Plant Archives Vol. 19, Supplement 2, 2019 pp. 2195-2200 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

A SYSTEMATIC REVIEW ON NOVEL NANOMEDICINES TO TARGET BREAST CANCER

Yogita Kumari, Gurmandeep Kaur, Clarisse Ayinkamiye, Sachin Kumar Singh, Rajesh Kumar*, Ankit Kumar Yadav, Chandan Bhogendra Jha and Surajpal Verma

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara -144411, Punjab, India

*Corresponding author email id: rajksach09@gmail.com Contact: +91-9855976499

Abstract

Breast cancer is amongst the most common type of malevolent tumour in females, constituting about 30% of all cancers in females worldwide. Incidence rate of disease has increased by 20% since 2008 globally. In the past few years, mortality rate of disease has been reduced significantly due to adoption of various treatments like surgery, radiation, chemotherapy etc. and emergence of breast cancer screening. At present, chemotherapy is the most efficient treatment for disease. However, their side effects cause a long term provocation on patient's health. Thus, there is a need to develop a new treatment strategy that can only target the malignant cells without causing any harm to the adjacent body cells. Nanomedicines are auspicious alternative for treatment of breast cancer. Nanomedicines refer to materials having biomedical applications and have size range below 100nm. A variety of nanocarriers are available like polymeric nanoparticles, dendrimers, nanotubes, liposomes, etc. Some of the nanocarriers like liposomes (Doxil) and nanoparticles (Abraxane) are successfully used for breast cancer treatment. These nanomedicines hold immense potential to refine treatment strategies against breast cancer. They can enhance the pharmacodynamics and pharmacokinetics profiles of conventional treatments and may optimize the efficacy of existing drugs. Site specific delivery of anticancer drugs using nanocarriers results in increased therapeutic efficiency of conventional drugs. Nanomedicines based approaches are used to understand the interaction of cancerous cells with their surrounding cells. Current review provides insight knowledge about the targeted drug delivery for breast cancer using nanomedicines approach to conquer the limitations of conventional therapy.

***Keywords*:** Nanomedicines, breast cancer, targeted delivery, conventional method, limitations.

Introduction

Breast cancer is amongst the most common types of malevolent tumors in women, accounting for about 30% of all cancers in women worldwide. The incidence rate of the disease has increased by 20% since 2008 worldwide (Agarwal *et al.*, 2008). Most cases of breast cancer are invasive carcinomas, but also other less frequent molecular subtypes attract attention due to their aggressiveness and recurrence in patients (Kydd *et al.*, 2017). Targeted breast cancer therapies include materials or drugs that inhibit cancer growth by blocking the functions of particular molecules required for multiplication and survival of malignant cells. Over-expression of particular receptors by breast cancer cells may initiate a downstream signaling pathway leading to the proliferation, growth and survival of the cancerous cell and may also initiate other signalling pathways. There are several types of breast cancer, such as positive estrogens or positive progesterone (hormone receptors). The estrogen receptor is present in 75% of breast cancer cases. Hormone-sensitive breast carcinoma, such as human epidermal growth factor receptor 2 (HER2), has a strong connection to low-grade tumor, bone and tissue metastasis. In hormone positive breast cancer, the multigenic test is performed to decide the treatment strategy for complementary therapy and the detection of those patients who would undergo endocrine therapy. Member of the receptor epidermal growth factor receptor tyrosine kinases, HER2 and EGFR are highly expressed and are responsible for the aggressive behavior of the tumor (Masoud *et al.*, 2017).

