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Exploring new Horizons in overcoming P-glycoprotein-mediated multidrug-resistant breast cancer via nanoscale drug delivery platforms



Paras Famta^{a,1}, Saurabh Shah^{a,1}, Esha Chatterjee^b, Hoshiyar Singh^b, Biswajit Dey^b, Santosh Kumar Guru^b, Shashi Bala Singh^b, Saurabh Srivastava^{a,*}

^a Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, India

^b Department of Pharmacology, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, India

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ABSTRACT

The high probability (13%) of women developing breast cancer in their lifetimes in America is exacerbated by the emergence of multidrug resistance after exposure to first-line chemotherapeutic agents. Permeation glycoprotein (P-gp)-mediated drug efflux is widely recognized as the major driver of this resistance. Initial *in vitro* and *in vivo* investigations of the co-delivery of chemotherapeutic agents and P-gp inhibitors have yielded satisfactory results; however, these results have not translated to clinical settings. The systemic delivery of multiple agents causes adverse effects and drug–drug interactions, and diminishes patient compliance. Nanocarrier-based site-specific delivery has recently gained substantial attention among researchers for its promise in circumventing the pitfalls associated with conventional therapy. In this review article, we focus on nanocarrier-based co-delivery approaches encompassing a wide range of P-gp inhibitors along with chemotherapeutic agents. We discuss the contributions of active targeting and stimuli responsive systems in imparting site-specific cytotoxicity and reducing both the dose and adverse effects.

1. Introduction

Breast cancer (BC) has become the most prevalent type of cancer among women in recent years. In the year 2020, of the total 2.3 million diagnosed cases of BC worldwide, 685,000 resulted in death. By the end of 2020, a total of 7.8 million women were reported to be diagnosed with BC in the previous 5 years (Rosenqvist, 2021). These alarming statistics indicate that BC is the most prevalent cancer worldwide. The categorization of BC into particular subtypes depends on the expression of receptors such as estrogen receptors and progesterone receptors. Subtype classification also depends on the expression of the human epidermal growth factor receptor 2 (HER2) oncogene and cell proliferation marker Ki-67 labeling index in BC cells (Table 1) (Awadelkarim et al., 2012).

The incidence of luminal cancer is highest (70%) and is followed by HER2-positive (15–20%) and triple-negative (15%) cancer, whereas the odds of recurrence are highest in triple-negative cancers. The treatment for luminal cancers includes endocrinology-based therapy, and chemotherapy is also used depending on the tumor response (Harbeck and Gnant, 2017). Patients with non-luminal BC receive HER2-targeted

antibody supplemented with chemotherapy (Loibl and Gianni, 2017). Chemotherapy is a prominent treatment for triple-negative BC (Wahba and El-Hadaad, 2015). Surgical ablation followed by radiation therapy is commonly used in the treatment of non-metastatic tumors (Waks and Winer, 2019). A recent clinical study in China has reported that the permeation-glycoprotein (P-gp) gene is most commonly overexpressed in the TNBC subtype (40.9% of total cases), followed by luminal A (27.6%), luminal B (17.0%), and HER2+ (14.6%) (Zhao et al., 2020).

Multidrug resistance (MDR) is the predominant reason for the failure of various chemotherapeutic treatments. MDR leads to resistance toward anticancer agents in various blood cancers and solid tumors, including BC (Bugde et al., 2017). Various mechanisms for MDR generation in cancer cells have been observed, such as high expression of drug efflux transporter proteins, modulation of cellular metabolism, drug detoxification, DNA repair pathway alterations, modulation of anti-apoptotic proteins, and chemical changes in targets (Markman et al., 2013; Miller et al., 2021). MDR has two types: acquired and intrinsic. Acquired MDR is nonspecific and is characterized by overexpression of efflux transporters, which pump the chemotherapeutic agents out of cancer cells (Ledwith et al., 2016). Cancer cells with intrinsic MDR undergo hyperactive

* Corresponding author. Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Balanagar, Hyderabad, 500037, Telangana, India.

E-mail address: saurabh@niperhyd.ac.in (S. Srivastava).

¹ Authors contributed equally.

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Abbreviations			
ABC	ATP binding cassette	NO	nitric oxide
AgNPs	silver nanoparticles	PDOX	palmitoyl doxorubicin
BC	breast cancer	PTX	paclitaxel
CD44	cluster determinant 44 receptor	P-gp	P-glycoprotein
DOC	docetaxel	PLA	polylactic acid
DOX	doxorubicin	PUFA	polyunsaturated fatty acids
FR	folic acid receptor	ROS	reactive oxygen species
FAL	folic acid decorated liposomes	SNELS	small nanoemulsifying lipids
HER2	human epidermal growth factor receptor 2	TPGS	tocopheryl polyethylene glycol succinate
HA	hyaluronic acid	TME	tumor microenvironment
HIF	hypoxia-inducible factors	TR	transferrin receptor
MDR	multidrug resistance	TR1	transferrin receptor-1
NPs	nanoparticles	TR2	transferrin receptor-2
		VER	verapamil hydrochloride
		VESOO	vitamin E succinate modified octahistidine-octaarginine

Table 1

Molecular subtypes of BC. (+) indicates presence, and (–) indicates absence. (+ or –) indicates that a marker may or may not be present.

Cancer subtype	Estrogen receptor	Progesterone receptor	HER2	Ki-67	General characteristics
Luminal A	+	+ or –	–	–	Most common type of BC with good prognosis
Luminal B	+	+ or –	+ or –	+	Worse prognosis than luminal A
Non-luminal	–	–	+	–	Less common and highly aggressive subtype placing young women at risk
Triple negative	–	–	–	–	Very aggressive subtype with a high tendency to metastasize

detoxification processes, such as high oxidant scavenging and the downregulation of pro-apoptotic proteins (Indran et al., 2011). Tumors comprise both drug-sensitive and drug-resistant cells. A course of chemotherapy kills the sensitive cells, thus leaving a population of resistant cells. Over time, these resistant cells develop into drug-resistant tumors (“Cancer Multidrug Resistance,” 2000).

MDR cancer cells are characterized by hyperactive mitochondria (Farnie et al., 2015) with increased mass and ATP production ability. Mitochondria undergo oxidative phosphorylation, thereby imparting energy to cells via ATP generation. Mitochondria are the main source of reactive oxygen species (ROS) and play important roles in oxidative signaling and consequently cell division. MDR cancer cells, compared with normal cells and non-MDR cancer cells, are characterized by greater mitochondrial bulk and hyperpolarized mitochondria (Dartier et al., 2017; Henkenius et al., 2017). Because P-gp efflux transporters require ATP to pump the chemotherapeutic agents out of cells, mitochondrial targeting is an attractive approach to kill MDR cancer cells (Indran et al., 2011; Weinberg and Chandel, 2015). The various reasons for the amplification of the P-gp transporter on MDR cancer cells comprise faulty regulation of gene expression, enhanced biostability of *MDR1* gene messengers, epigenetic pathways, and modulation of the P-gp encoding genomic locus (Sike et al., 2014).

2. The menace of P-gp facilitated MDR in breast cancer

Structurally, P-gp is a glycoprotein containing 1280 amino acids. P-gp is composed of two intracellular homologous nucleotide-binding domains (NBDs) and two transmembrane domains (TMDs). Each TMD comprises six transmembrane domains and two ATP binding sites joined by a flexible linker polypeptide (Alam et al., 2019; Hoosain et al., 2015; Y. Kim and Chen, 2018). The P-gp inhibitor may act as competitive blocker or a non-competitive antagonist by occupying the drug binding sites or binding chemosensitizer sites, respectively (Ford et al., 1996); sometimes the inhibition is allosteric. Importantly, P-gp has multiple drug binding sites in TMDs (Mittra et al., 2017). Furthermore, the inhibitors act by altering the mobility of cell membrane lipids and interfering with membrane fluidity and ATP hydrolysis (Fig. 1(A)) (Hamed

et al., 2019; Jun Yu et al., 2016). P-gp was discovered in 1976, when Chinese hamster ovary cells were found to show resistance to colchicine and a wide range of amphiphilic drugs. Surface labeling studies indicated that the resistant cells had a carbohydrate containing protein with a molecular weight of 170,000 Da (Juliano and Ling, 1976). P-gp is an ATP binding cassette (ABC) transporter genetically encoded as *MDR1* and *ABCB1*, which is encoded by the gene *ABCB1* (Ji et al., 2019). This membrane glycoprotein acts as an efflux transporter pumping the substrate, i.e., chemotherapeutic agents, out of cancer cells (Fruci et al., 2016). The source of energy for these transporters is ATP hydrolysis. The substrates for P-gp include ions and various endogenous or exogenous molecules, particularly hydrophobic drugs. Cancer cells with P-gp overexpression show simultaneous resistance to a wide range of structurally unrelated chemotherapeutic agents. Overexpression of P-gp is the basis for resistance to chemotherapeutic agents, including taxanes, anthracyclines, vinca alkaloids, and epipodophyllotoxins (Sosnik, 2013; Szakács et al., 2006). The MDR action of P-gp is assisted by enzymes such as glutathione *S*-transferases, which promote drug resistance by antagonizing mitogen-activated protein kinase (Borrie et al., 2017). P-gp expression is 2.72-fold higher in MDR BC cell lines than in drug-sensitive cancer cells (Mechetner et al., 1998).

Meta-analysis results have indicated that patients with BC are likely to be MDR-positive after treatment, thus further suggesting that treatment induces the expression of P-gp (Trock et al., 1997). Some patients with BC appear to show a naturally more aggressive phenotype even before treatment. Elevated baseline P-gp expression is a major hallmark of this aggressiveness (Clarke et al., 2005). Several causes of upregulation of P-gp have been reported, such as epigenetic mechanisms, intrinsic cancer genomic instability, gene rearrangements, tumor mutational burden, and inflammatory stressors in the tumor microenvironment (TME). These factors might regulate the upregulation of P-gp via modulating the promoter region of the *ABCB1* gene (Fig. 1(B)). Oncogenes, including p53, Ras, and c-Raf, as well as nuclear receptors, such as pregnane X receptor and constitutive androstane receptor, participate in P-gp expression initiation (Nanayakkara et al., 2018; Robinson and Tiriveedhi, 2020). Beyond cancer cells, P-gp is also present in normal cells, where it performs roles necessary for normal body function. P-gp is

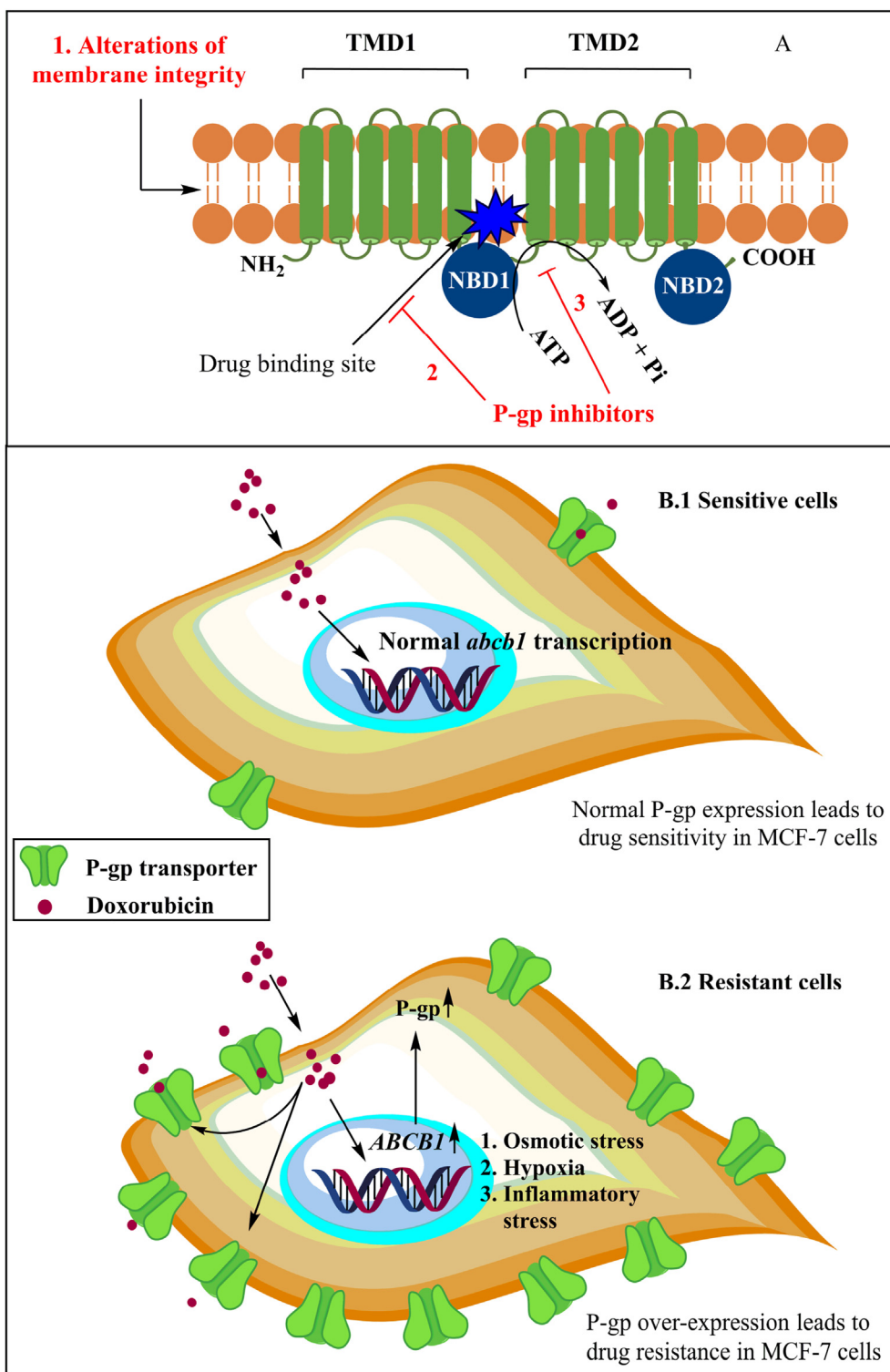


Fig. 1. (A) The P-gp efflux transporter and its inhibitory sites. The P-gp transporter consists of two transmembrane domains (TMD1 and TMD2) and two intracellularly located nucleotide binding domains (NBD1 and NBD2). Each TMD contains two ATP binding sites. P-gp inhibitors may act by inhibiting drug binding sites, changing membrane fluidity and permeability, or inhibiting ATP hydrolysis. (B) P-gp-mediated chemoresistance. (B.1) In sensitive cells, DOX first accumulates within the cells. (B.2) The *ABCBI* gene is upregulated after the chemotherapeutic (DOX) treatment of cancer cells, which makes cancer cells resistant to chemotherapy. The expression of P-gp protein is upregulated, thus leading to the efflux of chemotherapeutic drugs (DOX). Importantly, additional factors including osmotic stress, hypoxia, and inflammatory stress aid in overexpression P-gp protein, excess drug efflux, and chemoresistance.

present in several organs in the human body, and it functions by exporting toxic materials out of healthy cells. P-gp is extensively present at physiological barriers such as the blood–brain barrier, placental barrier, and intestinal barrier (Y. Lai, 2013). Inhibition of the P-gp transporters in these physiological barriers may disrupt normal physiology and affect the pharmacokinetics of various drugs; hence, targeted anti-P-gp therapy in cancer cells is important to circumvent the adverse effects (Guo et al., 2017). Nanoscale formulations play essential roles in such specific drug delivery.

