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REVIEW ARTICLE

Exosomes: special nano-therapeutic carrier for cancers, overview on anticancer drugs

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Abstract

Chemotherapy drugs are the first line of cancer treatment, but problems such as low intratumoral delivery, poor bioavailability, and off-site toxicity must be addressed. Cancer-specific drug delivery techniques could improve the therapeutic outcome in terms of patient survival. The current study investigated the loading of chemotherapy drugs loaded into exosomes for cancer treatment. Exosomes are the smallest extracellular vesicles found in body fluids and can be used to transfer information by moving biomolecules from cell to cell. This makes them useful as carriers. As the membranes of these nanoparticles are similar to cell membranes, they can be easily transported to carry different components. As most chemotherapy drugs are not easily soluble in liquid, loading them into exosomes can be a suitable solution to this problem. This cancer treatment could avert the injection of high doses of drugs and provide a more appropriate release mechanism.

Keywords Cancer · Exosome · Chemotherapy drugs · Carrier

Abbreviations

EXO	Exosome
MSC	Mesenchymal stromal cell
PI3K/Akt/mTOR	Phosphatidylinositol 3-kinase/phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin
CTX	Cabazitaxel
DTX	Docetaxel
CRPC	Castration-resistant prostate cancer
IPSCS	Induced pluripotent stem cells
NSCLC	Non-small cell lung cancer
OXA	Oxaliplatin
TEM	Temozolomide
DEC	Decitabine
CEL	Celastrol
GEM	Gemcitabine
CRC	Colorectal cancer
MIT	Mitoxantrone
GBM	Glioblastoma multiform
BBB	Blood–brain barrier
AML	Myeloid leukemia
CRC	Colorectal cancer

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Introduction

Despite being effective tumor suppressors, chemotherapy drugs are subject to low intratumoral delivery, poor bioavailability, and off-site toxicity. Systemic chemotherapy is a common method for slowing the spread of cancer, but it has several side effects. Targeted drug delivery systems have undergone extensive research as a way to reduce the side effects of chemotherapy. In order to improve the therapeutic results in terms of patient survival, cancer-specific drug delivery strategies could be used.

Therapies that reduce systemic toxicity can increase the effectiveness of treatment for people with breast cancer [1]. Pharmaceuticals have been successfully encapsulated in tumor-targeting material by Jang et al. [2], and

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doxorubicin-loaded exosomes and nanovesicles have been employed as efficient cytotoxic drug delivery systems.

Small extracellular vesicles (sEVs) have recently been increasingly used for targeted drug delivery and therapies (Fig. 1).

Three main elements make up an sEV-based delivery system: vesicles, cargoes, and surface decorations. Either passive loading or active loading can be used to add medicines to exosomes. For passive loading, in order for the medications to be present in exosomes that are produced by maternal cells, the drugs either must be transferred into the cells or be grown alongside them (Fig. 2). Active loading involves physical processes such as ultrasound, electroporation, extrusion, and freeze–thaw techniques that can be used to load pharmaceuticals into exosomes [3, 4].

Doxorubicin (DOX)

Doxorubicin is a highly effective anthracycline antibiotic that is commonly used in its liposomal formulation (Doxil) to treat hematological malignancies and solid tumors. However, the significant cardiotoxicity associated with long-term doxorubicin exposure limits its therapeutic use. Encapsulation of the drug to prevent non-specific uptake and improve the drug's pharmacokinetic properties is one strategy for preventing doxorubicin uptake into cardiac cells [5, 6].

The HER2, MDA-MB-231, and MFC-7 [7, 8] breast cancer cell lines are among the malignancies studied using doxorubicin nanocarriers. Some of this research has been carried out on mouse models of breast cancer [9]. The efficient delivery of doxorubicinloaded targeted exosomes in vitro has been verified by the considerable reduction in the tumor growth rate in a mouse breast cancer model [10].

Heat stress has been shown to increase the amount of doxorubicin-containing exosomes released by tumor cells and the antitumor effect of doxorubicin-treated tumor cell exosomes [7]. In vitro and in vivo studies on ectopic model C26 (mouse colon cancer) in BALB/c mice have indicated that a single intravenous injection of DOX@exosome reduced tumor growth substantially more than free DOX [11].