Various treatment strategies are involved for breast cancer such as; targeted therapy, surgery, radiation therapy (RT), chemotherapy (CT) and endocrine (hormone) therapy (ET) (Nounou *et al.*, 2015). The first drug approved by FDA in 1988 for treating HER2 positive breast cancer is Trastuzumab (Herceptein) (Rojo *et al.*, 2008). Conventional chemotherapy function by obstructing DNA synthesis and mitosis leading to the death of cancerous cell, but these agents are non-selective and can also damage other healthy tissues causing undesirable side effects which can cause a long-term provocation on patient's health. Therefore, it is required to develop a new treatment strategy that can by active or passive targeting can specifically target cancer cells, thereby causing less adverse effects and better therapeutic efficacy. Nanomedicine plays an important role by delivering anti-cancer drugs to specific site of disease without causing any systematic toxicity (Wu *et al.*, 2017). This technology of using nanosized particles could be a better therapeutic approach for breast cancer patients. Different types of nanocarriers that are commonly used such as polymeric nanoparticles, quantum dots, liposmes and micelles. Over Past few deacdes, major advancements in nanomedicines and drug carriers provide a safe and effective treatment strategy for breast cancer as compared to conventional therapeutic modalities (Wu *et al.*, 2017).

Conventional modalities for treatment of breast cancer

For treatment of breast cancer surgery is most common approach. It is followed by neoadjuvant therapy to diminish tumour bulk. After neoadjuvant therapy it is followed by adjuvant therapy for reducing the chance of metastases. Cancer cells that are not visible by surgery can be killed by radiation therapy thus preventing recurrence. In radiation therapy (RT) cancer cells are exposed to radiation directly. But there are some limitations of RT like peeling, itching and redness (Sharma *et al.*, 2013). Figure 2 compiles a list of chemotherapeutics used for treating breast cancer depending upon the targets.

Adjuvant therapy

Adjuvant therapy depends upon two main factors: a) Patient risk of relapse, b) sensitivity to specific method. Final decision should be based upon patient health, age and comorbidities. As per St. Gallen guidelines, decision depends on inherent phenotype which is evaluated by ER/PR and HER2 evaluation. In 2013, St. Gallen suggested that

endocrine therapy (ET) is required for endocrine responsive histology and chemotherapy is required for non-responsive endocrine. Figure 1 represents different adjuvant therapy required for the disease (Kaklamani *et al.*, 2005).

1) Endocrine therapy (ET): This therapy is required either for blocking or balancing hormones. Choice of therapy also depends on patient's menopausal status. In premenopausal patients, use of Tamoxifen 20mg/day is recommended. Chemotherapy can be used as an alternative. In postmenopausal patients, tamoxifen as well as anastrozole can be used in combinations.

2) Chemotherapy (CT): CT is suggested in majority of triple negative breast cancer and HER2 positive cases. Four rotations of doxorubicin, cyclophosphamide (AC) are found equal to six cycles of cyclophosphamide, methotrexate and fluorouracil (CMF).

3) HER2 directed therapy: Trastuzumab in combination with AC and CMF minimize the chance of recurrence in patients with HER2. Due to its adverse effects Trastuzumab should not be administered routinely. It can also be given in combination with ET and RT which is found to be safe (Teshome *et al.*, 2014).

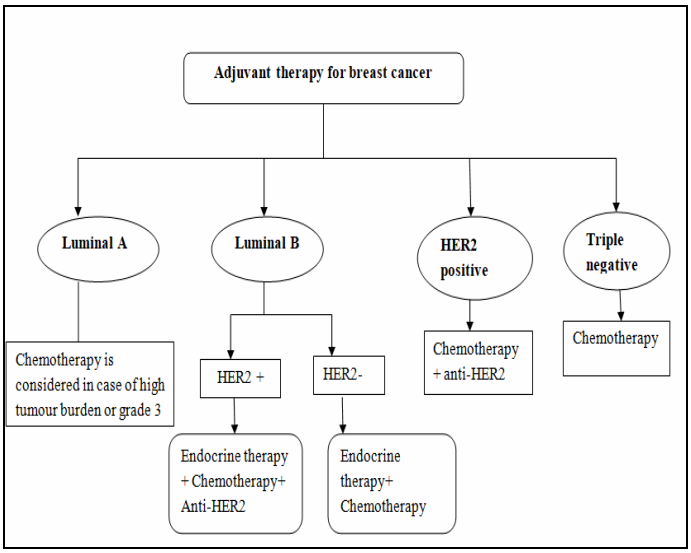

Fig. 1 : Different adjuvant therapies used for treatment based upon intrinsic phenotype, Neo-adjuvant therapy

This therapy is required in localized or advanced cancers, where mastectomy may be required due to cancer size; neo-adjuvant is mostly required for minimizing the extent of surgery. Treatment strategy employed in adjuvant therapy like CT, ET and targeted therapy are used efficiently. In HER2 breast cancer, Trastuzumab along with taxane part of CT regimen is being given thus improving chances of getting complete response. Just like adjuvant therapy, neo-adjuvant also minimizes the chance of tumour recurrence (Chatterjee *et al.*, 2017).