The exogenous substrates of P-gp efflux are predominantly lipophilic or amphipathic (Eckford and Sharom, 2009). The lipophilic substrates accumulate within the lipid bilayer, whereas the amphipathic substrates align in the interfacial region. P-gp has been shown to efflux drugs from the cell membrane itself rather than the intracellular vicinity. In addition, transport by P-gp has also been proposed to occur from the intracellular vicinity (Sharom, 2014). On the basis of several hypotheses and observations, three models have been established: the pore-forming, flippase, and hydrophobic vacuum cleaner models. The pore-forming model

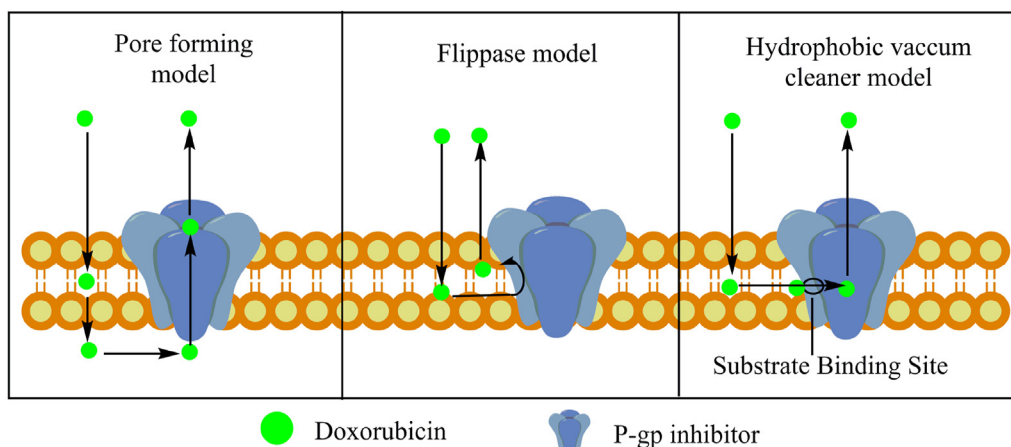


Fig. 2. Three models (pore-forming, flippase, and hydrophobic vacuum cleaner model) depicting the efflux of chemotherapeutic agents from MDR BC cells. Reproduced from Dewanjee et al. licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/legalcode>) Copyright © 2017 (Dewanjee et al., 2017). Saikat Dewanjee, Tarun K. Dua, Niloy Bhattacharjee, Anup Das, Moumita Gangopadhyay, Ritu Khanra, Swarnalata Joardar, Muhammad Riaz, Vincenzo De Feo and Muhammad Zia-Ul-Haq. Published by Molecules, MDPI.

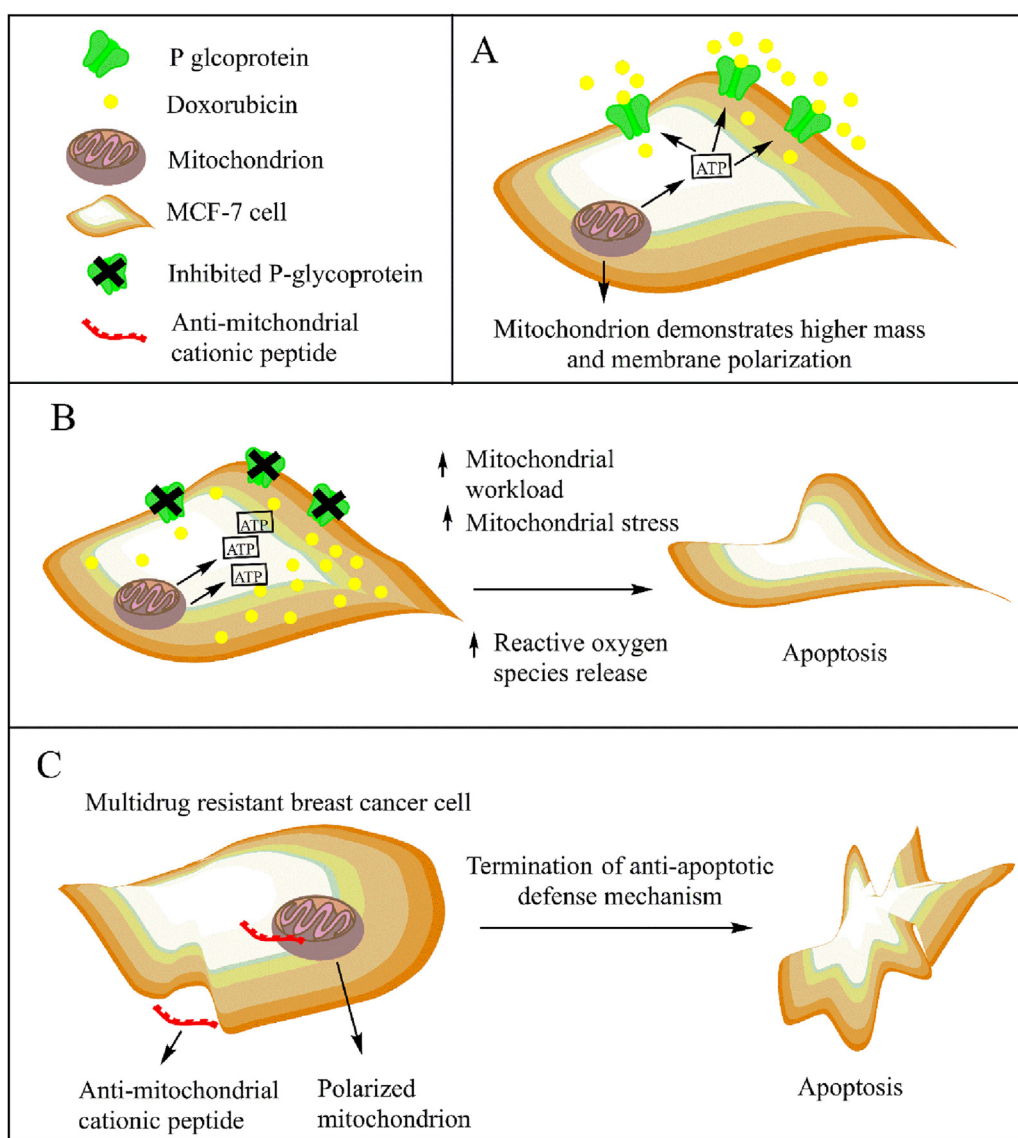


Fig. 3. Pictorial illustrations of the applications of mitochondrial targeting to reverse MDR. (A) Illustrates the DOX-resistant MCF-7 cells; the mitochondrion is depicted to provide ATP for the functioning of overexpressed P-gp transporters. Resistant cells are characterized by mitochondria with higher mass and more polarized membranes. (B) Depicts a P-gp transporter-inhibited MCF-7 cell. In such cells, the stress on the mitochondria is increased, thus increasing ATP production to facilitate P-gp transporter function. This greater mitochondrial stress results in ROS generation and ultimately apoptosis. (C) Depicts cationic peptide conjugates to deliver chemotherapeutic agents to over-polarized mitochondria. The mitochondrial targeted delivery leads to the termination of anti-apoptotic pathways and the discontinuation of the ATP generation necessary for P-gp functioning and other basic cell metabolic reactions.

proposes that drugs associated with P-gp are released from the cell directly through a protein channel. In the flippase model, drug efflux occurs by flipping of drug molecules from the inner leaflet to the outer

leaflet of the plasma membrane. Here, the flipping is performed by P-gp via interaction of the drug with the substrate binding pocket, as shown in Fig. 2. A clear concentration gradient is also created, wherein the outer

Table 2
Clinical studies of drugs used as P-gp inhibitors along with their generation.

P-gp inhibitor	Generation	Phase	NCT identification number
Simvastatin	First	Phase 2	NCT04418089
Lansoprazole	First	Phase 3	NCT04874935
Cyclosporine	First	Phase 1	NCT03768609
Valspodar	Second	Phase 1	NCT00001302
11C-JNJ-63779586	Third	Phase 1	NCT03089918
Tariquidar	Third	Phase 1	NCT00001944
Tariquidar	Third	Phase 2	NCT00048633
Laniquidar	Third	Phase 2	NCT00028873
Annamycin	Third	Phase 1/2	NCT00012129

leaflet contains a greater drug concentration than the inner leaflet of the membrane. The drug molecules then diffuse from the outer leaflet to the extracellular matrix of cancer cells. The hydrophobic vacuum cleaner model describes the recognition of intramembranous lipophilic foreign drug molecules by P-gp. The drug molecules then enter the P-gp receptor through the membranous site and are released from the cell to the extracellular space (Fig. 2) (Constantinides and Wasan, 2007; Hoosain et al., 2015). Moreover, P-gp actively potentiates MDR by perturbing tumor necrosis factor- and caspase-related apoptosis pathways (Galski et al., 2013; Souza et al., 2015). BC is heterogeneous in nature, and its clinical and pathological conditions consequently vary greatly among patients (Turashvili and Brogi, 2017). Hence, finding an efficient combination of chemotherapeutic drug and P-gp inhibitor is a challenge for physicians and scientists (see Fig. 3).

3. P-gp inhibitors investigated for chemosensitization in MDR BC

Because the P-gp transporter is widely recognized to transport drugs out of MDR BC cells, P-gp inhibitors have been extensively explored for

the sensitization of chemotherapeutic agents. Chemosensitizer therapy is successful only when it can target tumors while avoiding normal tissue (Nanayakkara et al., 2018). Various inhibitors, both synthetic and natural, have been studied as active pharmaceutical excipients for their P-gp inhibitory potential. The mode of action of different chemosensitizers also varies, because they do not target P-gp exclusively. P-gp inhibitors act as competitive blockers or as non-competitive antagonists, or bind the allosteric site (Ford et al., 1996). Inhibitors may also act by altering the mobility of cell membrane lipids, thereby interfering with membrane fluidity and ATP hydrolysis (Jun Yu et al., 2016). Beyond inhibiting P-gp, these inhibitors may modulate other pathways and consequently inhibit the propagation of tumors in BC. For example, quercetin promotes chemosensitivity by reversing MDR in cancer cells by impeding Y-box binding protein 1 activity and constraining P-gp mediated drug efflux (S. Li et al., 2018). Rutin arrests the cell cycle at G2/M and G0/G1 phases, and promotes apoptosis of cancer cells (Guestini et al., 2017). However, one P-gp inhibitor may promote the action of one or several specific chemotherapeutic drugs, but not all drugs. Therefore, many factors underlie the use of a specific inhibitor, thus potentially explaining why few P-gp inhibitors identified in preclinical observations and computer simulations have been successful in all phases of clinical trials (Nanayakkara et al., 2018; Robinson and Tiriveedhi, 2020). Various P-gp inhibitors investigated in different phases of clinical trials are summarized in Table 2.

The inhibitors are broadly divided into three generations: first, second, and third generation. An ideal P-gp inhibitor should be nontoxic and should lack pharmacological activity beyond P-gp inhibition (Binkhathlan et al., 2012). Tsuruo and co-workers first introduced P-gp inhibition for the reversal of chemoresistance in cancer cells. They have reported an enhanced intracellular accumulation of vincristine when incorporated with verapamil (VER) and trifluoperazine in P388 leukemia cells (Tsuruo et al., 1981). Several P-gp inhibitors have been introduced.

Table 3
Recent use of first-, second-, and third-generation P-gp inhibitors co-delivered with common chemotherapeutic agents to re-sensitize drug-resistant BC cells.

