cells had significant effect on cancer cells. One study showed that exosomes may be engineered as AQP5, which are designed to act as receptors for specific miRNAs and as a peptide to block cancer cell metastasis (see Table 1 at the same time) [140].

Recent increase in cancer treatment efficacy with the utilization of modified exosomes has driven scientists to construct hybrids of such bio vesicles with more excellent selectivity while at the same time decreasing their attention to detail [141]. When speaking about hybrid exosomes (HE), the term "fusion product" means the composition resulting from exosomal phospholipid molecules joining such a lipid-based chemically synthesized nano-drug carrier. Another example of using exosomes to target cancer cells would be if the plasma cell membrane of macrophages produced exosomes with specialized targeting ability were fused with liposomes to produce hybrid exosomes [142]. When hybrid exosomes loaded with doxorubicin are delivered to the proximity of cancer cells, they display improved toxicity, making them ideal delivery vehicles for DOX in the pH-regulated fashion [143] .

Hybrid exosomes provide a pH-sensitive characteristic that can be studied to improve delivery models for targeted treatments to bind clumps of different cancer cells [144]. Due to the extensive metabolic processes that tumor cells perform for their growth and proliferation, the pH of the cancer cells is generally acidic. Not only do metastases and chemoresistance contribute to the deaths of breast cancer patients, but so do recurrences after treatment, leading to additional deaths all over the world. Recurrence is managed by exosomes transporting oncogenes from the premetastatic niche into the cells that make up the niche. This cancer cell membrane component can be targeted by a hybrid HE (the fusion of chemically synthesized CBSA/siRNA nanoparticle and plasma membrane of

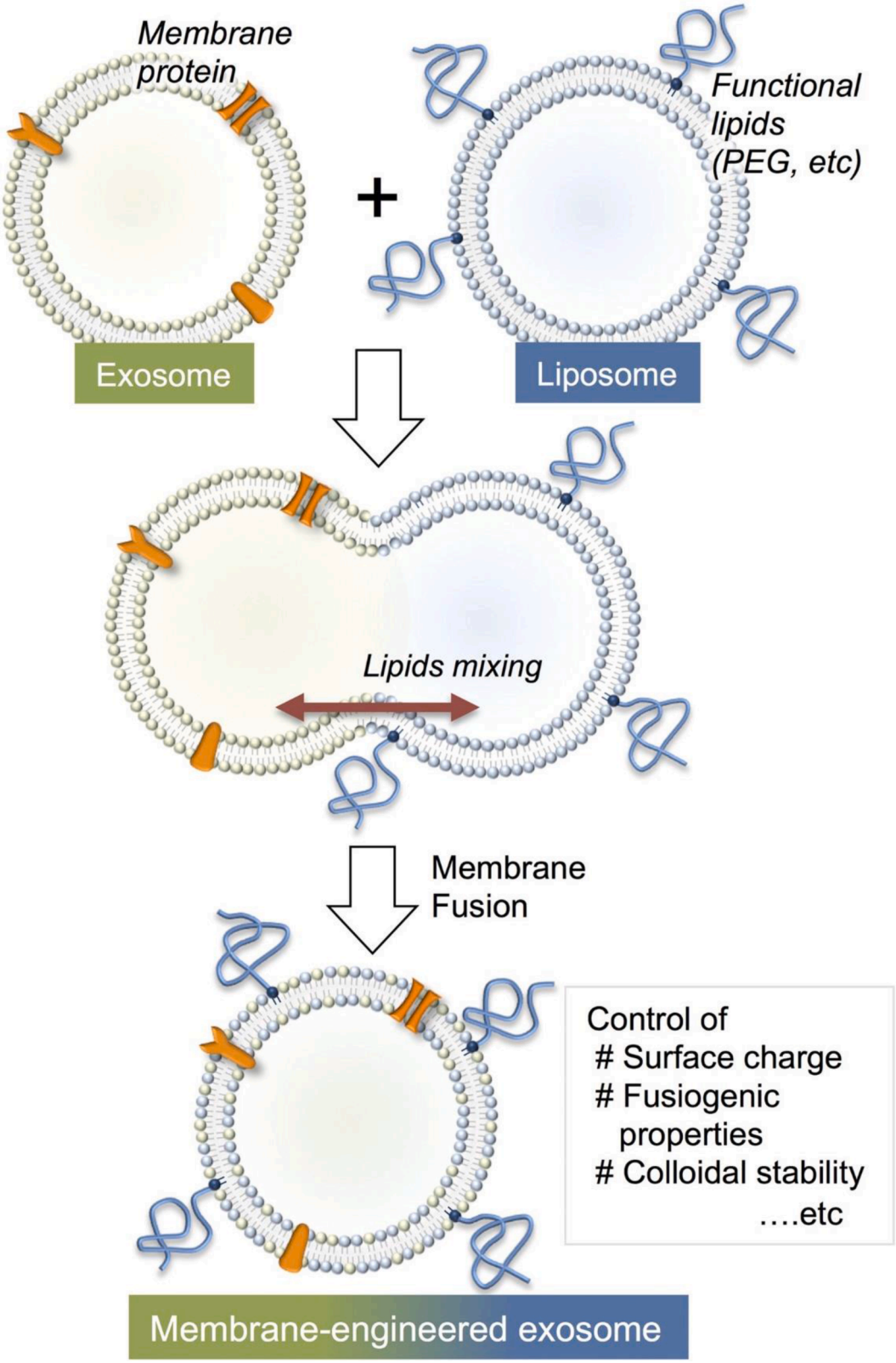

Fig. 5. Systematic synthesis of hybrid exosomes (Published under the term of common creative license [145]).

cancer-derived exosomes) that's created from the mixture of the plasma cell membrane of cancer-derived exosomes and the chemical synthesis of CBSA/siRNA nanoparticle [145] (Fig. 5). As with the transport of oncogenic genes and proteins, the generated HE now provides inhibitory siRNA cargos in the same manner. Which can help control the creation of a premetastatic niche, decrease the recurrence of breast cancer after surgery, and help extend the survival of breast cancer patients [146]. Additionally, nanovesicles derived from non-tumorigenic cells have been shown to have the same physiologic features, and they may be employed to deliver a siRNA that checks for cellular division in breast cancer patients [147].

6. Exosomes based alternative protocols

Kupffer cells, found in the human liver, also known as human phagocytic cells, hamper targeted medication delivery by exosomes and nanocarriers. Due to liver cell filtration, which decreases the bioavailability of the medicine at the tumor site, these delivery vehicles must be processed through the liver before they can reach the tumor. FourT1-derived exosomes (co-administered with DDL: DOPE liposome) were used with the DOPE liposome encapsulating medication DOTAP: DOPE liposome (DDL) to boost the entire medicinal bioavailability at the location [148]. By co-administering two different types of exosomes, for example, standard or hybrid or combination, the medicine has a higher bioavailability and gets beyond filtering of decoy exosomes. The decoy exosome is part of a systemic regulatory process that regulates the operation of the Kupffer cells, while the drug-loaded exosome can avoid being targeted by the Kupffer cells and delivers cargos straight to the breast cancer cells. The decoy system is the only one of the two decontamination methods that additionally include regulatory exosomes, which slows down the nanovector distribution in Kupffer cells, allowing them to deliver their therapeutic payloads more effectively [149].

High integrin specificity can be found in the exosomes in which treatment regimens incorporate exosomes as part of a synergistic treatment regimen. With the anti-cancerous medications, such as doxorubicin with small RNA interfering biomolecules loaded on these exosomes, having shown effectiveness and few or no side effects in animal models, the TNBC therapeutic effects were augmented with low or no toxicity in humans [150,151]. While it is true that immunotherapy and therapeutic immunization work synergistically, immunotherapy can also be defined as the ultimate step in cancer therapy advancement. In this procedure, a solution containing modified exosomes with targetable markers is applied to the cancer cells, triggering the endogenous immune cells to attack and kill the cancer cells [152]. When they encounter a breast cancer cell, exosomes first bind to the target cell using an antibody specific to the coreceptor. With recruitment and activation of cytotoxic T cells at the site, followed by the administration of an alternate anti-CD3, reduced adverse effects can be associated with chemotherapy treatments [153].

Cancer-associated endogenous and exogenous exosomes regulation

Exosomes are a vital part of the cells' overall homeostasis, acting as delivery vehicles for nuclear DNA, which helps maintain cell homeostasis. When the cytoplasm becomes overloaded with nuclear DNA, it causes ROS formation and cell cycle inhibition and/or apoptosis [154]. Exosomes, as a component of cell-to-cell communication, also contribute to paracrine signaling-mediated prevention of tumor growth in BC cells by suppressing angiogenesis [155]. Another aspect worth mentioning is that Li et al. discovered that miR-770 is capable of transferring to and carrying out changes in the RNA transcript levels of the *in-vitro* and *in-vivo* dox induced chemoresistance TNBC cells by means of targeting the stathmin1 gene [156]. Efforts made by different research groups to isolate exogenous exosomes obtained from camels' milk have proven successful in combating tumor growth and metastasis. The administration of camel milk-derived exosome prevents inflammatory response, parthenogenesis, and metastasis and, besides, enhanced apoptosis when supplied to MCF-7 cell lines [157]. It is not known whether there are any beneficial endogenous exosomes (microvesicles) in breast cancer regulation and reduction. To answer this question, a significant conceptual and experimental investigation is required. These investigations will assist us in finding macromolecules that may help with the treatment of cancer.