Possible side effects of Chemotherapeutics

Depending upon medication and dose various side effects are being observed in breast cancer patients undergoing chemotherapeutics such as (web source)-

a) Hair loss

b) Fatigue

c) Menstrual changes

d) Nerve damage

The table 2 given below compiles various chemotherapeutics used for treatment of breast cancer (Singh *et al.*, 2017).

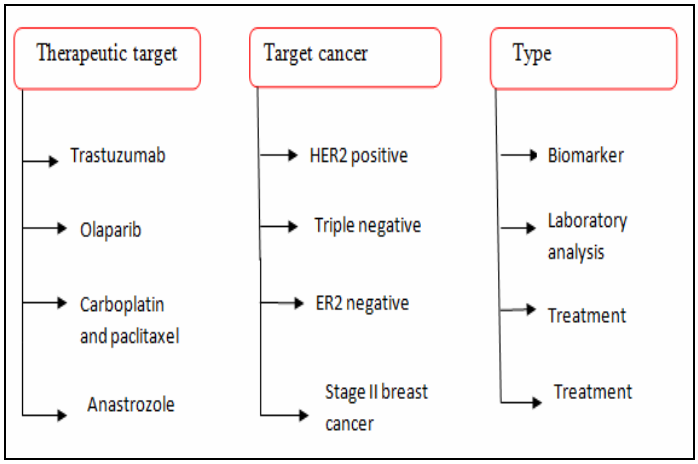

Fig. 2 : List of various chemotherapeutics used for treatment

Nanomedicines for breast cancer treatment

Nanotechnology plays a crucial role for delivering chemotherapeutics to specific site in a targeted manner, thereby minimizing specific toxicity of conventional drugs and decreasing health related quality of life. A nanomedicine is defined as the interaction of components (molecular and cellular); arrangement of atoms and molecules into smaller particles having size range between 1-100 nm (Saadeh *et al.*, 2014).

Over past few years, major development in nanomedicines and novel drug carriers has found safe and effective treatment strategies for breast cancer. To add on, advancement in molecular biology provides insight knowledge of breast cancer**.** As compared to conventional anti-cancer drugs, nanosized drug carriers have ability to conquer the limitations of chemotherapeutics by enhancing treatment efficacy while decreasing toxicity in normal body cells. Due to their characteristic feature such as high selective penetration in tumours, through enhanced permeability and retention effect (EPR). These nanomedicines hold immense potential to refine treatment strategies against breast cancer. The most common approach for delivery of drugs to targeted site using nanocarriers depends upon inorganic and organic particles. Different organic particles employed for delivery applications are dendrimers, liposomes, nanogels, micelles etc. They have flexible building blocks used for endocytosis and drug loading. They also have multifunctional surface property that helps to carry cell to tumour vasculature. Figure 5 presents drug delivery approaches using nanoparticles for treatment of breast cancer. The approach of encapsulating anticancer drugs using nanocarriers is a better approach with respect to reduced side effects and better bioavailability of conventional drugs (Hare *et al.*, 2017).