P-gp inhibitor	Anticancer drug	Nanotherapeutic approach	Cancer models used for investigations	Outcome	Reference
First generation P-gp inhibitor					
Verapamil	DOX	PLGA NPs	MCF-7 BC cell line	Increased cytotoxicity achieved with the combination	Ahmadi et al. (2019)
Verapamil	DOX	Reduction-sensitive liposomes	MCF-7/ADR cell lines, tumor spheroids and <i>in vivo</i>	Increased DOX uptake in cancer cells; low DOX-mediated toxicity <i>in vivo</i>	Tang et al. (2016)
Verapamil	PTX	-	MCF-7/ADR cancer cell line	3-fold increase in the cytotoxicity of MCF-7/ADR cell lines through co-delivery of VER and PTX	P. Li et al. (2019)
Verapamil	DOC	Reduction-sensitive micelles	MCF-7/ADR cancer cell line	3.52-fold increased cytotoxic activity in MDR BC cell lines	Yuanyuan Guo et al. (2017)
Diltiazem	DOX	-	MCF-7 cell line	4-fold increased cytotoxicity with 20 µg/mL treatment	Al-malky et al. (2019)
Quinidine	DOX	Methoxy-PEG-glycine-quinidine conjugate	MDA-435/LC-6 WT cell lines and <i>in vivo</i> preclinical studies	Excellent MDR reversal with an IC ₅₀ of 4.61 µg/mL	Snyder et al. (2020)
Second generation P-gp inhibitors					
Valspodar	DOX	PEGylated liposomes	T47D/TAMR-6-resistant human BC cell line	Higher cytotoxicity for the combination versus free DOX	Bajelan et al. (2012)
Third generation P-gp inhibitors					
Tariquidar	PTX	Biotin coated PLGA NPs	JC-resistant murine BC cell line	Decrease in IC ₅₀ value of PTX from more than 300 nM (free PTX) to 40 nM	Patil et al. (2009)
Tariquidar	PTX	E-tocopheryl polyethylene glycol succinate micelles	MCF-7/ADR-resistant BC cell line <i>in vitro</i>	Improved cytotoxicity and decreased IL-10 levels with co-delivery of tariquidar with PTX	(B. Y. Liu et al., 2016)
Tariquidar	DOX	Hyaluronic acid functionalized dendritic polyglycerol conjugated, mesoporous silica nanocarriers	MDA-MB 231 breast cells: adherent and mammosphere cell cultures <i>in vitro</i>	Increased cytotoxicity of DOX with co-delivery	Pan et al. (2020)
Tariquidar	PTX	Folic acid modified erythrocytes	<i>In vitro</i> and <i>in vivo</i> investigations in PTX-resistant MCF-7/taxol cells	Superior cytotoxic profile through inducing apoptosis in 69.8% MCF-7/taxol cells <i>in vitro</i> (IC ₅₀ = 6.30 µM)	Zhong et al. (2020)
Elacridar	PTX	Transferrin coated PLGA NPs	EMT6/AR1.0-resistant BC cell line	Sensitization of resistant cell line to PTX	Tonbul et al. (2019)
Zosquidar	DOX	pH-sensitive albumin conjugate	MCF-7/ADR and MT-3/ADR DOX-resistant BC cell line	Re-sensitization of cancer cell line to DOX	Abu Ajaj et al. (2012)

DOC = docetaxel; DOX = doxorubicin; PTX = paclitaxel.

Table 4

Recent use of phytochemicals as P-gp modulators in various nanoformulations.

Phytochemical	Anticancer drug	Formulation	Cancer models used for investigation	Pharmacological activity	Reference
Co-delivery of flavonoids along with various chemotherapeutic agents for MDR reversal					
QUE	ADR	PEGylated liposomes	ADR-resistant MCF-7 and HL-6 cell lines <i>in vitro</i> ; BC tumor <i>in vivo</i>	3.21-fold enhanced cytotoxicity of ADR in drug-resistant MCF-7 cells	Jiaqi Yu et al. (2019)
QUE	DOX	Biotin coated gold nanocages	MCF-7/ADR-resistant cells	Reversal of MDR and high toxicity (IC ₅₀ 1.5 µg/mL) in MCF-7/ADR cells <i>in vitro</i>	Z. Zhang et al. (2018)
QUE	DOX	Biotin coated poly (ethylene glycol)-b-poly (ε-caprolactone) NPs	DOX-resistant MCF-7 BC cell line <i>in vitro</i> and <i>in vivo</i>	IC ₅₀ of 0.26 µg/mL, 136- and 94-fold higher than that of free DOX and free DOX + QUE, respectively	Lv et al. (2016)
QUE	DOX	Biotin conjugate modified liposomes	Drug-resistant MCF-7/ADR BC cell line	Enhanced accumulation of DOX in the cytoplasm, owing to P-gp inhibition leading to elevated toxicity	Jiulong Zhang et al. (2016)
QUE	DOC	Hyaluronic acid functionalized PLGA-polyethyleneimine NPs	4T1 BC cells <i>in vitro</i> and <i>in vivo</i>	95.6% decrease in cell migration and 99.3% decrease in cell invasion	(J. Li et al., 2017)
QUE	DOC	Bovine serum albumin NPs	MCF-7 and MDA-MB 231 BC cell line <i>in vitro</i> and <i>in vivo</i>	2.5-fold increase in DOC bioavailability with better tumor reduction ability; downregulation of P-gp expression in both MCF-7 and MDA-MB 231 cells	Desale et al. (2018)
Silymarin	DOX	Liposomes	4T1 BC cells	Synergistic anticancer properties with downregulation of cell proliferation and P-gp expression	Gheybi et al. (2019)
Curcumin	DOX	Biotin functionalized self-assembled NPs made of poly (curcumin dithiodipropionic acid)-b-PEG-biotin	Drug-resistant MCF-7/ADR BC cell line xenograft	Synergistic cytotoxicity and chemosensitization; Inhibition of ATP generation in cancer cells; downregulation of P-gp transporters	(S. Guo et al., 2016a)
Co-delivery of terpenes and terpenoids along with various chemotherapeutic agents for MDR reversal					
Oleanolic acid	DOX	Folic acid functionalized chitosan and oleanolic acid copolymer self-assembled NPs	MDA-MB-231 drug-resistant BC cell line <i>in vitro</i> and <i>in vivo</i>	Improved internalization in MDA-MB-231 cancer cells <i>in vitro</i> with NPs; minimal uptake in HUVECs; 4.33-fold higher cytotoxicity with DOX-loaded NPs compared with free DOX	Niu et al. (2019)
Boswellic acid	DOC	DOC-loaded frankincense oil oral nanoemulsion	MDA-MB-231 BC cell line	Greater internalization (5 times) and lower IC ₅₀ 2.5 µg/mL (4.3-fold) than the marketed taxotere®	Pandey et al. (2017)
Ethanol extract of pachymic acid and dehydro-tumulosic acid	DOX	Liposomes	Drug-resistant MCF-7 cancer cell line <i>in vitro</i> and <i>in vivo</i>	IC ₅₀ of DOX decreased by 1.66-, 13.92-, and 39.99-fold with co-delivery of 5, 25, and 50 µg/mL ethanolic extract, respectively	Yanan Li et al. (2020)

ADR = adriamycin; DOX = doxorubicin; DOC = docetaxel; QUE = quercetin; NPs = nanoparticles.

The first-generation P-gp inhibitors were pharmacologically active agents repurposed for P-gp inhibition activity, including structurally diverse agents such as calcium channel blockers (VER), anti-hypertensive agents (reserpine), immunomodulators (cyclosporine A) (Warren et al., 2000), and selective estrogen receptor modulators (tamoxifen). Wang and colleagues first co-loaded VER and doxorubicin (DOX) in PEGylated liposomes. The drug loading has been found to be 70%, thus enabling a 13-fold dose reduction. VER-mediated cardiotoxicity has been successfully avoided through use of the liposomes. VER has successfully re-sensitized MDR cancer cells to DOX and significantly decreased the IC₅₀ (J. Wang et al., 2005). Most recently, Ahmadi and co-workers have developed DOX and VER co-loaded poly lactic-co-glycolic acid (PLGA) nanoparticles (NPs) for the controlled release of the drug combination in P-gp upregulated BC cells. The PLGA NPs substantially decrease the IC₅₀ value of DOX and VER combination in MCF-7 BC cells *in vitro*. This PLGA formulation has excellent potential for investigations in *in vivo* models and clinical studies, in which it may enable the combination drug's dose to be further decreased, owing to increased drug solubility and enhanced permeation and retention effects of the PLGA NPs (Ahmadi et al., 2019).

Various quinazoline derivatives such as gefitinib V and erlotinib VI have been approved by the US FDA as clinical anticancer agents (W.-W. Li et al., 2010). Abdel-Rahman and co-workers have synthesized quinazolin-4(3H)-one/Schiff base derivatives to inhibit phosphodiesterase-4. The quinazolinone derivative (QZD) 2-(4-methoxyphenyl)-3-((2, 3, 4-trihydroxy-benzylidene) amino) quinazolin-4-(3H)-one has potent anti-phosphodiesterase enzyme activity, with an IC₅₀ of 0.14, 0.08, and 0.32 µM in breast, lung, and colon cancer cell lines, in comparison with DOX, which has an IC₅₀ of 0.11, 3.13, and 2.75 µM, respectively (Abdel-Rahman et al., 2014). Motivated by the potent anticancer activity

of this QZD, El-Menshawe and co-workers have loaded DOX and QZD in carnauba wax solid lipid NPs (SLN) for the reversal of MDR in BC MDA-231/ADR cell lines. SLN has been found to ameliorate the therapeutic efficacy of the combination drugs by increasing the solubility and cell internalization, and bypassing P-gp-mediated drug efflux. DOX- and QZD-loaded SLN has been found to reverse MDR in BC cells and improve the potency by decreasing the IC₅₀ concentration of DOX and QZD by 19.7-fold (El-Menshawe et al., 2020). These agents are non-selective and weakly potent, and they precipitate toxic effects at the concentrations required for P-gp inhibition. Hence, the search for an ideal inhibitor resulted in the introduction of newer generations of glycoprotein inhibitors.

The second-generation P-gp inhibitors lack pharmacological activity of their own (Palmeira et al., 2012). In comparison to the first-generation inhibitors, they show potent P-gp binding. Agents such as dexverapamil (R-isomer of VER), elopamil, and valspodar (non-immunosuppressive analog of cyclosporine A) have been studied (Binkhathlan et al., 2012; Cagliero et al., 2004). However, these agents precipitate cytochrome P 450 3A-mediated pharmacokinetic alterations of the chemotherapeutic agents. The third-generation inhibitors circumvent the limitations of the first- and second-generation inhibitors, and demonstrate potent binding. These agents selectively bind P-gp and have highly potent inhibitory activity in the nano-molar range. Tariquidar (Kannan et al., 2011), annamycin, elacridar (Hyafil et al., 1993), and laniquidar are examples of this generation (J.-I. Lai et al., 2020). The third-generation P-gp inhibitors have not been widely explored and require efficient targeted nanodelivery to chemosensitize MDR BC (Silva et al., 2015). Table 3 classifies various P-gp inhibitors that re-sensitize MDR BC cells, according to their generation.

3.1. P-gp inhibitors of natural origin

The hunt for pharmacologically nontoxic P-gp inhibitors led to the exploration of herbal medicines. The long history of the consumption of plant-based medicines supports their safety. The interactions of grape juice with drugs launched the exploration of P-gp modulation by various classes of natural products. Scientists worldwide have reported the chemosensitization of MDR cancer cells by different classes of natural products, such as flavonoids, stilbenes, coumarins, alkaloids, terpenoids, and saponins (Dewanjee et al., 2017). These phytochemicals are classified as third-generation inhibitors (Jun Yu et al., 2016). Polyphenolic compounds such as flavonoids and stilbenes are a topic of interest among scientists because of their excellent P-gp inhibitory activity. Flavonoids such as rutin (Mohana et al., 2016), quercetin (QUE), genistein (Xue et al., 2014), silymarin (V. P. E. Colombo et al., 2011), silychristin A (Viktorová et al., 2019), morin, naringenin (F. Y. Zhang et al., 2009), naringin (H. S. Park et al., 2011), taxifolin (H.-J. Chen et al., 2018), hesperetin (Sarmoko et al., 2014), and kaempferol (Yi Wang et al., 2005) have been exhaustively investigated for their re-sensitizing potential against resistant cancer cells and improvements in the pharmacokinetic profiles of various chemotherapeutic agents (Choi et al., 2011; Mu, Fu, et al., 2019). Co-delivery of DOX with resveratrol (Stilbenoid polyphenol) diminishes its IC_{50} from $0.96 \pm 0.02 \mu\text{M}$ to $0.52 \pm 0.05 \mu\text{M}$, with upregulation of p53 and Bax genes (Khaleel et al., 2016). Mohana and co-workers have screened 40 flavonoids and reported that QUE and rutin have the best P-gp inhibition potential (Mohana et al., 2016). QUE reverses drug resistance and improves the cytotoxicity of DOX, paclitaxel (PTX), and vincristine in DOX-resistant MCF-7 cells *in vitro* (S. Li et al., 2018). Owing to its P-gp modulatory action, QUE has been used in recent formulations to neutralize MDR in BC (Table 4).