Paclitaxel (PTX)

Paclitaxel (PTX) is a microtubule-stabilizing agent that is used as an anticancer drug for both advanced and early-stage malignancies, including breast cancer [12] and glioblastoma multiforme (GBM) [13]. PTX therapy, however, is known to have features that harm healthy cells (cardiotoxicity, myelosuppression, and neurotoxicity) [14]. Hence, targeted PTX delivery to malignant tissues is preferable to avoid possible side effects in healthy cells.

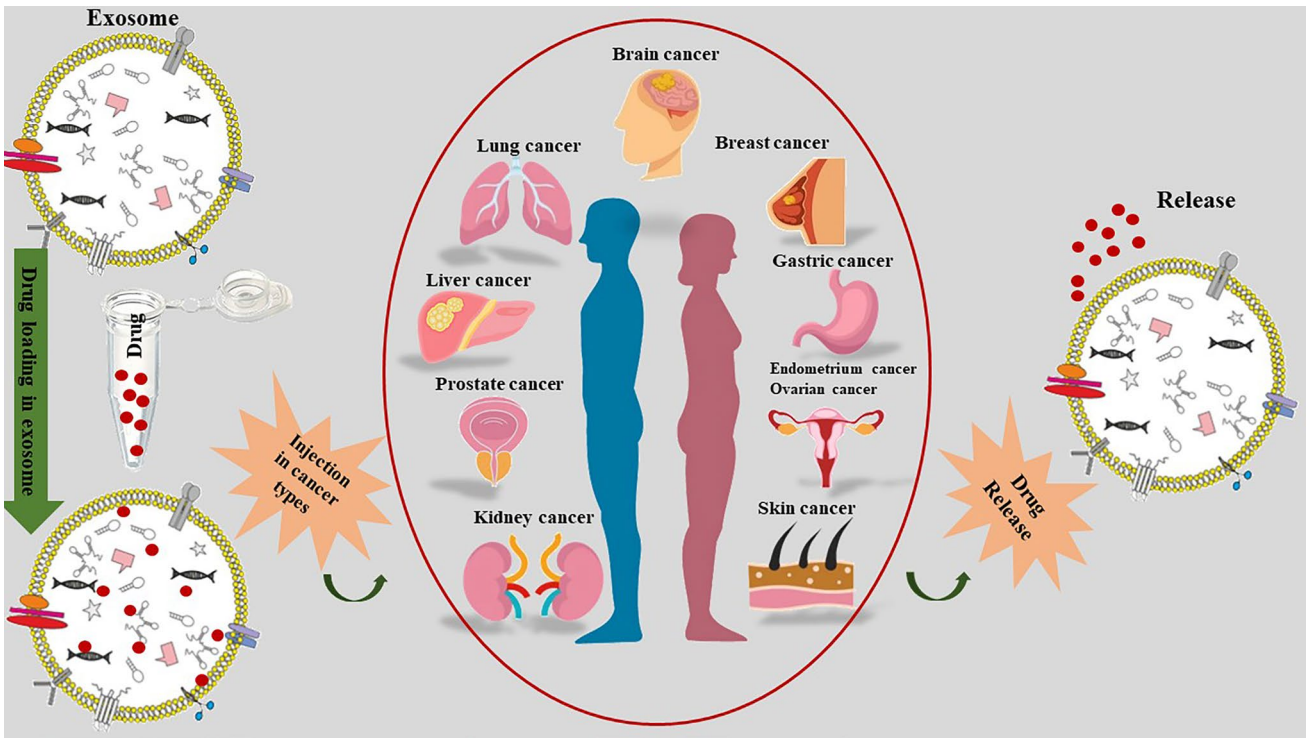

Fig. 1 Schematic figure that shows the use of exosomes as a drug carrier for targeted drug delivery and therapies