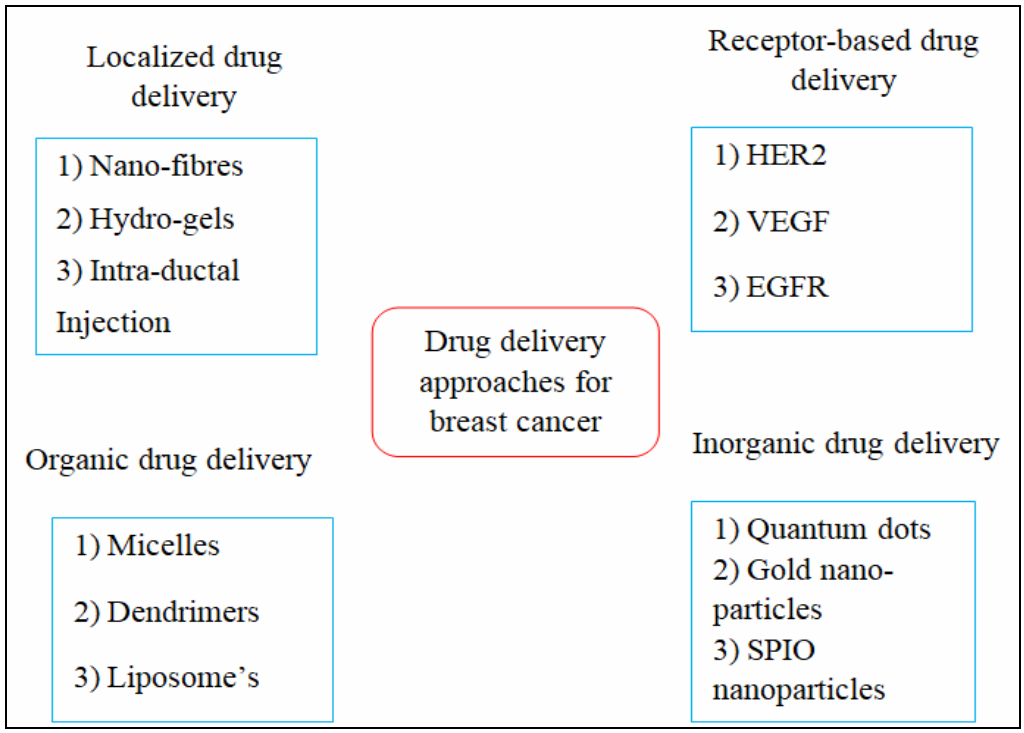

Fig. 3 : Various drug delivery approaches using nanocarriers for treatment of breast cancer

Surface of nanoparticles can be modified easily, which allows nanocarriers to target specific cells, resulting in active targeting of particles. Molecules like peptides, antibodies are widely used to carry nanoparticles to specific site. Use of nanocarriers for delivery of drugs offers various advantages related to free administration of drugs like; a) protecting drugs from degradation and b) better absorption inside body. Recently some nanocarrier have been found approved by US Food and Drug administration (FDA) for treating breast cancer like (Doxil®) which is a first liposomal nanocarriers approved by FDA. Another is (Abraxane®), a chemotherapeutic drug paclitaxel in combination with albumin is being used for targeting breast cancer which was approved by FDA in 2005 (Vieira *et al.*, 2016). Based on nanomedicine approach, the most relatable strategies for site specific targeting in anti-cancer drug resistant cancer cells are shown in figure 4 below.

