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REVIEW

Recent advances of nanotechnology for the delivery of anticancer drugs for breast cancer treatment

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Abstract

Background Breast cancer is one of the most common causes of death for women worldwide. While chemotherapy is the treatment option for most cancers, surgery, chemotherapy, and radiotherapy are the three main therapeutic strategies for the treatment of breast cancer. In recent years, nanotechnology applications for cancer treatments have attracted a lot of attention.
Area covered This review focuses on the various nanoparticle types, such as liposomes, micelles, polymeric nanoparticles, solid lipid nanoparticles, and gold nanoparticles, and their applications for the treatment of breast cancer.
Expert opinion In recent decades, nanotechnology has developed and been applied to cancer treatments. Currently, nanotechnology plays an important role in the targeted delivery of drugs for cancer treatments, including breast cancer. Nanoparticles can target tumors and control the release of drugs to precise sites, thereby improving the therapeutic efficiency of drugs and decreasing the toxicity to normal tissues or organs. In addition, nanoparticles are also able to activate immune cells against tumors. Therefore, nanoparticles are a promising tool for future cancer research and treatment.

Keywords Nanoparticles · Breast cancer · Drug delivery · Anticancer drugs

Introduction

Cancer is one of the leading causes of death worldwide and is defined as a disease that begins when cells grow uncontrollably and crowd out normal cells. Cancer can develop anywhere in the body, such as in the lungs, breasts, or liver. The World Health Organization predicted that the burden of cancer will increase to 23.6 million new cases annually by 2030 (World Health Organization 2014). Thus, cancer treatment has become a prominent issue over the past several decades. For women, breast cancer is one of the most commonly diagnosed cancers globally. In 2018, approximately 266,120 new cases of invasive breast cancer were estimated in women constituting 30% of all cancer cases (878,980 total cases); in addition, 40,920 of these breast cancer cases were estimated to be fatal (American Cancer Society 2018). Breast cancer is usually classified on the basis of the type of receptor overexpression present on the cancer cell membrane (Fig. 1), including progesterone (PR) and estrogen (ER) hormone receptors and HER2 receptors, with HER2 being a member of the human epidermal growth factor receptor family. Breast cancers that present the overexpression of these receptors are called either PR−, ER−, or HER2-positive, depending on the type of receptor overexpression. Patients that show PR−, ER−, HER2-positive breast cancer cells are said to have triple-positive breast cancer. In addition, triple-negative breast cancer group exists that is composed of breast cancers that are neither PR/ER-positive nor HER2-positive. It has been reported that the primary cause of deaths due to breast cancer is the result of its potential metastasis to distant organs such as the liver, lungs, lymph nodes, bones, and brain (Carty et al. 1995; Grobmyer et al. 2012).

Currently, surgery (in which whole breast is removed, called a mastectomy, or in which only the tumor and surrounding tissues are removed, called a breast-conserving lumpectomy), chemotherapy (in which drugs are used to kill cancer cells), and radiotherapy (in which high-energy waves are used to kill cancer cells) are the three main cancer treatment strategies (Shewach and Kuchta 2009). Among them, chemotherapy is more popularly used for treating most types of cancer. Chemotherapy can kill many cancer cells throughout the body, eradicate microscopic disease at the

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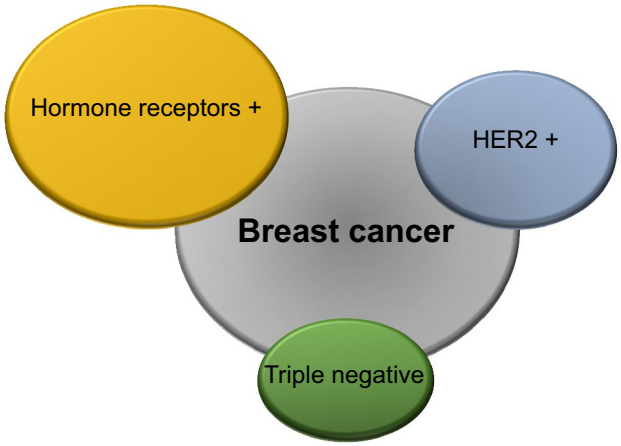

Fig. 1 Receptor-based breast cancer classification

edges of tumors that may not be seen by a surgeon, and be used in combination with other therapies.

Many anticancer drugs such as tamoxifen, paclitaxel, docetaxel, doxorubicin, and methotrexate have been approved for the treatment of breast cancer (Colleoni et al. 2002; Patt et al. 2006; Gradishar 2012; Jordan 2014; Gabizon et al. 2016). However, the poor aqueous solubility and permeability of these drugs have resulted in low bioavailability and decreased treatment efficiency. Thus, the controlled release and tumor-targeted delivery of these anticancer drugs via the use of nanoparticles represent two important strategies to improve therapeutic efficacy and reduce the side effects of cancer treatments.