Terpenoid compounds are another group of natural compounds studied for potential P-gp inhibition. These compounds are classified on the basis of the number of isoprene units in the parent chain. Studies on P-gp modulation by this class began with the repurposing of the anti-malarial sesquiterpene artemisinin. The P-gp modulation of artemisinin and its derivatives have been reviewed by Wang and co-authors (Yulin Wang et al., 2019). Isopetasin and S-isopetasin, additional sesquiterpenes isolated from *Petasites formosanus*, have dual roles in anticancer therapy: P-gp inhibition and cytotoxicity (Abdelfatah et al., 2020). Abdelfatah and co-workers have reported high affinity binding at key amino acids on the P-gp transporter *in silico*. P-gp inhibition increases the mitochondrial workload, thus generating more ATP in the MDA-MB-231 cell line. The prolonged stress on the mitochondria leads to ROS production, thus eventually resulting in cell death (Abdelfatah et al., 2020). Boswellic acid, a pentacyclic terpenoid, modulates the P-gp transporter (Weber et al., 2006). Recently, boswellic acid has been co-delivered with DOC in an oral nanoemulsion and found to increase the oral bioavailability and reversal of resistance in the MDA-MB-231 BC cell line. Boswellic acid co-delivery increases the bioavailability of DOC by $182.58 \pm 4.16\%$ and has a lower IC_{50} value than the marketed formulation taxotere (Pandey et al., 2017). Tomentodione M, a monoterpene, downregulates P-gp in the resistant MCF-7 BC cells by inhibiting the p38 MAPK signaling pathway. The co-delivery of tomentodione M with DOC, DOX and rhodamine 123 increases their intracellular retention and reverses MDR in a concentration- and time-dependent manner (X. W. Zhou et al., 2017). Hu and co-workers have isolated 15 diterpenoids from the fruits of *Euphorbia sororia* and identified euphosorophane A as the compound with maximum P-gp inhibition potential and drug-like pharmacokinetic properties. This compound triggers P-gp-ATPase activity and competitively inhibits P-gp, with an excellent EC_{50} value of $92.68 \pm 18.28 \text{ nM}$ (R. Hu et al., 2018). Ursolic acid, a pentacyclic triterpenoid, elevates the intracellular accretion of DOX by P-gp inhibition and disruption of the normal metabolism of glucose and amino acids, thus leading to an energy crisis that affects the functioning of ABC transporters (Zong et al., 2019).

In Chinese herbal medicine, *Poria cocos* (PC) extract is used as a diuretic and sedative (Ríos, 2011). Kim et al. have investigated the P-gp

inhibition activity of the triterpenoid-rich ethanol extract of PC in MDR1 overexpressing LLC-PK1 cells. The extract shows excellent P-gp inhibition properties and has been found to significantly decrease digoxin and daunorubicin efflux at $100 \mu\text{g/mL}$ (J. H. Kim et al., 2011). Recently, Li et al. have co-delivered DOX and alcohol extract of PC containing pachymic acid and dehydrotumulosic acid via liposomes. The extract, in comparison to other chemotherapeutic agents, has excellent safety features and successfully sensitizes MDR cells to DOX. A substantial decrease in the P-gp expression has been observed after treatment with loaded liposomes, whereas treatment of free DOX increases caveolin-1, which is linked to the P-gp transporter. Hence, DOX treatment induces P-gp overexpression, whereas DOX- and PC-extract-loaded liposomes inhibit P-gp expression (Yanan Li et al., 2020).

Alkaloids are secondary metabolites in fungi, plants, and bacteria. Their characteristic nitrogen atom containing heterocyclic ring in the chemical structure is necessary for the P-gp inhibitory properties (Coqueiro and Verpoorte, 2015). The use of alkaloids as P-gp inhibitors started with the first generation of P-gp inhibitors, specifically quinolone and quinazoline alkaloids. Quinine and its derivatives have been extensively researched to develop potent P-gp inhibitor molecules. Initially, piperine (a constituent of black pepper) was found to have high P-gp inhibition activity at a $50 \mu\text{M}$ concentration. Oral administration decreases the liver P-gp expression in Wistar rats (Han et al., 2008). However, the low aqueous solubility of piperine has limited its use. Nanocarrier-mediated delivery of piperine along with DOX increases the cytotoxicity of DOX by 6.38-fold (Pillai et al., 2020). Most recently, wilforine extracted from *Cynanchum wilfordi* has been studied for its P-gp inhibitory activity. Wilforine shows concentration-dependent competitive P-gp inhibition. *In silico* docking studies have confirmed the binding of wilforine to the THR176, LYS887, LEU884, and ASN172 residues of the P-gp transporter (Y. T. Chang et al., 2020).

Coumarins have also shown potential to modulate the P-gp transporter. The presence of a phenyl group at position C4 of the coumarin chemical structure has been reported to be critical for P-gp modulation. Various coumarins, including GUT-70, praeruptorin A, decursinol, and farnesiferol, have been studied for their influence on drug pharmacokinetics and pharmacodynamics (Abdallah et al., 2015). Unfortunately, their potential in MDR BC has rarely been studied. Kasaian and co-workers have reported that the ring-opened drimane-type sesquiterpene coumarins are the most potent inhibitors of the P-gp transporter among those tested. Lehnferin, farnesiferol B, and farnesiferol C significantly increase the accumulation of rhodamine 123 in DOX-resistant MCF-7 BC cells (Kasaian et al., 2015). Guo and co-workers have synthesized new derivatives of 3-benzyl coumarins by merging them with their B-ring derivatives. The NO donating derivative has high anti-proliferative activity in the P-gp overexpressing MCF-7 BC cell line (Yalan Guo et al., 2018).

3.2. Nitric oxide (NO)-mediated sensitization of BC cells

NO is crucial in the inhibition of DNA synthesis and cell cycle progression, and the induction of apoptosis (Kim et al., 2001). Researchers have used NO as a pro-apoptotic and cytotoxic agent in MDR cancer therapy. DOX produces NO-mediated cytotoxicity in cancer cells (Kali-vendi et al., 2001). The ability of MDR cancer cells to resist this activity of DOX is one of the main causes of DOX resistance in cancer cells (C. F. Chang et al., 2015). For cellular acclimatization to hypoxia, the expression of O_2 -regulated genes, such as VEGF, endothelin-1, glycolytic enzymes, platelet-derived growth factor- β , heme oxygenase-1, and tyrosine hydroxylase, is required (Wenger, 2002). Furthermore, hypoxia-inducible factors (HIF) are key transcriptional regulators of those genes, which are required for the adaptive response to hypoxia (Choudhry and Harris, 2018). However, under normal physiological conditions, O_2 is needed for the production of NO from citrulline and arginine by NO synthase in the cell, whereas NO may obstruct elements of the adaptive response to HIF, which tends to be associated with tumor

malignancy, and also increases resistance to radiotherapy and chemotherapy (Masoud and Li, 2015). Thus, hypoxia-induced drug resistance appears to develop through suppression of endogenous NO production, whereas NO is associated with chemosensitivity in cancer cells (Mathews et al., 2001).

Both *in vitro* and *in vivo* data suggest that exposure to NO and NO mimetic agents in cancer cells can productively restore the sensitivity of resistant populations of cancer cells to the cytotoxic effects of chemotherapeutic agents (Bonavida, 2017). Mechanistically, NO chemo-sensitizers promote vascular changes that increase blood delivery and oxygenation in tumors; retard transcription factors, such as HIF-1; inhibit various drug efflux transporters, such as P-gp, and DNA repair enzymes; and have anti-tumorigenic effects. These effects of NO have been demonstrated in various cancers, including BC (Sullivan and Graham, 2008). Experimental data also show that NO mimetic agents, such as glyceryl trinitrate and isosorbide dinitrate, decrease hypoxia-induced resistance to 5-fluorouracil and DOX in the BC model by promoting a signaling pathway leading to the production of cGMP (Abaza et al., 2015).

DOX-resistant cancer cells underexpress the NO synthase enzyme. Riganti and co-workers first reinforced DOX by co-delivery with atorvastatin, a NO production stimulating agent. They have reported that P-gp overexpressing MDR cancer cell lines resist an increase in the production of NO, and hence DOX is unable to internalize and produce cytotoxicity in HT29-dx cancer cells. The co-delivery of atorvastatin increases the retention of DOX in cancer cells by inhibiting P-gp, thus facilitating DOX efflux and potentiating NO-mediated cytotoxicity (Riganti et al., 2005). Later, the same research group synthesized NO donating DOX prodrugs by substituting the NO donor moieties such as nitroxy and phenyl sulfonyl furoxan on the DOX molecule. They have confirmed the importance of NO synthesis in the retention of DOX in cancer cells and have found that NO inhibits P-gp's activity by nitration of the critical tyrosine residues in its chemical structure (Chegaev et al., 2011). In further studies, NO donating DOX prodrugs have been actively delivered to MDR cancer cells by light-induced NO release (stimuli responsive smart delivery) and a folic acid immobilized carrier (active targeting) (Gazzano et al., 2018) for improved spatial control release. DOX has been derivatized with 4-nitro-3-(trifluoromethyl)aniline to impart photosensitivity. The photosensitive prodrug, when excited with visible light (wavelength = 400 nm), releases NO in tumors (Chegaev et al., 2017).

3.3. Mitochondrial targeting for MDR reversal

Mitochondria perform a central role in cancer cell multiplication and metastasis (Farnie et al., 2015). As cancer cells develop MDR, the consumption of ATP increases manyfold. To meet these increased requirements, MDR cancer cells have higher mitochondrial membrane potential, more mitochondrial bulk, and higher metabolic rates (Henkenius et al., 2017). The dysfunctional mitochondria alter cellular metabolism in the cells, thus playing a crucial role in anti-apoptotic defense mechanisms in cancer cells (Griguer and Oliva, 2011). The more polarized mitochondria are an attractive target to counter MDR in cancer cells (Galluzzi et al., 2006). However, penetrating the mitochondria is challenging, because their internal hydrophobic membrane acts as a barrier to the diffusion of the therapeutic moieties. Lipid-conjugated cationic peptides can cross this barrier (Fernández-Carneado et al., 2005). Cationic molecules are attracted to the hyperpolarized mitochondrial membrane potential. One such lipid-conjugated cationic peptide was developed by Horton and co-workers, who have used arginine (A) and lysine (L) to impart a positive charge on the conjugate; meanwhile, phenylalanine (P) and cyclohexyl alanine (C) provide the necessary hydrophobicity for membrane permeation. The peptide with the amino acid sequence (CACLCACL) has demonstrated the highest mitochondrial internalization in MCF-7 BC cell lines (Horton et al., 2008). Recently, Czupiel and co-workers have explored the anti-mitochondrial and ultimately P-gp inhibiting ability of vitamin E succinate modified

Table 5

List of various ligands used for site-specific delivery of chemotherapeutic agents and P-gp inhibitors in drug-resistant BC.

Ligand	Nanoformulation	Therapeutic benefits	Reference
Hyaluronic acid-mediated carrier delivery			
Hyaluronic acid	DOX-loaded mesoporous silica NPs	The targeted mesoporous silica NPs demonstrated superior internalization by the MDA-MB-231 cells <i>in vitro</i> .	Pan et al. (2020)
Hyaluronic acid	QUE and DO co-loaded PLGA-polyethyleneimine NPs	Actively targeted NPs accumulated in the breast tumor and lungs.	(J. Li et al., 2017)
Hyaluronic acid	QUE and DOX co-loaded D- α -tocopheryl polyethylene glycol succinate micelles	HA-mediated targeting showed superior therapeutic activity, such as a 2.95-fold decline in the IC ₅₀ value, accumulation of DOX in the nuclei, and increased apoptosis.	Soltantabar et al. (2020)
Hyaluronic acid	PTX-loaded D- α -tocopheryl polyethylene glycol succinate micelles	The micelles exhibited high internalization and cytotoxicity in MCF-7/ADR cells <i>in vitro</i> and <i>in vivo</i> .	Hou et al. (2019)
Transferrin receptor 1-mediated endocytosis			
7pep	Transferrin receptor-1-targeted 7pep-conjugated hybrid peptide composed of an extracellular signal-regulated kinase inhibitor	The conjugate demonstrated high selectivity for tumor cells, with 72.2 \pm 4.6% inhibition in the xenografts <i>in vivo</i> .	Sheng et al. (2016)
7pep	Rapamycin and PTX co-loaded DSPE-PEG micelles	Superior MCF-7 BC cell uptake was observed, thus leading to higher antitumor and autophagic cell death <i>in vitro</i> and <i>in vivo</i> .	Mei et al. (2019)
7pep	Micelles developed from podophyllotoxin, methoxy-PEG and 7 pep conjugate	Targeted delivery improved the maximum tolerated dose of toxic podophyllotoxin by 5.3-fold <i>in vivo</i> .	Yongfei Li et al. (2019)
Transferrin	PTX- and elacridar-loaded PLGA NPs	Transferrin-coated PLGA NPs demonstrated high cytotoxicity with a 16-fold decrease in IC ₅₀ value.	Tonbul et al. (2019)
Folic acid-mediated active drug delivery			
Folic acid	PTX and tariquidar co-loaded folic acid modified erythrocytes	Better cytotoxicity was observed <i>in vitro</i> and <i>in vivo</i> investigations in taxol-resistant MCF-7/taxol cells in comparison to folic acid free erythrocytes. The folic acid-mediated active delivery ensured site-specific drug delivery <i>in vivo</i> ; hence, no weight loss or other toxic effects were observed.	Zhong et al. (2020)
Folic acid	Folic acid functionalized DOX-loaded self-assembled chitosan-oleoic acid copolymeric micelles	The formulation was actively internalized by FR overexpressing MDA-MB-231 cancer cells, but was not internalized by HUVECs.	Niu et al. (2019)

(continued on next page)

Table 5 (continued)

Ligand	Nanoformulation	Therapeutic benefits	Reference
Folic acid	DOX and elacridar co-loaded PEG-polycaprolactone micelles	Enhanced accumulation was observed in MCF-7/ADR BC cells <i>in vitro</i> .	C. Zhang et al. (2018)
Folic acid	DOX-loaded folic acid functionalized liposomes	The targeted liposomes circumvented the P-gp efflux of DOX and reversed MDR in MDA-MB-231 BC cells.	Gazzano et al. (2018)
Biotin-avidin technology-based targeting			
Biotin	Tariquidar and PTX co-loaded PLGA NPs	Enhanced internalization was observed in avidin overexpressing MCF-7/ADR BC cells.	Patil et al. (2009)
Biotin	QUE and DOX co-loaded PEG-polycaprolactone micelles	The biotin functionalized micelles exhibited 136- and 94-fold the cytotoxicity of free DOX and free DOX + QUE, respectively.	Lv et al. (2016)
Biotin	Self-assembled poly (curcumin dithiodipropionic acid)-b-PEG-biotin NPs	High ptake by MCF-7 cells led to cytotoxicity, downregulation of ATP activity and inhibition of P-gp-mediated drug efflux.	(S. Guo et al., 2016b)

DOX = Doxorubicin; DOC = docetaxel; QUE = quercetin; PTX = paclitaxel.

octahistidine-octaarginine (VESOO) and H8-R8. Unconjugated H8-R8 peptide has an IC₅₀ cytotoxic concentration of 300 μM, whereas VESOO has a lower IC₅₀ value in EMT6/AR-1 DOX-resistant MDR BC cell lines. These findings have confirmed the necessity of a lipophilic moiety to target the mitochondria. Conjugation of hydrophilic PEG to the H8-R8 peptide resulted in a loss of all cytotoxic potential (P. P. Czupiel et al., 2019). Abdelfatah and co-workers have reported that the P-gp increase in intracellular chemotherapeutic accumulation due to P-gp dysfunction induces mitochondrial stress and the generation of more ATP. This stress triggers mitochondria to release ROS inside MDR cells, thereby leading to their apoptosis (Abdelfatah et al., 2020).