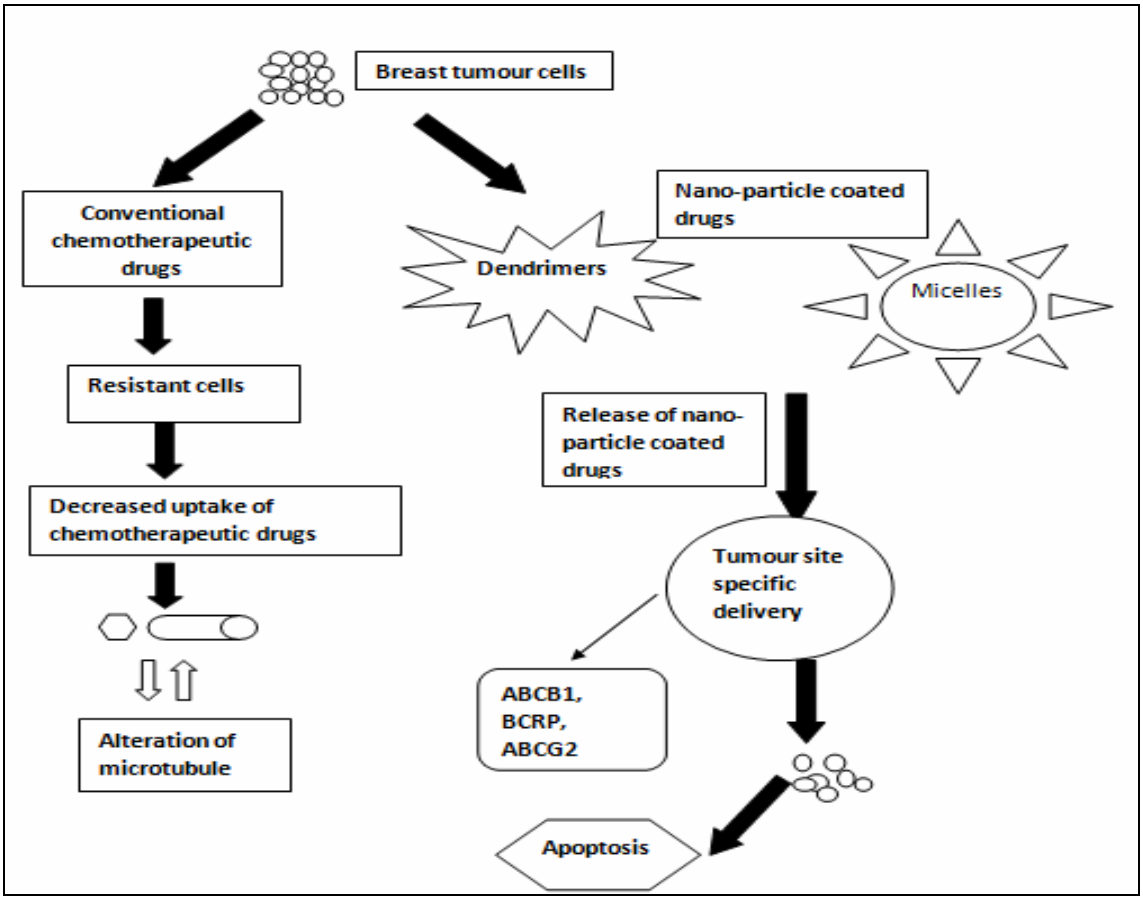

Fig. 4 : Treatment strategies for nanocarriers in drug-resistant cancer cells

Delivery of chemotherapeutics to specific site is being achieved through two main process; passive and active targeting. Figure 5 shows targeting of nanocarriers to tumour site by active and passive targeting.

Passive targeting

Targeted delivery for anticancer drugs has capability to minimize toxicity and increased treatment efficacy. Targeting of breast cancer cells can be achieved by active and passive targeting. Passive targeting is highly associated to circulation time. It depends upon the physiochemical nature of cancer cells. Leaky vasculatures of cancer cell results into large pores which help nanoparticles to get accumulate near the tumour cell. Vascular permeability of malignant cell is also known as enhanced permeability retention (EPR) effect. Nevertheless, for passive targeting EPR effect is required for targeted delivery of anticancer drugs. EPR effect is heterogeneous and its diversity may reduce delivery of drugs to specific site. Nanomedicines focus to improve the circulation time of conjugated drugs. Nanocarriers that only respond to malignant cells and deliver drugs at cancer site are part of passive targeting (Bazak *et al.*, 2014; Pawar *et al.*, 2014)

Active targeting

For enhancing targeting efficiency of nanocarriers active targeting was introduced. Targeting molecules like protein or antibodies is being attached to nanocarrier or direct targeting of particular receptors by these drugs. This mechanism is based upon ligand-receptor interactions. Overexpression of antigens in tumour is a potential target to attain drug uptake by endocytosis. In few cases, ligand like folic acid is being attached to nanocarriers which are also essential for tumour growth (Bhargav *et al.*, 2013).

