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REVIEW OF PEGYLATED LIPOSOMAL DRUG'S EFFECTIVENESS FOR OVERCOMING CHEMORESISTANCE OF BREAST CANCER.

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ABSTRACT

Breast cancer-related women mortality in the Ukraine accounts 18263 per year, or 22.2% of all cancer-related deaths. The existing breast cancer (BC) therapy suffers from various issues including recurrence and relapse. 30% BC patients develop chemoresistance throughout their treatment. Nanomedicine technologies provide a promising alternative while also overcoming the limitations posed by conventional therapies. Absence of available drugs targeting the chemoresistant BC cells, and the incapacity of drugs to be localized inside the tumor, developing alternative targeted therapies to deliver therapeutic agents is required. There is a need for development of suitable and effective drug delivery systems which can derive maximum benefits from a certain class of anti-cancer drug as well as reduce all the possible limitations amid the cancer therapy. Liposomes (nanostructured lipid carriers, solid lipid nanoparticles, micelles, and nanoemulsions) provide a variety of pharmaceutical benefits, including encapsulation of both hydrophobic and hydrophilic chemical moieties, improved solubility and stability, better bioenvironmental protection, modified drug release, and site-specific delivery of chemotherapeutics. PEGylation has been shown to increase the systemic residence duration of nanocarriers. The aim is emphasizing the direct administration of different medications to tumor cells for chemoresistant advanced breast cancer, fighting drug resistance. The PubMed database and available materials on the Internet searched for relevant issue for this review. Standard chemotherapy procedures have been shown several adverse effects and flaws during treatment. On the background of the chemotherapeutic agent's

administration, resistant BC cells acquire an aggressive phenotype with invasive and migratory abilities, but nanomedicine could overcome chemoresistance of conventional chemotherapy, and reduce the toxicity by tumor targeting of nanocarriers. Many nanoplatforms are at various phases of pre-clinical and clinical study. However, there is still a need for pharmaceutical nanoplatform and nanocarriers system development and manufacturing unification.

Keywords: breast cancer; chemoresistance; liposomes; nanomedicine; drug delivery; therapeutic approaches and drug discovery.

Aim - emphasizes the direct administration of different medications to tumor cells for chemoresistant advanced breast cancer, fighting drug resistance.

INTRODUCTION

Breast cancer (BC) is the most common form of cancers amongst all types with 2.3 million cases diagnosed annually [1]. BC-related women mortality in the Ukraine accounts18263 per year, or 22.2% of all cancer-related deaths [2]. BC starts with physiologically and molecularly diverse conditions in the breast, risk factors varying according to the type and genetic predisposition [3].

Inhibitors of downstream pathways such as PI3K/AKT/mTOR and RAS/MEK/ERK have the potential to be used therapeutically in some cases. Several of targeted medications showed significant improvements in the common and relapse-free survival and prognosis of BC patients [4]. However, the existing BC therapy suffers from various issues including recurrence and relapse. Identifying and blocking the pathways that promote or perpetuate the proliferation and invasion of breast carcinoma cells is required for long-term efficacy [5]. Nonetheless, 30% BC patients develop chemoresistance throughout their treatment [6]. The acquisition of resistance by tumor cells, which develops in response to one or more chemotherapeutic agents, adversely affects the efficacy of chemotherapeutic agents. Chemotherapeutic agents primarily promote tumor regression, although chemoresistance is inevitable. Chemoresistant tumor cells evade drug exposure by recruiting intracellular and extracellular molecular mechanisms and enabling them to manifest an invasive phenotype, thus promoting metastases and resulting in ineffective treatment [7].

BC relapse is mainly due to the resistance to conventional chemotherapeutic drugs, and it is the leading cause of mortality despite significant research breakthroughs in the therapy [8]. Pharmacokinetics and metabolism of the tumor changes lead to drug resistance in various ways. Due to an absence of available drugs targeting the chemoresistant BC cells specifically and the incapacity of drugs to be localized inside the tumor, developing alternative targeted therapies to deliver therapeutic agents is required [9].

Numerous techniques are being adopted to overcome the drug resistance including application of nanotechnology, development of novel synthetic analogues of currently used drugs, repurposing drugs, combination of drugs and methods. Among these techniques, application of nanotechnology in preparing the nanoformulations of existing synthetic and natural anticancer molecules has garnered much attention and significant advancements have been made in this field [10]. As time progresses, nanotechnology aids in the discovery of novel research methodologies in oncology, even at the molecular level. Nanoparticles are unique in different ways, and they can be used as nanomedicine in therapeutic applications [11]. These can act as chaperones in localizing chemotherapeutic drugs within the immunosuppressive tumor microenvironment (TME) or directly target the cancer cell receptors [12].