Chen and co-workers have recently injected mitochondria in MCF-7 MDR BC cell lines to target both intrinsic and extrinsic MDR. Healthy mitochondria from healthy MCF-12A BC cells were surface engineered with a layer-by-layer technique. Two layers of polyelectrolytes were coated over the mitochondria to confer injectable properties. P-gp small interfering RNA was integrated in the polyelectrolyte layers through ionic interactions. The developed biologic agent successfully suppressed both the intrinsic and extrinsic MDR pathways in BC cells. Meanwhile, RNA-induced silencing inhibited the expression of the P-gp transporters; the injected healthy mitochondria restored the normal drug-induced apoptotic pathways (W. Chen et al., 2019).

4. Ligands used to target carriers to MDR BC cells

Ligands have been repeatedly used to surface-functionalize a wide range of novel anticancer nanocarriers to impart site-specific drug release and protect healthy tissues against exposure to cytotoxic chemotherapeutic agents (Ashfaq et al., 2017). This section reviews previously used ligands for active targeting in MDR BC cells. Table 5 summarizes the use of various ligands in MDR BC cell therapy. Fig. 4 depicts the ligands commonly used in the active targeting of carriers to MDR BC.

4.1. Hyaluronic acid (HA)

HA, also known as hyaluronan, is an anionic glycosaminoglycan mucopolysaccharide. It occurs naturally in the body and functions as a

cushion in synovial joints and a moisture preserver in the eyes (Dicker et al., 2014). HA plays a major role in cell signaling, cell migration, angiogenesis, tissue structure, and wound healing in the TME (Chanmee et al., 2016); hence, cluster determinant 44 (CD44) receptors with high affinity for HA are overexpressed on BC cells. A correlation between HA production by stromal cells and breast tumor growth further highlights the importance of HA in BC therapy (Heldin et al., 2013). The HA forms hydrogen bonds and hydrophobic interactions with various amino acids in the N-terminus of the CD-44 receptor (Misra et al., 2015). HA also binds hyaluronan-mediated motility receptor and hyaluronan receptor with high affinity, thus resulting in endocytosis (Malavia et al., 2021). Because of the high binding potential of HA in the BC microenvironment, nanocarriers are frequently functionalized with HA for active targeting to BC cells (Wickens et al., 2017). Recently, Liu and co-workers have functionalized extracellular vesicles with lipid grafted HA for tumor site-specific delivery of DOX to MCF-7/ADR cells. The nanosystem actively accumulates inside MCF-7/ADR cells via CD44 receptor-mediated targeting. The nanosystem has been found to replicate the excellent tumor targeting activity *in vivo* and actively penetrate tumor xenografts. The “magic bullet” type of drug delivery system successfully eliminates the myocardial cytotoxicity of DOX. The functionalization of vesicles with lipid grafted HA improves the cytotoxicity in MCF-7/ADR cells. DOX-loaded extracellular carriers have an IC₅₀ value of 13.1 μg/mL, whereas the loaded carriers targeted with HA conjugate show a lower IC₅₀ value of 5.5 μg/mL *in vitro*. Similarly, *in vivo*, the targeted system has been found to yield an 89% decrease in tumor mass, in comparison to a 66% reduction with the untargeted system (J. Liu et al., 2019).

4.2. Transferrin receptors

Transferrin is a glycoprotein that regulates the translocation of iron in the plasma. The concentration of transferrin in human serum is ~2.5 mg/mL (Leibman and Aisen, 1979). It binds two transferrin receptors (TRs): transferrin receptor-1 (TR1) and transferrin receptor-2 (TR2). TR2 is found in the intestinal wall and absorbs iron from the diet, whereas TR1 is overexpressed on cancer cells (Malavia et al., 2021). TRs are hydrophilic and contain a cationic binding domain. The TRs are dimeric surface receptors comprising two monomers joined through a disulfide linkage between cysteine 89 and cysteine 98 (Shen et al., 2018). Because of the excessive iron requirements for cell proliferation in tumors, TR1 expression is upregulated in most tumors, including BC. A further increase in the expression of TR1 receptors with the emergence of MDR in BC has been reported (Yang et al., 2014). Because endocytosis of the bound nanocarrier follows TR1 binding, TR1 presents an attractive targeting site for BC therapy (Nogueira-Librelotto et al., 2016). Recently, an oligopeptide containing seven peptides (histidine-alanine-isoleucine-tyrosine-proline-arginine-histidine; 7pep) has been used by several research groups to target the overexpressed TR1 on BC cells (Gao et al., 2017; Yongfei Li et al., 2019; Mei et al., 2019). Nanocarriers functionalized with 7pep demonstrate tumor-specific uptake and improved cytotoxic activity in MDR BC cells.

4.3. Folic acid

Folic acid is an essential nutrient required by cells for the biosynthesis of the nucleotides (Hwang et al., 2018). Owing to the excess cell proliferation requirement in BC cells, the receptors for this nutrient are overexpressed on the tumor cell surface (Scaranti et al., 2020). The folic acid receptors (FRs) are glycoproteins found in three isoforms in the body: FRα, FRβ, and FRγ (Quici et al., 2015). The FRα isoform is predominantly found on BC cells, and more than 50% of the receptors on BC cells are of this isoform (Depau et al., 2017). BC cells express 100–300-fold higher FRα receptors than do healthy cells (Azzi et al., 2013). Healthy cells express FRs on the apical side, thus presenting an excellent opportunity to deliver a chemotherapeutic load specifically to BC cells. The nanocarriers bound to the FRα receptors are internalized via

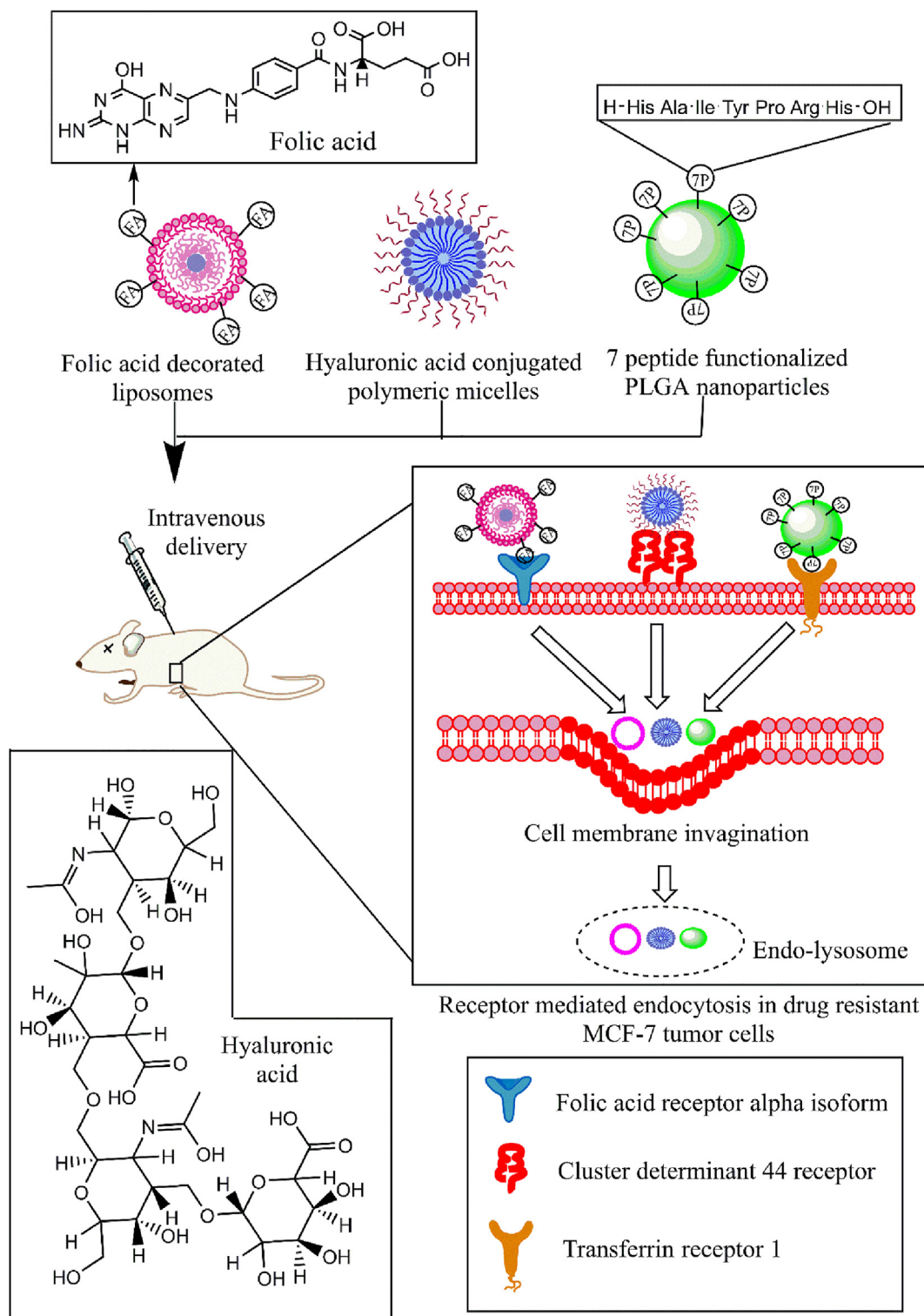


Fig. 4. Pictorial representation of receptor-mediated endocytosis of folic acid, HA, and 7-pep functionalized carriers inside MDR BC cells.

clathrin-mediated endocytosis (Assaraf et al., 2014; Ramzy et al., 2017). A wide range of folic acid functionalized carriers have displayed excellent cytotoxic activity in BC cells *in vitro* and *in vivo* (Bhanumathi et al., 2018; Tagde et al., 2020; Vinothini et al., 2019; M. Wang et al., 2020).

4.4. Biotin-avidin complex

Avidin is mainly isolated from chicken egg-whites and is secreted by some species of *Streptomyces*. In drug delivery, avidin is mainly used for

its strong binding to biotin (Jain and Cheng, 2017), an essential enzymatic cofactor commonly known as vitamin H. Avidin and biotin are characterized by similar secondary and tertiary structures (Lesch et al., 2010). One molecule of avidin strongly binds one molecule of biotin. For efficient use of this biotin-avidin complex, target cancer cells are first evaluated for the expression of avidin on their surfaces or are biotinylated through the immobilization of the biotin-antibody complex on cancer cells. The use of this complex ensures site-specific drug delivery (Fairhead and Howarth, 2015). Guo and co-workers have prepared