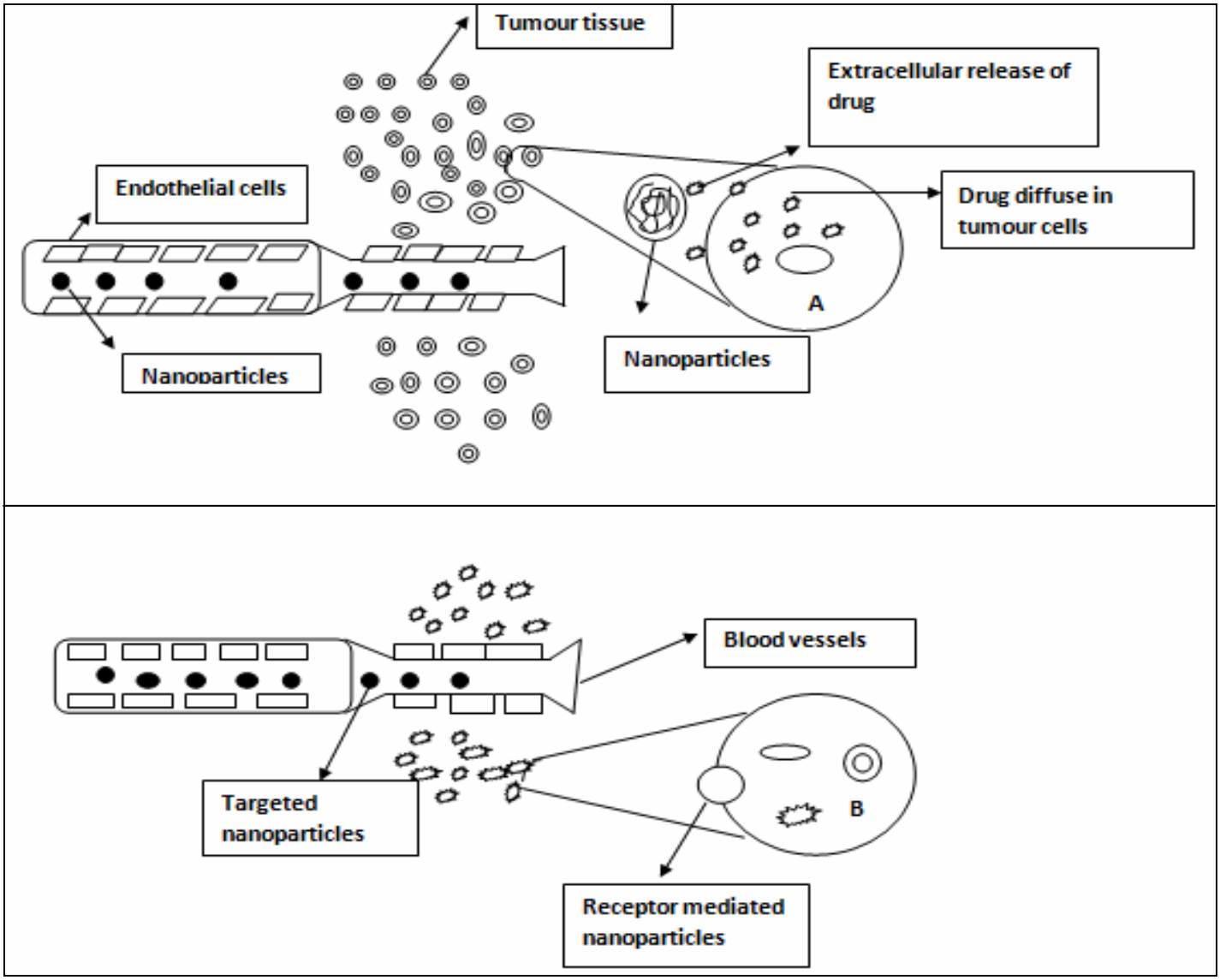

Fig. 5 : Drug targeting mechanisms of nanocarriers: a) Active targeting; b) Passive targeting

