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Chapter 1: Introduction to Nanomedicines in Breast Cancer: Evolution and Emerging Frontiers

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Abstract

Breast cancer has been one of the prevalent and life-threatening cancer in women all over the world. Non specific toxicity, drug resistance, and poor therapeutic effect tend to be observed in some of the applications of conventional methods of treatment including surgery, chemotherapy, and radiation. Such deficiencies have heralded the advent of nanomedicine which has opened up a transformative approach in the therapy of breast cancer and this approach has arrived in the form of target, control and sustained drug delivery with augmented biocompatibility and reduced systemic toxicity. An advancement has been giant in the pharmacokinetics and biodistribution of anti-cancer agents using contemporary development of nanocarriers- such as liposome, dendrimers, polymeric nanoparticle, micelles and solid lipid nanoparticle. The newer advances include ligand-guided imaging, pH-sensitive delivery and theranostic capabilities, allowing imaging addable to treatment. Moreover, the development of smart nanomedicines that can be triggered by the factors of tumor microenvironment (pH, enzymes, temperature) is also indicative of the move towards personalized and precision oncology. Though the laboratory evidence is promising and at least a couple of nanoformulations have been approved by FDA, clinical translation is challenging due to the complex regulatory demands, issues of mass reproducibility and safety. The trends in history, present affairs and prospect of nanomedicine in the treatment of breast cancer were discussed in this chapter.

Keywords: *Breast cancer, nanomedicine, targeted drug delivery, nanoparticles, tumor microenvironment, nano-theranostics.*

1. Introduction

It cannot be doubted that breast cancer is the most common diagnosed cancer in women around the globe (Sung *et al*., 2021). In 2020, around 2.3 million new cases of BC were reported and the numbers of deaths made 685 000, which constituted a sixth of cancer deaths (Perou *et al*., 2000); (MC, 2009); (Harbeck *et al*., 2019). Overall, the treatments used in the treatment of BC described as multidisciplinary include the systemic (chemotherapy, endocrine therapy, HER2 targeted therapy etc (Waks & Winer, 2019). The choice of therapeutic plan is dependent on the variety and stage of BC (Shien & Iwata 2020). Although, due to the optimization of such treatment schemes, the cure opportunity has grown by about 70 to 80 percent of the patients with early BC, metastatic BC, up until today, is still considered to be incurable (Hashemi *et al*., 2017). Moreover, many disadvantages are associated with the endeavors to manufacture the conventional anti-cancer drugs (Fraguas *et al*., 2019). Thus, the approaches of treatment which are not only less toxic but also more effective may be studied more thoroughly in order to develop individual treatment of BC. The constraints that accompanied the current conventional treatment anti-cancer treatment depicted the need to investigate the study of nanotechnology in the treatment of cancer. Having such nanotechnology it could be more powerful and much safer, at that it is called nanomedicine (Shi *et al*., 2017); (Afzal *et al*., 2021). It has demonstrated that the treatments related to nanotechnologies provide it with certain comparative advantages over conventional chemotherapy and chemical stability, an extended stay in the circulation, reduced toxicity due to antineoplastic effect, inhibition of drug resistances mechanisms (Fu *et al*., 2022); (Jiang *et al*., 2022). Nanomedicines has been incorporated as it has gained its wide usage during the past decades whose nanotechnology was developing (Gradishar *et al*., 2005). To give an example, Abraxane 120 PN was waved in 2005 to be employed as a routine therapeutics in the management of metastatic BC. The study to use nanotechnology to cure cancer came as a result of inherent vulnerability of the established used conventional anti-cancer therapy. This nanotechnology tends to be more efficient and more secure as it is known as nanomedicine (Boix *et al*., 2021). Nanomedicine has previously been aggressively applied in basic research and clinical research and since nanotechnology has been developing in rapid speed throughout the past decades, it has become highly promising and ubiquitous as a method of treating cancer. It is a nanoscale level albumin-bound pac litaxel that was also found to be biologically interactive and the research findings were that it has better curing effect and extremely reduced toxicity in introducing treatment of BC as compared to free PTX (Liu *et al*., 2018). In addition, other previously clinically applied nanomedicines in the treatment of BC also revealed high levels of efficacy in preventing the occurrence of the BC (Gupta *et al*., 2021); (Banthia *et al*., 2022). We fully described and discussed in this chapter on the major challenges that were met in the process of using the ancient BC treatment techniques and the potential roles that nanomedicine plays in the improvement of the BC treatment procedure by clearing up impediments of the current BC treatment. Also, the