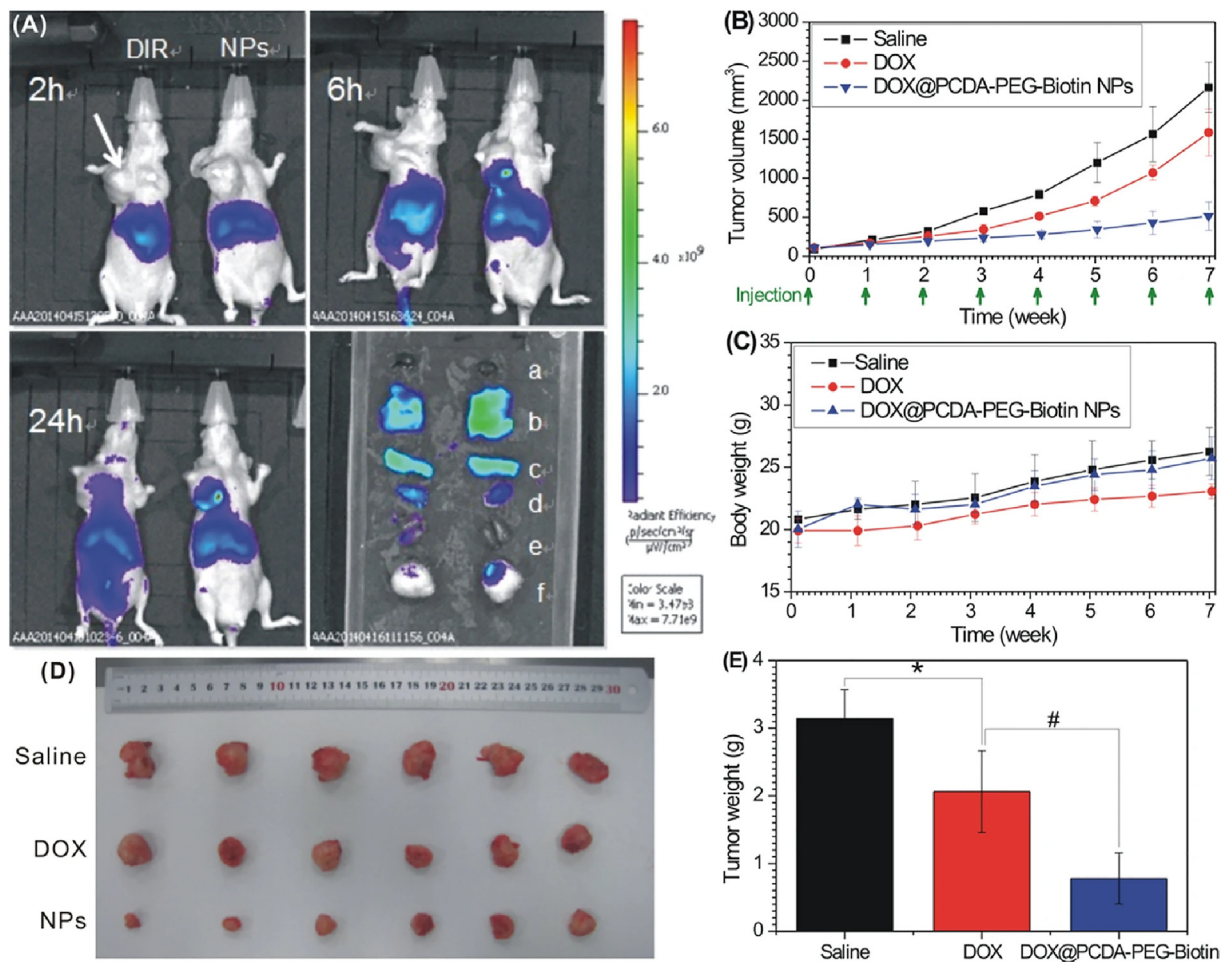


Fig. 5. Biotin functionalized micelles demonstrate better accumulation in tumors *in vivo*. (A) *In vivo* imaging results showing better accumulation of DiR functionalized micelles than free DiR in the tumor. The inset depicts *ex vivo* fluorescence studies of tumors and other organs; a–f represent the heart, liver, spleen, lung, kidneys, and tumor; (B) and (C) show the tumor growth curve and body weight variation, respectively, after the administration of saline, free DOX, and biotin functionalized DOX-loaded micelles. (D) Appearance and (E) weight of the tumor after saline, DOX, or biotin functionalized micelle treatments. Reprinted from Guo et al. (S. Guo et al., 2016a) licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/legalcode>) Copyright © 2016. Shengrong Guo, Li Lv, Yuanyuan Shen, Zhongliang Hu, Qianjun He and Xiaoyuan Chen. Published by Scientific reports, Springer Nature.

biotin-guided DOX- and curcumin-loaded micelles that bind the over-expressed biotin receptors on BC cells. The actively targeted delivery of the drugs leads to better cytotoxic action *in vivo* (Fig. 5) (S. Guo et al., 2016a) (see Fig. 6).

4.5. Recent formulation-based strategies to address P-gp facilitated MDR in BCs

Researchers have investigated and evaluated numerous nano-formulations to address the problem of P-gp-mediated MDR in BC cells. Such novel formulations are focused on delivering P-gp modulators exclusively inside the tumoral compartment (Kou et al., 2018). The drugs encapsulated in the NP carrier are transported to the cytoplasm via receptor-mediated endocytosis, thus avoiding encounters with P-gp transporters (Mirza and Karim, 2021). Co-delivery of P-gp inhibitor in the carrier is increasingly used with the aim of developing an “all-in-one” approach to chemosensitize and kill MDR cancer cells with one carrier formulation. Selected examples of such formulations are discussed in this section.

5.1. Polymeric nanoparticles

Polymeric NP-based carriers have been extensively used for delivering diagnostic and therapeutic agents since the turn of this century.

Various limitations such as short half-life and unwanted adverse effects associated with protein, peptide, and nucleic acid-based nanocarriers have led to the advent of polymeric NPs. The drug bearing polymeric NPs have various favorable qualities such as biodegradability, sustained release, prolonged circulation, and *in vivo* stability (Kamaly et al., 2016; Z. Wang et al., 2014). The physicochemical properties of polymeric NPs can be tuned to obtain carriers with a broad range of particle sizes and surface charges. Their surfaces can be easily functionalized to immobilize targeting ligands (Indoria et al., 2020). Various polymeric NPs have been used to deliver drugs in MDR BC. Recently, poly (lactic acid) (PLA) NPs have been developed for the delivery of bioperine, a natural alkaloid sourced from piperine. Piperine has been extensively investigated for its P-gp inhibitory properties (Han et al., 2008) and its ability to re-sensitize MDR cancer cell lines to chemotherapeutic agents (Bezerra et al., 2008; C. Li et al., 2018). However, its hydrophobic characteristics limit its clinical use. PLA NPs have been further coated with chitosan and PEG polymers to protect them from phagocytic cells (F. Q. Hu et al., 2008). Hydrophilic PEG coatings form a hydrated shell around the NPs (Otsuka et al., 2003), thereby preventing protein adsorption on the NPs and conferring a long circulatory period. X-ray diffraction studies have revealed that bioperine loses its crystalline nature when loaded in the PLA formulation, owing to the excellent partitioning of bioperine in the PLA. The loss of crystallinity and potential formation of nanosized PLA-bioperine solid dispersions increases the aqueous solubility of the

hydrophilic drug. The NPs exhibit a pH-dependent release profile with sustained release under acidic pH. Cell internalization studies conducted on MDA-MB 453 MDR BC cell lines have demonstrated time-dependent internalization of coumarin 6 tagged NPs. The NPs are internalized through adsorption-mediated transcytosis. Compared with free bioperine, the bioperine-loaded NPs exert the same therapeutic activity at 6.38 times lower doses, owing to the loss of the crystalline structure of the drug and better cancer cell internalization. The formulation has been compared with the marketed P-gp inhibitor VER. In 453 MDA-MB cell lines pretreated with VER and the formulation and further treated with DOX, VER has been found to decrease the cell viability to 41.66% after 48 h, whereas the PLA-bioperine formulation exhibits better therapeutic activity by decreasing the cell viability to 29.16%. Immunofluorescence staining studies have shown a better decrease in P-gp expression in case of bioperine in comparison to VER. PTX, a semi-synthetic taxane widely used in therapy for BC, is a substrate for P-gp-mediated drug removal from cancer cells (Rossi et al., 2008; Singla et al., 2002). PTX therapy has been reported to enhance the P-gp expression in various cancer cells (Higgins, 2007). However, it has the drawback of poor bioavailability, owing to its low aqueous solubility and poor intestinal permeability (Bhardwaj et al., 2009). To address this problem, Tonbul et al. have developed actively targeted PLGA NPs for delivery of PTX and elacridar. Elacridar is a third-generation P-gp inhibitor used to curb the P-gp-mediated efflux of PTX from BC cells (Hyafil et al., 1993). Dual drug-loaded PLGA NPs have been surface functionalized by transferrin to target BC cells with overexpressed transferrin receptors (Frasco et al., 2015). The novel PLGA NPs show a biphasic release pattern, with an initial accelerated release leading to 55% drug release in the first hour. The release is then sustained, thereby leading to a cumulative release of 80% in 24 h. *In vitro* cytotoxicity assays have been performed on EMT6/AR1.0 BC cell lines, which are resistant to PTX therapy because of their overexpression of P-gp transporters. The presence of elacridar in the novel formulation sensitizes resistant EMT6/AR1.0 BC cell lines to PTX chemotherapy. The actively targeted novel PLGA NPs show significant cytotoxicity (cell viability, 33.77%) (Tonbul et al., 2019). Zhu and co-workers have reported porous PLGA NPs for the co-delivery of DOC and vitamin E tocopheryl polyethylene glycol succinate (TPGS). TPGS has been used as a P-gp inhibitor as well as a pore-forming agent. Pore formation leads to greater drug encapsulation and rapid drug release. *In vitro* investigations have demonstrated 5.57-fold higher cytotoxicity in MCF-7 cells in comparison to the free DOC. TPGS-loaded PLGA NPs have demonstrated 52.7-fold higher cytotoxicity, owing to rapid drug release and P-gp inhibitory capability. The formulation loaded with 20% TPGS has shown the highest cytotoxicity in the xenograft model *in vivo* (Zhu et al., 2014).

5.2. Polymeric micelles

Polymeric micelles are self-assembling nanostructures 1–100 nm in diameter (Kaur et al., 2021), thus making them ideal carriers for BC delivery. Micelles' small particle sizes allow them to evade the reticulo-endothelial system in the circulation and accumulate at tumor sites via enhanced permeation and retention (Rao et al., 2019). Self-assembly of amphiphilic copolymers leads to the formation of micelles with hydrophobic anticancer agents trapped in the core (Kaur et al., 2021). The copolymers are readily conjugated with targeting moieties to enable site-specific accumulation in cancer cells (Keskin and Tezcaner, 2017). Stimuli responsive micelles have also been developed to ensure rapid drug release in the TME (Hanafy et al., 2018). Czupiel et al. have synthesized poly (D,L-lactide-co-2-methyl-2-carboxytrimethylene carbonate)-graft poly (ethylene glycol)-azide (LCCPEG), an amphiphilic derivative of PEG, through ring opening polymerization (Logie et al., 2014). LCCPEG NPs have been used to deliver VESOO and a pH-sensitive prodrug of DOX, palmitoyl doxorubicin (PDOX). VESOO was used because of its tumor targeting attributes and its ability to inhibit MDR by depolarizing the mitochondria and inhibiting the P-gp transporter (P. P. Czupiel et al., 2019). PDOX was synthesized to decrease the aqueous

solubility of DOX hydrochloride. The decrease in solubility led to a decline in the leakage from the polymeric LCCPEG NPs at physiological pH. VESOO and PDOX have demonstrated synergy in killing the EMT6/AR-1 MDR BC cell lines. The synergistic mechanism kills EMT6/AR-1 MDR BC cell lines through ROS induction, DOX retention by P-gp inhibition, mitochondrial depolarization, and apoptosis. The formulation restricts drug release at physiological pH, and less than 20% of the drug is released in 48 h *in vitro*. However, 81% of PDOX has been found to be released in simulated lysosomal media pH 5 *in vitro*, thereby ensuring that the polymeric NPs carry the PDOX to cancer cells and release it only under the lysosomal conditions (P. Czupiel et al., 2020).

Tingting and co-workers have developed DOX-loaded stearic acid grafted chitosan nanomicelles and tested their potential in tricyclic therapy. The study was performed in three phases to replicate the clinical use of the chemotherapy. The expression of P-gp in MCF-7/ADR MDR BC cell xenografts did not increase, whereas the parallel DOX treatment demonstrated P-gp overexpression. The authors have reported that MDR1 gene transcription is triggered by free DOX treatment, which increases MDR1 mRNA by several thousandfold. The nanomicelles demonstrated high potential to keep P-gp overexpression in check; hence, this nanomicelle formulation has excellent potential for clinical trials (Meng et al., 2019).

Guo and co-workers have prepared a TME-targeted reduction-sensitive micellar formulation for the co-delivery of docetaxel (DOC) and VER. A reduction-sensitive mPEG-PLGA-SS-DOC conjugate has been used to develop VER-loaded micelles. VER is released rapidly, thereby deactivating the P-gp transporter, and reduction-sensitive sustained release of DOC has been observed. The dual release mode with initial rapid release of VER helps retain high DOC concentrations in MCF-7/ADR MDR BC cells. MTT assays have confirmed that the VER-loaded micelles are more cytotoxic than both the micelle and DOC solution, thus indicating the importance of the P-gp inhibitor in the success of micellar formulations. The IC₅₀ values of mPEG-PLGA-SS-DOC and mPEG-PLGA-SS-DOC/VER micelles have been reported to be 6.75 and 3.6 times lower than that of free DOC in non-resistant MCF-7 cells. In MCF-7/ADR cells, the IC₅₀ value of micellar DOC is similar to that of free DOC in micelles without VER, whereas VER-loaded micelles show a 3.52 times lower IC₅₀ (Yuan-Guo et al., 2017). Zhou and co-workers have delivered podophyllotoxin by conjugating it to a poly (L-glutamic acid)-g-methoxy poly (ethylene glycol) copolymer. The conjugate self-assembles, yielding micelles of 100 nm in aqueous media. *In vitro* and *in vivo* investigations in the MCF-7/ADR cell line and Western blot analysis have confirmed that the prepared NPs significantly inhibit the expression of P-gp in drug-resistant cells. The resistance indices have demonstrated a several fold reduction in the resistance of MCF-7/ADR cells after conjugate NP treatment, in comparison to DOC and PTX (H. Zhou et al., 2018). Zhang and co-workers have reported folate functionalized PEG-polycaprolactone nanomicelles for site-specific active co-delivery of DOX and the third-generation P-gp inhibitor elacridar to MCF-7/ADR cells *in vitro* and *in vivo*. The nanomicelles have demonstrated enhanced accumulation of DOX inside MCF-7/ADR cells, owing to their small particle size (~35 nm) and inhibition of P-gp-mediated efflux from resistant BC cells (C. Zhang et al., 2018).

5.3. Liposomes

Liposomes are used to deliver both hydrophobic and hydrophilic drugs to cancer cells (Kiaie et al., 2020). They are made of phospholipid bilayers, and their structure varies from uni-lamellar to multi-lamellar. A typical liposome is prepared with two components: phospholipids and cholesterol (Large et al., 2021). Because both these components are endogenous to the body, liposomes display excellent biocompatibility. Doxil (DOX-loaded PEGylated liposomes) was the first liposomal formulation approved by the US FDA for marketing in America (Alavi and Hamidi, 2019). Various liposome-based nanoformulations used in the treatment of MDR BC are discussed below.

