Int. J. Pharm. Investigation, 2022; 12(2) : 145-150 Review Article

Nanotechnology-based Therapeutic Strategies for Breast Cancer

Majidah Aljadani
Department of Chemistry, College of Science and Arts, King Abdulaziz University, Rabigh, SAUDI ARABIA.

ABSTRACT
Breast cancer is the most prevalent cancer among women and is considered a societal burden. The current treatment strategies are limited to chemotherapy, radiotherapy, and surgery, governed by the tumor's size, stage, and properties of biomarkers. Nanotechnology can be used as an alternative and focused approach for treating various cancers. It provides a more effective and less toxic treatment regime than other conventional methods. It has gained enormous attention to precisely diagnose and treat cancers. Nanocarriers are ideally engineered to target the cancer cells specifically, thus improving the drug's efficacy. They can overcome the problems associated with conventional drug delivery, non-specific to cancer cells, and have severe side effects. Since these nanocarriers have higher biocompatibility and therapeutic efficiency, they have shown promising results in cancer therapy. Although several nanocarriers are being developed and validated, only a few have been approved for clinical trials in cancer treatment. This review focuses on nanocarriers used in the drug delivery system and their applications in breast cancer treatment. The conventional biomarkers for early diagnosis of breast cancer and their molecular profiling by nanoparticles are also discussed. This review helps understand the promising use of nanoparticle-based technology in breast cancer treatment.

Keywords: Breast Cancer, Nanocarriers, Drug-delivery, Biomarkers, Liposomes, Polymeric nanoparticles.

Correspondence

Majidah Aljadani
Department of Chemistry, College of Science and Arts, King Abdulaziz University, Rabigh, SAUDI ARABIA.

Email id: maaljadani@kau.edu.sa

DOI: 10.5530/ijpi.2022.2.27

INTRODUCTION

Breast cancer is the most common cancer and a leading cause of cancer-associated death in women.[1] Approximately 1.7 million people are diagnosed with breast cancer, and it accounts for 450,000 estimated deaths worldwide per annum.[2] Despite many treatment options and targeted therapies, the mortality rate remains high. Breast cancer cells metastasize commonly to lymph nodes, liver, lungs, and bone.[3] Some common breast cancer biomarkers are progesterone, estrogen, and Human Epidermal Growth Factor Receptor-2 (HER2).[4] Their expression pattern plays a crucial role in breast cancer etiology and is also an important genetic marker and target for the therapy.[5] The treatment strategies highly depend on the tumor's receptor status and stage.[3] Traditional therapies include chemotherapy, radiotherapy, surgery, and adjuvant endocrine therapy and have a partial impact on the patient's survival rate.[6-7]

Nanotechnology is a rapidly developing field bringing promising strategies for diagnosing and treating cancer.[7] The application of nanomaterials in cancer diagnosis and treatment is known as nano-oncology.[8] Several nanomaterials or nanocarriers are used to precisely deliver the chemotherapeutic drugs to minimize the toxicity to healthy cells.[9] Nanoparticles or nanomaterials have incredible potential in cancer therapeutics due to their size, shape, and surface chemistry. The nanoparticles used for drug delivery in breast cancer treatment are shown in Figure 1.

Food and drug administration (FDA) have approved the nanotechnology-based drug doxil®, which is a novel PEGylated liposomal (poly-ethylene glycol coated) doxorubicin formulation for the treatment of breast and ovarian cancers.[7] Other drugs approved by the FDA for breast cancer are Myocet (Liposome encapsulated-doxorubicin), LEP-ETU, EndoTAG-1, Lipoplatin, Genexal-PM, Nektar -102.[10] Nanoparticle loaded with chemotherapeutic drugs has the advantage of efficient target site delivery and could potentially circumvent the drug resistance in cancer cells.[11] This review discusses nanoparticles-based systems used in the diagnosis and treatment of breast cancer. Further, it also highlights the biomarkers used to diagnose breast cancer and reviews their limitations and challenges in clinical applications.

CONVENTIONAL METHODS OF BREAST CANCER TREATMENT AND THEIR LIMITATIONS

The standard methods to diagnose breast cancer include clinical examination, imaging, and pathological assessment. The clinical or physical examination techniques involve family medical history, menopausal status, blood count, liver and kidney function analysis, and manual palpation. The pathological assessment includes collecting and staining biomarkers in tissue biopsy obtained from patients, whereas the imaging technique involves breast ultrasound and mammography.[12] The prognosis and treatment depend on the tumor's size, location, immunohistochemistry (IHC), and histology studies.[13] Women with BRCA1 and BRAC2 mutations have an increased risk for breast cancer, and their management includes prophylactic bilateral total mastectomy and reconstruction to reduce the risk. The HER2-positive patients are treated with trastuzumab combined with other chemotherapeutic agents.[14-15]

However, these treatment strategies have limitations of lack of specificity and significant toxicity to the normal cells. Further, solid tumors form a barrier in transcapillary transport, leading to low penetration of drugs and, consequently, biodistribution.[15] Previous studies have shown that the drug accumulates 10 to 20 times higher in normal cells than the cancer cells proving that many anti-tumor drugs cannot cross 40 mm thick tissues. Subsequently, this leads to multi-drug resistance

Figure 1: Different types of nanocarriers based drug delivery system.

in the cancer cells.[16] Nanocarriers are potentially used for imaging and treatment applications in cancers to overcome these problems and for the drug's site-specific delivery.

NANOPARTICLES FOR DIAGNOSIS AND DRUG DELIVERY IN BREAST CANCER

Nanoparticles exhibit unique physical, chemical, and mechanical properties and are utilized as delivery agents by encapsulating and attaching drugs. They have optimum and regulated *in-vivo* distribution, specificity, intracellular penetration, bioavailability, and low toxicity. The nanoparticles are classified into three types (1) Lipid, (2) Polymeric, and (3) Inorganic. Depending on their size, colloidal state, and reasonable movement time, they have diverse applications in imaging, drug delivery, ablation of photothermic tumors, and radiation sensitizers.[17-19] Figure 2 represents the characteristics of nanoparticles used in breast cancer therapy.