combination therapies that nanomedicine undergoes with the current medication of BC are discussed. Conventional treatments of breast cancer are shown in figure 1.1 are as follows

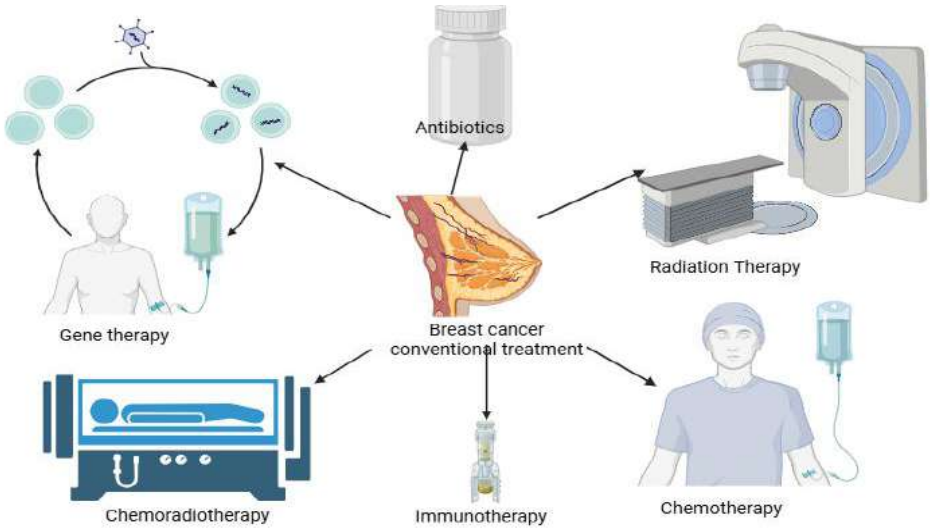

Figure 1.1 Breast Cancer Conventional Treatment: This diagram details different conventional treatment options for breast cancers such as the use of different antibiotics, radiation therapy, gene therapy, chemotherapy, immunotherapy and chemoradiotherapy (Gao & Swain, 2018).

2. The current curative instruments of BC were applied

2.1 Molecular basis regarding the different types of BC

These types are defined by different markers and each with different genetic profile, cellular pathways and clinical manifestation.

Luminal A: The Luminal A tumor tends to be well differentiated and usually slow growing, and this has the best prognosis in all the tumors (Gao & Swain, 2018); (Schettini & Prat, 2021).

Luminal B: Luminal B is aggressive as compared to Luminal A and hence they may require hormonal and chemotherapy (Gao & Swain, 2018). It has a common alteration in TP53, PIK3CA, and CCND1, which provides elevated cell proliferation and poor response to endocrine therapy. In fact, HER2-positive breast cancer is of high grade and aggressive nature. Most frequent genomic alteration is amplification in ERBB2 and PIK3CA and mutation in PIK3CA and TP53 (Derakhshan & Reis-Filho, 2022).
Triple-Negative Breast Cancer: The last type is most prevalent in young women and mutant BRCA1 (Derakhshan & Reis-Filho, 2022). High grade tumors are aggressive,

grows fast, and poor prognosis, which are mean by the tumors. As far as molecular level TNBC has usually been associated with BRCA1/2 alteration, TP53 mutation and the defect of DNA repair pathways, a factor due to which they are sensitive both to platinum-based chemotherapies (Dilruba & Kalayda, 2016) and PARP inhibitors (Bergin & Loi, 2019).