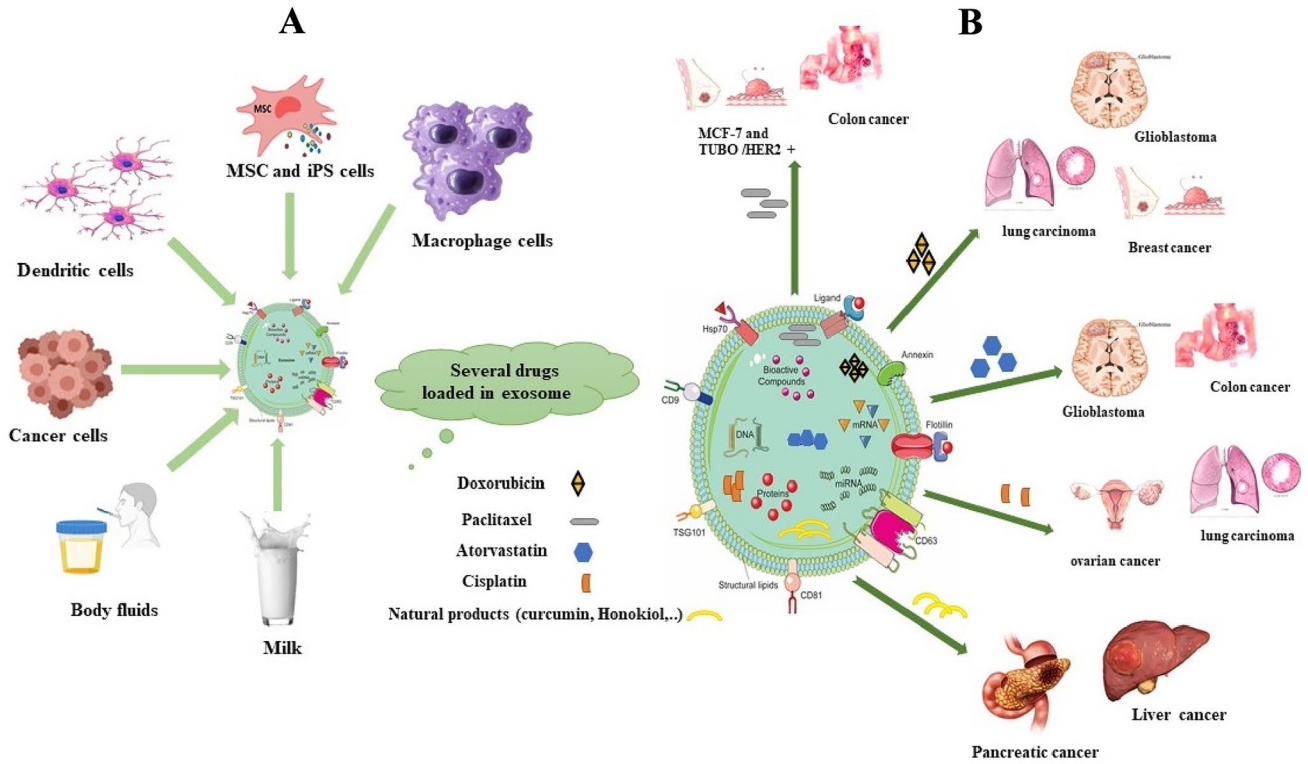

Fig. 2 **A** Exosomes from various sources will be used as a specific drug delivery system. **B** Exosomes in treatment of several malignancies

In a rat model of lung cancer, paclitaxel-encapsulated exosomes were reported to have greater antineoplastic effects than free paclitaxel [15]. Some studies have reported that PTX has low bioavailability and cannot cross the blood–brain barrier (BBB). However, in a zebrafish model, exosomes generated from a brain endothelial cell culture were able to increase doxorubicin and PTX penetration across the BBB [16].

In addition to inhibiting breast tumors, PTX loaded into MSC-derived exosomes was able to prevent metastasis to other tissues to a large extent. Systemic injection of these drug-loaded exosomes into mice with breast cancer (MDA-hyb1), in addition to the reducing tumor size more than 60%, was able to prevent metastasis to the lung, kidney, liver, and spleen (more than 50%) [17]. Doxorubicin and paclitaxel are the most widely used chemotherapy drugs. The information about these drugs is collected in Table 1.

Cabazitaxel (CTX)

Cabazitaxel is a taxane derivative with anticancer properties. This drug induces apoptosis in cancer cells by inhibiting the phosphorylation of the PI3K/Akt/mTOR pathway. It has shown better anticancer activity than other drugs in this category because of its low tendency to exhibit multidrug resistance 1 (MDR1). However, this drug does not dissolve well in solvents; thus, its use as an anticancer agent is limited. Loading CTX into exosomes could overcome this problem [31]. CTX loading into MSC-derived EXO has been shown to effectively inhibit the growth of oral squamous cell carcinoma in vitro and in vivo [32].

Cisplatin

Cis-diamminedichloroplatinum (II), or cisplatin is organometallic platinum that was discovered to have powerful anti-neoplastic effects on tumor cells after its antibacterial activities were initially described [33]. Patients with lymphomas, breast, testicular, ovarian, head, neck, and cervical cancers, and sarcomas are currently treated with cisplatin and other platinum-based drugs, including oxaliplatin and carboplatin, as first-line therapy. Its cytotoxicity is triggered by its interaction with DNA, which results in the formation of adducts and causes apoptosis [34]. Its nephrotoxicity, neurotoxicity, hepatotoxicity, and myelosuppression have limited the use of cisplatin as an effective anticancer medication [35, 36].

