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Invited Mini Review

Plant-derived extracellular vesicles as nanocarriers for combination therapy enhancing paclitaxel-based regimens in breast cancer

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Breast cancer remains a leading cause of morbidity and mortality worldwide. Triple-negative breast cancer (TNBC) presents unique challenges owing to its aggressiveness and limited treatment options. Paclitaxel-based chemotherapy is widely used in breast cancer treatment. However, its efficacy is often limited by toxicity, multidrug resistance, and lack of targeted delivery. In response to these challenges, recent studies have focused on the use of extracellular vesicles (EVs), particularly plant-derived EVs, as innovative drug delivery systems capable of enhancing therapeutic outcomes and reducing adverse effects. Plant-derived EVs offer significant advantages owing to their biocompatibility, low immunogenicity, and scalability. They provide a natural platform for delivering chemotherapeutics such as paclitaxel and doxorubicin directly to tumor cells. This review explores the therapeutic potential of plant-derived EVs in breast cancer treatment, focusing on TNBC by examining their ability to improve drug stability, bioavailability, and selective targeting of cancer cells. Key studies on EVs derived from plants such as grapefruit, ginger, and tea leaves have demonstrated their capacity to deliver chemotherapeutic agents effectively while mitigating common side effects associated with conventional delivery methods. Although the use of plant-derived EVs is still in early stages of research, findings suggest that that these nanocarriers can serve as transformative tools in oncology, providing a versatile and efficient platform for precise cancer treatment. This review highlights current landscape of research on plant-derived EVs, their application in breast cancer therapy, and future directions required to translate these findings into clinical practice. [BMB Reports 2025; 58(2): 53-63]

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INTRODUCTION

Cancer remains the leading cause of death worldwide, with significant variation in its incidence across types. Globally, lung cancer is leading in frequency, with approximately 2.48 million new cases in 2022 and the highest mortality rate of 18.7%. Breast cancer follows closely with approximately 2.3 million new cases, significantly affecting women's quality of life and resulting in high morbidity and mortality rates (1).

Treatment options for breast cancer have evolved to include surgery, radiation, hormone therapy, and chemotherapy, all of which have contributed to improved outcomes. Chemotherapy plays a pivotal role in treating high-risk and metastatic cases (2-5). Paclitaxel (PTX), a microtubule-stabilizing agent, has become a cornerstone of chemotherapeutic regimens for breast cancer. Recognized for its therapeutic efficacy across multiple disease stages, PTX is employed in both neoadjuvant and adjuvant contexts, considerably enhancing survival outcomes and decreasing recurrence rates when it is incorporated into combination therapy protocols (3, 4, 6). Nonetheless, challenges persist, including resistance and toxicity, which continue to drive research on optimizing PTX-based regimens. This review aims to explore the therapeutic potential of plant-derived extracellular vesicles (EVs) in breast cancer treatment, focusing on triple-negative breast cancer (TNBC) by examining these EVs' ability to improve drug stability, bioavailability, and selective targeting of cancer cells.

TAXANE-BASED CHEMOTHERAPY IN BREAST CANCER TREATMENT

Taxanes such as PTX are widely used in breast cancer therapy both in early stage and advanced diseases. They are often combined with other chemotherapeutic agents (7). In cervical cancer, PTX is combined with a platinum-based drug such as carboplatin or cisplatin. In addition, PTX has applications in non-small cell lung, ovarian, and gastric cancers by combining it with other agents (7, 8).

Breast cancer cells may display heightened sensitivity to microtubule stabilization compared with other tumor types. PTX can stabilize microtubules and block cell division. This

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mechanism is particularly valuable in metastatic breast cancer and TNBC. Given that TNBC lacks estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) receptors, making hormone- and HER2-targeted therapies ineffective, PTX offers a vital alternative as it targets microtubules independent of receptor status (9, 10).

In breast cancer treatment protocols, surgery remains fundamental. It is complemented by adjuvant chemotherapy post-surgery or neoadjuvant chemotherapy pre-surgery to reduce tumor size and recurrence risk (11). Moreover, PTX demonstrates notable synergy when it is combined with another agent such as doxorubicin (DOX) or carboplatin, specifically in breast cancer. In the setting of combined use of different types of anticancer drugs in the treatment of breast cancer, PTX has become the center of various treatment strategies due to its efficacy. Extensive clinical research has established the efficacy and safety of PTX in breast cancer treatment, providing optimized protocols that can improve disease-free and overall survival rates of patients with breast cancer. These studies underscore the critical role of PTX in enhancing treatment outcomes in breast cancer (12).

Chemotherapeutic agents are designed to target rapidly dividing cells, meaning that they can affect both cancer and healthy cells. This nonspecific action often results in side effects such as alopecia, nausea, diarrhea, and immunosuppression, with normal cell damage increasing as treatment intensity escalates (13, 14). Moreover, cancer cells frequently develop resistance to these agents over time, diminishing their therapeutic efficacies and complicating treatment efforts.