Basal-like: The tumors counterpart with TNBC but their characterization uses gene expression patterns and expression of high basal cytokeratins (CK5/6, CK14) and epidermal growth factor receptor (EGFR) (Hormones & Breast Cancer Collaborative Group, 2013). They are not genomic stable and it is usually aberration of TP53 and chromosome rearrangement (Łukasiewicz *et al*., 2021).

Normal-like: It is a vaguely defined subtype that is similar to normal breast one in gene expression. It has largely reduced proliferation rates and enhanced prognosis although its clinical usefulness is limited through its lack of consistency in characterization (Zelnak & O'Regan, 2015).

2.2 Current popular treatment regimens of BC

Various treatment regimens are listed below and figure 1.2 represents current popular treatment regimen of breast cancer are as follows-

2.2.1.1 Endocrine treatment

The endocrine treatment tries to block the effects of estrogen that cause cell proliferation like that of such cancer cells. In the case of the advanced/ metastatic scenario severity, it is normally used as an adjuvant therapy (that is following surgery) with an intent of reducing re-occurrence or even in the endeavor of the dispersion of disease progression (Zelnak & O'Regan, 2015); (Lerebours., Cabel., & Pierga, 2021). Selective estrogen receptor modulators (SERMs) have been endocrine therapies such as tamoxifen that target the receptors of estrogens, the aromatase inhibitors such as anastrozole, letozole and exemestane that curtail the level of estrogens in women after menopause and selective estrogen receptor degraders like fulvestrant that destroys ERs (Lumachi *et al*., 2011). Menopause status, side effect profile and stage of disease determine the use or non-use of treatment. The endocrine therapy is tolerated quite well yet hot flashes, loss of bone density, joint pains and fatigue are some of the side effects. The overall role played by endocrine therapy is enormous, according to the survival of hormone receptor-positive BC and significant with respect to the treatment of this disease in the long run (Reinbolt *et al*., 2015).

2.2.1.2 Treatment with Chemotherapy

In the breast cancer treatment, chemotherapy plays an essential role especially when the cancer is aggressive (Omidi *et al*., 2022). It entails using cytotoxic drugs which kill fast growing cancer cells. Chemotherapy may be applied in different contexts such as neoadjuvant (prior to surgery to shrink tumors), adjuvant (after cancer surgery to

eradicate remaining cancer cells) and in a metastatic form of breast cancer to suppress spread and alleviate the symptoms (Chabner & Roberts, 2005). These are widely used, e.g. cyclophosphamide (alkylating agent), doxorubicin (anthracycline), paclitaxel (taxane), 5-fluorouracil (antimetabolite) and others. Often, these agents can be used as combinations to enhance efficacy and decrease the resistance possibility (Saloustros., Mavroudis., & Georgoulias, 2008). HER2-targeted drugs such as trastuzumab and pertuzumab is usually done to improve outcome related to treatment (Penel., Adenis., & Bocci, 2012). In TNBC, chemotherapy therapy is the preferred systemic treatment (and in the relapsed setting the sole modality), and platinum-containing regimens (such as carboplatin) are very popular as a result of their success in treating BRCA-mutated carcinomas (Yamaguchi *et al*., 2015). Unlike surgery, chemotherapy is systemic, which implies a possibility to attack cancer cells all over the body, which makes it particularly helpful in situations when the metastasis is a possibility (Garutti *et al*., 2019). Nevertheless, owing to its impact on any fast dividing cells, and not only cancerous ones, chemotherapy has a number of side effects. Figure 1.2 represents current popular treatment resigmen of breast cancer are as follows-