Liposomes

Bangham *et al.* identified Liposomes,[20] the first nanocarrier to be clinically approved by the FDA to deliver chemotherapeutic drugs, such as DaunoXomeTM.[21] *Liposomes* are phospholipids consisting of small vesicles made of a vital aqueous and a lipid bilayer with membranes.[20] Bilayer membrane and hydrophobic molecules are intercalated, whereas hydrophilic molecules are entrapped in the aqueous medium, making it an excellent drug transporter (Torchilin, 2005). It is coated with inert polymers like Polyethylene glycol, which improves its stability and thus prolongs circulation in the blood.[22] The first FDA-approved liposomes-based nanomedicines were Doxil®, which comprises PEGylated-doxorubicin.[23] Although there are numerous advantages of liposomes, some studies have reported high absorption by the reticuloendothelial system and Kupfer cells of the liver within 15-30 min after intravenous injections,[24-25] batch-to-batch variation, stability, and sterilization limitations.[26]

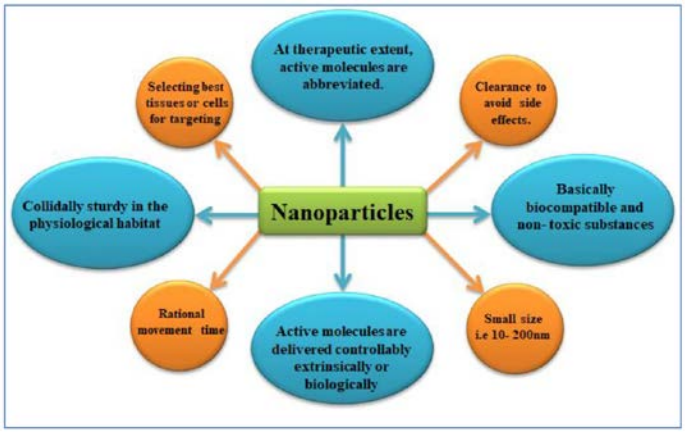

Figure 2: Properties of nanoparticles for used in the breast cancer therapy.

Polymeric Nanoparticles

Polymeric nanoparticles like PLGA (Poly D L-lactic-co-glycolic acid), PEG (Polyethylene glycol), and PLA (Poly D L-Lactic acid) are made from biodegradable and biocompatible polymers.[27] Polysaccharides like pectin, chitosan, and alginate have encapsulated these nanostructures.[28-29] These polymeric nanoparticles are articulated to encapsulate drugs with either hydrophobic or hydrophilic properties. It helps in surface alterations and pH-reliant controlled drug release. Dendrimers are the macromolecules of polymeric nanomaterials with many arms extending from a midpoint with a distinct topological arrangement.[30] These consist of three essential components – (1) a central core having two or other groups, which are called generations; (2) the peripheral functional groups on the surface which regulate the physicochemical possessions of a dendrimer; and (3) peripheral clusters, which can be modified to attain a vital lipophilic and hydrophilic function.[31] Genexol®-PM, Paclitaxel-formulated with polymeric micelle, is under clinical trial for treating breast cancer (Clinical Trials Database). *Paclitaxel* is an antimitotic chemotherapeutic drug that hinders the depolymerization of the microtubule, cell motility, and transport and is the first line of treatment for breast, lung, and ovary cancer.[32] However, its limitation includes low specificity to cancer cells, poor solubility, and poor permeability.[33]

Inorganic Nanoparticles

The inorganic nanoparticles have emerged as a novel drug delivery system due to their unique properties, such as chemical alignment, surface dimensions, physiochemical possessions, affluence of functionalization, virtuous constancy, and more excellent surface-to-volume ratio. Some inorganic nanoparticles are carbon nanotubes, magnetic, quantum dots, gold, and silica.[20] Gold nanoparticles are more attractive as nanocarriers because of their unique characteristics. They can be effortlessly synthesized, and their size can be actively controlled by tuning the synthesis.[34] The gold particles are resistant to oxidation within physiological conditions and thus are ideal for biological applications. The size and shape of the gold nanoparticles can be regulated to penetrate the cell membrane efficiently. These functionalized nanoparticles show increased transport kinetics, biocompatibility, circulation, and adsorption by tumor cells. An example of inorganic nanoparticles is Quantum dots (QD). These are semiconductor inorganic luminous nanocarriers whose surface can be modified with several ligands or molecules for the targeted therapy. These biocompatible nanocrystals range from 1-20 nm in size.[35-36]

ADVANCEMENTS OF CARBON NANOMATERIALS FOR TREATING BREAST CANCER

One of the nanomaterials with greater importance is carbon nanomaterials.[37] Carbon nanomaterials are inorganic nanomaterials and have excellent thermal and mechanical properties. They are used in photothermal therapy due to their strong ability to absorb in the infrared range.[38] The carbon nanomaterials such as graphene, carbon nanotubes (CNTs), and fullerenes, when chemically functionalized, exhibit enhanced solubility, thus enabling a controlled drug delivery.[39-41] The delivery of chemotherapeutic agents like taxol and doxorubicin using these carbon nanomaterials reduces toxicity as they have enhanced transmembrane permeability.[42-49] These nanomaterials are an excellent matrix for imaging agents like radionuclides and fluorescent tags for early-stage detection of breast cancer.[50-54] Buckyball or Buckminsterfullerene is a carbon allotrope that can absorb light in the ultraviolet region and generate reactive oxygen species upon illumination, which allows them to act as a potent photosensitizer. These tumor-specific photosensitizers are used in photodynamic therapy.[55] It involves photosensitizer and illumination of specific wavelength light, is an alternate tumor ablative treatment that can exert a robust cytotoxic action on malignant cells.[56] To replace the conventional invasive treatment for removing breast cancer cells recently, nanomaterials have been employed in photodynamic therapy.[57-65] Biosensors can detect tumor indicators or markers even at low concentrations as compared to conventional imaging; and several studies have highlighted the utilization and advantages of using carbon nanotubes (CNTs) as biosensors.[66-69]