Although chemotherapy may temporarily reduce or eliminate tumor cells, recurrence remains a significant risk, with relapsed cancer often exhibiting heightened resistance, complicating the prospects for a complete cure. Consequently, chemotherapy is often administered in combination with surgery, radiation, or other therapeutic modalities to enhance efficacy. However, this multimodal approach increases the complexity of treatment plans and may introduce unexpected interactions between therapies. This variability highlights the need for tailored therapeutic strategies to optimize outcomes and minimize adverse effects for each patient.

ADVANTAGES OF EXTRACELLULAR VESICLES (EVs) IN DRUG DEVELOPMENT

Cancer remains the leading cause of mortality worldwide. Its treatment options are largely confined to surgical resection, chemotherapy, radiotherapy, and immunotherapy. Traditional monotherapies face considerable challenges, particularly in addressing cancer recurrence, metastasis, and multidrug resistance. TNBC is a malignant tumor with a poor prognosis and limited treatment options, and recurrence or metastasis can occur, so combination therapy is often necessary (15).

Among chemotherapy treatments for TNBC, conventional PTX-based chemotherapy is often combined with other drugs such as DOX to increase antitumor efficacy. Research efforts have focused on the development of nanocarriers that can improve therapeutic outcomes and reduce chemotherapy-associated side effects (15).

Key developments in this area include the use of albumin-bound PTX (nab-PTX) and liposomal formulations of DOX. Although nab-PTX has demonstrated efficacy in several cancers including metastatic breast cancer, it is associated with a higher incidence of peripheral neuropathy than solvent-based PTX, sometimes requiring dose reduction or treatment discontinuation (4). Additionally, severe neutropenia is more frequently reported after nab-PTX treatment. Liposomal DOX has shown improved delivery to tumor sites and a better safety profile than conventional DOX. However, its efficacy is similar to that of standard DOX (16).

To overcome limitations of synthetic nanomaterials and achieve more precise drug targeting, EVs as naturally derived classes of nanoscale vesicles have emerged as promising and sophisticated drug delivery platforms. EVs offer a biocompatible and potentially more effective approach than conventional anticancer chemotherapy agents for targeted drug delivery, presenting an opportunity to address the limitations of existing nanocarriers and improve therapeutic precision in cancer treatment.

Therefore, EV-based therapies have emerged as a promising frontier for cancer treatment. EVs are lipid bilayer-enclosed nanoscale structures (typically 40-160 nm) secreted by most cell types. They can carry diverse cargo of nucleic acids, proteins, enzymes, and metabolites. These vesicles are recognized for their capacity to mediate intercellular communication over both short and long distances, making them potential vectors for targeted therapeutic delivery (17). EVs offer exceptional biocompatibility owing to their endogenous cellular origin, enabling stable function within the body with minimal immunogenicity even after repeated administration (18). In addition, when enclosed within a lipid bilayer, EVs can protect their cargo, whether therapeutic drugs or nucleic acids, thereby enhancing their stability and ensuring that therapeutic agents remain intact until they reach the intended site (19).

In addition, EVs can recognize specific target receptors and facilitate highly selective delivery to specific cells or tissues (20). This selectivity can reduce adverse effects on healthy cells while enhancing therapeutic efficacy at the target site. EVs are versatile carriers capable of delivering several therapeutic molecules including proteins, RNA, and DNA, making them suitable for complex treatment strategies. For instance, EVs can co-deliver chemotherapeutic agents and gene therapies, providing a sophisticated platform for multimodal cancer treatment (21). Furthermore, EVs derived from a patient's own cells can support personalized therapeutic approaches tailored precisely to the patient's genetic and tumor-specific profiles. This strategy aligns with principles of precision medicine, fostering therapies that are optimally adapted to each patient's unique biological characteristics and ultimately enhancing therapeutic outcomes (22).

Inherent biocompatibility and ability of EVs to deliver multiple bioactive molecules to specific target cells present an innovative approach for enhancing therapeutic precision and efficacy, offering the potential to overcome limitations associated with conventional cancer therapies. Given these unique characteristics, EVs have drawn significant attention for their potential application in the treatment of challenging diseases, particularly cancer.

THERAPEUTIC POTENTIAL OF EVs IN CANCER THERAPY

Functionally, EVs can facilitate intercellular communication by transferring biomolecules that modulate activities of recipient cells. Owing to their inherent targeting ability, EVs can selectively deliver drugs to cancer cells, thereby minimizing off-target effects and immune responses (23, 24). Their biocompatible lipid bilayer can enhance their stability and their capacity to carry multiple therapeutic agents can simultaneously support combination therapy approaches. EVs are particularly valuable in treating complex cancers such as TNBC where multifaceted treatment strategies are often necessary.