6.1. Challenges associated with exosome based nano drugs and alternative approaches

Although exosomes have some benefits as drug delivery vehicles, there are still obstacles to overcome in terms of scale production, standard purification techniques, cargo reloading, storage stability, and modifying costs for artificial exosomes [158]. The International Union of EV suggests storing EV in phosphate-buffered saline at a temperature of −80 °Celsius [159]. This is because EVs' biological and physical stability is typically only maintained for short periods. However, these circumstances are not ideal for storing anything, as they negatively affect energy usage, transportation, and, most significantly, clinical applications. The widespread consensus is that freeze-thaw will undermine the stability of EVs, for instance, by altering their form, function, particle size, and concentration [160]. Studies that involve freezing and thawing have indicated that glucose or potassium phosphate buffers are superior to phosphate buffer solution or phosphate buffer saline in terms of improving the stability of colloidal EVs [161]. pH near neutral inhibits aggregation and fusing of vesicles more than pH near acidic or alkaline values. In addition, the purification procedure requires a significant amount of time. It cannot be easy to separate exosomes from other EVs since some share size and density characteristics with exosomes. As a result, mass production and purification of exosomes are challenging [162].

The improved permeability and retention impact of the nano-drug delivery system (NDDS) on malignant tissue allows it to concentrate in tumors through blood arteries. NDDS, however, are cytotoxic and immunogenic [163]. Exosomes have significant benefits in treating cancer since they are natural medication carriers. First, somatic cells' exosomes, and vesicles, have high stability and excellent biocompatibility [164]. Secondly, exosomes can target certain organs or tissues, allowing for the accumulation of medications loaded onto them. Three methods exist for directing exosomes toward tumors: receptor-ligand interactions, antigen-antibody binding, and microenvironmental targeting.

Furthermore, we know the tumor-homing capabilities of exosomes produced by tumor cells. Exosomes released by one cell type are

Table 2
Studies that investigated the use of exosomes for cancer therapy [194].

Source of Exosomes	Disease Type	Drugs	Isolation Methods
Raw 264.7 macrophages (mouse)	Multi-drug resistant cancers (*in vitro* and mouse models)	Doxorubicin and paclitaxel	Low-speed centrifugation with precipitating reagents and purifying column
Primary dendritic cells (mouse)	Breast cancer (*in vitro* and mouse models)	VEGF siRNA	Differential centrifugation and UC
Neutrophils	Malignant glioma	Doxorubicin	Ultracentrifugation
MSC	Colorectal cancer	Doxorubicin	Ultracentrifugation
Milk (bovine)	Lung cancer (*in vitro* and mouse models)	Paclitaxel	Differential gradient centrifugation and UC
MCF-7 breast carcinoma cells (human)	Breast carcinoma (*in vitro*)	Doxorubicin	Differential gradient centrifugation
LNCaP and PC-3 prostate cancer cells (human)	Prostate cancer (*in vitro*)	Paclitaxel	Differential centrifugation
Lewis lung carcinoma cells (mouse)	Lung cancer (*in vitro*)	Methotrexate	Differential gradient centrifugation
Immature dendritic cells (mouse)	Breast cancer (*in vitro* and mouse models)	Doxorubicin	Ultrafiltration, UC, and gradient centrifugation
HeLa cervical cancer cells (human)	Cervical cancer (*in vitro*)	Dextran	Precipitating reagents (total exosome isolation kit, Invitrogen)
H22 hepatocarcinoma cells (mouse)	Hepatocarcinoma (*in vitro* and mouse models)	Cisplatin	Differential gradient centrifugation
Gastric cancer (SKBR-3)	Gastric cancer	Trastuzumab	Ultracentrifugation
EL-4 lymphoma cells (mouse)	Tumor-induced inflammation (*in vitro* and mouse models)	Curcumin	Sucrose gradient centrifugation
	Lung cancer (*in vitro*)	TRAIL	Filtration
Bone-marrow-derived MSCs (human)	Pleural mesothelioma (*in vitro*)	TRAIL	Filtration
	Renal cancer (*in vitro*)	TRAIL	Filtration
	Breast adenocarcinoma (*in vitro*)	TRAIL	Filtration
	Neuroblastoma (*in vitro*)	TRAIL	Filtration
B16-F10 melanoma cells (mouse)	Melanoma (*in vitro*)	Superparamagnetic iron oxide nanoparticles	Ultracentrifugation (UC)
B16BL6 melanoma cells (mouse)	Melanoma (*in vitro* and mouse models)	CpG DNA	Filtration and differential UC
ADR/MCF-7 breast carcinoma cells (human)	Breast carcinoma (*in vitro*)	Cisplatin	Differential gradient centrifugation
A549 lung carcinoma cells (human)	Lung carcinoma (*in vitro*, mouse models, and stage IV human patients)	Doxorubicin	Differential gradient centrifugation
M1 macrophage	Pancreatic cancer	Gemcitabine/Deferasirox	Ultracentrifugation
Human breast cancer cell line (EFM-192A)	Breast cancer	Trastuzumab	Ultracentrifugation

typically taken up by cells of the same kind. As a result, exosomes from tumors frequently assemble at tumor locations. Furthermore, the exosomal protein CD47 can attach to signal regulatory protein (SRP), which causes a "don't eat me" signal that delays the clearance of exosomes by the monocyte-macrophage system [165]. By injecting an exosome blocker before delivering modified exosomes, it is possible to prevent macrophage absorption of exosomes, stop exosomes from aggregating in large numbers in the spleen and liver, and boost the efficiency with which engineered exosomes reach their intended destination [166]. Based on these benefits, drug-loaded exosomes can considerably reduce tumor growth compared to free medications with nanocarrier-coated drugs (such as liposome-coated drugs) [167].

Researchers have done many experiments and created a wide variety of strategies to boost exosome production. Examples include isolating and loading exosomes as cells are grown on cell nano chips [168]. This technique resulted in a 50-fold increase in exosome synthesis compared to electroporation drug loading. Synthetic lipids used in extrusion boost the number of exosomes by a factor of 6–43 without compromising their ability to carry out their intended targets. Nanovesicles fashioned in the shape of exosomes are being developed with the express purpose of boosting output [169]. A huge quantity of nanovesicles imitating exosomes can be created by continuously expelling cells through nanosized vesicles or filter membranes. The productivity can be multiplied by 100. The discovery of synthetic chimeric exosomes offers another potential answer to the issue of inadequate exosome production [170,171].

In order to create artificial chimeric exosomes, membrane proteins from different cells are integrated into phospholipid bilayers. These exosomes can then acquire the diverse targeting abilities of both mother cells and can be manufactured in large quantities [172]. Example: chimeric exosomes produced by fusing transmembrane proteins mostly from red blood cell types and McF-7 cancer cells express CD47 protein and acquire the ability to evade clearance by macrophages from the body. While those mentioned above simulated exosomal nanovesicles differ from natural exosomes in certain ways, they may provide a promising route for future research and development to address a major flaw in exosomes [173].

The therapeutic efficacy of drug-loaded exosomes can be influenced by several factors, including the cell sources of exosomes, the isolation process of exosomes, the drug loading method, and the delivery route. All of these factors must be considered to select the most advantageous course of therapy.

Table 3
Lists clinical studies on the application of exosomes to cancer patients [195].

Status	Remarks	Reference
Completed	Use of exosomes as reliable biomarkers for the diagnosis of men with prostate cancer	NCT02702856
Unknown	Combination of computed tomography and exosomes for diagnosis of early stage lung cancer	NCT03542253
Active, not recruiting	Use of exosomes present in blood plasma to diagnose lung cancer in patients	NCT04529915
Unknown	Use of circulating exosomes for diagnosis of advanced gastric cancer	NCT01779583
Recruiting	New diagnostic method for colorectal cancer using exosomes	NCT04394572
Recruiting	Presence of exosomes in tumor-draining vein and their molecular profiling	NCT04939324
Recruiting	Use of plant exosome for delivery of curcumin in the treatment of colon cancer	NCT01294072

6.2. Clinical applications of exosomes

Exosomes' potential utility as cancer therapeutic has received interest due to the growing of preclinical and clinical research evidence demonstrating their function in cancer progression (see Table 2). Due to these characteristics, anticancer medicines incorporated into exosomes are more effective than the medications alone *in vitro* and clinical investigations [174].

Just like conventional pharmaceuticals, exosomes have multiple routes of administration [175]. The majority of exosomes (78%) were injected intravenously (IV), with intraperitoneal (IP) injections being the second most common mode of administration for *in vivo* dispersion investigation. Exosomes seldom enter the body through intranasal, hock, subcutaneous, or retroorbital sinus pathways. The tissues with the greatest accumulation of exosomal volume following intravenous injection are the liver, lung, spleen, and kidney.

According to a recent experiment, Exosomes from lung cancer cells were shown to include the essential signaling networks Hippo, Rap1, and Wnt [176]. Another study found that the PRPS2 protein can cause cisplatin resistance and is found in high concentrations in exosomes from non-small cell lung cancer. Exosomes containing PRPS2 can also cause macrophages with a bad prognosis to polarize M2 [177]. Patients with breast cancer have high quantities of the exosomes mirNA-3362, mirNA-146A, and mirNA-1290, which are involved in lymph node metastases and clinical staging. QSOX1 is less prevalent in plasma exosomes in colorectal cancer patients, which can be exploited as a diagnostic indicator [178]. These findings show that exosomes can be used to assess cancer patients' prognoses (Table 3).

7. Conclusions and future prospective

Cancer is an unregulated cell growth disorder induced by environmental and genetic alterations. Due to immunological evasion, metastasis, and tolerance of cancer cells towards medicines, people with cancer still have low survival rates despite multiple treatments. It is rather easy to determine the exosome's composition, function, isolation, and characterization based on decades of research. Several studies have been done on exosomes and exosomes could be employed as carriers for the administration of medication. As a new type of medication carrier, exosomes in the field of cancer therapy have garnered a lot of attention. New targeted cancer therapy utilizing nano-sized drug carriers is the beginning to show promise as a technique to compensate for conventional cancer therapy's inherent limitations. Recently, researchers discovered that as a waste disposal mechanism, the exosomes are a natural nanocarrier with tremendous advantages for drug administration because of their physiologically targeted and intrinsic capabilities to target breast cancer cells. These bioengineered exosomes are isolated and have been enhanced to increase their capability of delivering a diverse range of pharmaceuticals, natural plant extracts, proteins, and nucleic acid. Exosomes used in BC therapy give a better bioavailability, efficacy, and efficiency than non-delivered exosomes. Despite this, as a therapeutic delivery mechanism for breast cancer, the use of exosomes has multiple problems. There is still more work to be done. Researchers know less about the importance of extracellular cargo and tumor surface indicators in tumor formation than is currently known.