DIAGNOSTIC AND PROGNOSTIC BREAST CANCER BIOMARKER AND NANO-BASED PROFILING OF BIOMARKERS

Cancer expresses tissue-specific protein biomarkers that can detect different types of cancers. Biomarkers have all the information on tumor types and can be potential prognostic and diagnostic predictors.[70]

HER2

Human Epidermal Growth Factor Receptor-2 is a tyrosine kinase transmembrane receptor and is a potential predictive and prognostic biomarker in breast cancer.[71] Slamon *et al.* have found that those breast cancers in which HER2 is overexpressed are less responsive to chemotherapy.[72] HER2 subtype tumors account for 20% to 30% of breast cancer patients and are also linked with enhanced chemo-resistance.[73-74] Trastuzumab (Herceptin®) is a monoclonal antibody that targets the HER2 receptor.[75] It has two specific antigen-binding sites inhibiting the dimerization of HER2 and the activation of tyrosine-kinase.[77] The clinical data of HER2-positive patients treated with Trastuzumab in primary and metastatic stages showed an improved response and lower recurrence[77-79] Studies have also suggested that HER2-targeted therapy in cancer patients reduces the mortality rate by one-third. Though the development of the monoclonal antibody Trastuzumab increased prognosis in patients, few other patients have shown resistance and advance in disease progression.[80] Lapatinib and pertuzumab are alternative monoclonal antibodies used in Trastuzumab-resistant breast cancer cells.[80]

Estrogen Receptor

The estrogen receptor (ER) is considered the most important biomarker for classifying breast cancer, and ER-positive patients show a better treatment response for anti-estrogen or aromatase therapy than ER-negative patients.[81]

It is also an important prognostic factor for predicting breast cancer recurrence. It plays a vital role in the progression of carcinogenesis, and ER-positive tumors account for 70% of the primary breast cancer cases. It has been reported that ER-positive tumors are less aggressive and are associated with better outcomes after surgery.[82]

Progesterone Receptor

The progesterone receptors are ligand-induced transcriptional factors that activate pro-proliferative signaling pathways in breast cancers. Only a few reported tumors are positive for progesterone receptor (PR) and negative for estrogen receptor (ER). Studies have shown that PR-positive tumors comprise 65-75% of breast cancers. Endocrine inhibition therapy is more effective and more responsive in the progesterone receptor and estrogen receptor-positive (PR+ER+) patients as compared to only estrogen receptor-positive patients (ER+PR-).[83] Further, the patients who are PR upbeat show better responses to Tamoxifen. PR-negative and ER-positive tumors are more aggressive and are associated with Tamoxifen resistance.[84]

PROLIFERATIVE MARKERS

Ki-67 Biomarker

Ki-67 is the proliferation marker present in all actively dividing cells. It is a nuclear non-histone protein, the expression of which varies throughout the cell cycle.[85] It is considered one of the important markers in breast cancer and has been used to predict the outcome of hormonal adjuvant therapy and the risk of recurrence after chemotherapy.[86-87] Several studies have suggested Ki-67 as a predictive and prognostic biomarker in breast cancer patients treated with neoadjuvant chemotherapy.[88-89] It has been noted that Ki-67 should be used in combination with ER, PR, and HER2 to classify breast cancer better.

Cyclin D1 Biomarker

Cyclin D1 is a promising prognostic and diagnostic biomarker in breast cancer. The cyclin D1 (CCND1) gene is amplified in about 15% of the estrogen receptor-positive breast cancers and overexpression of its protein in 50% of cancer patients. Tumors with high expression of CCND1 are found to show resistance to endocrine therapy.[90] The expression of cyclins D, E, and A is crucial for the cell cycle transition (G1, S, and G2/M phase).[91] The cell cycle proteins and their associated proteins, cyclin-dependent kinases, govern the division of the cells.[92] However, as there have been conflicting reports of the correlation between cyclin D1 levels and patient survival, further studies are required to elucidate the clinical value of cyclin D1 in breast cancer.

Cyclin E

Cyclin E has similar actions as Cyclin D1, i.e., it is involved in regulating the cell cycle.[93] The overexpression of the Cyclin E gene has been identified in several breast cancer cell lines, and it has been proven that it plays a significant role in tumorigenesis.[94-96] It regulates the G1-S checkpoint and has been shown as a potent oncogene driving unregulated cellular proliferation (Table 1).[97-98]

Molecular Profiling of Biomarkers with Quantum Dots

The subtyping of breast cancer into different subtypes is based on immunohistochemistry (IHC) markers and gene expression array data. As these methods are semi-quantitative and variable, new molecular profiling technologies were developed.[99] The individual tumor can be analyzed for a panel of biomarkers for precision medicine or personalized treatment with advanced profiling techniques. Numerous studies have

Table 1: Types of prognostic and diagnostic breast cancer marker.