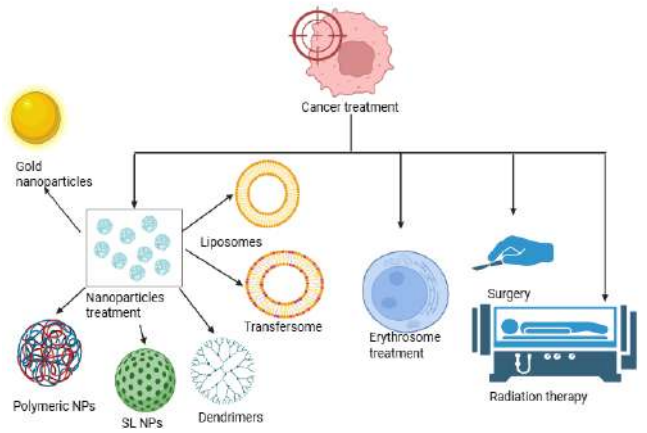

Figure 1.2 Current cancer treatments: This diagram represents the current popular treatment regimen of breast cancer are as surgery, radiation therapy, endocrine treatment and most popularly nanoparticles treatment which further include gold nanoparticles, polymeric NPs, Silver nanoparticles, solid lipid nanoprticles, transferosoms, dendrimers, liposomes and so on (Garutti *et al*., 2019).

These can be fatigue, nausea, hair loss, neutropenia (low white blood cells), anemia, neuropathy and may include cardiotoxicity usually only with anthracyclines (Zagouri *et al*., 2013). The side effects have been addressed with the help of developing supportive care (growth factors, antiemetics, etc.), which allows patients to maintain a good quality of life throughout treatment (Junnuthula *et al*., 2022). Chemotherapy is increasingly becoming personalized, especially on a basis of tumor genetics and molecular profiling

over the past few years (Wang & Mao, 2020); (Davey *et al*., 2021). It is most effective when applied together with a multimodal treatment course that involves surgery, radiation, hormonal therapy or a targeted therapy according to the subtype of cancer (Sun, *et al*., 2022); (Bredin., Walshe., & Denduluri, 2020).

2.2.1.3 HER2 targeted treatment

The most prominent aspect of the HER2 enriched subtype is the excess production of HER2 on the cells which results in accelerated advancement of the tumor, its severe course, and the indication of the poor survival rates of individuals with these HER2 types compared to Luminal A and B ones (Ahmad *et al*., 2022).

2.2.1.4 Vaccine-based treatment

An impending type of this treatment on breast cancer is the use of vaccines, where it is intended to use the vaccine to make the immune system of the body react with the cancer cell and kill them. In contrast to preventive vaccines (against HPV or hepatitis B), cancer vaccines are therapeutic and meant to treat already developed cancer by stimulating tumor-associated antigens (TAA) which are either over-expressed or uniquely expressed on breast cancer cells (Navarro *et al*., 2022). Various kinds of breast cancer immunizations are being examined: The peptide-based vaccines are based on the short segments of particular antigens such as HER2/neu, MUC1 and CEA that trigger the T-cells response towards cancerous cells. Vaccines based on DNA aim to stimulate tumor antigen (encoded in genetic material contained) production, and subsequent immune response, on the realization that genetic material would be introduced into the body. Dendritic cell vaccines are where dendritic cells which are removed and then sensitized against breast cancer antigens by incubating them and it is then injected back into a patient and causes an immune response that destroys tumours. Among the best studied targets is the HER2 which is usually over-expressed in the aggressive forms of breast cancer (Gavas., Quazi., & Karpiński, 2021).
Early clinical trials of HER2 vaccines, including E75 (NeuVax) have been promising particularly in the prevention of recurrence in HER2-low or HER2-positive patients of breast cancer. There are also more advanced substance possibilities to form vaccines against MUC1, a glycoprotein hyper-expressing in most of the breast tumors (Kwapisz, 2021). Moreover, combination therapies combining vaccines with immune checkpoint inhibitors such as, anti-PD1 or anti-CTLA4, or chemotherapies are also expected to improve immune activation and eliminate tumor immune evasion (Sharma *et al*., 2010); (Early Breast Cancer Trialists' Collaborative Group, 2012). The combination therapies are especially critical in triple-negative breast cancer (TNBC), with no hormone or HER2 targets but with greater immunogenicity. No such breast cancer vaccine has yet been full approved, but a number of candidate vaccines are under clinical trial, demonstrating safety and limited efficacy. There are still hurdles such as immune

tolerance, heterogeneity of tumors and immunosuppressive tumor microenvironment, yet developments in nanotechnology, personalized neo-antigen vaccines, and combination immunotherapy may overcome these obstacles (Sharma *et al*., 2010).