It has been demonstrated that exosomes are nanosized lipid-based small EVs that can be used as a diagnostic tool and as a transport vehicle for various bioactives such as small molecules, proteins, DNAs and RNAs such as mRNAs, miRNAs, etc., to the tumor microenvironment and which can modulate cellular communication. Additionally, surface functionalized exosomes offer a novel strategy to ensure their specific accumulation at the site of interest, minimizing off-target effects on the body and facilitating more effective treatment of various cancers including breast cancer.

Furthermore, to use exosomes as a therapeutic delivery system, it is essential to identify and eliminate tumor-associated elements before administering exosomes as a pharmaceutical delivery system, particularly for *in vivo* research. Furthermore, a limited option exists for the effective load of therapeutic cargos inside exosomes, and to improve loading efficiency, the creation of different loading techniques should be a focus of future research. Though this usage of exosomes for a nanotherapeutic vehicle is impressive and intriguing, it aligns with previous developments that focused on exosomes as nanotherapeutics. The logical conclusion to draw from this finding is that, soon, exosomes will be looked at as a suitable alternative to a nano- drug carrier for *in vivo* experiments and human studies.

References

[1] M.I. Khan, M.I. Hossain, M.K. Hossain, M. Rubel, K. Hossain, A. Mahfuz, M.I. Anik, Recent Progress in Nanostructured Smart Drug Delivery Systems for Cancer Therapy: A Review, ACS Appl. Bio. Mater. 5 (2022) 971–1012.

[2] M.I. Khan, F. Batool, R. Ali, Q.u.A. Zahra, W. Wang, S. Li, G. Wang, L. Liu, S.U. Khan, M. Mansoor, M. Bilal, W. Ding, A. Kazmi, F. Li, B. Qiu, Tailoring radiotherapies and nanotechnology for targeted treatment of solid tumors, Coord. Chem. Rev. 472 (2022), 214757, https://doi.org/10.1016/j.ccr.2022.214757.

[3] Y. Zhao, M. Bilal, M. Qindeel, M.I. Khan, K. Dhama, H. Iqbal, Nanotechnology-based immunotherapies to combat cancer metastasis, Mol. Biol. Rep. 48 (2021) 6563–6580.

[4] P.T. Kutoka, T.A. Seidu, V. Baye, A.M. Khamis, C.T. qizi Omonova, B. Wang, Current Nano-Strategies to Target Tumor Microenvironment (TME) to Improve Anti-Tumor efficiency, OpenNano (2022), 100041.

[5] A. Nayak, N.M. Warrier, P. Kumar, Cancer Stem Cells and the Tumor Microenvironment: Targeting the Critical Crosstalk through Nanocarrier Systems, Stem Cell Rev. Rep. (2022) 1–25.

[6] N. Pandey, P. Anastasiadis, C.P. Carney, P.P. Kanvinde, G.F. Woodworth, J.A. Winkles, A.J. Kim, Nanotherapeutic treatment of the invasive glioblastoma tumor microenvironment, Adv. Drug. Deliv. Rev. (2022), 114415.

[7] S.U. Khan, M.U. Khan, M.I. Khan, F.A. Abraham, A. Khan, S. Gao, M. Bilal, F. Li, Role of circular RNAs in disease progression and diagnosis of cancers: An overview of recent advanced insights, Int. J. Biol. Macromol. (2022), https://doi.org/10.1016/j.ijbiomac.2022.08.085.

[8] M. Mahmoudi, A. Hoseinzadeh, Z. Rezaieyazdi, J.T. Afshari, A. Mahmoudi, S. Heydari, Cross Talk between Mesenchymal Stem/Stromal Cells and Innate Immunocytes Concerning Lupus Disease, Stem Cell Rev. Rep. (2022) 1–16.

[9] C. Zhao, H. Deng, X. Chen, Harnessing Immune Response Using Reactive Oxygen Species-Generating/Eliminating Inorganic Biomaterials for Disease Treatment, Adv. Drug. Deliv. Rev. (2022), 114456.

[10] Q. Wu, L. You, E. Nepovimova, Z. Heger, W. Wu, K. Kuca, V. Adam, Hypoxia-inducible factors: master regulators of hypoxic tumor immune escape, J. Hematol. Oncol. 15 (2022) 1–18.

[11] J. Liu, T. Chen, S. Li, W. Liu, P. Wang, G. Shang, Targeting matrix metalloproteinases by E3 ubiquitin ligases as a way to regulate the tumor microenvironment for cancer therapy, Seminars in Cancer Biology, Elsevier (2022).

[12] S.Z. Alshawwa, A.A. Kassem, R.M. Farid, S.K. Mostafa, G.S. Labib, Nanocarrier Drug Delivery Systems: Characterization, Limitations, Future Perspectives and Implementation of Artificial Intelligence, Pharmaceutics 14 (2022) 883.

[13] M. Nehra, U.T. Uthappa, V. Kumar, R. Kumar, C. Dixit, N. Dilbaghi, Y.K. Mishra, S. Kumar, A. Kaushik, Nanobiotechnology-assisted therapies to manage brain cancer in personalized manner, J. Control Release 338 (2021) 224–243, https://doi.org/10.1016/j.jconrel.2021.08.027.

[14] Q.U.A. Zahra, Z. Luo, R. Ali, M.I. Khan, F. Li, B. Qiu, Advances in gold nanoparticles-based colorimetric aptasensors for the detection of antibiotics: An overview of the past decade, Nanomaterials 11 (2021) 840.

[15] Y. Mao, M. Qamar, S.A. Qamar, M.I. Khan, M. Bilal, H.M. Iqbal, Insight of nanomedicine strategies for a targeted delivery of nanotherapeutic cues to cope with the resistant types of cancer stem cells, J. Drug Delivery Sci. Technol. 64 (2021), 102681.

[16] Z. Chen, R.K. Kankala, Z. Yang, W. Li, S. Xie, H. Li, A.-.Z. Chen, L. Zou, Antibody-based drug delivery systems for cancer therapy: Mechanisms, challenges, and prospects, Theranostics 12 (2022) 3719.

[17] M.I. Khan, Q.u.A. Zahra, F. Batool, F. Kalsoom, S. Gao, R. Ali, W. Wang, A. Kazmi, L. Lianliang, G. Wang, M. Bilal, Trends in Nanotechnology to improve therapeutic efficacy across special structures, OpenNano 7 (2022), https://doi.org/10.1016/j.onano.2022.100049.

[18] R. Kumar, K.R. Aadil, K. Mondal, Y.K. Mishra, D. Oupicky, S. Ramakrishna, A. Kaushik, Neurodegenerative disorders management: state-of-art and prospects of nano-biotechnology, Crit. Rev. Biotechnol. (2021) 1–33, https://doi.org/10.1080/07388551.2021.1993126.

[19] A.K. Dubey, V. Kumar Gupta, M. Kujawska, G. Orive, N.-.Y. Kim, C.-z. Li, Y. Kumar Mishra, A. Kaushik, Exploring nano-enabled CRISPR-Cas-powered strategies for efficient diagnostics and treatment of infectious diseases, J. Nanostruct. Chem. (2022) 1–32.

[20] J.-.J. Xu, W.-.C. Zhang, Y.-.W. Guo, X.-.Y. Chen, Y.-.N. Zhang, Metal nanoparticles as a promising technology in targeted cancer treatment, Drug Deliv. 29 (2022) 664–678.

[21] Z. Wang, H. Mo, Z. He, A. Chen, P. Cheng, Extracellular vesicles as an emerging drug delivery system for cancer treatment: Current strategies and recent advances, Biomed. Pharmacother. 153 (2022), 113480.

[22] J.L. Hood, S.A. Wickline, A systematic approach to exosome-based translational nanomedicine, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 4 (2012) 458–467, https://doi.org/10.1002/wnan.1174.

[23] H. Cao, M. Yi, H. Wei, S. Zhang, Construction of Folate-Conjugated and pH-Responsive Cell Membrane Mimetic Mixed Micelles for Desirable DOX Release and Enhanced Tumor-Cellular Target, Langmuir (2022).

[24] G. Forte, V. Giuffrida, A. Scuderi, M. Pazzaglia, Future Treatment of Neuropathic Pain in Spinal Cord Injury: The Challenges of Nanomedicine, Supplements or Opportunities? Biomedicines 10 (2022) 1373.

[25] M.U. Saeed, N. Hussain, I. Zulfiqar, A. Raza, M.A. Ghauri, M. Bilal, Tumor cell dormancy: Molecular mechanisms, and pharmacological approaches to target dormant cells for countering tumor, J. Drug Delivery Sci. Technol. (2022), 103645.

[26] J.L. Hood, Post isolation modification of exosomes for nanomedicine applications, Nanomedicine (Lond) 11 (2016) 1745–1756, https://doi.org/10.2217/nnm-2016-0102.

[27] M. Khan, F. Batool, F. Kalsoom, R. Ali, F. Li, J. Wang, Z. Haider, M. Bilal, M. Rajput, A. Kazmi, New insights on unique therapeutic potentialities of prostacyclin and prostacyclin synthase, Mater. Today Chem. 16 (2020), 100258, https://doi.org/10.1016/j.mtchem.2020.100258.

[28] R.M. Johnstone, M. Adam, J. Hammond, L. Orr, C. Turbide, Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes), J. Biol. Chem. 262 (1987) 9412–9420.