Biomarkers	Types	Sample taken from, for identification
Serum Markers	CA 15-3, CA 27.29 CEA	Blood
Hormone Receptors	Estrogen receptors Progesterone receptors	Tissue
Oncoproteins	HER-2	Tissue
Gene mutations	BRCA1 and BRCA2	Blood
Tumor suppressor	p53	Tissue
Potential Proteins	MUC1 and Mammoglobin	Blood

documented the properties of quantum dots in immunostaining of the tissues. This method has the advantage of multicolor excitation, better brightness, and stability than photobleaching.[99] Yezhelev *et al.* reported conjugation of the quantum dots with breast cancer biomarkers ER, PR, and HER2. The multiplexed detection of these biomarkers in single paraffin-embedded tissue is closely correlated with immunohistochemistry, western blotting, and fluorescent *in-situ* hybridization (FISH). It was also suggested that quantum dots-based technology could be used for diagnostic applications with further improvements.[99] The nanocrystal-based quantum dots offer advantages over conventional imaging approaches, including signal amplification, enhanced binding affinity, specificity, and targeting efficiency. *In situ* hybridization (FISH) used the quantum dots-based fluorescence to detect HER2 biomarkers in breast cancer. It was found that the quantum dot model has more photostability than other probes like fluorescein or texas red.[59]

Wang *et al.* demonstrated molecular sentinel (MS) probes to detect breast cancer biomarkers HER2 and Ki67. The surface-enhanced Raman Scattering-based molecular sentinel (SERS) nanoprobes have enhanced specificity in breast cancer diagnosis. The MS-based nanoprobe technique is valuable for multiplexed DNA detection and high throughput-bioassays in cancer.[100, 101]

FUTURE PERSPECTIVE

With their unique biological properties and tunable surface characteristics, nanoparticles provide enhanced opportunities to improve breast cancer diagnosis and treatment. Many nanotechnology applications have transformed clinical oncology through enhanced detection, diagnosis, drug delivery, and treatment. This review has discussed various applications of nanoparticles in cancer therapy, current limitations, and future perspectives to improve the nanomedicine translation from bench to bedside.

CONCLUSION

To translate laboratory research of nanoparticles-based cancer therapeutics into clinical trials, some of the hurdles should be overcome, including improving concentration and encapsulation efficiency. It is essential to characterize the nanoparticles for their safety by analyzing their physiochemical, pharmacological, and immunological properties before being approved for clinical trials. The most challenging impediment to using nanoparticles associated with their use is toxicity; therefore, short-term and long-term studies should be performed in cell culture and animal models to assess their human use.

Another compounding factor that hinders the scaling-up of nanoparticle formulation for clinical use is batch-to-batch variation and biological equivalence. The improved strategies of a nanoformulation-based system to deliver therapeutics when breast cancer cells spread to bone, lung, liver, and breast should be invented to improve the patient outcome. Overcoming these challenges will pave for the augmented role of nanoparticles in the fight against cancer.

CONFLICT OF INTEREST

The author declare that there is no conflict of interest.

REFERENCES

1. Grobmyer SR, Zhou G, Gutwein LG, Iwakuma N, Sharma P, Hochwald SN. Nanoparticle delivery for metastatic breast cancer. Nanomedicine. 2012;8; Suppl 1:S21-30. doi: 10.1016/j.nano.2012.05.011, PMID 22640908.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29. doi: 10.3322/caac.21208, PMID 24399786.
3. Tanaka T, Decuzzi P, Cristofanilli M, Sakamoto JH, Tasciotti E, Robertson FM, *et al.* Nanotechnology for breast cancer therapy. Biomed Microdevices. 2009;11(1):49-63. doi: 10.1007/s10544-008-9209-0, PMID 18663578.
4. Pindiprolu SKSS, Krishnamurthy PT, Chintamaneni PK, Karri VVSR. Nanocarrier based approaches for targeting breast cancer stem cells. Artif Cells Nanomed Biotechnol. 2018;46(5):885-98. doi: 10.1080/21691401.2017.1366337, PMID 28826237.
5. Allahverdiyev AM, Bagirova M, *et al.* Aldehyde dehydrogenase: Cancer and stem cells, dehydrogenases. Rosa Angela Canuto. IntechOpen, 2012. doi: 10.5772/48591.
6. Aljadani MajidahA, Alkhatib MH, Sawsan H. Mahassni 'evaluation of the proliferation and invasion of human hepatocellular carcinoma cells subjected to epirubicin formulated with natural oils in nanoemulsion'. Asian J Pharm. 2020;14(1):1-9.
7. Falagan-Lotsch P, Grzincic EM, Murphy CJ. New advances in nanotechnology-based diagnosis and therapeutics for breast cancer: An assessment of active-targeting inorganic nanoplatforms. Bioconjug Chem. 2017;28(1):135-52. doi: 10.1021/acs.bioconjchem.6b00591, PMID 27973767.
8. Prabhakar U, Maeda H, Jain RK, Sevick-muraca EM, Zamboni W, Farokhzad OC, *et al.* Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology. Cancer Res. 2013;73(8):2412-7. doi: 10.1158/0008-5472.CAN-12-4561, PMID 23423979.
9. Yezhelyev MV, Al-Hajj A, Morris C, Marcus AI, Liu T, Lewis M, *et al. In situ* molecular profiling of breast cancer biomarkers with multicolor quantum dots. Adv Mater. 2007;19(20):3146-51. doi: 10.1002/adma.200701983.
10. Pillai G. Nanomedicines for cancer therapy: An update of FDA approved and those under various stages of development. SOJPPS. 2014. doi: 10.15226/2374-6866/1/2/00109.
11. Adair JH, Parette MP, Altinoglu EI, Kester M. Nanoparticulate alternatives for drug delivery. ACS Nano. 2010;4(9):4967-70. doi: 10.1021/nn102324e, PMID 20873786.
12. Aebi S, Davidson T, Gruber G, Cardoso F, ESMO Guidelines Working Group. Primary breast cancer: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22;Suppl 6:vi12-24. doi: 10.1093/annonc/mdr371, PMID 21908498.
13. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart MJ, *et al.* Panel Members. Tailoring therapies–improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015;26(8):1533-46. doi: 10.1093/annonc/mdv221, PMID 25939896.
14. Hartmann LC, Lindor NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Engl J Med. 2016;374(5):454-68. doi: 10.1056/NEJMra1503523, PMID 26840135.
15. Heldin CH, Rubin K, Pietras K, Östman A. High interstitial fluid pressure - an obstacle in cancer therapy. Nat Rev Cancer. 2004;4(10):806-13. doi: 10.1038/nrc1456, PMID 15510161.
16. Bosslet K, Straub R, Blumrich M, Czech J, Gerken M, Sperker B, *et al.* Elucidation of the mechanism enabling tumor selective prodrug monotherapy. Cancer Res. 1998;58(6):1195-201. PMID 9515805.
17. Ferrari M. Cancer nanotechnology: Opportunities and challenges. Nat Rev Cancer. 2005;5(3):161-71. doi: 10.1038/nrc1566, PMID 15738981.
18. Duncan R. The dawning era of polymer therapeutics. Nat Rev Drug Discov. 2003;2(5):347-60. doi: 10.1038/nrd1088, PMID 12750738.
19. LaVan DA, McGuire T, Langer R. Small-scale systems for *in vivo* drug delivery. Nat Biotechnol. 2003;21(10):1184-91. doi: 10.1038/nbt876, PMID 14520404.
20. Bangham AD, Horne RW. Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. J Mol Biol. 1964;8(5):660-8. doi: 10.1016/s0022-2836(64)80115-7, PMID 14187392.
21. Forssen EA, Ross ME. Daunoxome® Treatment of Solid Tumors: Preclinical and Clinical Investigations. Journal of Liposome Research. 1994;4(1):481-512. doi: 10.3109/08982109409037058.

22. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov. 2005 Feb;4(2):145-60. doi: 10.1038/nrd1632, PMID 15688077.
23. Barenholz YC. Doxil®—the fi rst FDA-approved nano-drug: Lessons learned. J Control Release. 2012;160(2):117-34. doi: 10.1016/j.jconrel.2012.03.020, PMID 22484195.
24. Laverman P, Carstens MG, Boerman OC, Dams ET, Oyen WJ, Van Rooijen N, *et al*. Factors affecting the accelerated blood clearance of polyethylene glycol-liposomes upon repeated injection. J Pharmacol Exp Ther. 2001;298(2):607-12. PMID 11454922.
25. Litzinger DC, Buiting AM, Van Rooijen NV, Huang L. Effect of liposome size on the circulation time and intra organ distribution of amphipathic poly(ethylene glycol)-containing liposomes. Biochim Biophys Acta. 1994;1190(1):99-107. doi: 10.1016/0005-2736(94)90038-8, PMID 8110825.
26. Allen TM, Hansen C, Martin F, Redemann C, Yau-Young A. Liposomes containing synthetic lipid derivatives of poly(ethylene glycol) show prolonged circulation half-lives *in vivo*. Biochim Biophys Acta. 1991;1066(1):29-36. doi: 10.1016/0005-2736(91)90246-5, PMID 2065067.
27. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. Colloids Surf B Biointerfaces. 2010;75(1):1-18. doi: 10.1016/j.colsurfb.2009.09.001, PMID 19782542.
28. Arora D, Sharma N, Sharma V, Abrol V, Shankar R, Jaglan S. An update on polysaccharide-based nanomaterials for antimicrobial applications. Appl Microbiol Biotechnol. 2016 Mar;100(6):2603-15. doi: 10.1007/s00253-016-7315-0, PMID 26830099.
29. Vora A, Wojtecki RJ, Schmidt K, Chunder A, Cheng JY, Nelson A, *et al*. Development of polycarbonate-containing block copolymers for thin film self-assembly applications. Polym Chem. 2015;7(4):940-50. doi: 10.1039/C5PY01846C.
30. Satija J, Mukherji S. Dendrimeric nano-glue material for localized surface plasmon resonance-based fiber-optic sensors. Appl Nanosci. 2012;2(3):293-7. doi: 10.1007/s13204-012-0107-7.
31. Bai J, Li Y, Du J, Wang S, Zheng J, Yang Q, *et al*. One-pot synthesis of polyacrylamide-gold nanocomposite. Mater Chem Phys. 2007;106(2-3), 15 412-4152007. doi: 10.1016/j.matchemphys.2007.06.021.
32. Mackler NJ, Pienta KJ. Drug Insight: Use of docetaxel in prostate and urothelial cancers. Nat Clin Pract Urol. 2005;2(2):92-100; quiz 1 p following 112. doi: 10.1038/ncpuro0099, PMID 16474654.
33. Shao K, Singha S, Clemente-casares X, Tsai S, Yang Y, Santamaria P. Nanoparticle-Based Immunotherapy for cancer. ACS Nano. 2015;9(1):16-30. doi: 10.1021/nn5062029, PMID 25469470.
34. Das M, Saxena N, Dwivedi PD. Emerging trends of nanoparticles application in food technology: Safety paradigms. Nanotoxicology. 2009;3(1 (Mar)):10-8. doi: 10.1080/17435390802504237.
35. Zhang H, Yee D, Wang C. Quantum dots for cancer diagnosis and therapy: Biological and clinical perspectives. Nanomedicine (Lond). 2008;3(1):83-91. doi: 10.2217/17435889.3.1.83, PMID 18393668.
36. Geszke-Moritz M, Moritz M. Quantum dots as versatile probes in medical sciences: Synthesis, modification and properties. Mater Sci Eng C Mater Biol Appl. 2013;33(3):1008-21. doi: 10.1016/j.msec.2013.01.003, PMID 23827537.
37. Casais-Molina ML, Cab C, Canto G, Medina J, Tapia A. Carbon nanomaterials for breast cancer treatment. J Nanomater. 2018;2018:1-9. doi: 10.1155/2018/2058613.
38. Chen D, Dougherty CA, Zhu K, Hong H. Theranostic applications of carbon nanomaterials in cancer: focus on imaging and cargo delivery. J Control Release. 2015;210:230-45. doi: 10.1016/j.jconrel.2015.04.021, PMID 25910580.
39. Singh A, Choudhary M, Kaur S, Singh SP, Arora K. Molecular Functionalization of Carbon Nanomaterials for Immuno-diagnosis of Cancer. Materials Today: Proceedings. 2016;3(2):157-61. doi: 10.1016/j.matpr.2016.01.050.
40. Lucafò M, Gerdol M, Pallavicini A, Pacor S, Zorzet S, Da Ros T, *et al*. Profiling the molecular mechanism of fullerene cytotoxicity on tumor cells by RNA-seq. Toxicology. 2013;314(1):183-92. doi: 10.1016/j.tox.2013.10.001, PMID 24125657.
41. Alkhatib MH, Bawadud RS, Gashlan HM. Incorporation of docetaxel and thymoquinone in borage nanoemulsion potentiates their antineoplastic activity in breast cancer cells. Sci Rep. 2020;10(1):18124. doi: 10.1038/s41598-020-75017-5. PMID 33093596.
42. Shao W, Arghya P, Yiyong M, Rodes L, Prakash Carbon S. Nanotubes for use in medicine: Potentials and limitations, syntheses and applications of carbon nanotubes and their composites, Satoru Suzuki. IntechOpen; 2013. doi: 10.5772/51785.
43. Al Faraj A, Shaik AP, Shaik AS. Magnetic single-walled carbon nanotubes as efficient drug delivery nanocarriers in breast cancer murine model: Noninvasive monitoring using diffusion-weighted magnetic resonance imaging as sensitive imaging biomarker. Int J Nanomedicine. 2015;10:157-68. doi: 10.2147/IJN.S75074, PMID 25565811.
44. Zhou X, Tian Z, Li J, Ruan H, Ma Y, Yang Z, *et al*. Synergistically enhanced activity of graphene quantum dot/multi-walled carbon nanotube composites as metal-free catalysts for oxygen reduction reaction. Nanoscale. 2014;6(5):2603-7. doi: 10.1039/c3nr05578g, PMID 24477654.