Enhanced tumor targeting and efficacy

The use of EVs in cancer therapy has attracted considerable interest because of their natural affinity for tumor cells and enhanced drug delivery capabilities (25). A study by Tian *et al.* highlighted the potential of EVs as drug carriers in oncology to improve target specificity and showed that EVs derived from mouse immature dendritic cells effectively encapsulated DOX and delivered it effectively to cancer cells, enhancing drug accumulation and inhibiting tumor growth. Proven that it can be done (26). In another notable study, Kim *et al.* used macrophage-derived EVs as carriers for a chemotherapeutic drug

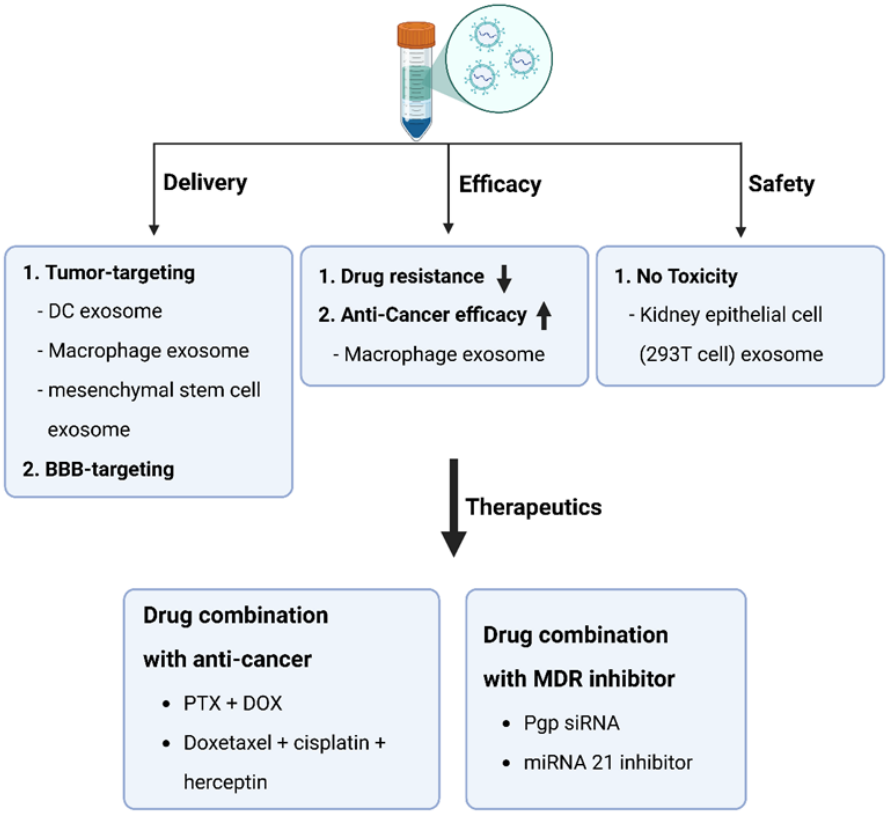

Fig. 1. Overview of a combination drug therapy via EV. EV-based drug delivery systems offer distinct advantages in delivery, efficacy, and safety. In terms of delivery, EVs enable precise targeting of tumors and efficient crossing of the blood-brain barrier. Regarding efficacy, EV-mediated drug delivery overcomes drug resistance by utilizing alternative uptake mechanisms and enhances intracellular drug retention, resulting in prolonged anticancer effects. From a safety perspective, EVs demonstrate proven *in vivo* biocompatibility. These attributes support the development of combination therapies, including those involving anticancer drugs with MDR inhibitors, for achieving significant therapeutic efficacy. Overall, the application of EVs as drug carriers offers a highly effective and innovative approach for enhancing current combination cancer therapies.

PTX, targeting specifically metastatic lung cancer cells. Results showed that PTX encapsulated within EVs selectively reached metastatic sites, improving therapeutic efficacy and reducing systemic toxicity (27). This target specificity can enhance anticancer efficacy and reduce toxicity (Table 1). In practical applications, DOX-loaded EVs have shown reduced toxicity, allowing for higher therapeutic concentrations and markedly suppressing the growth of MDA-MB-231 tumors in mouse xenograft models (28). The therapeutic efficacy of Exo-PTX for lung metastasis has been demonstrated in Lewis Lung Carcinoma mouse models, showing that intratracheal EV administration can result in significant co-localization with metastatic sites. Targeted intratumoral accumulation was confirmed by tracking EV-loaded DOX in cancer cells. It was attributed to specific surface molecules on macrophage-derived EVs that facilitated selective targeting and communication with cancer cells (29, 30). These findings aligned with those of a study by Parolini *et al*., who demonstrated that EVs preferentially fused in acidic tumor microenvironments (TMEs), enhancing Exo-PTX uptake and exerting robust inhibitory effects on metastatic lung tumor growth (31). Pascucci *et al*. have further substantiated the therapeutic potential of EVs, showing that mesenchymal stem cell-derived EVs could effectively deliver PTX in breast cancer treatment, highlighting EVs as efficient carriers for chemotherapeutic agents (32).