Table 1 Doxorubicin and paclitaxel loaded in various exosomes for the treatment of different kinds of cancers

Drug	Exosome sources	Cancer type/cell line	Finding	Ref
Doxorubicin	Bone marrow mesenchymal stem cells	TUBO/HER2+	MTT assay showed that cytotoxicity of targeted doxorubicin-loaded exosomes was higher than free doxorubicin at 72 h/efficient delivery of targeted doxorubicin-loaded exosomes in vitro, corroborated with a significant reduction of murine breast cancer model tumor growth rate	[10]
	MDA-MB-23 cell line	MDA-MB-23/mouse model	ExoDOX increase tolerability and efficacy of DOX/Myocardial endothelial cells limit exoDOX crossing, avoiding accumulation of drug in the heart. The kinetics of myocardial endothelial extravasation are slower in exoDOX compared with DOX	[9]
	Tumor-cell-derived exosomes	MFC-7	Heat stress increased the quantity of doxorubicin-containing exosomes from tumor cells, /enhanced the anti-tumor effect of exosomes from the doxorubicin-treated tumor cells	[7]
	Mouse bone marrow MSCs	C26 (mouse colon cancer)	Single dose intravenous injection of DOX @ exosome suppressing C26-tumor growth	[11]
	U-87 MG	Zebrafish embryos	Zebrafish treated with exosome delivered doxorubicin had a significantly smaller area of the U-87 MG/suppressed the RNAs of VEGF in brain tumor model in zebrafish	[16]
	MDA-MB-231 and HCT-116 cell lines	Xenograft tumor MDA-MB-231 cells in nude mice	ExoDOX was less toxic than DOX through its altered bio distribution/exoDOX showed no cardiotoxicity	[18]
Paclitaxel	RAW 264.7 macrophages	MDR cells	Incorporation of PTX into exosomes increased cytotoxicity more than 50 times in drug-resistant $MDCK_{MDR1}$ (Pgp+) cells	[15]
	RAW 264.7 macrophages	C57BL/6 mice/injected 3LL-M27 cells/Lung Carcinoma pulmonary metastases	Confocal images revealed exosomes were co-localized with lung metastases, indicating efficient targeting of exoPTX in vivo	[15]
	Exosome-like sequential-bioactivating prodrug nanoplatform (EMPCs)	MDA-MB-231, MCF-7 and RAW264.7 cells/and breast cancer mouse model	Efficient targeting of circulating tumor cells (CTCs)/enhanced breast cancer metastasis inhibition	[19]
	A549 cells/adenocarcinomic human alveolar basal epithelial cells	In vitro and in vivo of lung cancer	Paclitaxel encapsulated in autologous extracellular provides a selective cancer cell tropism and contributes to enhancing PTX anticancer effects in vitro and in vivo	[20]
	Human bone marrow-derived MSCs	Breast cancer (MDA-MB-231) cells	PTX-MSCEMs significantly decreased the viability of MDA-MB-231 cells/in vivo tumor growth was significantly inhibited	[1]
	Bovine milk-derived exosomes	Human lung cancer (A549 and H1299), breast cancer (MDA-MB-231 and T47D)	A biocompatible and cost-effective source of exosomes. Enhanced anticancer and anti-inflammatory effects	[21]
	RAW 264.7 macrophages	Mouse model of pulmonary metastases	PTX-loaded exosomes with incorporated aminoethylanisamide-polyethylene glycol (AA-PEG-exoPTX) showed high anticancer efficacy	[22]
	Brain neuronal glioblastoma-astrocytoma U-87 MG, endothelial bEND.3, neuroectodermal tumor PFSK-1/glioblastoma A-172 cell lines	U-87 MG, and bEND.3, Zebrafish embryos	In zebrafish in vivo, exosome delivery allowed doxorubicin and paclitaxel to cross the blood brain barrier (BBB), whereas when given alone neither drug showed brain uptake	[16]
	U87 glioblastoma cells	Cell line of glioblastoma, U87 and T98G	Cytotoxicity of PTX on U87 cells was increased/while on T98 cells exosomal formulation of PTX could not increase PTX toxicity	[23]
	RAW264.7 macrophage	Murine breast cancer cells 4T1/xenograft tumors in murin model	PTX -M1-Exos provided a pro-inflammatory environment which enhanced the antitumor activity via caspase-3 mediated pathway	[24]