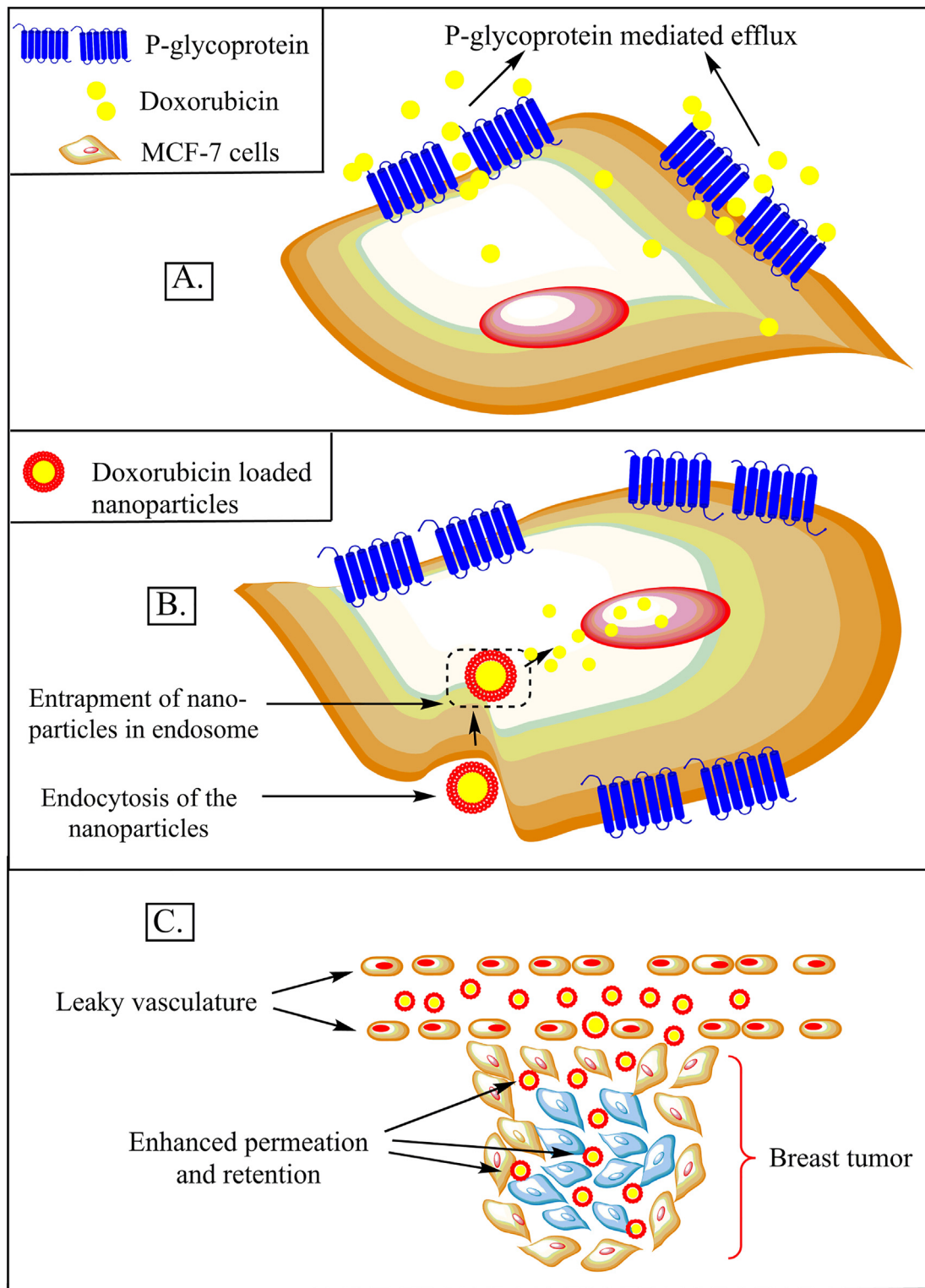


Fig. 6. Mechanistic insights into nanocarriers demonstrating greater cytotoxicity in the MDR BC than the conventional dosage forms. (A) Depicts the biological fate of DOX administered in a conventional form in drug-resistant MCF-7 cells. P-gp transporters efflux the drug out of cells, thus leading to a loss of therapeutic action. (B) Depicts the delivery of DOX encapsulated in a carrier. The carrier is internalized in BC cells by receptor-mediated endocytosis, thus further protecting the drug from P-gp transporters and leading to higher DOX delivery to the nucleus. (C) Illustrates the enhanced permeation and retention of the nanosized carriers in BC. The leaky vasculature allows small carriers to escape from the blood circulation and accumulate in the tumor compartment.

Most diagnosed BC cases receive chemotherapy, but only a small fraction actually benefit from this therapy (P. E. V. Colombo et al., 2011). BC develops drug resistance through different mechanisms, but P-gp drug efflux plays a major role. DOX is an effective drug against BC, but P-gp

efflux, myelosuppression, and cardiotoxicity limit its use (Minotti et al., 2004). To alleviate the toxicity and improve the pharmacokinetics, a PEGylated liposomal formulation has been developed for the delivery of DOX in MDR BC. The designed biocompatibility enables avoidance of the

reticuloendothelial system. The enhanced permeation and retention in cancer tissue leads to the accumulation of liposomes in tumors. Both DOX and the novel liposomal formulation treatment are ineffective in P-gp expressing cell lines such as P388/ADR and A-431-B1 *in vitro*. The P-gp inhibitor tariquidar restores DOX sensitivity, thus affirming the role of P-gp in chemoresistance. The formulation has been found to prolong survival in a physiologically relevant mouse model generated by orthotopic transplantation of mammary tumors. The liposomes have demonstrated a 6-fold increase in relapse free survival. All DOX treated tumors relapsed within 60 days, whereas only two of ten relapsed in the liposome treated groups. The tumors in which the liposomes formulation failed had 200–400-fold greater in P-gp expression than that in the control group. On the basis of these observations, better therapeutic results of DOX liposomes can be attributed to the superior pharmacokinetics. The liposomes enable 60% greater DOX administration, thus leading to a 35-fold increase in the maximum plasma concentration. Although the half-life of DOX is very low, the liposomes maintain high blood DOX concentrations even after 7 days. The liposomes can increase the bioavailability of DOX by ~2600 times (Füredi et al., 2017).

Recently, Rolle and co-workers have used liposomes to co-deliver disulfiram and DOX to re-sensitize DOX in human BC cells, MCF-7, human triple-negative BC cells, MDA-MB 231, and murine triple-negative BC cells and JC cells. Disulfiram is a non-competitive inhibitor of the P-gp transporter. Its metabolites bind P-gp inhibitor through covalent bonds on cysteines 431 and 1074, thus ultimately leading to the ubiquitination of the transporter (Loo et al., 2004). However, the hydrophobicity of disulfiram limits its use. The developed liposomes trap disulfiram in the phospholipid bilayer, and DOX is incorporated in the aqueous core. Faster release of disulfiram than DOX has been reported to result in inhibition of P-gp before DOX release, thus increasing the intracellular accumulation of DOX beyond that with the free mixture of the two drugs (Rolle et al., 2020).

Gazzano and co-workers have prepared folic acid decorated liposomes (FAL) for delivering DOX in P-gp overexpressing MDR BC cells. The FAL were designed to bypass P-gp-mediated efflux, where free DOX and PEGylated liposomes (Caelyx®) were ineffective. FR are upregulated in MDR cancer cells compared with drug-sensitive cancer cells. In P-gp overexpressing MDA-MB-231 and TUBO MDR BC cells, FAL, PEGylated liposomes, and free DOX are internalized in the order of FAL > PEGylated liposomes > free DOX. DOX levels in cells are stable after 72 h after FAL administration, whereas the levels decrease after treatment with free DOX. The FAL treatment has been found to induce the highest nitrite release in BC cells, thus indicating the highest cytotoxicity (Gazzano et al., 2018).

5.4. Self-nanoemulsifying lipids (SNELS)

SNELS are lipid-based drug delivery systems used for the oral delivery of hydrophobic drugs (Akhtar et al., 2020). These systems, when administered orally, form clear nanosized emulsions in the gastrointestinal tract. The drug solubilized in oil is absorbed through the action of biliary salts (Chaturvedi et al., 2020). SNELS presents an excellent opportunity to deliver hydrophobic chemotherapeutic agents (Rehman et al., 2017). Recent advancements in SNELS-based drug delivery for MDR BC therapy are discussed below. Recently, polyunsaturated fatty acid (PUFA)-based lipid systems have been extensively studied for their ability to improve the oral bioavailability and biodistribution of hydrophobic anticancer drugs. PUFA-rich lipid-based formulations containing omega-6 and omega-3 fatty acids solubilize the hydrophobic drugs in micellar solution. These drug solubilized micellar solutions are absorbed via lymphatic pathways (Elgart et al., 2012), thus ultimately avoiding the first pass metabolism of the hydrophobic drugs (Muchow et al., 2009). PUFA lipids have been reported to increase the anticancer efficacy of chemotherapeutic agents (Ramasamy et al., 2017) and inhibit the metastasis of BCs (Bougnoux et al., 2010). Sandhu and co-workers have formulated tamoxifen and naringenin-loaded SNELS and investigated

their activity in MCF-7 MDR BC cell lines. SNELS demonstrates >80% loaded drug release within the first 30 min. The formulation exhibits high internalization by Caco-2 cells, thus confirming high uptake of the formulation from the gastrointestinal tract. Coumarin-6 tagged SMELS also show high internalization in MCF-7 cells. The drug-loaded SNELS have shown 22 times greater cytotoxicity than that of the free drugs. This increase in cytotoxic activity is attributed to both the excellent SNELS formulation and inhibition of the P-gp transporter by the loaded naringenin (Sandhu et al., 2017). In a series of studies, Khurana and co-workers have developed DOC-loaded SNELS for the treatment of MDR BC. The DOC-loaded SNELS demonstrate better and faster cytotoxic activity in MCF-7 cancer cells (4.7-, 5.96-, and 8.68-fold higher IC₅₀ values at 24, 48, and 72 h, respectively) than free DOC. In comparison, the DOC-loaded SNELS demonstrate a 1.87-, 2.09-, and 3.35-fold higher IC₅₀ value than free DOC at 24, 48, and 72 h, respectively, in MDA-MB-231 cells. DOC-loaded SNELS show higher cytotoxicity in MDR MCF-7 cancer cells than in the triple-negative BC MDA-MB-231 cells. The decrease in the dose required for anticancer activity is attributed to the high SNELS internalization efficiency and the ability of the designed SNELS to avoid MDR-mediated efflux. Cell cycle flow cytometry studies have demonstrated that DOC-loaded SNELS triggered the accumulation of cells in the G2/M phase (2.21-fold increase) and a significant decrease in cells in the G0/G1 phase. SMELS interfere with the microenvironment of the P-gp transporter and inhibit P-gp-mediated DOC efflux, as confirmed by rhodamine 123 dye assays demonstrating high dye concentrations in MCF-7 MDR BC cancer cell lines (Khurana et al., 2018).

5.5. Silver nanoparticles (AgNPs)

AgNPs have been extensively studied as anticancer and antimicrobial agents, owing to their cytotoxic characteristics. They have been reported to kill cancer cells via different pathways, including ROS generation, cellular redox balance disruption, anti-angiogenesis, cell cycle arrest, and apoptosis (E. J. Park et al., 2010). AgNPs have also been reported to result in accumulation of misfolded proteins in cancer cells, thus causing endoplasmic reticulum stress. These anticancer activities of the AgNPs are attributed to their size, shape, and surface coating. Nanosized particles induce cancer cell death through cellular oxidative imbalance and damage other organelles by releasing toxic silver ions (Gluga et al., 2014). Studies have found that MDR cancer cells are unable to resist the anticancer effects of AgNPs. These particles inhibit MDR in cancer cells by blocking P-gp expression as well as inhibiting the activity of the P-gp glycoproteins, and re-sensitizing cancer cells to traditional chemotherapeutic agents (Kovács et al., 2016). Motivated by these results, Gopisetty and co-workers have verified the size-dependent effect of AgNPs on P-gp activity, reporting that 75 nm sized AgNPs decrease P-gp-mediated drug efflux by depleting the calcium stores in the endoplasmic reticulum, and hence triggering endoplasmic reticulum stress and decreasing expression of the P-gp transporter on the MDR BC cell membrane (Gopisetty et al., 2019).