Targeting the brain via blood–brain barrier (BBB) penetration can be achieved by enhancing the specificity of EVs. EVs have demonstrated their ability to cross biological barriers such as the BBB, significantly enhancing their potential for delivering therapeutics to the brain. This capability is particularly promising for treating brain metastases, which affect nearly one-third of patients with TNBC and present a considerable clinical challenge. EVs can traverse the BBB via adsorption-mediated transcytosis, a process in which EVs can interact with BBB endothelial cells to facilitate transcytotic transport (33-35).

Through the presentation of specific surface ligands, EVs can also enable receptor-mediated targeting and facilitate precise modulation of signaling either through activation or inhibition in recipient cells. Notably, Kim *et al*. have conducted pivotal studies to illustrate these properties (36). Additionally, studies have demonstrated that EVs derived from immature dendritic cells modified with αv integrin-specific RGD peptide and loaded with DOX have significant therapeutic efficacy in a breast cancer model (37).

Overcoming drug resistance

Kim *et al*. confirmed the potential for resistance suppression to overcome p-glycoprotein-mediated drug efflux that causes drug resistance (36). This study showed that when DOX, a substrate of p-glycoprotein, was loaded into EVs, free DOX levels increased and drug accumulation in multidrug-resistant cells increased significantly, even in the presence of the p-glycoprotein inhibitor verapamil.

The increase in cytotoxicity of Exo-PTX was significantly greater in resistant cells (relative risk index [RRI] = 53.33) than in sensitive cells (RRI = 18.35). However, for naked PTX, its cytotoxicity almost showed no difference in between resistant (RRI $>$ 5.85) and sensitive cancer cells (RRI = 6.17). The higher cytotoxic effect of Exo-PTX on resistant cancer cells than on sensitive cells might be due to different internalization pathways of naked PTX and Exo-PTX. Although naked PTX is absorbed into cells through endocytosis, PTX encapsulated in EVs achieves superior absorption owing to adhesion molecules such as tetraspanins, integrins, immunoglobulins, proteoglycans, and lectins known to be absent in artificial nanoparticles. Consequently, loading an anticancer drug into EVs means that EVs can absorb a significantly larger amount of a drug than liposomes or polystyrene nanoparticles to overcome anticancer drug resistance (36).

High safety of EVs

Cell-free EV-based chemotherapy has the advantage of avoiding serious toxicities such as cytokine release syndrome and immune effector cell-related neurotoxicity syndrome, which are problems associated with cell-based chemotherapy such as chimeric antigen receptor T.

Additionally, although the efficacy of cell-based therapies can be altered by an immunosuppressive and acidic environment of the TME, EVs have the advantage of being essentially unresponsive to the host TME because they are unable to self-replicate. However, they have an advantage in that EV membrane of the EV can protect the cargo from the environment, maintain it for a long time, and increase *in vivo* stability of the delivered material.

No signs of toxicity were observed in their study, demonstrating a high tolerability of EVs and supporting their therapeutic applicability. This favorable safety profile suggests that EVs have significant potential as independent therapeutic agents and advanced drug delivery vehicles for cancer treatment (38).

In summary, EVs provide a sophisticated, biocompatible platform for targeted drug delivery in cancer therapy with significant potential to enhance treatment specificity, overcome drug resistance, and address challenging metastatic sites including the brain. The multifunctional capacity of EVs can make them transformative tools in precision oncology, thereby supporting effective therapeutic strategies for cancer (Fig. 1).

EVs as a cost-effective anticancer therapeutic strategy

Immune checkpoint inhibitors have recently been introduced as an innovative anti-cancer treatment method, showing very promising results in the treatment of TNBC. Pembrolizumab, a representative immune checkpoint inhibitor, is a monoclonal antibody that binds to the PD-1 protein expressed on the surface of T cells. Pembrolizumab is commonly prescribed for patients with advanced non-small cell lung cancer positive for PD-L1 expression, particularly among those with an expression rate of more than 50% whose cancer has progressed despite treatment with platinum-based chemotherapy. It is also used as

a treatment for various other types of cancer, including metastatic melanoma, Hodgkin lymphoma, urothelial cancer, and triple-negative breast cancer (39), since this treatment utilizes the patient's immune system to affect cancer cells, it is associated with few of the side effects typical of existing anticancer drugs. However, treatment with immune checkpoint inhibitors activated the immune response, with activated cells targeting not only cancer cells, but also the healthy liver, pancreas, thyroid gland, and pituitary gland, leading to hepatitis and thyroiditis. Consequently, side effects may occur, including fatigue, decreased appetite, gastrointestinal disorders such as diarrhea, breathing difficulties, and pneumonia (40).