2.2.2 Local therapy/local treatment of BC

2.2.2.1 Surgery

The SLNB, which is somewhat a strategy of excluding the existence of axillary metastases, has currently replaced the ALND to serve as the best or primary method of evaluating the axilla in most early BC peoples (Lovelace., McDaniel., & Golden, 2019).

2.2.2.2 Radiotherapy

The treatment using the woman with locally advanced BC was the first method to be used to apply radiation to the tumor cells and today, the radiation became the central part of the BC treatment Sharma *et al*., 2010). Radiation therapy includes mainly two types of treatment which includes, EBRT or internal radioisotope therapy (RIT) (Lovelace., McDaniel., & Golden, 2019). Table 1.1 and figure 1.3 contains some illustrations of over local treatment of BC:

Table 1.1: Local treatment of BC (Michaels., Worthington., & Rusiecki, 2024).

Therapy	Type	Application Site	Mechanism	Goal
Surgery	Physical removal	Tumor site	Excision of tumor tissue	Curative / Palliative
Radiation therapy	Ionizing radiation	Breast/chest wall	DNA damage to cancer cells leading to apoptosis	Curative (often post-surgery)
Intratumoral chemotherapy	Pharmacological	Within tumor	Direct delivery of cytotoxic agents	Reduce systemic toxicity
Topical drug delivery	Pharmacological	Skin over/near tumor	Passive/active permeation through skin	Local control of superficial tumors
Thermotherapy (e.g., hyperthermia)	Physical	Tumor site	Heat-induced damage to tumor cells	Enhances effect of other therapies
Intraductal therapy	Pharmacological	Mammary ducts	Local instillation of drugs via ducts	Treat/prevent ductal carcinoma
Photodynamic therapy (PDT)	Photo-activated	Tumor	Light-activated drug generates ROS to kill tumor cells	Targeted tumor ablation

Figure 1.3 contains some illustrations of over local treatment of breast cancer are as follows:

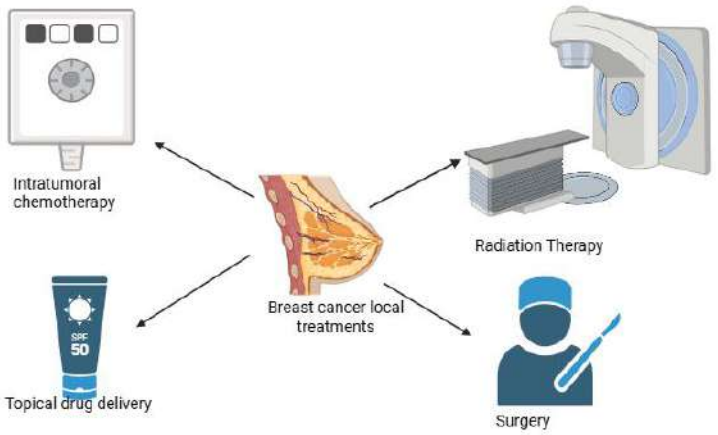

Figure 1.3 Breast cancer local treatment: This diagram illustrate local breast cancer treatments such as topical drug delivery, radiation therapy, surgery and intratumoral chemotherapy use (Li *et al*., 2015).