Each treatment approach is associated with certain flaws like inappropriate site-specific targeting, improper biodistribution of therapeutic, limited efficacy, instability in bioenvironment and adjuvant toxicities [13]. BC being heterogenous in nature, with complex pathophysiological changes happening throughout the metastasis and thus the treatment requires precise medicine. Also, there is a need for development of suitable and effective drug delivery systems which can derive maximum benefits from a certain class of anti-cancer drug as well as reduce all the possible limitations amid the cancer therapy [14]. In order to avoid these obstacles, the nanocarriers have emerged as favourable classes of therapeutic agents for BC treatment that could sort out the shortcomings of the

drugs and help in achieving accurate drug delivery to different sites of primary and metastatic breast cancer, including tumor vasculature, stromal cells, cancer and immune cells [15].

Liposomes (nanostructured lipid carriers, solid lipid nanoparticles, micelles, and nanoemulsions) provide a variety of pharmaceutical benefits, including encapsulation of both hydrophobic and hydrophilic chemical moieties, improved solubility and stability, better bioenvironmental protection, modified drug release, and site-specific delivery of chemotherapeutics [16].

PEGylation has been shown to increase the systemic residence duration of nanocarriers. Some of the key benefits of using nano-lipidic carriers in BC therapy are increased chemodrug biological half-life, increased internalization and tumor accumulation of nanocarriers, higher therapeutic plasma concentration, increased bioavailability, and decreased toxicity [17].

Certain medications, such as Dopolo®, Abraxane®, Doxil®, Myocet®, Depocyt®, and Genexol® PM, have been approved by various regulatory bodies across the world, and many others are currently in the clinical stage [18].

Nanotechnology is one of the world's fastest-expanding technologies, with an effect on practically every field of research. The study of manipulating materials, lipids, polymers. The nanometric range (typically less than 100 nm) is known as nanotechnology. Nanotechnology-based delivery systems are expected to rise at a 22.6% annual pace, amounting to a $130.4 billion increase over the next decade [19].

Doxorubicinum is a non-selective anthracycline antineoplastic antibiotic used in the BC treatment. Anthracyclines' cytotoxic mechanism of action is due to two phenomena: first, the drug intercalates between the base pairs of DNA, inhibiting the function of the enzyme topoisomerase II and thus halting replication and RNA transcription; and second, the drug induces apoptosis by producing radicals and reactive oxygen species (ROS) capable of damaging the cell membrane, organelles, and DNA. Unfortunately, while being among the most therapeutically efficient chemotherapeutic drugs, anthracyclines are highly associated with multidrug resistance and cardiotoxicity [20].

Nano-based colloidal drug delivery methods, such as lipid nanocapsules and liposomes, have sparked considerable interest in the scientific community. Drugs can be dissolved, adsorbed, covalently bound, encapsulated, and embedded within these delivery systems, as well as functionalized peptides, antibodies, proteins, aptamers, ligands, and antigens that target cancer via the cell surface, intracellular, and tumoral environment. These developments not only enhance medication pharmacokinetics, but also increase drug safety, offer prolonged release, improve solubility, and decrease adverse effects and drug waste [21].

MATERIAL AND METHODS

The PubMed database and available materials on the Internet was searched for relevant issue for this review. The search criteria were "Liposomal, pegylated drugs, nanotechnology, chemoresistant breast cancer" with additional filtering for papers published between 2018 and 2023. The search was done in Febrary 2024, and suitable items were manually reviewed. 67 articles identified through PubMed database and available on the Internet. Excluded 22 articles: not related: Liposomal, pegylated drugs (10); Nanocarriers systems (9); Breast cancer chemoresistance (3). 45 articles included. Figure 1 depicts a flowchart for the literature search method.