[29] G. Raposo, H.W. Nijman, W. Stoorvogel, R. Liejendekker, C.V. Harding, C. Melief, H.J. Geuze, B lymphocytes secrete antigen-presenting vesicles, J. Exp. Med. 183 (1996) 1161–1172.

[30] H. Valadi, K. Ekström, A. Bossios, M. Sjöstrand, J.J. Lee, J.O. Lötvall, Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells, Nat. Cell Biol. 9 (2007) 654–659.

[31] C. Théry, K.W. Witwer, E. Aikawa, M.J. Alcaraz, J.D. Anderson, R. Andriantsitohaina, A. Antoniou, T. Arab, F. Archer, G.K. Atkin-Smith, Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines, J. Extracell. Vesicles 7 (2018), 1535750.

[32] C. He, S. Zheng, Y. Luo, B. Wang, Exosome theranostics: biology and translational medicine, Theranostics 8 (2018) 237.

[33] N.P. Hessvik, A. Llorente, Current knowledge on exosome biogenesis and release, Cell. Mol. Life Sci. 75 (2018) 193–208.

[34] S. Heydarzadeh, S.K. Kia, M. Zarkesh, S. Pakizehkar, S. Hosseinzadeh, M. Hedayati, The Cross-Talk between Polyphenols and the Target Enzymes Related to Oxidative Stress-Induced Thyroid Cancer, Oxid. Med. Cell. Long. 2022 (2022).

[35] C.E. DeSantis, J. Ma, M.M. Gaudet, L.A. Newman, K.D. Miller, A. Goding Sauer, A. Jemal, R.L. Siegel, Breast cancer statistics, 2019, CA Cancer J. Clin. 69 (2019) 438–451.

[36] L. Wilkinson, T. Gathani, Understanding breast cancer as a global health concern, Br. J. Radiol. 95 (2022), 20211033.

[37] P. Samadi, S. Saki, F.K. Dermani, M. Pourjafar, M. Saidijam, Emerging ways to treat breast cancer: will promises be met? Cell. Oncol. 41 (2018) 605–621.

[38] N. Dastmalchi, R. Safaralizadeh, B. Baradaran, M. Hosseinpourfeizi, A. Baghbanzadeh, An update review of deregulated tumor suppressive microRNAs and their contribution in various molecular subtypes of breast cancer, Gene 729 (2020), 144301.

[39] C.Y. Goh, C. Wyse, M. Ho, E. O'Beirne, J. Howard, S. Lindsay, P. Kelly, M. Higgins, A. McCann, Exosomes in triple negative breast cancer: Garbage disposals or Trojan horses? Cancer Lett. 473 (2020) 90–97.

[40] H. Yao, G. He, S. Yan, C. Chen, L. Song, T.J. Rosol, X. Deng, Triple-negative breast cancer: is there a treatment on the horizon? OncoTargets Ther. 8 (2017) 1913.

[41] L.E. Pace, N.L. Keating, A systematic assessment of benefits and risks to guide breast cancer screening decisions, JAMA 311 (2014) 1327–1335.

[42] K.D. Miller, L. Nogueira, A.B. Mariotto, J.H. Rowland, K.R. Yabroff, C.M. Alfano, A. Jemal, J.L. Kramer, R.L. Siegel, Cancer treatment and survivorship statistics, 2019, CA Cancer J. Clin. 69 (2019) 363–385.

[43] E. Chen, H. Abu-Sbeih, S. Thirumurthi, N. Mallepally, S. Khurana, D. Wei, M. Altan, V.K. Morris, D. Tan, C.H. Barcenas, Clinical characteristics of colitis induced by taxane-based chemotherapy, Ann. Gastroenterol. 33 (2020) 59.
[44] N.R. Palukuri, R.P. Yedla, S.C. Bala, S.P. Kuruva, R. Chennamaneni, M.L. Konatam, S. Gundeti, Incidence of febrile neutropenia with commonly used chemotherapy regimen in localized breast cancer, South Asian J. Cancer 9 (2020) 4.
[45] N. Esfandiari, M.K. Arzanani, M. Soleimani, M. Kohi-Habibi, W.E. Svendsen, A new application of plant virus nanoparticles as drug delivery in breast cancer, Tumour Biol. 37 (2016) 1229–1236.
[46] D. Bhavsar, J. Gajjar, K. Sawant, Formulation and development of smart pH responsive mesoporous silica nanoparticles for breast cancer targeted delivery of anastrozole: In vitro and in vivo characterizations, Microporous Mesoporous Mater. 279 (2019) 107–116.
[47] P. Kulkarni, D. Rawtani, Application of Box-Behnken Design in the Preparation, Optimization, and In Vitro Evaluation of Self-assembly–based Tamoxifen-and Doxorubicin-loaded and Dual Drug–loaded Niosomes for Combinatorial Breast Cancer Treatment, J. Pharm. Sci. 108 (2019) 2643–2653.
[48] P.Y. Liyanage, S.D. Hettiarachchi, Y. Zhou, A. Ouhtit, E.S. Seven, C.Y. Oztan, E. Celik, R.M. Leblanc, Nanoparticle-mediated targeted drug delivery for breast cancer treatment, Biochim. Biophys. Acta 1871 (2019) 419–433.
[49] L. Martínez-Jothar, N. Beztsinna, C.F. van Nostrum, W.E. Hennink, S. Oliveira, Selective cytotoxicity to HER2 positive breast cancer cells by saporin-loaded nanobody-targeted polymeric nanoparticles in combination with photochemical internalization, Mol. Pharmaceut. 16 (2019) 1633–1647.
[50] A. Schneeweiss, V. Moebus, H. Tesch, C. Hanusch, C. Denkert, K. Luebbe, J. Huober, P. Klare, S. Kuemmel, M. Untch, Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto—GBG 84): A randomised phase III trial, Eur. J. Cancer 106 (2019) 181–192.
[51] Y. Zhao, D.Y. Alakhova, X. Zhao, V. Band, E.V. Batrakova, A.V. Kabanov, Eradication of cancer stem cells in triple negative breast cancer using doxorubicin/pluronic polymeric micelles, Nanomed. Nanotechnol. Biol. Med. 24 (2020), 102124.
[52] U.S. Gaharwar, R. Meena, P. Rajamani, Biodistribution, clearance and morphological alterations of intravenously administered iron oxide nanoparticles in male wistar rats, Int. J. Nanomed. 14 (2019) 9677.
[53] D.-.Q. Ng, Y. Chu, S.-.W. Tan, S.-.L. Wang, Y.-.P. Lin, C.-.H. Chu, Y.-.L. Soo, Y.-.F. Song, P.-.J. Chen, In vivo evidence of intestinal lead dissolution from lead dioxide (PbO 2) nanoparticles and resulting bioaccumulation and toxicity in medaka fish, Environ. Sci.: Nano 6 (2019) 580–591.
[54] O. Lyass, B. Uziely, R. Ben-Yosef, D. Tzemach, N.I. Heshing, M. Lotem, G. Brufman, A. Gabizon, Correlation of toxicity with pharmacokinetics of pegylated liposomal doxorubicin (Doxil) in metastatic breast carcinoma, Cancer: Interdisciplinary International Journal of the American Cancer Society 89 (2000) 1037–1047.