Nanotechnology has been widely used over the last decades and nanoparticle drug delivery is considered a promising tool for cancer treatments due to the high loading capacity, reduced toxicity, stability, efficacy, specificity, and tolerability of drug-loaded nanoparticles compared to conventional chemotherapy drugs. Anticancer drug loaded nanoparticles can be used to actively or passively deliver drugs to tumors during breast cancer treatments (Singh et al. 2017). The advantages to using nanoparticles are not only due to their ability to be created in a range of small sizes but also to their capacity to be made from various substances, such as lipids (e.g., solid lipid nanoparticles, liposomes), polymers (e.g., polymeric nanoparticles), and inorganic materials (e.g., gold nanoparticles). Among the various types of nanoparticles, liposomes, micelles, polymeric nanoparticles, solid lipid nanoparticles, and gold nanoparticles are popularly used in the treatment of breast cancer. Thus, this review focuses on these nanoparticle types and discusses recent advances in the treatment of breast cancer.

Nanoparticle types and the treatment of breast cancer

To date, nanotechnology has rapidly developed to produce some of the most important cancer treatment strategies. Among the various nanoparticle types, the most popular nanoparticles used in breast cancer treatments are liposomes, micelles, polymeric nanoparticles, solid lipid nanoparticles, and gold nanoparticles (Fig. 2).

Liposomes

Liposomes were first developed in 1964 by Bangham and Horne (1964) and are spherical vesicles ranging in size from ~ 50 to 200 nm comprised of aqueous material contained by a phospholipid outer layer (Singh et al. 2017). Liposomes are used in the targeted drug delivery of both hydrophilic and hydrophobic drugs due to their phospholipid layers, which are composed of biocompatible, biodegradable, and non-immunogenic materials. Given their small particle size, liposomes easily pass through vascular pores to accumulate in tumors. In addition, it was reported when P-glycoprotein (P-gp) was inhibited by anionic membrane lipids and liposomes were loaded with rhodamine 123 to be used as a P-gp substrate, rhodamine retention in MCF-7/P-gp cells increased, suggesting P-gp is functional in transfer of its substrate (Kang et al. 2009). The representative examples

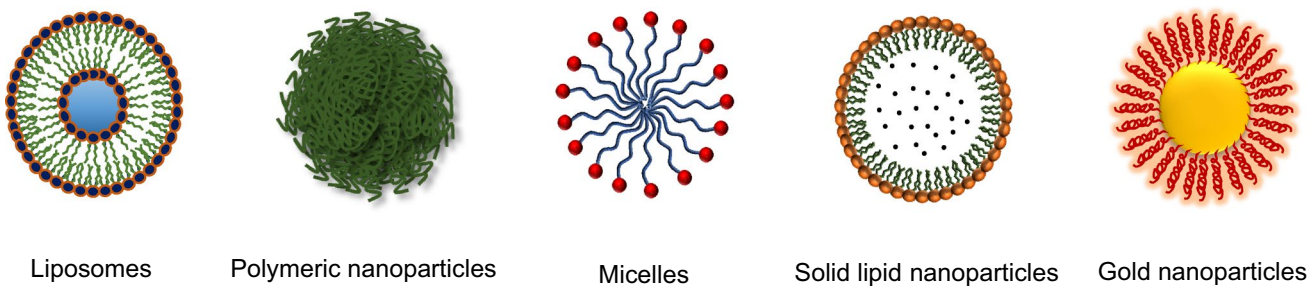

Fig. 2 Nanoparticle types commonly used in the treatment of breast cancer

of liposomes used for anticancer drug delivery to breast cancer cells are presented in Table 1. In 1965, a liposomal formulation of doxorubicin (Doxil®) was first approved by FDA for ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma (U.S. Food and Drug Administration 1995) and was recently approved for breast cancer (Gabizon et al. 2016). A paclitaxel-nanoliposome formulation was prepared using phosphatidylcholine and cholesterol, and the cytotoxicity of this liposome was evaluated in MCF-7 breast cancer cells (Esfahani et al. 2013). The results showed that the paclitaxel-liposomal formulation significantly destroyed a greater number of cancer cells compared to the free drug. Anders et al. studied the pharmacokinetics and efficacy of PEGylated liposomal doxorubicin (PLD) in an intracranial breast cancer model, and the results showed that the area under the curve (AUC) in the group treated with PLD was 1500-fold higher compared to the group treated with non-liposomal doxorubicin (Anders et al. 2013). In addition, PLD was detected in the plasma for a longer time (96 h) than non-liposomal doxorubicin (24 h). In another study by Jeong et al., pH-sensitive polymer-liposome complexes were prepared by using Pluronic P104-based multiblock copolymer as a pH-sensitive polymer to explore its potential in anticancer therapies in combination with doxorubicin and siRNA (Jeong et al. 2014). The results indicated that the cellular uptake of the pH-sensitive liposome in MCF-7 and MDA-MB-231 breast cancer cells was higher than with free doxorubicin. In addition, the in vitro cytotoxicity of doxorubicin in pH-sensitive liposomes delivered to cells was higher than that of free doxorubicin.