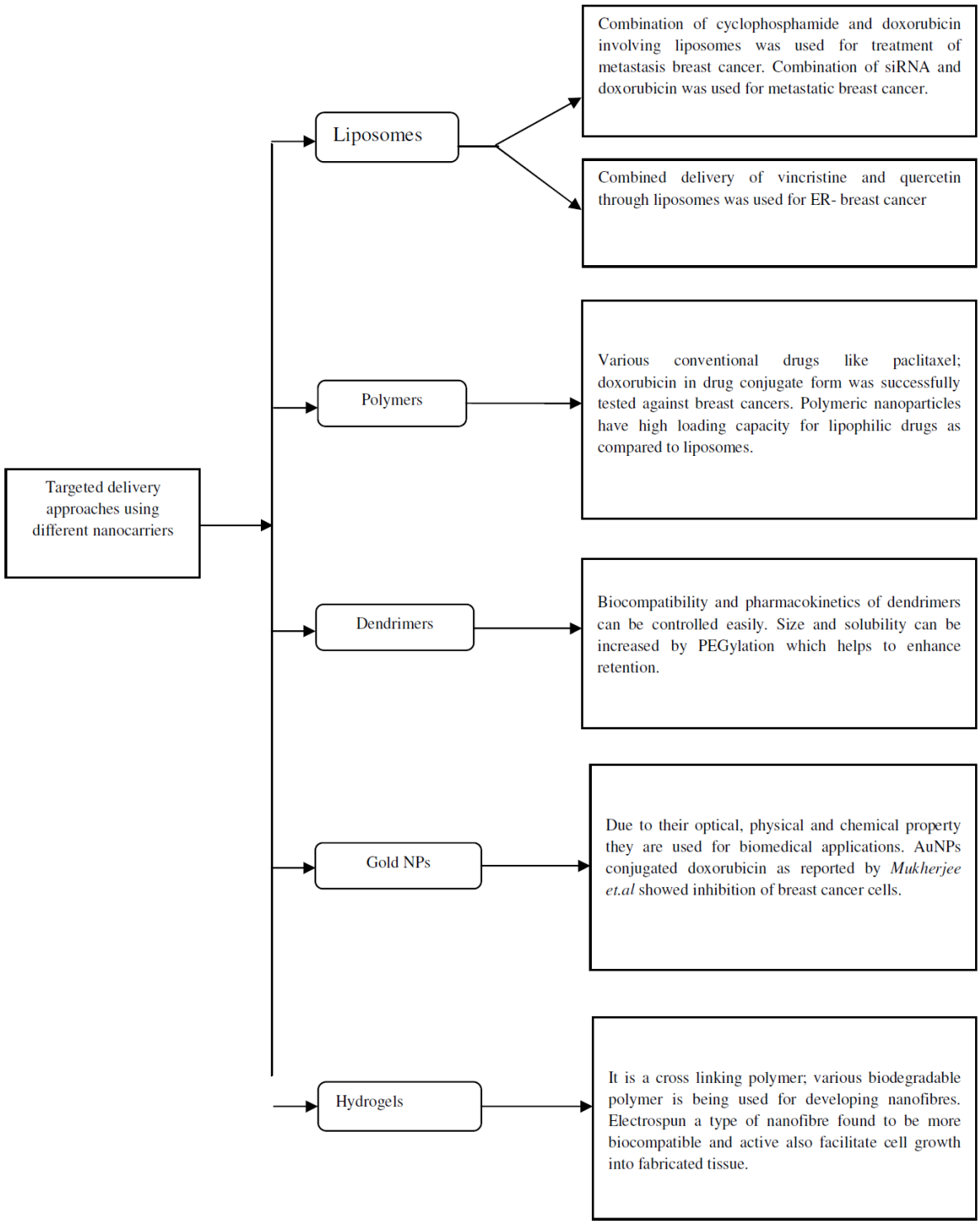

Fig. 6 : Overview of different nanocarriers used for delivery of drugs to specific site

Conclusion

From the review of literature, it can be concluded that conventional treatments for breast cancer involve various limitations and can cause life threatening adverse effects, hence to conquer these problems targeted therapies using nanocarriers which efficiently deliver chemotherapeutics to specific site without causing toxicity to other cells. Ongoing efforts by researchers and scientists in nanomedicines will consistently develop new platform for nanocarriers. In upcoming years, nanomedicine will showcase their potential not only in oncology but in various other fields also.