[55] L. Ansari, F. Shiehzadeh, Z. Taherzadeh, S. Nikoofal-Sahlabadi, A. Momtazi-Borojeni, A. Sahebkar, S. Eslami, The most prevalent side effects of pegylated liposomal doxorubicin monotherapy in women with metastatic breast cancer: a systematic review of clinical trials, Cancer Gene Ther. 24 (2017) 189–193.
[56] Y. Fan, Z. Li, Y. He, Exosomes in the Pathogenesis, Progression, and Treatment of Osteoarthritis, Bioengineering 9 (2022) 99.
[57] M.-.H. Chan, Z.-.X. Chang, C.-Y.F. Huang, L.J. Lee, R.-.S. Liu, M. Hsiao, Integrated therapy platform of exosomal system: hybrid inorganic/organic nanoparticles with exosomes for cancer treatment, Nanoscale Horiz (2022).
[58] J.J. Lai, Z.L. Chau, S.Y. Chen, J.J. Hill, K.V. Korpany, N.W. Liang, L.H. Lin, Y.H. Lin, J.K. Liu, Y.C. Liu, Exosome Processing and Characterization Approaches for Research and Technology Development, Adv. Sci. (2022), 2103222.
[59] G. van Niel, D.R. Carter, A. Clayton, D.W. Lambert, G. Raposo, P. Vader, Challenges and directions in studying cell–cell communication by extracellular vesicles, Nat. Rev. Mol. Cell Biol. (2022) 1–14.
[60] Y. Guo, Z. Gil, The Role of Extracellular Vesicles in Cancer–Nerve Crosstalk of the Peripheral Nervous System, Cells 11 (2022) 1294.
[61] D. Ferreira, J.N. Moreira, L.R. Rodrigues, New advances in exosome-based targeted drug delivery systems, Crit. Rev. Oncol. Hematol. (2022), 103628.
[62] M. Imanbekova, S. Suarasan, Y. Lu, S. Jurchuk, S. Wachsmann-Hogiu, Recent advances in optical label-free characterization of extracellular vesicles, Nanophotonics (2022).
[63] R. Xu, D.W. Greening, H.-.J. Zhu, N. Takahashi, R.J. Simpson, Extracellular vesicle isolation and characterization: toward clinical application, J. Clin. Invest. 126 (2016) 1152–1162.
[64] L. Mashouri, H. Yousefi, A.R. Aref, F. Molaei, S.K. Alahari, Exosomes: composition, biogenesis, and mechanisms in cancer metastasis and drug resistance, Mol. Cancer 18 (2019) 1–14.
[65] S.K. Limoni, M.F. Moghadam, S.M. Moazzeni, H. Gomari, F. Salimi, Engineered exosomes for targeted transfer of siRNA to HER2 positive breast cancer cells, Appl. Biochem. Biotechnol. 187 (2019) 352–364.
[66] M. Mughees, K. Kumar, S. Wajid, Exosome vesicle as a nano-therapeutic carrier for breast cancer, J. Drug Targeting 29 (2021) 121–130.
[67] C. Harding, P. Stahl, Transferrin recycling in reticulocytes: pH and iron are important determinants of ligand binding and processing, Biochem. Biophys. Res. Commun. 113 (1983) 650–658.
[68] M. Tschuschke, I. Kocherova, A. Bryja, P. Mozdziak, A. Angelova Volponi, K. Janowicz, R. Sibiak, H. Piotrowska-Kempisty, D. Iżycki, D. Bukowska, Inclusion biogenesis, methods of isolation and clinical application of human cellular exosomes, J. Clin. Med. 9 (2020) 436.
[69] T.L. Whiteside, Tumor-derived exosomes and their role in cancer progression, Adv. Clin. Chem. 74 (2016) 103–141.
[70] J.H. Hurley, ESCRT s are everywhere, EMBO J. 34 (2015) 2398–2407.
[71] J. Kowal, M. Tkach, C. Théry, Biogenesis and secretion of exosomes, Curr. Opin. Cell Biol. 29 (2014) 116–125.
[72] M.P. Bebelman, M.J. Smit, D.M. Pegtel, S.R. Baglio, Biogenesis and function of extracellular vesicles in cancer, Pharmacol. Ther. 188 (2018) 1–11.
[73] L. Gangoda, M. Liem, C.S. Ang, S. Keerthikumar, C.G. Adda, B.S. Parker, S. Mathivanan, Proteomic profiling of exosomes secreted by breast cancer cells with varying metastatic potential, Proteomics 17 (2017), 1600370.
[74] K. Vicikova, E. Petrovcikova, P. Manka, J. Drach, H. Stockinger, V. Leksa, Serum and urinary levels of CD222 in cancer: origin and diagnostic value, Neoplasma 65 (2018) 762–768.
[75] S.N. Tamkovich, N.V. Yunusova, E. Tugutova, A.K. Somov, K.V. Proskura, L.A. Kolomiets, M.N. Stakheeva, A.E. Grigor'eva, P.P. Laktionov, I.V. Kondakova, Protease cargo in circulating exosomes of breast cancer and ovarian cancer patients, Asian Pacific journal of cancer prevention: APJCP 20 (2019) 255.
[76] M. Mughees, H. Chugh, S. Wajid, Vesicular trafficking–related proteins as the potential therapeutic target for breast cancer, Protoplasma 257 (2020) 345–352.
[77] S. Adlat, F. Hayel, Y. Chen, R.K. Sah, Z.M. Oo, M. Al-Azab, M.Z.Z. Myint, N. Bahadar, F.B. Bah, N. Mi, Heterozygous loss of Dip2B enhances tumor growth and metastasis by altering immune microenvironment, Int. Immunopharmacol. 105 (2022), 108559.
[78] S. Ravi, A.M. Alencar Jr, J. Arakelyan, W. Xu, R. Stauber, C.-C.I. Wang, R. Papyan, N. Ghazaryan, R.M. Pereira, An Update to Hallmarks of Cancer, Cureus 14 (2022).
[79] Y. Zhou, S. Bréchard, Neutrophil Extracellular Vesicles: A Delicate Balance between Pro-Inflammatory Responses and Anti-Inflammatory Therapies, Cells 11 (2022) 3318.
[80] W. Zhang, Z. Jiang, D. Tang, The value of exosome-derived noncoding RNAs in colorectal cancer proliferation, metastasis, and clinical applications, Clin. Transl. Oncol. (2022) 1–14.
[81] X. Wang, W. Zhong, J. Bu, Y. Li, R. Li, R. Nie, C. Xiao, K. Ma, X. Huang, Y. Li, Exosomal protein CD82 as a diagnostic biomarker for precision medicine for breast cancer, Mol. Carcinog. 58 (2019) 674–685.
[82] M. Kumari, A. Anji, Small but Mighty—Exosomes, Novel Intercellular Messengers in Neurodegeneration, Biology 11 (2022) 413.
[83] M.P. Nikolova, E.M. Kumar, M.S. Chavali, Updates on Responsive Drug Delivery Based on Liposome Vehicles for Cancer Treatment, Pharmaceutics 14 (2022) 2195.
[84] A.M. Demell, Developing Viruses for Gene Editing to Study Virus-Specific Molecular Interactions in Nicotiana Species, 2019.
[85] S.T. Chuang, B. Conklin, J.B. Stein, G. Pan, K.-.B. Lee, Nanotechnology-enabled immunoengineering approaches to advance therapeutic applications, Nano Converg. 9 (2022) 1–31.
[86] Y.L. Tai, K.C. Chen, J.T. Hsieh, T.L. Shen, Exosomes in cancer development and clinical applications, Cancer Sci. 109 (2018) 2364–2374.