Liposomes have been also developed by combining two anticancer drugs to obtain synergistic anticancer effects. For instance, Eloy et al. developed co-loaded liposomes with paclitaxel and rapamycin, and evaluated their performance in breast cancer therapies in vitro and in vivo (Eloy et al. 2016). Soy phosphatidylcholine (SPC), cholesterol (Chol), and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethyleneglycol)-2000] (DSPE-PEG_{2000}) were used in the preparation of the co-loaded liposomes. The SPC/Chol/DSPE-PEG_{2000} liposome was successful in co-encapsulating paclitaxel and rapamycin. Liposomes were more cytotoxic (approximately twofold at lowest concentration) to 4T1 breast cancer cell lines than the free drug in vitro.

Micelles

Micelles present particle sizes that range from 10 to 100 nm are formed by the self-assembly of amphiphilic molecules comprised of hydrophilic heads and hydrophobic tails. The advantages associated with micelles include prolonged blood circulation times, low toxicity, and enhanced tumor accumulation; furthermore, they are commonly used for the delivery of anticancer drugs with poorly water solubility (Zhang et al. 2014). Pluronic block copolymers, a triblock copolymer of poly(ethylene oxide) and poly(propylene oxide), are widely used in the preparation of drug delivery micelles. As shown in Table 2, many anticancer drugs have been encapsulated in micelles for delivery to breast cancer cells. Batrakova et al. demonstrated that the exposure of cells to Pluronic P85 resulted in a substantial decrease in ATP level selectivity in multidrug-resistant (MDR) cells for the first time (Batrakova et al. 2001). In another study, teniposide-loaded polymeric micelles were prepared for breast cancer therapy, using monomethoxy-poly(ethylene glycol)-poly(ε-caprolactone-co-D,L-lactide) (MPEG-PCLA) copolymers with a thin-film hydration method to improve hydrophilicity and reduce systemic toxicity.

Table 1 Anticancer drug delivery by liposomes to breast cancer cells

Anticancer drug	Results	References
Paclitaxel	The cytotoxic effect of nanoliposomal paclitaxel (86.25 μg/mL) on the MCF-7 cell line was more than that of the standard form (142 μg/mL)	Esfahani et al. (2013)
Doxorubicin	The liposome nanoparticle of doxorubicin provided 1500-fold higher plasma and 20-fold higher intracranial tumor sum total doxorubicin AUC compared with free drug	Anders et al. (2013)
Docetaxel	After the IV administration of liposome formulations, the half-life was 10 times longer than that of docetaxel alone. The AUC increased 1.728-fold. IC_{50} value was found to be 20.3 ± 1.95 for free drug and 0.08 ± 0.4 μg/mL for liposome formulation	Raju et al. (2013)
Paclitaxel/rapamycin	Liposomes were more cytotoxic to the 4T1 breast cancer cell line than the free drugs (approximately twofold at lowest concentration). In addition, liposomes were better able to control tumor growth than the solution	Eloy et al. (2016)
Paclitaxel/doxorubicin	The liposome tumor inhibition ratios were observed for the treatments with free and co-encapsulated of two drugs in liposomes (66.87% and 66.52%, respectively) as compared to the control	Franco et al. (2019)
Quercetin/vincristine	Liposome formulations were physically stable and enhanced quercetin solubility 8.6-fold. In vitro MTT assays showed significant synergism, with a combination index of 0.113 and a dose-reduction index value of 115 at ED_{50} for vincristine	Wong and Chiu (2010)