Table 1 (continued)

Drug	Exosome sources	Cancer type/cell line	Finding	Ref
	LNCaP- and PC-3 prostate cancer cell	LNCaP and PC-3 PCa cell lines	Loading of paclitaxel to autologous prostate cancer cell-derived EVs increased its cytotoxic effect/Cancer cell-derived EVs can be used as effective carriers of Paclitaxel to their parental cells	[25]
	Milk-derived exosomes	Lung tumor xenografts by injecting human lung A549 cells to nude mice	ExoPAC delivered orally showed significant tumor growth inhibition/demonstrated remarkably lower systemic and immunogenic toxicities	[26]
	U-87 cell line	U-87 cell line	PTXloaded exosome significantly inhibited the growth of U-87 cell line by 59.92% compared to that of free PTX	[27]
	SR4987 (BM mesenchymal stromal cell line)	CFPAC-1 (human pancreatic adenocarcinoma)	MSCs are able to package and deliver active drugs through their MVs/SR4987PTX-derived-MVs (SR4987PTX-MVs) demonstrated a strong anti-proliferative activity on CFPAC-1	[28]
	MDAMB231(breast cancer Cells)	MDAMB231 cells	PTX-treated MDAMB231 cells consistently generated ~ 1.5-fold more exosomes compared to cells treated with DMSO alone/These Exosomes strongly promote cell survival	[29]
	F56-PTX-NP, by emulsion and solvent evaporation with a following surface functionalization	Human umbilical vein endothelial cells (HUVECs)/MDA-MB-231 breast cancer/BALB/c nude mice	Metronomic F56-PTXNP specifically targeted tumor vascular endothelial cells (ECs), pruned vessels with strong antiangiogenic activity and induced thrombospondin-1 (TSP-1) secretion from ECs/metronomic, actively-targeted nanomedicine can induce tumor vascular normalization and modulate the tumor microenvironment	[30]

Docetaxel (DTX)

Docetaxel is a taxoid antitumor agent that is used clinically as a cytotoxic manager in the treatment of many cancers. Raw264.7 macrophage-derived exosomes transfected with DTX and inactivated exosome loading for chemotherapy have been studied to treat castration-resistant prostate cancer (CRPC). CRPC has a high resistance to treatment and undergoes extensive progression and mortality. In vitro and in vivo models have shown acceptable results for cancer inhibition. Suppression of tumor growth was greater in groups conjugated to exosome-DTX folate. This technique prevented the widespread release of the drug into the body and reduced systemic toxicity [37].

Exosome-loaded DTX should be able to inhibit cancer cells by inducing apoptosis. The HELA cell line of cervical cancer frequently has been used in studies to find a treatment for this disease. In one study, exosomes derived from this cell were isolated, and cervical cancer was evaluated after loading with DTX. Increase mitochondrial apoptosis was reported in this treatment, as well as an increase in the expression of Bax and caspase-3 and a decrease in the expression of Bcl-2 [38].

DTX loaded into induced pluripotent stem cells derived exosomes inhibited metastatic prostate cancer cells in a mouse model relatively better than liposomes, resulting in significantly reduced tumor growth in this group. This approach was clearly more effective in inhibiting prostate cancer compared to free DTX [39].

DTX is a first-line of treatment for NSCLC cancer. Due to the poor solubility of this drug in water, it has been suggested to be loaded into exosomes. Lung cell-derived exosomes were loaded with DTX and examined in vitro and in vivo in a cancer model. Decrease in cell survival, tumor size, and weight occurred. This technique stopped the cell cycle in phase G and increased apoptosis. Exosome drug loading can be more effective than free DTX through its slow-release system for controlling cancer [40].

Oxaliplatin (OXA)

Oxaliplatin combined with 5-fluorouracil (5-Fu) is a prevalent systemic treatment for colorectal cancer CRC [41], and its use in targeted therapies has expanded [42]. The prospects of patients with metastatic CRC remain serious because of inherent or acquired resistance to the medication. Oxaliplatin is the first drug approved to treat colorectal cancer; however, it inhibits division and transcription, which results in cell death [43]. Resistance to oxaliplatin has become a major problem [44]. The exosome-mediated

mechanisms underlying the tumor microenvironment, distant cellular interaction, exosome heterogeneity, and the molecular mechanisms responsible for resistance and metastasis have become increasingly apparent. Designing new investigative approaches based on tumor background expands knowledge about exosome-mediated cancer treatment and prepares new and advantageous cures for cancer patients [45].