The cost of treatment of immunotherapy varies depending on the number and duration of administrations; for example, Pembrolizumab costs approximately 4 million KRW per treatment cycle. As neoadjuvant treatment before surgery, Pembrolizumab is generally administered 8 times every 3 weeks or 4 times every 6 weeks, while as an adjuvant therapy after surgery, it is administered 9 times every 3 weeks or 5 times every 6 weeks. In this case, a maximum of 17 cycles can be used. The associated cost per patient is approximately 70 million KRW in non-benefit benefits.

The current price per 100 mg is 2,103,620 KRW in South Korea, and each administration requires 200 mg. Consequently, the annual cost of treatment typically ranges from approximately 70 million to 80 million KRW. Due to this significant financial burden, chemotherapy agents such as taxanes and anthracyclines remain important options for cancer treatment. Further, there is a growing need to develop cost-effective traditional chemotherapy methods that minimize toxicity to normal cells, while maintaining high efficacy in targeting cancer tissues. In this context, the EV drug delivery system presents a promising alternative.

IMPLEMENTATION OF COMBINATION CHEMOTHERAPY REGIMENS THROUGH ANTICANCER DRUG CARGO LOADING IN EVs

EVs are cell-derived secretory vesicles containing membranes and internal cargo that play a pivotal role in intercellular signaling. They have demonstrated a strong potential for efficient anticancer drug delivery. The remarkable versatility and loading capacity of engineered EVs provide promising opportunities for integrating multiple cancer treatment strategies. Notably, employing more than one anticancer agent enables a multitargeted approach against cancer cells through various mechanisms, thereby enhancing therapeutic efficacy. For aggressive cancers such as TNBC, for which combination chemotherapy regimens are essential, the ability to co-load key anticancer drugs into EVs can significantly improve therapeutic outcomes. In the next section, we will review studies on co-loading of multiple chemotherapeutic agents into EVs.

Multidrug resistance (MDR) is a major cause of chemotherapy failure. To overcome this problem of multidrug resistance, emphasis has been placed on the use of MDR inhibitors or new anticancer drugs (41). Using engineered EVs can be considered a promising strategy to co-deliver MDR inhibitors and chemotherapy agents to effectively inhibit MDR and improve the efficacy of chemotherapy. The primary mechanism of MDR involves overexpression of efflux transporters such as P-glycoprotein (Pgp) in tumor cell membranes. Consequently, co-delivery of Pgp siRNA and anticancer drugs using engineered EVs might effectively inhibit drug resistance. For example, Wang *et al*. have developed an aptamer-based red blood cell-mimetic vesicle carrying both Pgp siRNA and DOX (an anticancer drug), demonstrating a strategy to counteract Pgp-mediated MDR (42). Additionally, Yong *et al*. have designed biocompatible, tumor-derived, exosome-based porous silicon nanoparticles (DOX@E-PSiNPs) to co-deliver DOX while simultaneously inhibiting Pgp expression (37). These findings have confirmed the effectiveness of engineered EVs in enhancing the efficacy of chemotherapy by delivering anticancer drugs along with Pgp inhibitors. This approach highlights that EVs are powerful tools for improving chemotherapeutic outcomes by overcoming MDR (37). Another significant study has reported that EVs engineered to target HER2-positive colorectal cancer cells that encapsulate both miR-21 inhibitors and 5-FU (a chemotherapeutic agent) can effectively circumvent drug resistance in colorectal cancer (43). In the clinical field, the concept of combination chemotherapy is applied in cancer treatment to kill as many cancer cells as possible within the toxicity range that the patient can tolerate for each anticancer drug, overcome drug resistance, and expand the range of application in resistant tumors. Considering the above research results, co-delivery of various anticancer drugs using EVs shows potential as a smart anticancer drug delivery vehicle that can effectively implement combination anticancer chemotherapy.

Combination regimen of paclitaxel and doxorubicin in breast cancer chemotherapy

The combination of PTX, a taxane anticancer drug, and DOX, an anthracycline anticancer drug, is a basic strategy for breast cancer chemotherapy. In current clinical practice, this regimen involves administering DOX at 50 mg/m^2 as an IV bolus on day 1, followed by PTX at 135 mg/m^2 over a 3-h IV infusion on day 2, with cycles repeated every 3 weeks. This protocol is designed to administer both agents at maximum tolerated doses.

Chemotherapy combining paclitaxel and doxorubicin may play an important role in the management of breast cancer (44), and Franco *et al*. co-encapsulated paclitaxel and doxorubicin in different optimal ratios to prevent pharmacokinetic interactions between the two drugs (45). It is suggested that efficacy can be improved rather than administering drugs at intervals and that the effect of reducing paclitaxel concentration can be obtained through combination. Using MTT assays, they analyzed a synergistic interaction between paclitaxel and doxorubicin and identified the optimal drug ratio for enhanced tumor targeting. Their findings indicate that co-encapsulated