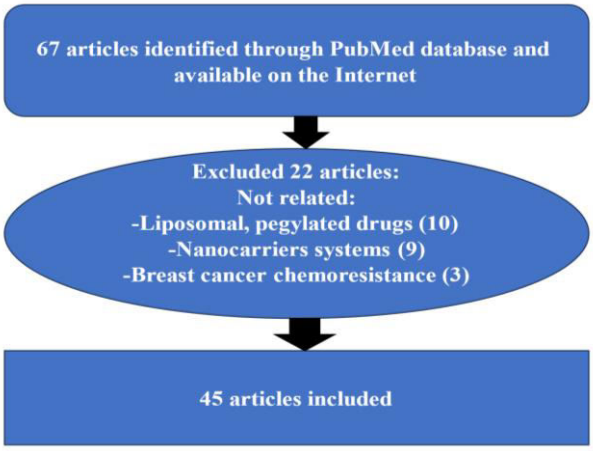

Figure 1: Flowchart representing the literature search process.

Currently, a large number of nanoparticles (NP), with different sizes, shapes, surface charge, microstructure and surface modification, are used as carriers to deliver the payload in the treatment of human diseases.

These NP include: a) organic NP (such as liposomes, polymeric nanoparticles, polymeric micelles, dendrimers); b) inorganic NP (such as carbon nanotubes, metallic nanoparticles, quantum dots). NP involved in the development of nanomedicines to treat BC are depicted in Figure 2.

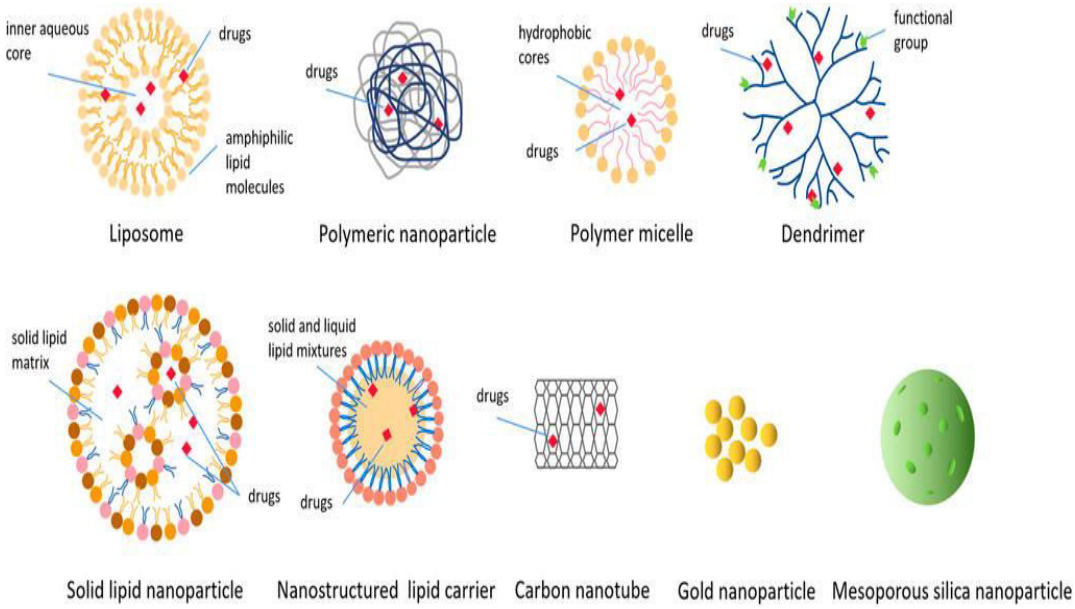

Figure 2: Types of nanoparticles used to deliver drugs in BC treatment

Currently, only few liposome-based treatments are clinically proven for use as BC therapies and have been approved for use: Dopolo®, Doxil®/Caelyx®, Myocet®, Lipodox® (Table 1).

Table 1: Liposome-based therapies for metastatic and advanced breast cancer currently in clinical use

Pharmaceutical name	Drug	Liposome, size	Components of delivery system
Dopolo® (IND)	Doxorubicinum hydrochloridum	PEGylated stealth liposomes, ~100 nm	cholesterin, hydrogenated soybean phosphatidylcholine, 1,2-distearoyl-

			sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000, ammonium sulfate, histidine, sucrose, sodium hydroxide, hydrochloric acid, water for injections
Doxil® (US)/Caelyx® (EU)	Doxorubicinum hydrochloridum	PEGylated stealth liposomes, 80–90 nm	cholesterin, hydrogenated soybean phosphatidylcholine, , 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000
Myocet liposomal	Doxorubicinum	Non-PEGylated, 150–250 nm	cholesterin,egg yolk phosphatidylcoline
Lipodox®	Doxorubicinum hydrochloridum	PEGylated stealth liposomes, ~100 nm	cholesterin, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-amino(polyethylene glycol)-2000

- Dopolo is manufactured by NATKO Pharma Ltd (Dr. Reddy's Laboratories Ltd) (India) as a generic equivalent of Doxil® since 2014.
- Lipodox® is manufactured by Sun Pharmaceuticals Industries Ltd. (India) and has been approved by the FDA as a generic equivalent of Doxil® since 2013.