3. Barriers of existing treatment options of BC

Treatment of the BC with current treatment methods is associated with some of its challenges (Fisher *et al*., 2002). Another disadvantage of the traditional chemotherapeutic agents is the drug tolerance that reduces the effectiveness of drug [56]. The timing in which they occur can be used as the foundation to differentiate intrinsic drug resistance or acquired drug resistance (Chidambaram., Manavalan., & Kathiresan, 2011). Table 1.2 and figure 1.4 indicates Barriers in BC: current treatment options are as follows:

Table 1.2: Barriers in current breast cancer treatment

Treatment Option	Barrier/ Limitation	Example	Reference
Chemotherapy	Non-specific cytotoxicity; severe side effects (nausea, myelosuppression, cardiotoxicity)	Doxorubicin-induced cardiotoxicity	(Chidambaram., Manavalan., & Kathiresan, 2011)
Hormone Therapy (e.g., Tamoxifen, Aromatase Inhibitors)	Resistance development; limited to hormone receptor-positive patients	Tamoxifen resistance in ER+ patients	(Carpenter & Conlan, 2021).
Targeted Therapy (e.g., Trastuzumab)	Limited efficacy in triple-negative BC; high cost; cardiotoxicity	HER2-targeted therapies	(Alibakhshi *et al*., 2017).

		ineffective in TNBC	
Radiotherapy	Radiation-induced fibrosis and secondary malignancies; limited in metastatic disease	Radiation-induced lung fibrosis post-mastectomy	Boyages, (2017).
Surgery	Risk of recurrence, lymphedema, cosmetic/psychological impact	Breast-conserving surgery with residual micro-metastases	(Lovelace., McDaniel., & Golden, 2019).
Immunotherapy (e.g., checkpoint inhibitors)	Low response rate in BC compared to other cancers; immune-related adverse events	PD-L1 inhibitors in TNBC with <25% response rate	(Davey *et al*., 2021).
Nanoparticle-based Drug Delivery	Poor clinical translation, stability issues, high cost	Albumin-bound paclitaxel (Abraxane®) limited by hypersensitivity	(Tagde *et al*., 2022).
Precision Medicine / Genomic Approaches	Requires expensive testing; not accessible to all; limited actionable mutations in some subtypes	BRCA testing limited in rural settings	(Li *et al*., 2015)

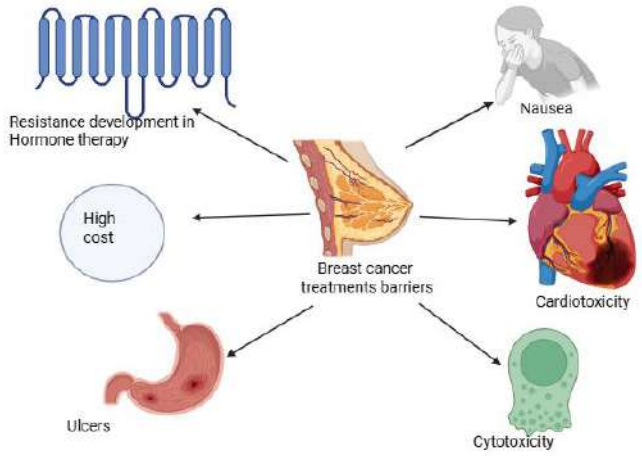

Figure 1.4 Barriers in breast cancer treatment: This image indicates various breast cancer treatments barriers such as ulcers, cytotoxicity, cardiotoxicity, nausea, high coast and resistance development in hormone therapy (Ecanow *et al*., 2013).