Temozolomide (TMZ)

Temozolomide is used to treat various types of cancer, including brain tumors. It is an alkylating drug that is an international standard for treating glioblastoma and halts cancer cells' growth. Glioblastoma is the deadliest human cancer and is the most common type of brain cancer. However, resistance to TMZ and subsequent tumor recurrence have become critical problems in the clinical treatment of glioblastoma [46]. Exosomes in human serum may serve as a possible diagnostic marker for therapy-refractory GBM.

Decitabine (DEC)

Decitabine hypomethylated DNA by inhibiting DNA methyltransferase. It functions in a similar manner to azacytidine, although decitabine can only be incorporated into DNA strands, while azacytidine can be incorporated into both DNA and RNA chains. Decitabine acts as a nucleic acid synthesis inhibitor. It is a medication for treating myelodysplastic syndrome, a class of conditions where certain blood cells are dysfunctional, and acute myeloid leukemia. Increased exosomal expression of miR-200c and miR-141 may be biomarkers for mesenchymal-epithelial transmission of CRC cells [47].

Gemcitabine (GEM)

Gemcitabine, with the molecular formula C9H11F2N3O4 [48], is an anticancer medicine that acts as an anti-metabolite and prevents the development of proteins that are essential for the growth of tumors. Gemcitabine is used to treat pancreatic, lung, and bladder cancers. M1Exo-GEM-DFX can be an effective strategy for the treatment of drug-resistant pancreatic tumors and provide insight into their mechanisms of action [49].

Carboplatin

An analog of cisplatin, carboplatin cis-diammine (1,1-cyclobutane-dicarboxylate platinum) is a second-generation platinum compound. The clinical efficacy of carboplatin and cisplatin for all tumor types may not be the same, although their methods of action and preclinical activity spectra are similar. In both species, platinum chemotherapeutic drugs have been the go-to treatment for osteosarcoma, either alone or in combination with other drugs. Similar mechanisms underlie resistance to both cisplatin and carboplatin [50].

Mitoxantrone (MIT)

Graphene oxide as a nanocarrier is widely used in drug delivery systems because it offers good properties, such as the creation of non-covalent bonds and hydrophobic interactions [51]. However, it does not show proper targeting. The use of exosomes as a drug delivery system should assist in this process, as studies have shown that MIT drug loading in graphene oxide and exosomes have reported effective antitumor effects and enhanced apoptosis [52]. All of these chemo-drugs are listed in (Table 2).

Natural substances

Natural substances such as curcumin and black bean extract loaded into exosomes also have been shown to inhibit cancer. Loading this extract into (HepG2) exosomes derived from the liver and (PC3) prostate cancer cells and then treating the cancer cells with this combination has shown a significant anti-proliferative effect [76]. Co-encapsulated (LPNs) lipid nanoparticles of (DTX)docetaxel and (CUR) curcumin were evaluated on PC3 tumor xenografts in mice (human prostate cancer-bearing Balb/c nude mice model). Compared to other groups, these strong nanoparticles greatly reduced tumor volume development while having no obvious negative effects. This combination may out to be a successful therapy for prostate cancer; it was determined [77]. The bioactive triterpenoid β-elemene, which is obtained from many plants, is another natural substance. There is a lot of interest in using β-elemene as chemotherapy due to its remarkable anticancer effects, which include the reversal of multidrug resistance [78].

Celastrol (CLT) is a compound with the chemical formula $C_{29}H_{38}O_4$ which is extracted from the root of *Tripterygium wilfordii*. While the plant itself is poisonous, it produces a variety of active compounds. Celastrol is a traditional herbal medicine that has the potential for the treatment of various cancers and the ability to inhibit the growth of tumor cells [79]. However, clinical use of CLT is extremely limited by its low solubility/penetrance, insignificant bioavailability, and potential for off-target toxicity. The development of nanotechnology has provided solutions to altering the oral bioavailability, remedial effects, and tissue-targeting of CLT [80]. This highlight the need to fully describe the

Table 2 Chemotherapeutic drugs loaded in exosomes from various sources for the treatment of different kinds of cancers