Table 2 Anticancer drug delivery by micelles to breast cancer cells

Anticancer drug	Results	References
Docetaxel	The therapeutic effects of docetaxel could be enhanced by micelle formulation, which were 205.6- and 223.8-fold higher than those of the commercial reference (Taxotere®) for MDA-MB-468 and MDA-MB-231 cell lines, respectively	Kutty and Feng (2013)
Dasatinib	Dasatibib micelles exhibited 1.35-fold increase in the in vitro cytotoxicity against triple-negative human breast cancer cell line (MDA-MB-231)	Sabra et al. (2019)
Teniposide	Teniposide micelles inhibited the growth of MCF-7 more than commercial formulation (VM-26). IC_{50} of VM-26 and micelles were 5.342 μg/mL and 3.248 μg/mL, respectively. The cellular uptake of micelles group was significantly higher than that of VM-26 group (1 h: 0.529 ± 0.044 mg vs. 0.126 ± 0.017 mg; 4 h: 1.829 ± 0.163 mg vs. 0.858 ± 0.160 mg)	Chu et al. (2016)
Paclitaxel/cisplatin	Paclitaxel/cisplatin micelles showed more active than either of the single drugs. IC_{50} of paclitaxel/cisplatin micelles was about 0.25 μg/mL while IC_{50} of paclitaxel and cisplatin were about 45 and 20 μg/mL, respectively	Wan et al. (2019)
Paclitaxel	The cell viability of paclitaxel micelles in MCF-7 cells showed significantly decreased from ~ 75% to ~ 30% when paclitaxel concentration increased from 0.01 μM to 0.25 μM. The tumor growth were significantly inhibited by super-antiresistant paclitaxel micelles for both intravenous (TIR = 45.90 ± 10.47%) and oral (44.62 ± 11.15%) administration routes	Zhang et al. (2017)
Doxorubicin	The IC_{50} values were found to be 0.13 μg/mL for free doxorubicin and 0.15 μg/mL for encapsulated doxorubicin	Rosch et al. (2019)

The results showed that the half-life of the micelle formulation was improved compared to the control drug. In addition, the cellular uptake and the distribution of micelles in MCF-7 breast cancer cells and in the tumor itself were increased when compared to the commercial drug. Besides, micelles proved safe with the maximum tolerated dose (50 mg/kg), which was 2.5-fold higher than the commercial drug (20 mg/kg) (Chu et al. 2016). Zhang et al. developed a novel super-antiresistant paclitaxel micelle formulation for oral administration and evaluated its ability to combat breast cancer (Zhang et al. 2017). As a result, super-antiresistant micelles showed higher cellular uptake efficiency, cytotoxicity, and antimitotic effects in MCF-7/ADR cells with compared to the control drug. In vivo, micelles significantly improved bioavailability after oral administration and inhibited tumor growth in multidrug-resistant xenografted MCF-7/ADR nude mice. In a study by Mishra and Dey, doxorubicin and docetaxel were co-loaded in the micelle using a poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) copolymer for the treatment of breast cancer with synergistic anti-tumor effects (Mishra and Dey 2018). The in vitro cytotoxicity result showed a distinct synergistic effect of drug-loaded micelles on the viability of MCF-7 cells. Only 33% of MCF-7 breast cancer cells were viable after 48 h of treatment with doxorubicin-docetaxel-PEG-PLA micelle nanoparticles.

Polymeric nanoparticles

Polymeric nanoparticles are solid colloidal systems with particle sizes less than 200 nm, in which anticancer drugs are dissolved, entrapped, encapsulated, or adsorbed into the composition of the polymer matrix (Joshi et al. 2015; Singh et al. 2017). The polymers used in the preparation of nanoparticles can be natural (e.g., chitosan, cellulose, alginate, and gelatin) or synthetic polymers [e.g., (poly-ε-caprolactone (PCL), polylactide (PLA), and poly(lactic-co-glycolic acid) (PLGA)]. The polymeric nanoparticles for anticancer drug delivery to breast cancer cells are shown in Table 3. To enhance the solubility and bioavailability of psoralen, which is a promising anticancer drug that is limited by its poor aqueous solubility and bioavailability, Du et al. used a combination of Tween 80 and soy lecithin in the preparation of polymeric nanoparticles. The effect of nanoparticle on breast cancer MCF-7 cells was also investigated (Du et al. 2019). In vivo results showed significantly lower tumor weights and tumor volumes in the BALB/c mice treated with psoralen-polymeric nanoparticles compared with mice in the control group. In another study, Shenoy and Amiji used poly(ethylene oxide)-modified poly(ε-caprolactone) (PEO-PCL) in the preparation of tamoxifen nanoparticles and the in vivo biodistribution was evaluated in Nu/Nu athymic mice bearing a human breast carcinoma xenograft, MDA-MB-231 using tritiated [^{3}H]-tamoxifen as radio-marker for quantification (Shenoy and Amiji 2005). Polymeric nanoparticles containing tamoxifen showed significantly greater accumulation in tumors and in systemic circulation compared to the control group; below 5% of control drug and over 15% of nanoparticles were accumulated in tumor and systemic circulation after 1 h, respectively. In a study by Jadon and Sharma, PLGA and DSPE-polyethylene glycol 2000 (PEG_{2000})-NH_2 were used in the preparation of docetaxel nanoparticles for breast cancer therapies (Jadon and Sharma 2019). The cytotoxicity of docetaxel lipid hybrid