45. Xu Z, Wang S, Li Y, Wang M, Shi P, Huang X. Covalent functionalization of graphene oxide with biocompatible poly(ethylene glycol) for delivery of paclitaxel. ACS Appl Mater Interfaces. 2014;6(19):17268-76. doi: 10.1021/am505308f, PMID 25216036.
46. Raza K, Kumar D, Kiran C, Kumar M, Guru SK, Kumar P, *et al*. Conjugation of docetaxel with multiwalled carbon nanotubes and codelivery with piperine: Implications on pharmacokinetic profile and anticancer activity. Mol Pharm. 2016;13(7):2423-32. doi: 10.1021/acs.molpharmaceut.6b00183, PMID 27182646.
47. Jiang H, Zhang D, He Z, Lian Q, Xue Z, Zhou X, *et al*. A novel sensitive electrochemical sensor for the simultaneous determination of hydroquinone and catechol using tryptophan-functionalized graphene. Anal Lett. 2015;48(9):1426-36. doi: 10.1080/00032719.2014.984188.
48. Shi H, Magaye R, Castranova V, Zhao J. Titanium dioxide nanoparticles: A review of current toxicological data. Part Fibre Toxicol. 2013;10(1):15. doi: 10.1186/1743-8977-10-15, PMID 23587290.
49. Hashemi M, Noie SH. Study of flow boiling heat transfer characteristics of critical heat flux using carbon nanotubes and water nanofluid. J Therm Anal Calorim. 2017;130(3):2199-209. doi: 10.1007/s10973-017-6661-1.
50. Al Faraj A, Shaik AS, Al Sayed B, Halwani R, Al Jammaz I. Specific targeting and non-invasive imaging of breast cancer stem cells using single-walled carbon nanotubes as novel multimodality nanoprobes. Nanomedicine (Lond). 2016;11(1):31-46. doi: 10.2217/nnm.15.182, PMID 26673059.
51. Ding H, Yu SB, Wei JS, Xiong HM. Full-color light-emitting carbon dots with a surface-state-controlled luminescence mechanism. ACS Nano. 2016;10(1):484-91. doi: 10.1021/acsnano.5b05406, PMID 26646584.
52. Singh A, Choudhary M, Singh SP, Arora K. (December): 1-6. Hernández-Rivera M, Zaibaq NG, Wilson LJ. Toward carbon nanotube-based imaging agents for the clinic. Biomaterials. Mol Functionalization Carbon Nanomater Immuno-Diagn Cancer. 2016;101:229-40. PMID 27294540.
53. Herrero-Latorre C, Barciela-García J, García-Martín S, Peña-Crecente RM. Graphene and carbon nanotubes as solid phase extraction sorbents for the speciation of chromium: A review. Anal Chim Acta. 2018;1002:1-17. doi: 10.1016/j.aca.2017.11.042, PMID 29306409.
54. Meng L, Xia W, Liu L, Niu L, Lu Q. Golden single-walled carbon nanotubes prepared using double layer polysaccharides bridge for photothermal therapy. ACS Appl Mater Interfaces. 2014;6(7):4989-96. doi: 10.1021/am406031n, PMID 24606763.
55. Lucky SS, Soo KC, Zhang Y. Nanoparticles in photodynamic therapy. Chem Rev. 2015;115(4):1990-2042. doi: 10.1021/cr5004198, PMID 25602130.
56. Dolmans DE, Fukumura D, Jain RK. Photodynamic therapy for cancer. Nat Rev Cancer. 2003; May;3(5):380-7. doi: 10.1038/nrc1071, PMID 12724736.
57. Wang Z, Yu J, Gui R, Jin H, Xia Y. Carbon nanomaterials-based electrochemical aptasensors. Biosens Bioelectron. 2016;79:136-49. doi: 10.1016/j.bios.2015.11.093, PMID 26703992.
58. Yan QL, Gozin M, Zhao FQ, Cohen A, Pang SP. Highly energetic compositions based on functionalized carbon nanomaterials. Nanoscale. 2016;8(9):4799-851. doi: 10.1039/c5nr07855e, PMID 26880518.
59. Xiao Y, Barker PE. Semiconductor nanocrystal probes for human metaphase chromosomes. Nucleic Acids Res. 2004;32(3):e28. doi: 10.1093/nar/gnh024, PMID 14960711.
60. Ogbodu RO, Limson JL, Prinsloo E, Nyokong T. Photophysical properties and photodynamic therapy effect of zinc phthalocyanine-spermine-single walled carbon nanotube conjugate on MCF-7 breast cancer cell line. Synth Met. 2015;204:122-32. doi: 10.1016/j.synthmet.2015.03.011.
61. Lin S, Chen L, Huang L, Cao S, Luo X, Liu K. Novel antimicrobial chitosan-cellulose composite films bioconjugated with silver nanoparticles. Ind Crops Prod. 2015;70:395-403. doi: 10.1016/j.indcrop.2015.03.040.
62. Fan W, Shi J, Bu W. Engineering upconversion nanoparticles for multimodal biomedical imaging-guided therapeutic applications. Springer S Biomater Sci Eng. 2016:165-95. doi: 10.1007/978-3-662-48544-6_5.
63. Eldridge BN, Bernish BW, Fahrenholtz CD, Singh R. Photothermal therapy of glioblastoma multiforme using multiwalled carbon nanotubes optimized for diffusion in extracellular space. ACS Biomater Sci Eng. 2016;2(6):963-76. doi: 10.1021/acsbiomaterials.6b00052, PMID 27795996.
64. Chakravarty P, Marches R, Zimmerman NS, Swafford ADE, Bajaj P, Musselman IH, *et al*. Thermal ablation of tumor cells with antibody-functionalized single-walled carbon nanotubes. Proc Natl Acad Sci USA. 2008;105(25):8697-702. doi: 10.1073/pnas.0803557105, PMID 18559847.
65. Nurunnabi M, Khatun Z, Moon WC, Lee G, Lee YK. Heparin based nanoparticles for cancer targeting and non-invasive imaging. Quant Imaging Med Surg. 2012;2(3):219-26. doi: 10.3978/j.issn.2223-4292.2012.09.01, PMID 23256083.
66. Chen X, Huang Y, Duan N, Wu S, Xia Y, Ma X, *et al*. Screening and identification of DNA aptamers against T-2 toxin assisted by graphene oxide. J Agric Food Chem. 2014;62(42):10368-74. doi: 10.1021/jf5032058, PMID 25265190.
67. Azimzadeh M, Rahaie M, Nasirizadeh N, Ashtari K, Naderi-Manesh H. An electrochemical nanobiosensor for plasma miRNA-155, based on graphene oxide and gold nanorod, for early detection of breast cancer. Biosens