paclitaxel and doxorubicin within liposomes may be a promising approach for the management of breast cancer, given its effectiveness against human breast adenocarcinoma cell lines MDA-MB-231, MCF-7, and SKBR-3. Delivering chemotherapeutic agents to TNBC cells remains a significant challenge in cancer therapy because TNBC lacks tumor-specific markers, making treatment particularly difficult. One promising strategy for enhancing delivery of essential chemotherapeutic agents such as PTX and DOX to TNBC cells is to use EVs to target cancer cells. For instance, Haney *et al*. have utilized macrophage-derived EVs loaded with PTX and DOX to specifically target cancer cells and demonstrated strong anticancer effects of such EVs in a mouse lung metastasis model (29). They optimized various loading conditions including pH, temperature, and ultrasound to develop and characterize a novel EV-based drug formulation. The selected EV formulation showed high drug-loading capacity, efficient accumulation within TNBC cells, and potent antiproliferative effects. These drug-loaded EVs effectively targeted TNBC *in vivo*, inhibiting the growth of orthotopic T11 tumors in immunocompetent BALB/c mice and human MDA-MB-231 tumors in athymic nu/nu mice. Mi *et al*. have developed a nanocarrier system of d-alpha-tocopheryl-co-poly (ethylene glycol) 1,000 succinate-cisplatin prodrug (HTCP) nanoparticles (HTCP NPs) conjugated with herceptin for targeted co-delivery of cisplatin, docetaxel, and herceptin in a multimodal treatment of HER2-overexpressing breast cancer (46). IC50 values for docetaxel + cisplatin + herceptin (0.0201 + 0.00780 + 0.1629 μg/ml) were significantly lower in HER2-overexpressing SK-BR-3 cells than in HER2-low NIH3T3 cells (0.225 + 0.0875 + 1.827 μg/ml), demonstrating the targeted efficacy of HTCP NPs.

Overall, this EV-based formulation provides a promising solution for unmet clinical needs. It has the potential to reduce morbidity and mortality of patients with TNBC.

However, the challenge of loading drugs onto EVs remains unresolved. Although pre-loading methods involving co-incubation have been investigated for incorporating various chemotherapeutic agents such as DOX and PTX, these approaches are limited by their relatively low loading efficiencies. Alternatively, post-loading, which involves direct insertion of cargo into isolated EVs, allows for greater customization and reduces inclusion of extraneous substances. However, this method presents a drawback of potentially compromising structural integrity and stability of EVs.

PLANT-DERIVED EVs AS TARGETED DRUG DELIVERY SYSTEMS FOR CANCER THERAPY

Although chemotherapeutic agents have led to considerable progress in cancer treatment, maximizing the therapeutic efficacy of cytotoxic chemotherapy remains a challenge. A promising approach to address this limitation is to use artificial nanoparticles or EVs as drug delivery systems. However, the use of animal-derived exosomes, particularly those derived from cancer cells, carries potential risks of promoting cancer and inducing resistance to anticancer drugs.

Risk factors for using animal-derived EVs

Therapeutic application of EVs in cancer treatment primarily relies on EVs derived from animal cells, which introduces a potential risk of neoplastic transformation in recipients. For instance, EVs originating from breast cancer cells can promote tumorigenesis by delivering miRNA cargo, whereas EVs from metastatic breast cancer cells are associated with increased metastatic potential (47, 48). Additionally, EVs can activate fibroblasts, thereby enhancing stromal signaling at metastatic sites and remodeling distant microenvironments to facilitate metastasis (49). EVs can also contribute to breast cancer cell metastasis through mechanisms such as integrin expression and activation of Wnt–planar cell polarity autocrine signaling pathways. For example, miR-105 in breast cancer-derived EVs can inhibit the expression of the endothelial tight junction protein zonular occludens 1, thereby increasing vascular permeability and promoting metastatic spread (50, 51). Additionally, the emergence of chemotherapeutic resistance mediated by cancer-derived EVs is a significant challenge. A significant concern in chemotherapy is the ability of cancer cell-derived EVs to promote resistance to various chemotherapeutic agents. For example, HER2-positive EVs have been implicated in resistance to HER2-targeted therapies, whereas EVs derived from colorectal cancer cells are associated with the development of chemotherapy resistance (52, 53).

An innovative approach to overcome these limitations involves the use of plant-derived EVs as carriers of chemotherapeutic agents. Plant-derived EVs represent a novel and potentially biocompatible platform for targeted drug delivery, offering new opportunities to enhance cancer therapy. Plant-derived EVs have a markedly safer profile than EVs derived from tumor cells. For example, grapefruit produces a higher yield of EVs than other sources such as grapes, tomatoes, cow's milk, and ginger (54). In a study conducted by Wang *et al*., grapefruit-derived nano vectors effectively delivered chemotherapeutic agents, nucleic acids, and proteins to various cell types, with co-delivery of folic acid and PTX showing therapeutic benefits in a colorectal cancer mouse model (55). Moreover, a phase I clinical trial (NCT01668849) has investigated the use of plant-derived EVs to prevent oral mucositis in patients undergoing chemoradiotherapy for head and neck cancer, highlighting the potential of plant-derived EVs to mitigate treatment-related side effects in oncology (56).