Dopolo® (a long-lasting pegylated liposomal version of doxorubicin hydrochloride) inhibits the development of BC resistant to free doxorubicinum and causes tumor parenchyma pathomorphosis. Enter the cancer cell cytoplasm by endocytosis (liposome membranes are made of natural phospholipids, which allow them to adhere to cell membranes and transfer liposome contents intracellularly) allows it to enter the to tumor cell cytoplasm. Because it does not increase P-gp expression in tumor cells, it avoids active removal from the cytoplasm with the aid of this protein. In other words, it offers benefits over free cytostatics in terms of accumulation and action on malignant cells. It can accumulate for a long time in the cytoplasm and nucleus of tumor cells with a treatment resistance phenotype [22]. Pegylated liposomes have surface-bound portions of the hydrophilic polymer methoxy polyethylene glycol (MPEG). These linear MPEG groups protrude from the liposome's surface, producing a protective shell that minimizes interactions between the lipid bilayer membrane and blood plasma components. This enables doxorubicin liposomes to circulate in the blood for an extended period. Direct liposomal doxorubicin assays demonstrate that at least 90% of the medication remains encapsulated in liposomes in the circulation. PEGylated liposomes are tiny enough (average diameter around 100 nm) to pass through the tumor's damaged blood arteries intact (extravasation) [23]

Doxil®/Caelyx® (trade name varies by country) is a PEGylated nanoliposomal drug delivery system that encapsulates Doxorubicinum hydrochloridum for the primary treatment of AIDS-related Kaposi's sarcoma, multiple myeloma, treatment-resistant or refractory ovarian cancer, and metastatic breast cancer, and was the first clinically used chemotherapeutic nanosystem. The liposomal formulation and PEGylation are regarded as revolutionary since they lowered the quantity of free Doxorubicinum in the blood, reducing its anticancer activity while expanding the chemotherapeutic agent's circulation time [24].

Myocet, a non-PEGylated liposomal drug delivery system encapsulating Doxorubicinum, has been used in the EU since 2000 for metastatic breast cancer in conjunction with cyclophosphamide. Myocet has been awarded "Fast Track" accelerated designation in the United States as a first-line therapy for HER+ metastatic breast cancer. Myocet approved because of its capacity to minimize drug-related cardiotoxicity rather than improve antitumor effectiveness. [25].

Lipodox®, a PEGylated Doxorubicinum hydrochloridum encapsulating liposomal formulation, was utilized as a replacement for Doxil® in the United States during a serious shortage in 2012 and is now considered a generic counterpart [26].

Liposomes and nanoparticles of roughly 8 nm size, flushed through the kidneys and removed, but those bigger than 8 nm are cleaned by mononuclear phagocytic systems in a process known as opsonization. Opsonization should nullified by covering the nanocarrier with an inert polymer (PEG), like shield on the nanoparticle's surface, disgusting intercommunion with blood components – "stealth" effect. Stealth inhibits the clearance processes of mononuclear phagocytic systems, resulting in better vascular circulation time and pharmacokinetic features of PEGylated delivery systems with a 100-fold higher clearance half-life than free Doxorubicinum [27].

Liposomes are spherical vesicles made up of one or more lipid bilayers with an aqueous core. Spherical nanovesicles with water interaction, to form particles with an inner aqueous core and resemble cellular membranes, deliver the loaded drugs to the cell. Consist of only phospholipids, one side of such lipid molecules is hydrophilic and the other side is hydrophobic, and they have reduced shelf-life. Liposomes size range 25nm - 2.5µm, this is a huge benefit for drug delivery [28] – Figure 3.