Bioelectron. 2016;77:99-106. doi: 10.1016/j.bios.2015.09.020, PMID 26397420.
68. Rajesh, Bisht V, Takashima W, Kaneto K. An amperometric urea biosensor based on covalent immobilization of urease onto an electrochemically prepared copolymer poly (N-3-aminopropyl pyrrole-co-pyrrole) film. Biomaterials. 2005;26(17):3683-90. doi: 10.1016/j.biomaterials.2004.09.024, PMID 15744952.
69. Ali J, Najeeb J, Asim Ali M, Farhan Aslam M, Raza A. Biosensors: Their fundamentals, designs, types and most recent impactful applications: A review. J Biosens Bioelectron. 2017;08(1). doi: 10.4172/2155-6210.1000235.
70. Polley MYC, Leung SCY, McShane LM, Gao D, Hugh JC, Mastropasqua MG, *et al.* International Ki67 in Breast Cancer Working Group of the Breast International Group and North American Breast Cancer Group. An international ki67 reproducibility study. J Natl Cancer Inst. 2013;105(24):1897-906. doi: 10.1093/jnci/djt306, PMID 24203987.
71. Meric-Bernstam F, Hung MC. Advances in targeting human epidermal growth factor receptor-2 signaling for cancer therapy. Clin Cancer Res. 2006;12(21):6326-30. doi: 10.1158/1078-0432.CCR-06-1732, PMID 17085641.
72. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235(4785):177-82. doi: 10.1126/science.3798106, PMID 3798106.
73. Tan M, Yao J, Yu D. Overexpression of the c-erbB-2 gene enhanced intrinsic metastasis potential in human breast cancer cells without increasing their transformation abilities. Cancer Res. 1997;57(6):1199-205. PMID 9067293.
74. Zhou BP, Hu MCT, Miller SA, Yu Z, Xia W, Lin SY, *et al.* HER-2/neu blocks tumor necrosis factor-induced apoptosis via the Akt/NF-kappaB pathway. J Biol Chem. 2000;275(11):8027-31. doi: 10.1074/jbc.275.11.8027, PMID 10713122.
75. Carter P, Presta L, Gorman CM, Ridgway JBB, Henner D, Wong WLT, *et al.* Humanization of an anti-p185HER2 antibody for human cancer therapy. Proc Natl Acad Sci U S A. 1992;89(10):4285-9. doi: 10.1073/pnas.89.10.4285, PMID 1350088.
76. Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JAW, *et al.* Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol. 2007;25(15):2127-32. doi: 10.1200/JCO.2006.10.3523, PMID 17513820.
77. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE, *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84. doi: 10.1056/NEJMoa052122, PMID 16236738.
78. Nahta R, O'Regan RM. Therapeutic implications of estrogen receptor signaling in HER2-positive breast cancers. Breast Cancer Res Treat. 2012;135(1):39-48. doi: 10.1007/s10549-012-2067-8, PMID 22527112.
79. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-92. doi: 10.1056/NEJM200103153441101, PMID 11248153.
80. Toss A, Cristofanilli M. Molecular characterization and targeted therapeutic approaches in breast cancer. Breast Cancer Res. 2015;17(1):60. doi: 10.1186/s13058-015-0560-9, PMID 25902832.
81. Tamoxifen for early breast cancer: An overview of the randomised trials. Lancet. 1998;351(9114):1451-67. doi: 10.1016/S0140-6736(97)11423-4, PMID 9605801.
82. Dai X, Xiang L, Li T, Bai Z. Cancer hallmarks, biomarkers and breast cancer molecular subtypes. J Cancer. 2016;7(10):1281-94. doi: 10.7150/jca.13141, PMID 27390604.
83. Elledge RM, Green S, Pugh R, Allred DC, Clark GM, Hill J, *et al.* Estrogen receptor (ER) and progesterone receptor (PgR), by ligand- binding assay compared with ER, PgR and pS2, by immuno-histochemistry in predicting response to tamoxifen in metastatic breast cancer: A Southwest Oncology Group study. Int J Cancer. 2000;89(2):111-7. doi: 10.1002/(SICI)1097-0215(20000320)89:2<111::AID-IJC2>3.0.CO;2-W, PMID 10754487.
84. Dowsett M, Houghton J, Iden C, Salter J, Farndon J, A'Hern R, *et al.* Benefit from adjuvant tamoxifen therapy in primary breast cancer patients according oestrogen receptor, progesterone receptor, EGF receptor and HER2 status. Ann Oncol. 2006;17(5):818-26. doi: 10.1093/annonc/mdl016, PMID 16497822.