Plant-derived EVs offer distinct advantages, particularly in terms of safety as they exhibit low toxicities. In addition, they are well-tolerated *in vivo*. From a production perspective, they offer scalability and cost-effectiveness because they can be readily extracted from plant byproducts. Moreover, as natural products, plant-derived EVs provide high biocompatibility with a reduced risk of immune response (18, 57). Therefore, the development of plant-derived EV-based drug delivery systems holds significant promise as a versatile and natural platform for

Table1. Exosome based chemotherapeutic agents for cancer

Therapeutics	EV source	Loading methods	*In vitro* model	Effect	*In vivo* model	Effect	Ref
Doxorubicin	HEK-293	Electroporati-on	HEK 293, SK-BR-3, BT20, HUVEC, PASMC, Cardiomyocytes	Enhanced anti-tumor effect selectively to cancer cells	NA	NA	(66)
	BM-MSC	Mixing	MG63, H9C2	Enhanced anti-tumor effect selectively to cancer cells	NA	NA	(67)
	Bovine milk	Electroporati-on	MDA-MB-231, MDA-MB-468, HCC 1806, HCC 1937	Reduced cell viability	NA	NA	(68)
	H1299, MRC9	Co-incubation	H1299, A549, MRC9, HCASM	Enhanced anti-tumor effect selectively to cancer cells	NA	NA	(69)
	Saccharomyces cerevisia expressing Her2 affibody	Physical adsorption	NIH3T6.7, SKOV3 MDA-MB-231	Reduced cell viability	HER2-overexpres-sing NIH3T6.7 mouse xenograft model	Suppression of tumor growth	(70)
	Ginger roots	Mixing	Colon-26 and HT-29	Enhanced anti-tumor effect	Colon 26 subcutaneous xenograft model	Inhibition of tumor growth	(71)
	Klebsiella pneumonia	Mixing	A549	Enhanced anti-tumor effect	A549tumor-bearing BALB/c nude mice	Increased anti-tumor activity	(72)
Paclitaxel	RAW 264.7	Ultrasound treat	MDCKMDR1, MDCKwt, and 3LL-M27	Enhanced anti-tumor effect selectively to cancer cells	C57BL/6 LLC model of lung metastases	Reduction in lung metastases	(36)
	RAW 264.7	Incubation and sonication	3LL-M27	Increased cellular uptake by receptor mediated endocytosis	C57BL/6 LLC model of lung metastases	Suppression of metastases and improved survival	(27)
	U87 GBM cells	Incubation and sonication	U87	Enhanced anti-tumor effects	NA	NA	(68)
	LNCaP- and PC-3 cells	Incubation	LNCaP, PC-3	Enhanced cytotoxic effects	NA	NA	(73)
Docetaxel	A549	Electroporation	A549	Suppressed the A549 cell proliferation	A549 xenograft mouse model by subcutaneously injected	Increased drug potency compared to PTX	(74)
5-FU	MSC	Incubation and sonication	CCA QBC939 cells	Enhanced anti-tumor effects	NA	NA	(75)
Withaferin A, Paclitaxel, Docetaxel	Bovine milk	Mixing	H1299, A549, MDA-MB-231, T47D	Enhanced efficacy and considerable growth inhibition	A549 lung tumor xenograft	Increased anti-tumor activity	(36)
Cisplatin	Bovine milk	Mixing	A2780CP	Enhanced anti-tumor effects	Ovarian tumor xenografts	Suppression of tumor growth	(76)

GBM: glioblastoma, BM-MCS: bone marrow-mesenchymal stem cells, "3LL-M27" Murine Lewis lung carcinoma cell subline, LNCaP cells are androgen-sensitive human prostate adenocarcinoma cells, PC-3 human prostate cancer cell line, MCF10A is an epithelial cell line that was isolated in 1984 from the mammary gland of a White, 36-year-old female with fibrocystic breasts, SK-BR-3 isa human breast cancer cell line that overexpresses the Her2 (Neu/ErbB-2) gene product. A549 cells are adenocarcinomic human alveolar basal epithelial cells, A2780 human ovarian cancer cell line.

innovative therapeutic applications using a wide range of plant sources. To date, research on plant-derived EVs for delivering formulated chemotherapeutics such as PTX remains limited. However, with continued advancements in the study of plant-derived EVs, these vesicles can potentially serve as a novel system for targeted delivery of anticancer agents such as PTX. Specific examples of plant-derived EVs used in anticancer drug delivery systems are described below.

Grapefruit-derived EVs

Wang *et al*. have explored nanovectors derived from grapefruit as carriers of anticancer drugs (58). These nanovectors have demonstrated high biocompatibility, low toxicity, and excellent stability and effectively delivered chemotherapeutic agents, such as PTX. These findings indicate that grapefruit-derived nanovectors can enhance the bioavailability of PTX, improve drug delivery efficiency, and optimize anticancer efficacy.