Table 3 Anticancer drug delivery by polymeric nanoparticles to breast cancer cells

Anticancer drug	Results	References
Tamoxifen	Nanoparticles exhibited significantly increased drug accumulation levels within tumors: below 5% of control drug and over 15% of nanoparticles were accumulated in tumor and systemic circulation after 1 h, respectively	Shenoy and Amiji (2005)
Docetaxel	In vitro cell studies showed increased cytotoxicity in nanoparticles compared with free drug. After 24 h, cell viability of nanoparticle and free drug was about 15% and 30%, respectively at concentration of 20 µg/mL. IC_{50} of docetaxel and nanoparticle were about 8 and 5 µg/mL after 24 h, respectively. Nanoparticle showed significantly cellular uptake compared with free drug	Jadon and Sharma (2019)
Psoralen	The tumor weight after administration with psoralen-polymeric nanoparticles (< 1 g) showed significantly decreased in comparison with control group (~ 4 g)	Du et al. (2019)
Erlotinib/doxorubicin	The cytotoxicity in MDA-MB-231 cell showed that the cell viability of erlotinib/doxorubicin nanoparticle (about 10%) was lower than that of doxorubicin nanoparticle (about 30%) after 48 h incubation at concentration of 1 µg/mL	Zhou et al. (2017)

nanoparticles in MDA-MB-231 breast cancer cells was significantly higher than that of the drug alone. In addition, the cellular uptake efficiency of docetaxel lipid hybrid nanoparticles (45–48%) was improved compared to the free drug (37–39%). The onset of early apoptosis in MDA-MB-231 breast cancer cells after treatment with docetaxel nanoparticles (11.3%) was 3.5-fold higher than that of the free drug (3.2%). In addition, the residual tumor burden for docetaxel nanoparticles (31.9%) after 3 weeks of treatment was lower than that for the free drug (69.9%). This result was correlated with in vitro cytotoxicity and cellular uptake results.

Solid lipid nanoparticles (SLNs)

SLNs were introduced as a novel drug carrier system for oral delivery (Mehnert and Mäder 2001). Over the years, SLNs have attracted special interest in cancer treatments. In particular, SLNs have several advantages, including a good release profile, biocompatibility, high drug content capacity, and high physical stability. SLNs is one of the novel potential colloidal carrier systems. By incorporating between colloidal nanoparticles and anticancer agents, resistances to drug action can overcome, the concentration of cancer drug in cancer cells including breast cancer cells can increase. Besides, the antitumor activity can enhance and their toxicity towards normal cells can reduce. They can be endocytosed/phagocytosed by cells, with resulting cell internalization of the encapsulated drug (Güney and Kutlu 2011). Therefore, SLNs are usually used to overcome the limitations associated with other formulations such as liposomes or polymeric nanoparticles. The applications of SLNs for anticancer drug delivery to breast cancer cells are listed in Table 4.

Guney Eskiler et al. prepared tamoxifen-SLNs using stearic acid and Tween 80 and evaluated the SLNs in MCF-7 Tam-resistant breast cancer cells (MCF-7-TamR) (Guney Eskiler et al. 2018). The cytotoxicity results showed that tamoxifen-SLNs significantly enhanced the efficacy of tamoxifen and reversed acquired tamoxifen resistance by inducing apoptosis and altering the expression levels of specific miRNAs and the related apoptosis-associated target genes in both MCF-7 and MCF-7-TamR cells without damaging the MCF-10A control cells. In another study, Xu et al. used egg L-α-phosphatidylcholine (PC) and DSPE–methyl(polyethylene glycol)-2000 ($mPEG_{2000}$) for the preparation of paclitaxel-SLNs and evaluated their performance in the drug-sensitive human breast cancer cell line MCF-7 and its MDR variant MCF-7/ADR (Xu et al. 2018). Paclitaxel-SLNs showed remarkably enhanced anticancer activity in the MCF-7/ADR cell lin compared to the control. In addition, the cellular uptake of paclitaxel-SLNs in MCF-7/ADR cells was also greater than that of the control. Quereshi et al. also developed docetaxel-loaded SLNs to improve the solubility and pharmacokinetics of docetaxel, and evaluated the in vitro cytotoxicity in MCF-7 breast cancer cells (Qureshi et al. 2017). The AUC of docetaxel-SLNs increased 3.7-fold in comparison with that of docetaxel-loaded micelles (commercial formulation, Taxotere®). In vitro cytotoxicity results showed that the half-maximal inhibitory concentration (IC_{50}) of docetaxel-SLNs (2.50 ± 0.14 µg/mL) for MCF-7 breast cancer cells was significantly lower (1.9-fols) than that of the commercial formulation (4.81 ± 0.15 µg/mL).