85. Nishimura R, Osako T, Okumura Y, Hayashi M, Toyozumi Y, Arima N. Ki-67 as a prognostic marker according to breast cancer subtype and a predictor of recurrence time in primary breast cancer. Exp Ther Med. 2010;1(5):747-54. doi: 10.3892/etm.2010.133, PMID 22993598.
86. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, *et al.* A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351(27):2817-26. doi: 10.1056/NEJMoa041588, PMID 15591335.
87. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, *et al.* Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006;24(23):3726-34. doi: 10.1200/JCO.2005.04.7985, PMID 16720680.
88. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: Prognostic and predictive potential. Lancet Oncol. 2010;11(2):174-83. doi: 10.1016/S1470-2045(09)70262-1, PMID 20152769.
89. De Azambuja E, Cardoso F, De Castro G, Colozza M, Mano MS, Durbecq V, *et al.* Ki-67 as prognostic marker in early breast cancer: A meta-analysis of published studies involving 12,155 patients. Br J Cancer. 2007;96(10):1504-13. doi: 10.1038/sj.bjc.6603756, PMID 17453008.
90. Tobin NP, Bergh J. Analysis of cyclin D1 in breast cancer: A call to arms. Curr Breast Cancer Rep. 2012;4(3):171-3. doi: 10.1007/s12609-012-0083-7, PMID 22924091.
91. Musgrove EA, Hamilton JA, Lee CS, Sweeney KJ, Watts CK, Sutherland RL. Growth factor, steroid, and steroid antagonist regulation of cyclin gene expression associated with changes in T-47D human breast cancer cell cycle progression. Mol Cell Biol. 1993;13(6):3577-87. doi: 10.1128/mcb.13.6.3577-3587.1993, PMID 8497271.
92. Matsushima S, Mori M, Adachi Y, Matsukuma A, Sugimachi K. S100 protein positive human breast carcinomas: An immunohistochemical study. J Surg Oncol. 1994;55(2):108-13. doi: 10.1002/jso.2930550210, PMID 8121183.
93. Koff A, Giordano A, Desai D, Yamashita K, Harper JW, Elledge S, *et al.* Formation and activation of a cyclin E-cdk2 complex during the G 1 phase of the human cell cycle. Science. 1992;257(5077):1689-94. doi: 10.1126/science.1388288, PMID 1388288.
94. Buckley MF, Sweeney KJ, Hamilton JA, Sini RL, Manning DL, Nicholson RI, *et al.* Expression and amplification of cyclin genes in human breast cancer. Oncogene. 1993;8(8):2127-33. PMID 8336939.
95. Keyomarsi K, Pardee AB. Redundant cyclin overexpression and gene amplification in breast cancer cells. Proc Natl Acad Sci USA. 1993;90(3):1112-6. doi: 10.1073/pnas.90.3.1112, PMID 8430082.
96. Bortner DM, Rosenberg MP. Induction of mammary gland hyperplasia and carcinomas in transgenic mice expressing human cyclin E. Mol Cell Biol. 1997;17(1):453-9. doi: 10.1128/MCB.17.1.453, PMID 8972226.
97. Duong MT, Akli S, Wei C, Wingate HF, Liu W, Lu Y, *et al.* LMW-E/CDK2 deregulates acinar morphogenesis, induces tumorigenesis, and associates with the activated b-raf-ERK1/2-mTOR pathway in breast cancer patients. PLOS Genet. 2012;8(3):e1002538. doi: 10.1371/journal.pgen.1002538, PMID 22479189.
98. Duong MT, Akli S, Macalou S, Biernacka A, Debeb BG, Yi M, *et al.* Hbo1 is a cyclin E/CDK2 substrate that enriches breast cancer stem-like cells. Cancer Res. 2013;73(17):5556-68. doi: 10.1158/0008-5472.CAN-13-0013, PMID 23955388.
99. Yezhelyev MV, Gao X, Xing Y, Al-Hajj A, Nie S, O'Regan RM. Emerging use of nanoparticles in diagnosis and treatment of breast cancer. Lancet Oncol. 2006;7(8):657-67. doi: 10.1016/S1470-2045(06)70793-8, PMID 16887483.
100. Wang HN, Vo-Dinh T. Multiplex detection of breast cancer biomarkers using plasmonic molecular sentinel nanoprobes. Nanotechnology. 2009;20(6):065101.

Article History: Submission Date : 18-02-2022; Revised Date : 06-04-2022; Acceptance Date : 01-05-2022.
Cite this article: Aljadani M. Nanotechnology-based Therapeutic Strategies for Breast Cancer. Int. J. Pharm. Investigation. 2022;12(2):145-50.