Drug	Exosome sources	Cancer type/cell line	Finding	Ref
Atorvastatin	Human endometrial stem cells (hEnSCs-EXOs)	U87 cells (gliomas)	The AtoEXOs were uptaken by U87 and generated significant apoptotic effects, while this inhibited tumor growth of U87 cells	[53]
	Human endometrial stem cells (hEnSCs-EXOs)	U87 tumor cells and Human Umbilical Vein Endothelial cells (HUVECs)	Effective anti-angiogenic effect and apoptotic improvement effect against glioblastoma cells/down-regulated expression levels of anti-apoptotic gene Bcl-2 and induced Bax expression level	[54]
Cyclophosphamide (CTX)	Mouse bone marrow-derived dendritic cells	DBA2 mice were injected subcutaneously with L1210 cells	Exosomes, in combination with CTX suppressed L1210 tumor growth in vivo and gave the greatest prolongation of survival time in tumor-bearing DBA2 mice	[55]
	MSC	Oral squamous cell carcinoma	Inhibition of PI3K/Akt/mTOR Signaling Pathway Increased apoptosis	[32]
Cisplatin	Me30966 and Me501 (human metastatic melanoma)	The mouse was injected subcutaneously with Me30966 melanoma cells	PPI pre-treatment increased cellular uptake of CisPt/it induced a clear inhibition of exosome release by tumor cells	[56]
	M1 macrophage-derived exosomes	In vitro (LLC cells) and in vivo Lewis lung cancer	Decreased proliferation and increased apoptosis in both in vitro and in vivo Lewis lung cancer models	[57]
	Human colorectal cancer (HCT 116), human lung cancer (A549), and macrophage-like cell lines (RAW 264.7)	Athymic nude mice were injected with HCT 116, A549, and RAW 264.7 cells	Cell-derived vesicles can be generated in high yields and easily loaded with various cargos. The ability of these vesicles to specifically target the same cell type from which they originated provides	[58]
	M1 macrophage	Mouse Lewis lung cancer (LLC) cells	Drug-loaded Exos are able to effectively inhibit the proliferation of tumor cells and induce their apoptosis, exerting an antitumor effect	[57]
	Mononuclear M1 and M2 macrophages from umbilical cord blood	A2780 and A2780/DDP human ovarian carcinoma cell lines	Loading of cisplatin into M2 exosomes increased its cytotoxicity by nearly 1.7×in drug-resistant A2780/DDP cells and 1.4×in drug-sensitive A2780 cells	[59]
	Exosomes released by A549 cells during DDP exposure	A549 cells	When DDP was added to A549 cells, exosomes secretion was strengthened/the addition of the secreted exosomes to other A549 cells increased the resistance of these A549 cells to DDP	[60]
Carboplatin	Carboplatin-resistant HMPOS cells	Carboplatin-sensitive HMPOS-S cells	Exosomes from the resistant HMPOS-2.5R cell line were found to transfer drug resistance to drug-sensitive HMPOS cells	[61]
MIT	MDA-MB-231 (breast cancer)	Breast cancer	Enhanced apoptosis	[52]
DTX	Raw264.7 macrophage	CRPC	Suppressed tumor growth	[37]
	HELA cell line (cervical cancer)	Cervical cancer	Increased mitochondrial apoptosis Increased Baxo and Caspase-3 expression Decreased Bcl-2 expression	[38]
	iPSC-MSCs	Prostate cancer	Decreased the tumor growth	[39]
	A549 cell line (lung cancer)	NSCLC	Stops the cell cycle in phase G2/M Increased apoptosis	[40]
	Bovine milk-derived exosomes	Human lung cancer (A549 and H1299), breast cancer (MDA-MB-231 and T47D)	A biocompatible and cost-effective source of exosomes. Enhanced anticancer and anti-inflammatory effects	[21]

Table 2 (continued)