[87] H.A. Adeola, I.O. Bello, R.T. Aruleba, N.M. Francisco, T.A. Adekiya, A.O. Adefuye, P.C. Ikwegbue, F. Musaigwa, The Practicality of the Use of Liquid Biopsy in Early Diagnosis and Treatment Monitoring of Oral Cancer in Resource-Limited Settings, Cancers 14 (2022) 1139.
[88] X. Yang, N. Wu, MicroRNAs and exosomal microRNAs may be possible targets to investigate in gestational diabetes mellitus, Diabetes Metab. Syndr. Obes. 15 (2022) 321.
[89] L. Chu, X. Shu, Y. Huang, T. Chu, M. Ge, Q. Lu, Sex Steroid Hormones in Urinary Exosomes as Biomarkers for the Prediction of Prostate Cancer, Clin. Chim. Acta (2022).
[90] B. Rath, A. Plangger, L. Klameth, M. Hochmair, E. Ulsperger, C. Neumayer, G. Hamilton, Small cell lung cancer: circulating tumor cell lines and expression of mediators of angiogenesis and coagulation, (2022).
[91] M.C. Klymiuk, N. Balz, M.I. Elashry, M. Heimann, S. Wenisch, S. Arnhold, Exosomes isolation and identification from equine mesenchymal stem cells, BMC Vet. Res. 15 (2019) 1–9.
[92] T.N. Lamichhane, R.S. Raiker, S.M. Jay, Exogenous DNA loading into extracellular vesicles via electroporation is size-dependent and enables limited gene delivery, Mol. Pharmaceutics 12 (2015) 3650–3657.
[93] R.K. Oskuee, M.R. Jaafari, Delivery of LNA-antimiR-142-3p by mesenchymal stem cells-derived exosomes to breast cancer stem cells reduces tumorigenicity, Stem Cell Rev. Rep. 16 (2020) 541–556.
[94] Y. Si, S. Kim, E. Zhang, Y. Tang, R. Jaskula-Sztul, J.M. Markert, H. Chen, L. Zhou, X. Liu, Targeted exosomes for drug delivery: biomanufacturing, surface tagging, and validation, Biotechnol. J. 15 (2020), 1900163.
[95] M. Pal, T. Muinao, H.P.D. Boruah, N. Mahindroo, Current advances in prognostic and diagnostic biomarkers for solid cancers: Detection techniques and future challenges, Biomed. Pharmacother. 146 (2022), 112488.
[96] V. Subramanian, R. Bairwa, P. Sharma, B. Bissa, Cancer cell's internal and external warriors: Autophagosomes and exosomes, Life Sci. (2022), 120552.
[97] A. Adib, R. Sahu, S. Mohta, R.E. Pollock, L. Casadei, Cancer-Derived Extracellular Vesicles: Their Role in Sarcoma, Life 12 (2022) 481.
[98] G. Kara, G.A. Calin, B. Ozpolat, RNAi-based therapeutics and tumor targeted delivery in cancer, Adv. Drug. Deliv. Rev. (2022), 114113.
[99] L. Chen, L. Wang, L. Zhu, Z. Xu, Y. Liu, Z. Li, L. Feng, Exosomes as drug carriers in anti-cancer therapy, Front. Cell Dev. Biol. (2022) 34.
[100] A. Papaefthymiou, A. Doukatas, M. Galanopoulos, Pancreatic cancer and oligonucleotide therapy: exploring novel therapeutic options and targeting chemoresistance, Clin. Res. Hepatol. Gastroenterol. (2022), 101911.
[101] M. Han, J. Hu, P. Lu, H. Cao, C. Yu, X. Li, X. Qian, X. Yang, Y. Yang, N. Han, Exosome-transmitted miR-567 reverses trastuzumab resistance by inhibiting ATG5 in breast cancer, Cell Death. Dis. 11 (2020) 1–15.
[102] J. Du, J. Fan, C. Dong, H. Li, B. Ma, Inhibition effect of exosomes-mediated Let-7a on the development and metastasis of triple negative breast cancer by down-regulating the expression of c-Myc, Eur. Rev. Med. Pharmacol. Sci. 23 (2019) 5301–5314.
[103] S.M. Kim, Y. Yang, S.J. Oh, Y. Hong, M. Seo, M. Jang, Cancer-derived exosomes as a delivery platform of CRISPR/Cas9 confer cancer cell tropism-dependent targeting, J. Controlled Release 266 (2017) 8–16.
[104] A. Mukherjee, B. Bisht, S. Dutta, M.K. Paul, Current advances in the use of exosomes, liposomes, and bioengineered hybrid nanovesicles in cancer detection and therapy, Acta Pharmacol. Sin. (2022) 1–18.
[105] D.I. Viswanath, H.-.C. Liu, D.P. Huston, C.Y.X. Chua, A. Grattoni, Emerging biomaterial-based strategies for personalized therapeutic in situ cancer vaccines, Biomaterials 280 (2022), 121297.
[106] M.-.H. Chan, Z.-.X. Chang, C.-Y.F. Huang, L.J. Lee, R.-.S. Liu, M. Hsiao, Integrated therapy platform of exosomal system: Hybrid inorganic/organic nanoparticles with exosomes for cancer treatment, Nanoscale Horiz 7 (2022) 352–367.
[107] A. Vahabi, J. Rezaie, M. Hassanpour, Y. Panahi, M. Nemati, Y. Rasmi, M. Nemati, Tumor Cells-derived Exosomal CircRNAs: novel cancer drivers, molecular mechanisms, and clinical opportunities, Biochem. Pharmacol. (2022), 115038.
[108] M. Entezari, M. Ghanbarirad, A. Taheriazam, M. Sadrkhanloo, A. Zabolian, M.A.S.B. Goharrizi, K. Hushmandi, A.R. Aref, M. Ashrafizadeh, A. Zarrabi, Long non-coding RNAs and exosomal lncRNAs: Potential functions in lung cancer progression, drug resistance and tumor microenvironment remodeling, Biomed. Pharmacother. 150 (2022), 112963.
[109] H. Nie, X. Xie, D. Zhang, Y. Zhou, B. Li, F. Li, F. Li, Y. Cheng, H. Mei, H. Meng, Use of lung-specific exosomes for miRNA-126 delivery in non-small cell lung cancer, Nanoscale 12 (2020) 877–887.
[110] J. Zhao, J. Ruan, G. Lv, Q. Shan, Z. Fan, H. Wang, Y. Du, L. Ling, Cell membrane-based biomimetic nanosystems for advanced drug delivery in cancer therapy: A comprehensive review, Colloids Surf. B (2022), 112503.
[111] F. Zhang, J. Guo, Z. Zhang, Y. Qian, G. Wang, M. Duan, H. Zhao, Z. Yang, X. Jiang, Mesenchymal stem cell-derived exosome: A tumor regulator and carrier for targeted tumor therapy, Cancer Lett. 526 (2022) 29–40.
[112] W.A. Alasmari, A. Abdelfattah-Hassan, H.M. El-Ghazali, S.A. Abdo, D. Ibrahim, N.A. ElSawy, E.S. El-Shetry, A.A. Saleh, M.A. Abourehab, H. Mahfouz, Exosomes Derived from BM-MSCs Mitigate the Development of Chronic Kidney Damage Post-Menopause via Interfering with Fibrosis and Apoptosis, Biomolecules 12 (2022) 663.
[113] S.Janho Dit Hreich, J. Benzaquen, P. Hofman, V. Vouret-Craviari, To inhibit or to boost the ATP/P2RX7 pathway to fight cancer-that is the question, Purinergic Signal 17 (2021) 619–631, https://doi.org/10.1007/s11302-021-09811-9.
[114] Z. Naseri, R.K. Oskuee, M.R. Jaafari, M.F. Moghadam, Exosome-mediated delivery of functionally active miRNA-142-3p inhibitor reduces tumorigenicity of breast cancer in vitro and in vivo, Int. J. Nanomed. 13 (2018) 7727.
[115] G. Almanza, J.J. Rodvold, B. Tsui, K. Jepsen, H. Carter, M. Zanetti, Extracellular vesicles produced in B cells deliver tumor suppressor miR-335 to breast cancer cells disrupting oncogenic programming in vitro and in vivo, Sci. Rep. 8 (2018) 1–10.
[116] M.J. Haney, Y. Zhao, Y.S. Jin, S.M. Li, J.R. Bago, N.L. Klyachko, A.V. Kabanov, E.V. Batrakova, Macrophage-derived extracellular vesicles as drug delivery systems for triple negative breast cancer (TNBC) therapy, J. Neuroimmun. Pharmacol. 15 (2020) 487–500.
[117] K.-.L. Li, H.-.Y. Huang, H. Ren, X.-.L. Yang, Role of exosomes in the pathogenesis of inflammation in Parkinson's disease, Neural. Regen. Res. 17 (2022) 1898.
[118] S. Salarpour, M. Barani, A. Pardakhty, M. Khatami, N.P.S. Chauhan, The Application of Exosomes and Exosome-nanoparticle in Treating Brain Disorders, J. Mol. Liq. (2022), 118549.
[119] A.R. Panigrahi, L. Srinivas, J. Panda, Exosomes: Insights and therapeutic applications in cancer, Transl. Oncol. 21 (2022), 101439.
[120] S. Pancholi, A. Tripathi, A. Bhan, M.M. Acharya, P. Pillai, Emerging Concepts on the Role of Extracellular Vesicles and Its Cargo Contents in Glioblastoma-Microglial Crosstalk, Mol. Neurobiol. (2022) 1–16.
[121] S. Kalimuthu, P. Gangadaran, R.L. Rajendran, L. Zhu, J.M. Oh, H.W. Lee, A. Gopal, S.H. Baek, S.Y. Jeong, S.-.W. Lee, A new approach for loading anticancer drugs into mesenchymal stem cell-derived exosome mimetics for cancer therapy, Front. Pharmacol. 9 (2018) 1116.
[122] H. Gomari, M.F. Moghadam, M. Soleimani, Targeted cancer therapy using engineered exosome as a natural drug delivery vehicle, Onco. Targets Ther. 11 (2018) 5753.
[123] B.T. Kreger, E.R. Johansen, R.A. Cerione, M.A. Antonyak, The enrichment of survivin in exosomes from breast cancer cells treated with paclitaxel promotes cell survival and chemoresistance, Cancers 8 (2016) 111.
[124] C. Melzer, V. Rehn, Y. Yang, H. Bähre, J. von der Ohe, R. Hass, Taxol-loaded MSC-derived exosomes provide a therapeutic vehicle to target metastatic breast cancer and other carcinoma cells, Cancers 11 (2019) 798.
[125] M. Barok, M. Puhka, G. Vereb, J. Szollosi, J. Isola, H. Joensuu, Cancer-derived exosomes from HER2-positive cancer cells carry trastuzumab-emtansine into cancer cells leading to growth inhibition and caspase activation, BMC Cancer 18 (2018) 1–12.
[126] Y. Zheng, M. Li, B. Weng, H. Mao, J. Zhao, Exosome-based delivery nanoplatforms: next-generation theranostic platforms for breast cancer, Biomater. Sci. (2022).
[127] H. Kim, H.-.J. Park, H.W. Chang, J.H. Back, S.J. Lee, Y.E. Park, E.H. Kim, Y. Hong, G. Kwak, I.C. Kwon, Exosome-guided direct reprogramming of tumor-associated macrophages from protumorigenic to antitumorigenic to fight cancer, Bioact. Mater. (2022).