Ginger-derived EVs

Man *et al*. have confirmed that ginger-derived EVs have excellent potential as drug delivery systems and demonstrated the potential value of ginger-derived EVs as natural nanocarriers (59). In addition, Zhu *et al*. have confirmed that DOX, a powerful anticancer drug with many side effects such as thrombocytopenia, could be encapsulated by interacting with negatively charged ginger EV-like nanoparticle (GELN) to form a double layer (60). In particular, DOX encapsulated in GELN has a high loading efficiency and biocompatibility, which might be owing to increased ability of GELN to deliver DOX to tumor tissues.

Collectively, these studies highlight the potential of plant-derived EVs as safe and effective drug delivery vehicles in oncology, offering improvements in drug stability, bioavailability, and targeting precision.

Application of plant-derived EVs in treatment of triple-negative breast cancer

Research on plant-derived EVs for treating TNBC is relatively new and promising. Anusha *et al*. have found that GELNs can induce apoptosis, cell cycle arrest, and antimetastatic effects in a TNBC cell line MDA-MB-231 (61). Chen *et al*. investigated tea leaf-derived exosome-like nanotherapeutics (TLNT) and demonstrated that TLNT has antioxidant and anticancer properties and can inhibit breast cancer growth through pro-apoptotic effects and microbiota regulation (62).

These findings highlight the potential of plant-derived EVs as innovative therapeutic agents for TNBC. These EVs offer a promising avenue for further research in natural product-based oncology. Grape-derived nanoparticles possess intrinsic anticancer properties with antitumor effects against TNBC cells. Additionally, grape-derived nanoparticles can induce autophagy and inhibit cancer cell proliferation (63).

Wang *et al*. reported that curcumin-containing nanoparticles exhibit higher antitumor efficacy against breast cancer compared to free curcumin. This discovery highlights the potent anticancer effects of curcumin nanoparticles derived from turmeric, emphasizing their promising role as an efficient approach for targeting cancer cells in cancer therapy (64).

However, these studies remain in their early stages, with most being conducted at the preclinical level. Plant-derived EVs have gained significant attention as potential anticancer agents owing to their high biocompatibility and safety. Although further research and clinical trials are required, this approach holds promise for advancing TNBC treatment, especially given that many essential chemotherapeutics currently in use are plant-derived.

EVs IN TUMOR TREATMENT CLINICAL TRIALS

The application of EVs in the clinic is still in its early stages, with most relevant studies being conducted at the preclinical level. However, due to its antitumor effects demonstrated in both *in vitro* and *in vivo* studies, as well as its nanocarrier characteristics, EV-based cancer therapy is considered a viable approach for clinical treatment. Examples of clinical trials using EVs as a registered drug delivery system include one employing ribociclib for Her-2 (−) breast cancer (NCT02278120), one using trastuzumab emtansine for Her-2 (+) breast cancer (NCT01772472), and one targeting TNBC with chemotherapy and atezolizumab (NCT02425891). Additionally, there is one trial targeting colon cancer using plant-derived EVs loaded with curcumin (NCT01294072) (65).

CONCLUSIONS

EVs are considered as highly promising tools for cancer therapy because of their biocompatibility, stability, and targeting capabilities. Given inherent limitations of current anticancer therapies and frequent need for combination regimens, leveraging unique properties of EVs can offer an effective approach for cancer treatment. In particular, plant-derived EVs show significant potential as natural product-based drug delivery systems. Although research on delivery of chemotherapeutics such as PTX through plant-derived EVs is still in its infancy, this strategy can play a crucial role in the development of safer and more effective cancer treatments. Overall, EVs have demonstrated significant potential as carriers for anticancer drugs. However, challenges remain, particularly in establishing the large-scale production and storage, and in obtaining regulatory approval of plant-derived EVs (PDEVs). Furthermore, clinical trials are still limited, leading to uncertainty regarding their efficacy in humans. Selecting appropriate plant cell sources will be essential to ensure successful and safe production. Additionally, no standardized isolation method has yet been established, and identifying reproducible characteristics, such as specific markers, of PDEV remains difficult. Therefore, standardization for both quantitative and qualitative analyses is crucial to facilitate large-scale commercial production and quality control. Current

extraction and purification methods, such as ultracentrifugation and density gradient centrifugation, are time-consuming, have low yield, and do not guarantee high purity. Furthermore, research on the changes in physicochemical properties and biological activity under various storage conditions remains insufficient. Along with these challenges, a clear understanding of the potential interactions between plant-derived EVs and the loaded drugs, as well as their physiological effects, is necessary to assess clinical applications.

With further research, the potential of a PTX delivery system using plant-derived EVs may become increasingly viable, ultimately advancing their clinical application as an anticancer therapy. This would provide a significant benefit for patients with hard-to-treat cancers such as TNBC, where treatment options are limited. It can markedly improve quality of life for patients.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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