The addition of 2-hydroxypropyl-β-cyclodextrin in SLNs improved the bioavailability, cellular uptake, and anticancer activity of paclitaxel in MCF-7 breast cancer cells via modification of paclitaxel-SLNs (Cho et al. 2015). Moreover, hyaluronic acid (HA)-coated docetaxel-SLNs were developed to overcome drug-resistance in tumor cells (Lee et al. 2019). Docetaxel-loaded HA-SLNs were shown to be effective in overcoming drug resistance in tumor cells and a considerable amount of CD44 expression was detected in MCF-7/ADR cells. Additionally, the in vitro cytotoxicity

Table 4 Anticancer drug delivery by solid lipid nanoparticles (SLNs) for to breast cancer cells

Anticancer drug	Results	References
Tamoxifen	The R↔ and R↑ cells were 4.9- and 3.7-fold resistant respectively ($P < 0.05$), to 1 μM of 4-OH tamoxifen, whereas the cells were 7- and 3.5-fold resistant respectively ($P < 0.05$), to 10 μM tamoxifen at 72 h. The maximum cytotoxicity against R↔ cells was 72.6% whereas the highest cytotoxic effects on R↑ cell was 81.8% ($P < 0.05$), with 10 μM tamoxifen-SLNs	Guney Eskiler et al. (2018)
Paclitaxel	Paclitaxel-SLNs showed remarkably enhanced anticancer activity in MCF-7/ADR compared to paclitaxel delivered in dimethyl sulfoxide (DMSO) and Cremophor EL-based vehicles. Verapamil increased 29.7% the cellular uptake of paclitaxel-SLNs into MCF-7/ADR	Xu et al. (2018)
Docetaxel	Docetaxel-SLNs reduced cytotoxicity, arrested cell cycle progression in the G2/M stage and induced more apoptosis in MCF-7 cells at a low dose compared to the control	Bi et al. (2014)
Doxorubicin	Doxorubicin-SLNs accumulated in MCF-7/ADR cells to a greater extent than did doxorubicin alone. The relative cellular uptake of doxorubicin-SLNs was 17.1-fold (60 min) and 21.6-fold (120 min) higher than that of free drug	Kang et al. (2010)
Methotrexate, mitoxantrone, paclitaxel	In vitro cytotoxicity of mitoxantrone-SLNs (IC_{50}/72 h = 1.25 ± 0.19 μM vs. 2.13 ± 0.37 μM) and methotrexate-SLNs (IC_{50}/72 h = 93.80 ± 6.54 nM vs. 53.16 ± 11.54 nM) was higher than that of free drug formulations. In vitro cytotoxicity of paclitaxel-SLNs and free drug formulation IC_{50}/72 h were similar	Zhuang et al. (2012)

and cellular uptake of docetaxel-loaded HA-SLNs in MCF-7/ADR cells were higher than those of other cells. Kang et al. prepared doxorubicin-loaded SLNs to overcome multidrug resistance in cancer therapy (Kang et al. 2010). In the preparation, doxorubicin-loaded SLNs were prepared by solvent emulsification-diffusion method in which glyceryl caprate (Capmul®MCM C10) was used as lipid core and curdlan was used as the shell material. Dimethyl sulfoxide (DMSO) was used to dissolve both lipid and drug, Solutol®HS15 was used as a surfactant (Subedi et al. 2009). As the result, doxorubicin decreased the percentage of cell viability in MCF-7/ADR cells; after treating with doxorubicin and doxorubicin-loaded SLNs (30 μM), the percentage of cell viability decrease from approximately 90% (doxorubicin) to approximately 10% (doxorubicin-loaded SLNs).

Gold nanoparticles

Gold nanoparticles are inert and non-toxic, contain a gold core, and are below 150 nm in size (Manju and Sreenivasan 2010). Gold nanoparticles have recently emerged as attractive candidates to deliver anticancer drugs due to their biocompatibility (Singh et al. 2017). Besides, there are several advantages associated with gold nanoparticles such as radiosensitization, photothermal therapy, etc. (Arvizo et al. 2010). The study by García Calavia et al. showed that phthalocyanine functionalized gold nanoparticles can be stabilized and dispersed in aqueous solutions using a lactose derivative. Gold nanoparticles were prepared and functionalized with a mixed monolayer of a zinc phthalocyanine and a lactose derivative (García Calavia et al. 2018). The functionalization of the phthalocyanine-gold nanoparticles with lactose led to the production of water-dispersible nanoparticles that can generate singlet oxygen and effect cell death upon irradiation. The targeting ability of lactose of the lactose-phthalocyanine functionalized gold nanoparticles has studied in vitro towards the galectin-1 receptor on the surface of MDA-MB-231 and SK-BR-3 breast cancer cells. The results showed the exciting potential of lactose as a specific targeting agent for galactose-binding receptors overexpressed on breast cancer cells. It has been reported that gold nanoparticles can conjugate with antibodies specific to antigens that are overexpressed on tumor cells (Lim et al. 2011). Examples of gold nanoparticles used for anticancer drug delivery to breast cancer cells are summarized in Table 5.