[128] T. Yu, H. Cheng, Z. Ding, Z. Wang, L. Zhou, P. Zhao, S. Tan, X. Xu, X. Huang, M. Liu, GPER mediates decreased chemosensitivity via regulation of ABCG2 expression and localization in tamoxifen-resistant breast cancer cells, Mol. Cell. Endocrinol. 506 (2020), 110762.
[129] D. Rodrigo, A. Tittl, N. Ait-Bouziad, A. John-Herpin, O. Limaj, C. Kelly, D. Yoo, N.J. Wittenberg, S.-.H. Oh, H.A. Lashuel, Resolving molecule-specific information in dynamic lipid membrane processes with multi-resonant infrared metasurfaces, Nat. Commun. 9 (2018) 1–9.
[130] G. He, X. Peng, S. Wei, S. Yang, X. Li, M. Huang, S. Tang, H. Jin, J. Liu, S. Zhang, Exosomes in the hypoxic TME: from release, uptake and biofunctions to clinical applications, Mol. Cancer 21 (2022) 1–22.
[131] N. Sharma, K. Bietar, U. Stochaj, Targeting nanoparticles to malignant tumors, Biochim. Biophys. Acta (2022), 188703.
[132] J. Wang, Y. Zheng, M. Zhao, Exosome-based cancer therapy: implication for targeting cancer stem cells, Front. Pharmacol. 7 (2017) 533.
[133] J. Thundimadathil, Cancer treatment using peptides: current therapies and future prospects, J. Amino Acids (2012) 2012.
[134] B. Besse, M. Charrier, V. Lapierre, E. Dansin, O. Lantz, D. Planchard, T.Le Chevalier, A. Livartoski, F. Barlesi, A. Laplanche, Dendritic cell-derived exosomes as maintenance immunotherapy after first line chemotherapy in NSCLC, Oncoimmunology 5 (2016), e1071008.
[135] M. Wang, K. Alberti, S. Sun, C.L. Arellano, Q. Xu, Combinatorially designed lipid-like nanoparticles for intracellular delivery of cytotoxic protein for cancer therapy, Angew. Chem. Int. Ed. 53 (2014) 2893–2898.
[136] W. Gu, F. Meng, R. Haag, Z. Zhong, Actively targeted nanomedicines for precision cancer therapy: Concept, construction, challenges and clinical translation, J. Controlled Release 329 (2021) 676–695.
[137] F. Vakhshiteh, F. Atyabi, S.N. Ostad, Mesenchymal stem cell exosomes: a two-edged sword in cancer therapy, Int. J. Nanomed. 14 (2019) 2847.
[138] Z. Yang, J. Shi, J. Xie, Y. Wang, J. Sun, T. Liu, Y. Zhao, X. Zhao, X. Wang, Y. Ma, Large-scale generation of functional mRNA-encapsulating exosomes via cellular nanoporation, Nat. Biomed. Eng. 4 (2020) 69–83.
[139] C. Liu, C. Su, Design strategies and application progress of therapeutic exosomes, Theranostics 9 (2019) 1015.
[140] E.J. Park, H.J. Jung, H.J. Choi, H.J. Jang, H.J. Park, L.N. Nejsum, T.H. Kwon, Exosomes co-expressing AQP5-targeting miRNAs and IL-4 receptor-binding peptide inhibit the migration of human breast cancer cells, FASEB J. 34 (2020) 3379–3398.
[141] M. Wu, M. Wang, H. Jia, P. Wu, Extracellular vesicles: Emerging anti-cancer drugs and advanced functionalization platforms for cancer therapy, Drug Deliv. 29 (2022) 2513–2538.
[142] S. Rayamajhi, T.D.T. Nguyen, R. Marasini, S. Aryal, Macrophage-derived exosome-mimetic hybrid vesicles for tumor targeted drug delivery, Acta Biomater. 94 (2019) 482–494.
[143] A. Chaudhuri, D.N. Kumar, R.A. Shaik, B.G. Eid, A.B. Abdel-Naim, S. Md, A. Ahmad, A.K. Agrawal, Lipid-Based Nanoparticles as a Pivotal Delivery Approach in Triple Negative Breast Cancer (TNBC) Therapy, Int. J. Mol. Sci. 23 (2022) 10068.
[144] H. Amjad, K. Rizwan, M. Baber, S. Iqbal, Organic–Inorganic Nanohybrids in Cancer Treatment, Hybrid Nanomaterials, Springer (2022) 107–132.
[145] Y.T. Sato, K. Umezaki, S. Sawada, S.-a. Mukai, Y. Sasaki, N. Harada, H. Shiku, K. Akiyoshi, Engineering hybrid exosomes by membrane fusion with liposomes, Sci. Rep. 6 (2016) 21933, https://doi.org/10.1038/srep21933.
[146] L. Zhao, C. Gu, Y. Gan, L. Shao, H. Chen, H. Zhu, Exosome-mediated siRNA delivery to suppress postoperative breast cancer metastasis, J. Controlled Release 318 (2020) 1–15.
[147] Z. Yang, J. Xie, J. Zhu, C. Kang, C. Chiang, X. Wang, X. Wang, T. Kuang, F. Chen, Z. Chen, Functional exosome-mimic for delivery of siRNA to cancer: in vitro and in vivo evaluation, J. Controlled Release 243 (2016) 160–171.
[148] X. Qiu, Z. Li, X. Han, L. Zhen, C. Luo, M. Liu, K. Yu, Y. Ren, Tumor-derived nanovesicles promote lung distribution of the therapeutic nanovector through repression of Kupffer cell-mediated phagocytosis, Theranostics 9 (2019) 2618.
[149] Q.-l. Wang, X. Zhuang, M.K. Sriwastva, J. Mu, Y. Teng, Z. Deng, L. Zhang, K. Sundaram, A. Kumar, D. Miller, Blood exosomes regulate the tissue distribution of grapefruit-derived nanovector via CD36 and IGFR1 pathways, Theranostics 8 (2018) 4912.
[150] C. Gong, J. Tian, Z. Wang, Y. Gao, X. Wu, X. Ding, L. Qiang, G. Li, Z. Han, Y. Yuan, Functional exosome-mediated co-delivery of doxorubicin and hydrophobically modified microRNA 159 for triple-negative breast cancer therapy, J. Nanobiotech. 17 (2019) 1–18.
[151] Y. Zheng, W. Zhang, L. Xu, H. Zhou, M. Yuan, H. Xu, Recent Progress in Understanding the Action of Natural Compounds at Novel Therapeutic Drug Targets for the Treatment of Liver Cancer, Front. Oncol. 11 (2022), 795548.
[152] Q. Sun, Z. Wang, B. Liu, F. He, S. Gai, P. Yang, D. Yang, C. Li, J. Lin, Recent advances on endogenous/exogenous stimuli-triggered nanoplatforms for enhanced chemodynamic therapy, Coord. Chem. Rev. 451 (2022), 214267.
[153] X. Shi, Q. Cheng, T. Hou, M. Han, G. Smbatyan, J.E. Lang, A.L. Epstein, H.-.J. Lenz, Y. Zhang, Genetically engineered cell-derived nanoparticles for targeted breast cancer immunotherapy, Mol. Ther. 28 (2020) 536–547.
[154] A. Takahashi, R. Okada, K. Nagao, Y. Kawamata, A. Hanyu, S. Yoshimoto, M. Takasugi, S. Watanabe, M.T. Kanemaki, C. Obuse, Exosomes maintain cellular homeostasis by excreting harmful DNA from cells, Nat. Commun. 8 (2017) 1–16.
[155] K. Pakravan, S. Babashah, M. Sadeghizadeh, S.J. Mowla, M. Mossahebi-Mohammadi, F. Ataei, N. Dana, M. Javan, MicroRNA-100 shuttled by mesenchymal stem cell-derived exosomes suppresses in vitro angiogenesis through modulating the mTOR/HIF-1α/VEGF signaling axis in breast cancer cells, Cell. Oncol. 40 (2017) 457–470.
[156] Y. Li, Y. Liang, Y. Sang, X. Song, H. Zhang, Y. Liu, L. Jiang, Q. Yang, MiR-770 suppresses the chemo-resistance and metastasis of triple negative breast cancer via direct targeting of STMN1, Cell Death. Dis. 9 (2018) 1–12.
[157] A.A. Badawy, M.A. El-Magd, S.A. AlSadrah, Therapeutic effect of camel milk and its exosomes on MCF7 cells in vitro and in vivo, Integr. Cancer Ther. 17 (2018) 1235–1246.
[158] A. Semaan, A. Maitra, Isolating Circulating Exosomes as Biomarkers: Challenges and Opportunities, Cell-Free Circulating DNA: Purification and Analysis Techniques (2022) 209–246.
[159] A. Amiri, R. Bagherifar, E. Ansari Dezfouli, S.H. Kiaie, R. Jafari, R. Ramezani, Exosomes as bio-inspired nanocarriers for RNA delivery: Preparation and applications, J. Transl. Med. 20 (2022) 1–16.
[160] B. Lu, J. Ku, R. Flojo, C. Olson, D. Bengford, G. Marriott, Exosome-and extracellular vesicle-based approaches for the treatment of lysosomal storage disorders, Adv. Drug. Deliv. Rev. (2022), 114465.
[161] Y. Ding, Y. Wang, Q. Hu, Recent Advances in Overcoming Barriers to Cell-Based Delivery Systems For Cancer immunotherapy, Exploration, Wiley Online Library, 2022, 20210106.
[162] Y. Wang, W. Wang, F. Kong, Q. Zhang, J. Xiao, Y. Zhang, B. Yan, Tango of dual nanoparticles: Interplays between exosomes and nanomedicine, Bioeng. Transl. Med. 7 (2022) e10269.
[163] R. Zhao, J. Liu, Z. Li, W. Zhang, F. Wang, B. Zhang, Recent Advances in CXCL12/CXCR4 Antagonists and Nano-Based Drug Delivery Systems for Cancer Therapy, Pharmaceutics 14 (2022) 1541.
[164] S. Roshancheshm, A. Asadi, S.M. Khoshnazar, A. Abdolmaleki, Z.Omar Khudhur, S.Wasman Smail, Application of natural and modified exosomes a drug delivery system, Nanomed. J. 9 (2022) 192–204.
[165] W. Fu, T. Li, H. Chen, S. Zhu, C. Zhou, Research Progress in Exosome-Based Nanoscale Drug Carriers in Tumor Therapies, Front. Oncol. 12 (2022).
[166] Q. Tang, S. Yang, G. He, H. Zheng, S. Zhang, J. Liu, S. Wei, Q. Fan, X. Peng, X. Li, Tumor-derived exosomes in the cancer immune microenvironment and cancer immunotherapy, Cancer Lett. (2022), 215823.
[167] S. Shan, J. Chen, Y. Sun, Y. Wang, B. Xia, H. Tan, C. Pan, G. Gu, J. Zhong, G. Qing, Functionalized Macrophage Exosomes with Panobinostat and PPM1D-siRNA for Diffuse Intrinsic Pontine Gliomas Therapy, Adv. Sci. (2022), 2200353.
[168] A. Akbar, F. Malekian, N. Baghban, S.P. Kodam, M. Ullah, Methodologies to Isolate and Purify Clinical Grade Extracellular Vesicles for Medical Applications, Cells 11 (2022) 186.
[169] G. Loch-Neckel, A.T. Matos, A.R. Vaz, D. Brites, Challenges in the development of drug delivery systems based on small extracellular vesicles for therapy of brain diseases, Front. Pharmacol. 13 (2022).