6. Tumor microenvironment responsive targeted drug delivery

The TME, the cellular and extracellular vicinity surrounding tumor cells, is essential for tumor cell proliferation and migration, thus playing a pivotal role in tumor physiology. It comprises various cells such as inflammatory cells, endothelial cells, dendritic cells, pericytes, and cancer stem cells (Thakkar et al., 2020). The signaling between the TME and tumor cells is essential for maintaining high proliferation and evading the body's defense mechanisms (Hanahan and Weinberg, 2011). Although all these factors have roles in cancer cell proliferation, researchers worldwide are showing interest in two TME conditions: acidic pH and induced hypoxia. Tumor cells use oxygen at higher rates than the normal cells, thus leading to hypoxic conditions in the TME. Furthermore, cancer cells increase glycolysis to meet the high oxygen demands, thereby increasing the glucose uptake by tumor cells and the local accumulation of lactic

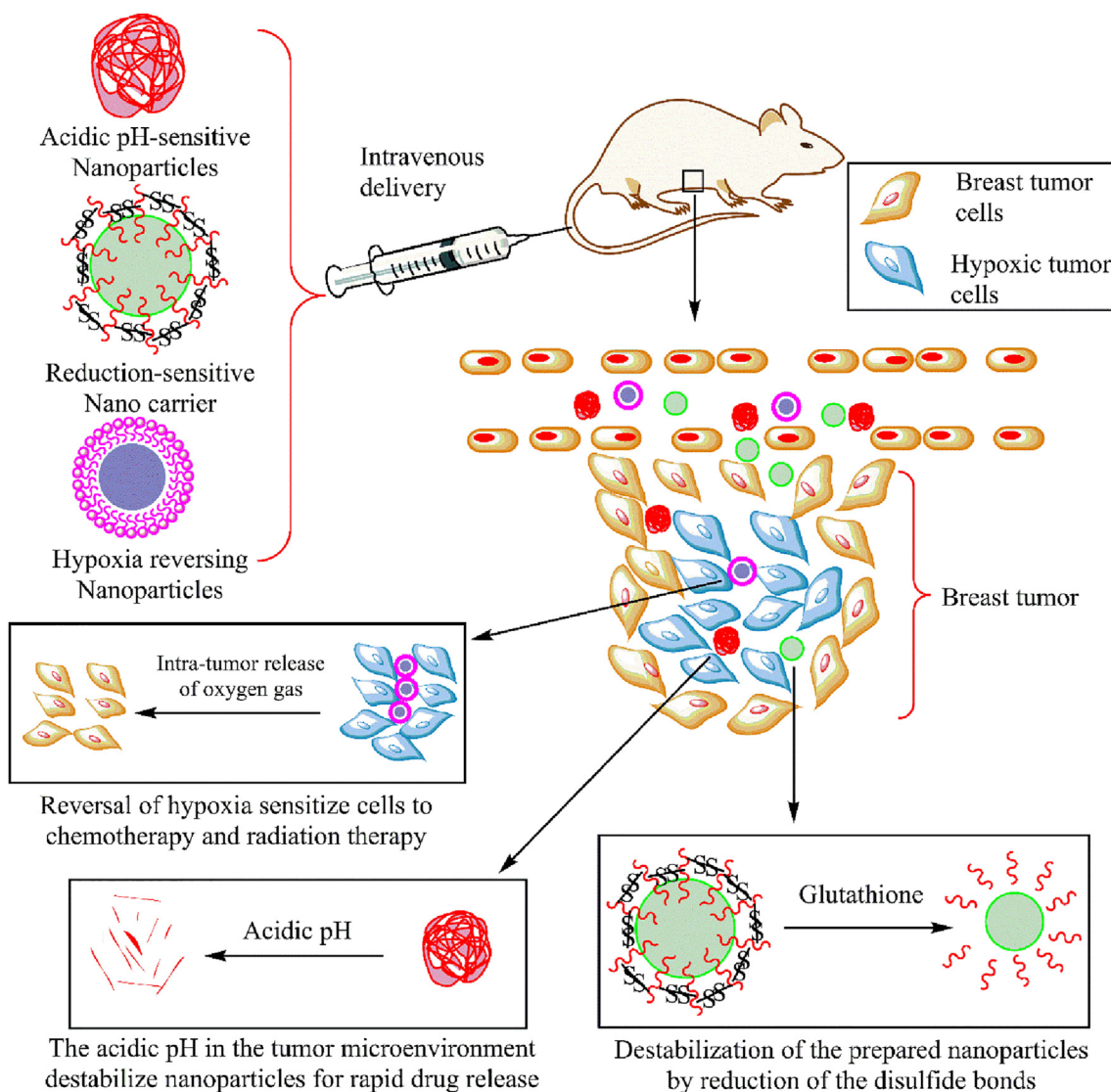


Fig. 7. Pictorial representation of TME-sensitive nanocarrier-mediated drug delivery to MDR BC cells.

acid, a by-product of glycolysis (Albini and Sporn, 2007). These processes are commonly known as the Warburg effect (Ferreira, 2010). Acidic and hypoxic local environments are associated with poor diagnosis and low response to chemotherapies (Bissell and Hines, 2011). The highly reducing environment of the TME also offers the potential for site-specific delivery. The concentration of glutathione can reach 10 mM in tumor cells and 20 μ M in the TME. Thus, the concentration of glutathione is 4-fold higher in the TME than in normal tissues (X. Guo et al., 2018). TME responsive drug delivery nanocarriers demonstrate superior tumor-specific drug release. They remain stable while circulating in the blood vessels, and release minimal amounts of the loaded chemotherapeutic agent. In the TME, drug release at a rapid rate yields high tumor drug concentrations. Site-specific release prevents the unnecessary exposure of healthy cells to the chemotherapeutic agents, thus minimizing the adverse effects (Q. He et al., 2020). Pictorial representation of TME targeting nanoformulations is done in Fig. 7.

Hypoxic conditions in the tumoral compartment are the root cause of resistance of cancer cells to chemotherapies (Y. He et al., 2019) and photo-thermal therapies (Larue et al., 2019). Reversal to oxygen-rich conditions has been found to decrease P-gp expression (Tian et al., 2017). To address this problem, Cheng et al. have developed a combined hybrid enzyme-prodrug actively targeted nanoformulation to alleviate the hypoxic conditions and simultaneously sensitize the MCF-7 BC cell

line to chemo- and photo-thermal therapies. The authors have conjugated lactobionic acid and the DOX prodrug onto the catalase side chain to manufacture an enzyme-prodrug-ligand conjugate. These conjugates were then co-assembled with chlorin e6 to form LA-DOX-CAT-C6 NPs. Lactobionic acid actively targets the NPs to BC cells. While catalase reacts with H_2O_2 to produce oxygen in situ, chlorin e6 acts as a photosensitizer inducing ROS formation. The reversal of hypoxic conditions down-regulates the overexpression of P-gp, thus leading to chemotherapeutic re-sensitization (Cheng et al., 2020).

PEG creates a region of steric hindrance around NPs, thus avoiding the adsorption of opsonins on the surface (Mozar and Chowdhury, 2018). Through this mechanism, the circulation time of the NPs in physiologic systems increases. PEG also increases the enhanced permeation and retention of NPs in tumors by increasing the circulation time and hence aids in the localization of NP systems in tumors (S. Chen et al., 2016). However, the steric hindrance developed around the NPs prevents the cellular internalization of the NPs (Greish, 2010; Hare et al., 2017). Joshi and co-workers have prepared hypoxia-sensitive micellar NPs made of PEG 2000, azobenzene, polyethylene imine, and 1, 2-dioleoyl-*sn*-glycerol-3-phosphoethanol amine amphiphilic units (PAPD) (Joshi et al., 2020). The PAPD sheds the PEG unit in the presence of hypoxic conditions and increases the cellular internalization of the micelles. The azobenzene groups confer the required hypoxia sensitivity on the micelles. The PAPD

Table 6
Summary of pH and redox-sensitive nanocarriers for the treatment of MDR BC.

P-gp inhibitor	Anticancer drug	Formulation	Cancer models used for investigation	Pharmacological activity	Reference
pH-responsive nanodrug delivery formulations					
QUE	DOX	pH-responsive chitosan-QUE nanomicelles	Drug-resistant MCF-7/ADR BC cell line	Rapid DOX release was observed at pH 4.5 <i>in vitro</i> . The micelles escaped lysosomes and released the drug in the cytoplasm, thus leading to increased cytotoxicity.	Mu, Wu, et al. (2019)
Adjudin	DOX	pH-sensitive graft copolymer poly (b-amino ester)-g- β -cyclodextrin NPs	Drug-resistant MCF-7/ADR cell line <i>in vitro</i> and <i>in vivo</i> xenografts	The prepared NPs were stable at physiological pH 6.8–7.4; however, weakly acidic pH led to the disruption of the nanoparticles' matrix and hence, leading to rapid drug release.	Q. Wang et al. (2019)
–	DOX	Terpolymer of polymethacrylic acid, starch and polysorbate 80	MDR1 expressing MDA-MB435/LCC6/MDR1 BC cell line <i>in vitro</i> investigations	The rapid DOX release rate at acidic pH was due to the loss of negative charge on the polymer below its pKa value. The site-specific rapid release against cancer cells caused the reversal of MDR.	Shalviri et al. (2012)
Oleanolic acid	DOX	Folic acid functionalized chitosan and oleanolic acid copolymer NPs	<i>In vitro</i> and <i>in vivo</i> investigations in the MDA-MB-231 drug-resistant BC cell line	<i>In vitro</i> drug release studies demonstrated 75% release in 24 h in TME simulated media (pH 5).	Niu et al. (2019)
Reduction-sensitive nanodrug delivery formulations					
QUE	DOX	Reduction-sensitive hyaluronic acid conjugated TPGS micelles	Drug-resistant MDA-MB-231/MDR1 and MCF-10 cell lines <i>in vitro</i> and <i>in vivo</i> tumor models	Nanomicelles released 93% and 95% of the loaded DOX and QUE, respectively, within 12 h in glutathione containing dissolution medium. Western blot analysis verified as much as a 12.89% downregulation of P-gp transporter expression after treatment <i>in vivo</i> .	Soltantabar et al. (2020)
QUE	PTX	Reduction-sensitive chondroitin sulfate coated mesoporous silica NPs	Drug-resistant MCF-7/ADR BC cell lines	The NPs were endocytosed actively via CD-44 receptors. Amelioration of the cancer cell cytotoxicity of PTX was exhibited, with lower IC ₅₀ , increased apoptosis, better G2/M phase arrest and stronger microtubule destruction.	(M. Liu et al., 2020)
TPGS	PTX	Reduction-sensitive hyaluronic acid conjugated TPGS micelles	MCF-7/ADR drug-resistant BC cell line <i>in vitro</i> and <i>in vivo</i>	The micelles demonstrated 21.05% and 72.7% PTX release in 48 h in the medium without and with 20 mM glutathione, respectively.	Hou et al. (2019)

DOX = doxorubicin; PTX = paclitaxel; QUE = paclitaxel; TPGS = tocopheryl poly (ethylene glycol) 1000 succinate.

construct assembled in aqueous media forms micelles that trap hydrophobic drugs as well as genetic material in the core, owing to ionic interactions with the cationic surface charges. The authors have reported the simultaneous delivery of DOX and P-gp siRNA MCF-7/ADR MDR BC cell lines. The hypoxia-targeted formulation demonstrates a 60% increase in the internalization of the formulation in MDR cancer cells. The P-gp siRNA delivery demonstrates 60% greater P-gp downregulation in hypoxic conditions. The combination demonstrates excellent cytotoxicity, yielding 80% cancer cell death in the hypoxic MCF-7 cancer cell lines (Joshi et al., 2020).

Ke and co-workers have developed acidic pH-responsive hollow PLGA NPs (HPs) for the delivery of DOX to MCF-7/ADR MDR BC cells. The HPs carry DOX and sodium bicarbonate, a gas-generating agent. The HPs generate carbon dioxide gas when trafficked via the acidic environment of endosomes and lysosomes. The generation of carbon dioxide bubbles triggers rapid release of DOX and its accumulation in the nuclei, thus leading to the death of MDR MCF-7/ADR cells. In contrast, treatment with free DOX has been found to lead to the peri-membrane accumulation of the drug and does not demonstrate any cytotoxicity, because the DOX is unable to reach the nuclei in MCF-7/ADR cells (Ke et al., 2013).

Zhang and co-workers have developed a conjugate to influence the TME. They have reported an actively targeted nano-conjugate comprising gold NP-PEG-RGD and a glucose oxidase enzyme. The functionalization with RGD ensures active targeting to DOX-resistant MCF-7R cells. The targeted conjugate consumes glucose and O₂ gas and releases H₂O₂ in cancer cells, thereby depleting the resources necessary for normal cancer cell physiology through starvation therapy. The depletion of the basic resources and the H₂O₂ gas formation retard cell proliferation and trigger cell apoptosis. The co-delivery of nano-conjugate along with

DOX leads to the killing of 80% of MCF-7R cells *in vitro*. The combination demonstrates synergy, with a combination index of less than 1, and hence has the potential to re-sensitize traditionally ineffective DOX in resistant BC cells (Jing Zhang et al., 2020). Table 6 indicates various pH and redox responsive nanocarriers to overcome resistance in BC.

7. Conclusion

The loss of sensitivity of first-line chemotherapeutic agents poses a severe problem in treating BC. Exposure to chemotherapeutic agents leads to upregulation of the P-gp transporter, which effluxes multiple chemically dissimilar chemotherapeutic agents. Co-delivery of a P-gp inhibitor has shown excellent results *in vitro* and *in vivo*. However, these results have not been replicated in clinical trials. Hence, scientists worldwide are turning to incorporation of chemotherapeutic and P-gp inhibitors in nanoscale carriers. In this article, we discussed various classes of P-gp inhibitors investigated in MDR BC, as well as deeper mechanistic insights. The discussed formulations, in comparison to free drugs, have demonstrated superior cytotoxicity in BC cells. Additionally, we discussed the importance of mitochondrial functional alterations for successful chemotherapy in resistant cancer cell lines. Several stimulus-responsive nanoformulations were discussed, with implications for tumor site-specific targeting and resistance reversal.

CRedit authorship contribution statement

Paras Fanta: Conceptualization, Data curation, Writing – original draft, Writing – review & editing, manuscript writing, data, Visualization, editing. **Saurabh Shah:** Conceptualization, Data curation,

manuscript writing, data, Writing – original draft, Writing – review & editing, Visualization, editing. **Essha Chatterjee**: Data curation. **Hoshiyar Singh**: Data curation. **Biswajit Dey**: Data curation. **Santosh Kumar Guru**: Supervision, Validation. **Shashi Bala Singh**: Supervision, Validation. **Saurabh Srivastava**: Supervision, editing and, Writing – original draft, Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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