As reported by Lee et al., antibody-conjugated gold nanoparticles were used for the surface-enhanced Raman spectroscopy imaging of tumor biomarkers that are overexpressed in MCF-7 breast cancer cells (Lee et al. 2009). Chloroquine gold nanoparticles were prepared, and their anticancer activity in MCF-7 breast cancer cells was explored (Joshi et al. 2012); interesting anticancer properties were found in vitro. The release of chloroquine from gold nanoparticles at a lower pH suggested that the lysosomal/endosomal uptake of chloroquine and the cytotoxicity of chloroquine nanoparticles in MCF-7 breast cancer cells was concentration-dependent (Joshi et al. 2012). In another study, docetaxel gold nanoparticles were prepared and evaluated in cancer cells (François et al. 2011), and the efficiency of docetaxel gold nanoparticle against MCF-7 breast cancer cells was 2.5-fold higher than that of docetaxel alone (François et al. 2011). Inulin-coated gold nanoparticles were also prepared for the selective delivery of doxorubicin to breast cancer cells (Licciardi et al. 2016). The anticancer activity toward MCF-7 breast cancer cells increased and inulin-coated gold nanoparticles preferentially accumulated in cancer cells rather than normal cells.

Table 5 Anticancer drug delivery by gold nanoparticles to breast cancer cells

Anticancer drug	Results	References
Tamoxifen	Antibody, folic acid, and tamoxifen components had complementary roles in the cell recognition, and, therefore, in the efficiency of the drug carrier nanosystem. The cytotoxicity of the drug was enhanced, in the presence of the nanostructured system, more than 20 times	Teixeira et al. (2018)
Chloroquine	Chloroquine gold nanoparticles exhibited concentration-dependent cytotoxicity in MCF-7 breast cancer cells. IC_{50} value of chloroquine gold nanoparticle was 30 ± 5 µg/mL	Joshi et al. (2012)
Docetaxel	Docetaxel gold nanoparticle was found to be 2.5-fold more efficient than docetaxel alone against MCF-7 cells	François et al. (2011)
Doxorubicin	Doxorubicin gold nanoparticles were able to be preferentially internalized into MCF-7 cells, which resulted in selective and higher cytotoxic effects on cancer cells. IC_{50} of free doxorubicin and gold nanoparticle in MCF-7 were 15.79 and 8.08 µM, respectively	Licciardi et al. (2016)

Recent advances in nanoparticles for the treatment of breast cancer

Nanoparticles have considerable potential for drug delivery and are widely used in the treatment of cancer. Nanoparticles have shown several advantages, such as good stability, high encapsulation, and the ability to incorporate both hydrophilic and hydrophobic drugs. However, nanoparticles have also shown some potential risks (Table 6). For example, nanoparticles with small particle size can easily pass through membranes, access many areas of the body, interact with cells in an unfavorable manner, and potentially cause intrinsic toxicity in many normal cells. In addition, materials can limit the preparation of nanoparticles. For instance, PLGA is a safe material with low toxicity, but it degrades quickly and does not circulate in tissues long enough for sustained drug/gene delivery resulting in decreased treatment efficiency (Jain et al. 2011; Nguyen 2011). Therefore, the disadvantage of PLGA can be overcame by changing the poly-lactic/glycolic acid ratio (Makadia and Siegel 2011). For example, with the ratio of 50:50 (PLA/PGA), PLGA exhibited a faster degradation than PLGA with a ratio 65:35 (PLA/PGA) due to preferential degradation of glycolic acid proportion assigned by higher hydrophilicity. Subsequently PLGA 65:35 (PLA/PGA) shows faster degradation than PLGA 75:25 (PLA/PGA) and PLGA 75:25 (PLA/PGA) than PLGA 85:15 (PLA/PGA). Therefore, the absolute value of the degradation rate depends on the ratio of

Table 6 Advantages and disadvantages of liposomes, micelles, polymeric nanoparticles, solid lipid nanoparticles, and gold nanoparticles