[170] S.R.K. Pandian, K.K. Vijayakumar, S. Kunjiappan, E. Babkiewicz, P. Maszczyk, Emerging role of exosomes in hematological malignancies, Clin. Exp. Med. (2022) 1–14.
[171] W. Zeng, Z. Wen, H. Chen, Y. Duan, Exosomes as Carriers for Drug Delivery in Cancer Therapy, Pharm. Res. (2022) 1–15.
[172] A. Esmaeili, M. Alini, M. Baghaban Eslaminejad, S. Hosseini, Engineering strategies for customizing extracellular vesicle uptake in a therapeutic context, Stem Cell Research & Therapy 13 (2022) 1–16.
[173] M.A. Di Bella, Overview and Update on Extracellular Vesicles: Considerations on Exosomes and Their Application in Modern Medicine, Biology 11 (2022) 804.
[174] C. Wang, J. Liu, Y. Yan, Y. Tan, Role of Exosomes in Chronic Liver Disease Development and Their Potential Clinical Applications, J. Immunol. Res. 2022 (2022).
[175] N.R. Dehkordi, N.R. Dehkordi, M.H. Farjoo, Therapeutic properties of stem cell-derived exosomes in ischemic heart disease, Eur. J. Pharmacol. (2022), 174839.
[176] C. Compagnoni, V. Zelli, A. Bianchi, A. Di Marco, R. Capelli, D. Vecchiotti, L. Brandolini, A.M. Cimini, F. Zazzeroni, M. Allegretti, MicroRNAs Expression in Response to rhNGF in Epithelial Corneal Cells: Focus on Neurotrophin Signaling Pathway, Int. J. Mol. Sci. 23 (2022) 3597.
[177] A. Allegra, C. Petrarca, M. Di Gioacchino, M. Casciaro, C. Musolino, S. Gangemi, Exosome-Mediated Therapeutic Strategies for Management of Solid and Hematological Malignancies, Cells 11 (2022) 1128.
[178] H. Zhou, L. Zhu, J. Song, G. Wang, P. Li, W. Li, P. Luo, X. Sun, J. Wu, Y. Liu, Liquid biopsy at the frontier of detection, prognosis and progression monitoring in colorectal cancer, Mol. Cancer 21 (2022) 1–21.
[179] M. Garcia-Contreras, R.W. Brooks, L. Boccuzzi, P.D. Robbins, C. Ricordi, Exosomes as biomarkers and therapeutic tools for type 1 diabetes mellitus, Riv. Eur. Sci. Med. Farmacol. 21 (2017) 2940–2956.
[180] Shabanali Khodashenas Limoni, Mehdi Forouzandeh Moghadam, Seyed Mohammad Moazzeni, Hosna Gomari, Fatemeh Salimi,, Engineered Exosomes for Targeted Transfer of siRNA to HER2 Positive Breast Cancer Cells, Applied Biochemistry and Biotechnology 187 (1) (2019) 352–364, https://doi.org/10.1007/s12010-018-2813-4.
[181] Liuwan Zhao, Chunyan Gu, Ye Gan, Lanlan Shao, Hongwei Chen, Hongyan Zhu, Exosome-mediated siRNA delivery to suppress postoperative breast cancer metastasis, Journal of Controlled Release 318 (2020) 1–15, https://doi.org/10.1016/j.jconrel.2019.12.005.
[182] Mingli Han, Jianguo Hu, Pengwei Lu, Hui Cao, Chao Yu, Xiangke Li, Xueke Qian, Xue Yang, Yunqing Yang, Na Han, Dongwei Dou, Fan Zhang, Mulin Ye, Changcheng Yang, Yuanting Gu, Huaying Dong, Exosome-transmitted miR-567 reverses trastuzumab resistance by inhibiting ATG5 in breast cancer, Cell death & disease 11 (1) (2020) 43, https://doi.org/10.1038/s41419-020-2250-5.
[183] K.P. O'Brien, S. Khan, K.E. Gilligan, H. Zafar, P. Lalor, C. Glynn, C. O'Flatharta, H. Ingoldsby, P. Dockery, A. De Bhulbh,, J.R. Schweber, K. St John, M. Leahy, J. M. Murphy,, W.M. Gallagher, T. O'Brien,, M.J. Kerin, R.M. Dwyer, Employing mesenchymal stem cells to support tumor-targeted delivery of extracellular vesicle (EV)-encapsulated microRNA-379, Oncogene 37 (16) (2018) 2137–2149, https://doi.org/10.1038/s41388-017-0116-9.
[184] Eui-Jung Park, Hyun Jun Jung, Hyo-Jung Choi, Hyo-Ju Jang, Hye-Jeong Park, Lene N Nejsum, Tae-Hwan Kwon, Exosomes co-expressing AQP5-targeting miRNAs and IL-4 receptor-binding peptide inhibit the migration of human breast cancer cells, FASEB Journal 34 (2) (2020) 3379–3398, https://doi.org/10.1096/fj.201902434R.
[185] Lei Yuan, Yuqiong Liu, Yunhui Qu, Lan Liu, Huixiang Li, Exosomes Derived From MicroRNA-148b-3p-Overexpressing Human Umbilical Cord Mesenchymal Stem Cells Restrain Breast Cancer Progression, Frontiers in Oncology 22 (9) (2019), 1076, https://doi.org/10.3389/fonc.2019.01076.
[186] Zahra Naseri, Reza Kazemi Oskuee, Mehdi Forouzandeh Moghadam, Mahmoud Reza Jaafari, Delivery of LNA-antimiR-142-3p by Mesenchymal Stem Cells-Derived Exosomes to Breast Cancer Stem Cells Reduces Tumorigenicity, Stem Cell Reviews and Reports 16 (3) (2020) 541–556, https://doi.org/10.1007/s12015-019-09944-w.
[187] J Du, J-J Fan, C Dong, H-T Li, B-L Ma, Inhibition effect of exosomes-mediated Let-7a on the development and metastasis of triple negative breast cancer by down-regulating the expression of c-Myc, European Review for Medical and Pharmacological Sciences 23 (12) (2019) 5301–5314, https://doi.org/10.26355/eurrev_201906_18197.
[188] Hosna Gomari, Mehdi Forouzandeh Moghadam, Masoud Soleimani, Targeted cancer therapy using engineered exosome as a natural drug delivery vehicle, OncoTargets and Therapy 12 (11) (2018) 5753–5762, https://doi.org/10.2147/OTT.S173110.
[189] Mark Barok, Maija Puhka, Gyorgy Vereb, Janos Szollosi, Jorma Isola, Heikki Joensuu, Cancer-derived exosomes from HER2-positive cancer cells carry trastuzumab-emtansine into cancer cells leading to growth inhibition and caspase activation, BMC Cancer 2 (18) (2018), 504, https://doi.org/10.1186/s12885-018-4418-2.
[190] Catharina Melzer, Vanessa Rehn, Yuanyuan Yang, Heike Bähre, Juliane von der Ohe, Ralf Hass, Taxol-Loaded MSC-Derived Exosomes Provide a Therapeutic Vehicle to Target Metastatic Breast Cancer and Other Carcinoma Cells, Cancers (Basel) 11 (6) (2019), 798, https://doi.org/10.3390/cancers11060798.
[191] Myung Soo Kim, Matthew J Haney, Yuling Zhao, Vivek Mahajan, Irina Deygen, Natalia L Klyachko, Eli Inskoe, Aleksandr Piroyan, Marina Sokolsky, Onyi Okolie, Shawn D Hingtgen, Alexander V Kabanov, Elena V Batrakova, Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells, Nanomedicine 12 (3) (2016) 655–664, https://doi.org/10.1016/j.nano.2015.10.012.
[192] Piaopiao Wang, Huihui Wang, Qianqian Huang, Can Peng, Liang Yao, Hong Chen, Zhen Qiu, Yifan Wu, Lei Wang, Weidong Chen, Exosomes from M1-Polarized Macrophages Enhance Paclitaxel Antitumor Activity by Activating Macrophages-Mediated Inflammation, Theranostics 9 (6) (2019) 1714–1727, https://doi.org/10.7150/thno.30716.
[193] Mengyu Yu, Chengcheng Gai, Zihaoran Li, Dejun Ding, Jie Zheng, Weifen Zhang, Shijun Lv, Wentong Li, Targeted exosome-encapsulated erastin induced ferroptosis in triple negative breast cancer cells, Cancer Science 110 (10) (2019) 3173–3182, https://doi.org/10.1111/cas.14181.
[194] Bohyun Moon, Suhwan Chang, Exosome as a Delivery Vehicle for Cancer Therapy, Cells 11 (3) (2022), 316, https://doi.org/10.3390/cells11030316.
[195] Mahshid Deldar Abad Paskeh, Maliheh Entezari, Sepideh Mirzaei, Amirhossein Zabolian, Hossein Saleki, Mohamad Javad Naghdi, Sina Sabet, Mohammad Amin Khoshbakht, Mehrdad Hashemi, Kiavash Hushmandi, Gautam Sethi, Ali Zarrabi, Alan Prem Kumar, Shing Cheng Tan, Marios Papadakis, Athanasios Alexiou, Md Asiful Islam, Ebrahim Mostafavi, Milad Ashrafizadeh, Emerging role of exosomes in cancer progression and tumor microenvironment remodeling, Journal of Hematology & Oncology 15 (1) (2022), 83.
[196] Haiyang Zhang, Yi Wang, Ming Bai, Junyi Wang, Kegan Zhu, Rui Liu, Shaohua Ge, JiaLu Li, Tao Ning, Ting Deng, Qian Fan, Hongli Li, Wu Sun, Guoguang Ying, Yi Ba, Exosomes serve as nanoparticles to suppress tumor growth and angiogenesis in gastric cancer by delivering hepatocyte growth factor siRNA, Cancer Science 109 (3) (2018) 629–641, https://doi.org/10.1111/cas.13488.
[197] Marie-Cécile Didiot, Lauren M Hall, Andrew H Coles, Reka A Haraszti, Bruno Mdc Godinho, Kathryn Chase, Ellen Sapp, Socheata Ly, Julia F Alterman, Matthew R Hassler, Dimas Echeverria, Lakshmi Raj, David V Morrissey, Marian DiFiglia, Neil Aronin, Anastasia Khvorova, Exosome-mediated Delivery of Hydrophobically Modified siRNA for Huntingtin mRNA Silencing, MOLECULAR THERAPY 24 (10) (2016) 1836–1847, https://doi.org/10.1038/mt.2016.126.
[198] Kyeongsoo Jeong, Yeong Jun Yu, Jae Young You, Won Jong Rhee, Jeong Ah Kim, Exosome-mediated microRNA-497 delivery for anti-cancer therapy in a microfluidic 3D lung cancer model, LAB ON A CHIP 20 (3) (2020) 548–557, https://doi.org/10.1039/c9lc00958b.
[199] Matthew J Haney, Natalia L Klyachko, Yuling Zhao, Richa Gupta, Evgeniya G Plotnikova, Zhijian He, Tejash Patel, Aleksandr Piroyan, Marina Sokolsky, Alexander V Kabanov, Elena V Batrakova, Exosomes as drug delivery vehicles for Parkinson's disease therapy, Journal of Controlled Release 207 (2015) 18–30, https://doi.org/10.1016/j.jconrel.2015.03.033.