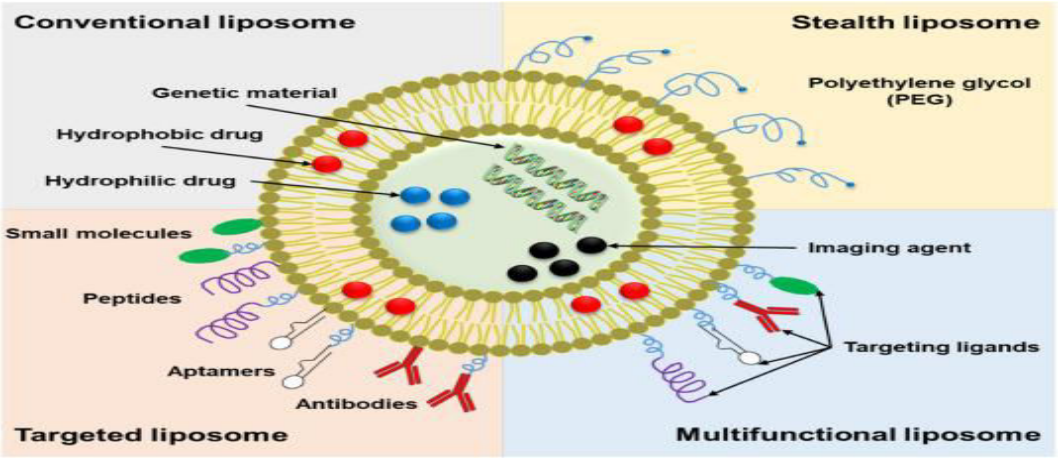

Figure 3: PEGylated liposomes.

Phospholipids, which can be of either synthetic or natural source, are the most commonly used lipids, with the addition of organic molecules to the phosphate head group producing a broad range of phospholipid species such as phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, and phosphatidylcholine [29]. Cholesterin is the most often utilized sterol, and its addition can significantly alter liposome fluidity, transparency, and stability [30]. Encapsulating acts as a protective drug delivery system, enhancing the stability of the encapsulated compounds by shielding them from environmental, enzymatic, and chemical changes, as well as providing a barrier against pH, temperature, and ion variations [31]. Liposomes can also be employed as co-delivery systems to carry chemotherapeutic medicines and inhibitors to malignant cells, rendering them susceptible to anticancer treatments [32].

Actively targeted liposomal drug delivery systems are a very intriguing idea since they can selectively target cancer cells. This precise targeting has several advantages, including selective cancer cell internalization and drug release, resulting in fewer side effects in healthy tissues and lowering the chance of multidrug resistance and the capacity to detect, visualize, and treat primary-resistant and/or recurrent breast cancer cells. Although the notion of generating targeted cancer therapy appears simple, active targeting is quite difficult. Liposomes must be grafted with appropriate targeting moieties for maximum affinity without concealing the required stealth characteristics in order to necessitate the existence of viable targets. Liposomes' surfaces are chemically changed with various reactive groups in order to functionalize them (covalently or non-covalently) with a wide range of targeted agents [33].

Bharti et al. loaded the synthetic "somatostatin analog 2" targeting agent diacerein, a medication used to treat joint swelling and discomfort, in liposome nanocarriers for the treatment of BC [34].

Fu et al. created a transferrin-functionalized co-loaded liposomal delivery system that delivered both sorafenib and Doxorubicinum for a more potent antitumor effect. Sorafenib, a hydrophobic medication placed in the liposome carrier's phospholipid bilayer, decreased tumor cell growth and stopped angiogenesis. The maximum absorption was seen with transferrin-functionalized liposomes, and the combination of the two medicines reduced tumor development more effectively than the monotherapy controls [35]

Huang et al. created a liposomal system that targets both biotin and glucose on a double-branched surface functionalized attachment and demonstrated better drug carrier absorption as compared to mono-targeting ligand-modified liposomes [36].

Seynhaeve A et al. loaded lysolipid-containing thermosensitive liposomes with marimastat, a synthetic inhibitor of collagenases and gelatinases, which are stable at 37^0C but degrade when subjected to moderate hyperthermia (39^0C). The use of hyperthermia is a well-established method for improving the accumulation of targeted entities in tumors, and it has been shown to improve blood perfusion and increase the pore size between endothelial cells of tumor microvessels; enhancing nanoparticle extravasation into the tumoral tissue's interstitial spaces. [37].

DISCUSSION

The drug delivery systems rely on the improved protection, stability, and circulation time afforded by liposomes and their PEGylation for therapeutic concentration in tumor tissue [38].

Nanoformulations include problems with laboratory-scale batch-to-batch variation, complex large-scale manufacturing processes that limit fabrication costs and throughput speeds, intellectual property disputes, a lack of clear and consistent governmental guidelines, and the cost-effectiveness of these formulations when compared to current therapies [39].