Nanoparticles	Advantages	Disadvantages
Liposomes	• Biodegradable and biocompatible • Wide range of drug delivery applications • Reduced drug toxicity	• Blurring of vision after intravenous injection, short half-life • Limited storage conditions • Cationic lipids cause toxicity
Micelles	• Biocompatibility • Biodegradability • Easy to prepare • Suitable for intravenously administered drug delivery systems	• Use only for lipophilic drugs • Low drug loading capacity • Dependency of critical micelle concentration • Limited number of polymers for use
Polymeric nanoparticles	• Incorporation of hydrophilic and hydrophobic drugs • Tunable chemical and physical properties • Existence of pH, enzymatic, hydrolysis, etc., sensitive properties when preferred proper polymers • High stability • Being many methods to prepare them	• Difficult for their scale-up • Insufficient of toxicological assessment in the literature • Degradation of the carrier
Solid lipid nanoparticles	• Good solubility and bioavailability due to organic makeup • Better control of drug release kinetic	• Low drug loading capacities • Possibly containing other colloidal
Gold nanoparticles	• Simple for diagnosis • Less invasive • Providing increased contrast for diagnosis • No photo bleaching	• Tumor targeting efficacy low • Toxicity • Optical signal not strong

glycolic acid. The amount of glycolic acid is a critical parameter in tuning the hydrophilicity of the matrix and thus the degradation and drug release rate (Park 1995; Lu et al. 1999, 2000). On the other hand, inorganic materials, such as carbon nanotubes, are durable and can persist in the body for weeks, months, or even years, making them potentially toxic and limiting their use for repeated treatments. In addition, some cancer cells can develop a resistance to the drug over the course of treatment, rendering the drug released from the nanoparticle ineffective (Nguyen 2011).

In recent years, the surfaces of nanoparticles have been modified using active targeting ligands to improve the distribution of anticancer drugs to target cells (Sohn et al. 2017; Choi and Park 2017). For example, a docetaxel liposome was prepared using D-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS) and further conjugated to trastuzumab for cellular uptake intended to produce cytotoxicity in SK-BR-3 cells, while in vivo pharmacokinetics were also investigated in rats (Raju et al. 2013). The IC_{50} value of a marketed preparation of docetaxel, TPGS liposomes, and trastuzumab-conjugated TPGS liposomes after a 24 h incubation with SK-BR-3 cells was 20.23 ± 1.95, 3.74 ± 0.98, and 0.08 ± 0.4 μg/mL, respectively. In addition, the half-life of trastuzumab-conjugated TPGS liposomes was tenfold higher compared to docetaxel alone in the pharmacokinetic study. In another study, PLA-TPGS was used as a polymer in the preparation of emtansine nanoparticle that were subsequently conjugated with trastuzumab for the treatment of HER2-positive breast cancer (Rong et al. 2017). The toxicity of emtansine nanoparticle-trastuzumab in breast cancer cells was higher that than of emtansine and trastuzumab alone. In vivo, the nanoparticle showed fewer toxic effects and inhibited tumor growth by 88% compared to the non-targeting group after administration in MDA-MB-453 xenograft-bearing mice. To modify the surface of the docetaxel-PLGA nanoparticles with Herceptin® (HCT), different methods such as adsorption, bio-conjugation, and charged adsorption were applied to enhance internalization and cytotoxicity in BT-474, SK-BR-3, and MCF-7 breast cancer cells (Choi et al. 2018a). The cellular uptake of HCT-bioconjugated nanoparticles in BT-474, SK-BR-3, and MCF-7 breast cancer cells was 5.0-, 4.4-, and 4.6-fold higher than that of the nanoparticles, respectively. In addition, the cytotoxicity of HCT-bioconjugated DTX-nanoparticles in BT-474, SK-BR-3, and MCF-7 breast cancer cells was higher compared to other formulations. Moreover, tumor-targeting gold nanorod (AuNR)-photosensitizer conjugates were designed using glutathione-sensitive linkages for effective photodynamic (PDT)/photothermal (PTT) therapies to improve active tumor-targeting activity and stability and in vitro cytotoxicity and cellular localization were also investigated in MCF-7 breast cancer cells (Choi et al. 2018b). The AuNR-photosensitizer conjugates presented good stability and biocompatibility. In addition, more than 99% of MCF-7 breast cancer cells showed AuNR-photosensitizer conjugate uptake in vitro.

Conclusions

Currently, nanoparticle research for the treatment of breast cancer has increased rapidly and has been primarily focused on using targeting ligands to achieve high accumulation with tumors. One of the most common cell surface receptors on breast cancer cells, is HER2 and this receptor is used as an effective target for traditional anticancer drugs, such as paclitaxel, docetaxel, and doxorubicin. By using targeting ligands in the preparation of nanoparticles, treatment efficiency is increased and toxicity is avoided in normal cells compared to nanoparticles without targeting ligands. Therefore, nanoparticles are a promising tool for the treatment of breast cancer and other cancers in the future.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Research involving human and animal rights This review does not contain any studies with human and animal subjects performed by any of the authors.

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