References

Agarwal, G. and Ramakant, P. (2008). Breast cancer care in India: The current scenario and the challenges for the future. Breast Care, 3 : 21-27.

Bazak, R.; Houri, M.; El Achy, S.; Hussein, W. and Refaat, T. (2014). Passive targeting of nanoparticles to cancer: A comprehensive review of the literature. Molecular and Clinical Oncology, 2 : 904-908.

Bhargav, E., Madhuri, N., Ramesh, K., Ravi, V (2013). Targeted Drug Delivery- a Review. World Journal of Pharmacy and Pharmaceutical Sciences, 3 : 150-169.

Chatterjee, A. and Erban, J.K. (2017). Neoadjuvant therapy for treatment of breast cancer: the way forward, or simply a convenient option for patients? Gland Surgery, 6 : 119-124.

Hare, J.I.; Lammers, T.; Ashford, M.B.; Puri, S.; Storm, G. and Barry, S.T. (2017). Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. Advanced Drug Delivery Reviews, 108 :

25-38.

Kaklamani, V.G. and Gradishar, W.J. (2005). Adjuvant therapy of breast cancer. Cancer Investigation, 23 : 548-560.

Kydd, J.; Jadia, R.; Velpurisiva, P.; Gad, A.; Paliwal, S. and Rai, P. (2017). Targeting strategies for the combination treatment of cancer using drug delivery systems. Pharmaceutics, 9 : 1-26.

Masoud, V. and Pagès, G. (2017). Targeted therapies in breast cancer: New challenges to fight against resistance. World Journal of Clinical Oncology, 8 : 120-134.

Nounou, M.I.; ElAmrawy, F.; Ahmed, N.; Abdelraouf, K.; Goda, S. and Syed-Sha-Qhattal, H. (2015). Breast Cancer: Conventional Diagnosis and Treatment Modalities and Recent Patents and Technologies. Breast Cancer (Auckl), 9 : 17-34.

Pawar, P.V.; Domb, A.J. and Kumar, N. (2014). Systemic Targeting Systems-EPR Effect, Ligand Targeting Systems. In: Domb, A.J., Khan, W. (eds.). Focal Controlled Drug Delivery, Springer, Boston, MA, 61-91.

Rojo, F.; Albanell, J.; Rovira, A.; Corominas, J.M. and Manzarbeitia, F. (2008). Targeted therapies in breast cancer. Seminars in Diagnostic Pathology, 25 : 245-261.

Saadeh, Y.; Leung, T.; Vyas, A.; Chaturvedi, L.S.; Perumal, O. and Vyas, D. (2014). Applications of Nanomedicine in Breast Cancer Detection, Imaging, and Therapy. Journal of Nanoscience and Nanotechnology, 14 : 913-923.

Sharma, A.; Jain, N. and Sareen, R. (2013). Nanocarriers for diagnosis and targeting of breast cancer. BioMed Research International, 2013 : 1-10.

Singh, S.K.; Singh, S.; Lillard, J.W. and Singh, R. (2017). Drug Delivery Approaches for Breast cancer. International Journal of Nanomedicine, 12 : 6205-6218.

Teshome, M. and Hunt, K.K. (20014). Neoadjuvant therapy in the treatment of breast cancer. Surgical Oncology Clinics of North America, 23 : 505-523.

Vieira, D.B. and Gamarra, L.F. (2016). Advances in the use of nanocarriers for cancer diagnosis and treatment. Einstein (Sao Paulo), 14 : 99-103.

Wu, D.; Si, M.; Xue, H.Y. and Wong, H.L. (2017). Nanomedicine applications in the treatment of breast cancer: current state of the art. International Journal of Nanomedicine, 12 : 5879-5892.

https://www.cancer.org/cancer/breast-cancer/treatment/chemotherapy-for-breast-cancer.html accessed on 5-10-18.