Another cause of problems with conventional therapy is the tumor's microenvironment and medication resistance. Drugs are transported more to healthy tissues, producing toxicity, and less to tumors, resulting in diminished effectiveness. Nanotechnology can be used to circumvent some of these restrictions since it has a higher surface area-to-volume ratio, which allows for better manipulation of drug surface characteristics [40].

Nanoparticles, due to their small size, can infiltrate cells and tissues and cause injury. Before nanoparticles may be used in therapeutic settings, they must be tested for toxicity and their impact on biological systems. The intricacy of nanoparticle production is a time-consuming and costly process that necessitates specialized equipment and expertise. The repeatability and scalability of nanoparticle production must also be addressed for them to be made on a bigger scale for broad application. Nanoparticles can clump together, affecting their characteristics and effectiveness. The regulatory landscape for nanoparticles is still changing, and no clear rules for their usage in clinical applications. This might cause uncertainties for researchers and corporations researching nanoparticulate medicines, thereby slowing their progress [41].

Bischoff H et al. – The goal was to show that the 2-weekly schedule outperformed the 4-weekly schedule in terms of 6-month PFS among the 209 metastatic breast cancer patients treated with PLD included in the study. Anthracyclines had previously been administered to 65% of patients (four cycles). The median duration of follow-up was 12.1 months (range: 6.0 to 18.2). The median PFS was 4.1 months (95% CI: 2.4 to 4.9), and the median overall survival was 14.2 months (95% CI: 9.6 to 15.3). In this severely pretreated MBC group, PLD appears to be a well-tolerated medication. The effectiveness and safety of the 2-weekly schedule provided no benefit, indicating that there was no desire to change the registered regimen [42].

Jiang H et al shown in their analysis of individuals with HER2-negative MBC PLD (Duomeisu®, generic doxorubicin hydrochloride liposome) 50 mg/m2 every 4 weeks until disease progression, intolerable toxicity, or completion of six cycles was given to patients who had previously undergone anthracycline and taxanes. From the

50 patients included, 40 and 38 were evaluable for safety and effectiveness, respectively. 70% had two metastatic locations, and 80% had visceral disease. PFS median was 3.9 months (95% CI: 3.1-4.3), and the median OS was 16.0 months (95% CI: 11.8-18.2). Neutropenia (8.1%), palmar-plantar-erythrodysesthesia (2.2%), and stomatitis (5.2%) were the most prevalent grade 3 AEs. In patients with HER2-negative MBC, PLD (Duomeisu®) 50 mg/m2 every 4 weeks was efficacious and well tolerated. Anthracycline and taxanes were used extensively, showing a potentially feasible therapy approach [43].

Liposomes are constantly being improved for application in tissue engineering as liposome-scaffold composite systems, programmable, multi-staged, or stimuli-triggered multi-drug eluting systems, and so on. The use of dual-targeted combination medicines that address many components of tumoral cells (e.g., targeting mitochondria and MDR processes) is also improving targeting tactics. Personalized medicine, which matches patients to the best treatment by screening for genes, proteins, receptors, and vascularization, is another promising option for targeted liposomal cancer medication delivery [44].

As a drug delivery system, liposomes have several distinct advantages, including the ability to self-assemble, load hydrophilic, hydrophobic, and amphiphilic compounds, improve solubility, protect the encapsulated drugs, provide biocompatibility and low toxicity at relative levels, biodegrade, and induce low immunogenicity [45].

CONCLUSION AND OUTLOOK

Standard chemotherapy procedures have been shown several adverse effects and flaws during treatment, the NPs-mediated drug delivery mechanism might be a contender for substitution as a new methodology.

On the background of the chemotherapeutic agent's administration, resistant BC cells acquire an aggressive phenotype with invasive and migratory abilities, but nanomedicine could overcome chemoresistance of conventional chemotherapy, and reduce the toxicity by tumor targeting of nanocarriers.

Even though nanomedicines have shown a promising application in the treatment of BC disease, there are still several issues that should be addressed before the nanomedicine can be used in clinical practice, such as long-term toxicity of nanomaterials, their impact on the immune system, pharmaceutical stability issues, and the reproduction of uniform nanoparticle batches.

Many nanoplatforms are at various phases of pre-clinical and clinical study. However, there is still a need for pharmaceutical nanoplatform and nanocarriers system development and manufacturing unification.

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