Drug	Exosome sources	Cancer type/cell line	Finding	Ref
OXA	Tumor–cell	Colorectal cancer	The novel structure of oxaliplatin stability provides a new biomarker for predicting drug treatment oxaliplatin sensibility in CRC	[62]
	Epithelial mesenchymal	Colorectal cancer	miR-128-3p, is promising diagnostic and prognostic marker for oxaliplatin-based chemotherapy	[63]
	Epithelial– mesenchymal	Colorectal cancer	Increased exosomal expression of miR-200c and miR-141,an could be indicator or biomarker candidate for mesenchymal–epithelial transition of CRC cells	[64]
	Supernatant of 293 T cells	Colon cancer	Engineered exosomes co-delivering PGM5-as1 and oxaliplatin reverse drug resistance in CRC	[65]
	Cell culture medium	Colon cancer	iRGD-modified exosomes have good prospects for clinical applications with high performance and low toxicity and can be widely used in the future	[66]
	The culture medium of treated or untreated cells	Colorectal cancer	Provide a novel mechanism for overcoming the drug resistance encountered in colorectal cancer	[67]
	NCM460, SW480, and SW480-OXA cells (human oxaliplatin-resistant colon cancer cell line)	Colorectal Cancer	Caused decrease of oxaliplatin-based chemosensitivity in CRC	[68]
	Cell culture medium	Colorectal cancer	Could be a potential therapeutic and prognostic target for intervention of therapy-refractory CRC	[69]
	L-OHP-resistant cells	Colon cancer	DNAJB8 from sEVs: is a promising therapeutic target for L-OHP resistance and a prognostic predictor of clinical response	[70]
TEM	GSCS(Glioblastoma stem-like cells)	Glioblastoma cells(Tumor brain)	Temozolomide treatment led to the enrichment of EVs with cargoes dedicated to cell adhesion processes increase the release of protumoral information	[71]
	Glioma-derived	Glioma cancer	a novel mechanism of resistance to TMZ in glioma, which could serve as a potential therapeutic target in the treatment of glioma patients	[72]
	Cell culture medium (depleted fetal bovine serum media supplement)?	GBM cells	Exosomes are foundation of gene fusion-based therapy for managing gbm	[73]
	GBM cell culture	GBM cells	Exosomal lncSBF2-AS1 in human serum may serve as a possible diagnostic marker for therapy-refractory GBM	[74]
DEC	Cell-cultured media	Colorectal cancer	increased exosomal expression of mir-200 c and mir-141 may be an indicator or biomarker candidate for CRC cells	[47]
GEM	M1 macrophage-derived exosomes	Pancreatic cancer	Co-delivery of gemcitabine and Deferasirox using M1Exo; offers an effective solution for treating drug-resistant pancreatic cancer	[75]

Table 3 Natural drugs loaded in exosomes for the treatment of different kinds of cancers

Drug	Exosome sources	Cancer type/cell line	Finding	Ref
Curcumin	Bovine milk-derived exosomes	Human lung cancer (A549 and H1299), breast cancer (MDA-MB-231 and T47D)	A biocompatible and cost-effective source of exosomes. Enhanced anticancer and anti-inflammatory effects	[21]
β-elemene (ELE)	Adriacin (Adr) resistant MCF-7 cells (MCF-7/Adr) and docetaxel (Doc) resistant MCF-7 cells (MCF-7/Doc)	(MCF-7/Adr) and (MCF-7/Doc) cells	Drug resistance can be reversed by β-elemene/alteration of the expression of some MDR-related miRNAs, including PTEN (increased) and Pgp (decreased)	[81]
Honokiol (from the Magnolia plant)	mesenchymal stem cell-derived exosomes	Pancreatic cancer (MiaPaCa, Colo357), breast cancer (MDA-MB-231), ovarian cancer (SK-OV-3), colon cancer (HT-29), and prostate cancer (LNCaP) cells	Alterations in the expression of cell cycle- and survival-associated proteins/Cell Cycle Arrest and Apoptosis/more intracellular accumulation of honokiol in cancer cells	[82]
Black bean	Liver (HepG2) and prostate (PC3) cancer cells line	Liver and prostate	Enhanced antiproliferative activity	[76]
CLT	Milk from pasture-fed Holstein and Jersey cows	Lung cancer	Celastrol is Chemotherapeutic potential in lung cancer, and CSL is to be an effective and promising antitumor agent in clinical practice for the treatment of breast cancer	[83]
	Cell culture	Breast cancer	CSL is likely to be an effective and promising anti-tumor agent in clinical practice for the treatment of breast cancer	[80]

physicochemical and biopharmaceutical properties of such nano-formulations. Before they can be used clinically to treat disease, their safety and efficacy profiles must be extensively studied in vivo (Table 3).

Conclusion

We reviewed the literature that used exosomes as a drug delivery system for the treatment of malignancies. Cancer-specific drug delivery techniques could improve the therapeutic outcome in terms of patient survival. Many researchers have recently considered various applications of exosomes, but the pharmaceutical aspects will need to be investigated further in the future. As most chemotherapy drugs are not easily soluble in liquid, loading them into exosomes can be a suitable solution to this problem. This cancer treatment could avert the injection of high doses of drugs and provide a more appropriate release mechanism.

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Declarations

Conflict of interest The authors declare no competing financial interests.

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