Chemoresistance fundamentals are very extensive and can be listed among some of its mechanisms which include: walking out more drugs, tumor variety, enhancement of damages within the DNA, epigenetic remodeling, death resistance (obstructing apoptosis) (Ecanow *et al*., 2013); (Jason & Formenti, 2018). Another contributing factor to chemotherapy effect is the chemotherapeutic drugs quality such that poor solubility and high toxicity mediate the treatment effect. The chemotherapy drugs are mainly plant source or synthetically prepared which is hydrophobic and needs a solvents to make up the dosage, therefore the drug preparations are more toxic in nature and dosage is limited (Carpenter & Conlan, 2021). Finally, short half-life and chemical instability also compromise the therapeutic effect of the chemotherapy agents as it affects the delivery and the rate of tumor site absorption and precludes the dose-effect (Saleh *et al*., 2021). In addition, it has been revealed that BC brain metastases have not been treated effectively since more than 99 percent of chemotherapy drugs do not diffuse across the blood brain barrier. As the most common side effects of the endocrine therapy, one could distinguish hot flashes and night sweats, vaginal dryness, the increased risk of thromboembolic events as well as the adverse events such as the bone ones including the osteoporosis (Chakraborty *et al*., 2025). As the resistance to the hormone therapies due to drugs, the problem of BC treatment occurs. Although both trastuzumab and pertuzumab have shown good promise in the treatment of HER2-enriched BC, intrinsic and acquired resistance is the very common phenomenon during treatment and it is worth looking deeper into the understanding of drug resistance at its depths with the aim of steering the search and development of new HER2-based treatment options (Rimawi., Schiff., & Osborne, 2015).

Similarly, drug resistance is one of the primary issues of therapeutic barriers of immunotherapy. Besides this, the manifestation of immune-preceded side effects that led to manifestation of multiple side effects in skin and gastrointestinal including rash, pruritus, diarrhea and colitis are other major drawbacks of immunotherapy particularly when taken in a combination therapy (Modi *et al*., 2021). In addition to the risk of a relapse, a solution that brings the short-term outcome surgery, in the long-term causes the undesired effects as a change in the anatomy, chronic, phantom breast pain, and lymphedema, etc (Chakraborty *et al*., 2025). The radiotherapy can always cause radiation dermatitis, radiation pneumonia, myelosuppression, cardiac and lung injuries, and establishment of cancer due to radiations, fatigue, edema and lymphedema and other negative effects, and that influence the activities of life living (Rimawi., Schiff., & Osborne, 2015); (Saleh *et al*., 2021). According to the pitfalls pointed above, several of problems already approached in the BC treatment area include the difficulties facing the management of the multidrug resistance and recurrence, and the decrease or prevention of the side-effects of the treatment. Therefore, the necessity to present novel methods of BC therapy would be essential to adequately treat the disease in order to meet the unmet medical need that BC patients feel.

4. Advantages of nanomedicines over current medicines

The recent past years, the nanomedicine has shown various advantages in meeting the inefficiencies of the conventional ways of treating BC. Nanotechnology introduces the prospect of dealing with materials, with at least one dimension in the range of less than 1 to 100 nm (Schettini & Prat, 2021). Some of the nanoparticle (NP) expertise lies in small size, large surface-to-volume ratio, ability to package high doses of drugs, increased circulation (at high doses, in more yards per deal), enhancement, retention, tumor targeting capability, control of the chemotherapy burden after release, biocompatibility, bioaccessibility, extended circulation time, and avoidance of the multidrug resistance, among others (Schettini & Prat, 2021). Moreover, due to the small size, nanoparticle can dissolve biological structures such as BBB and this would be an opportunity of treating BC patient with brain metastases. In table 1.3 Role of nanomedicine in promoting breast cancer treatment by eliminating current challenges in treatment processes are represented as follows:

Table 1.3: Role of Nanomedicine in Enhancing Breast Cancer (BC) Treatment by Overcoming Existing Therapeutic Challenges (Saleh *et al*., 2021)

Challenge in Existing BC Therapy	How Nanomedicine Addresses It	Nanomedicine Example
Non-specific cytotoxicity of chemotherapy	Enables targeted drug delivery, reducing off-target toxicity	Liposomal doxorubicin (Doxil®) selectively accumulates in tumor via EPR effect
Multidrug resistance (MDR)	Bypasses efflux pumps by endocytic uptake; co-delivers MDR inhibitors	Polymeric nanoparticles co-loaded with paclitaxel and verapamil
Poor solubility and bioavailability of drugs	Enhances solubility, controlled release and bioavailability	Nanocrystals of curcumin improve its absorption and anticancer effect
Ineffective delivery to tumor microenvironment (TME)	Modifies surface (e.g., PEGylation, ligand attachment) for tumor targeting and penetration	HER2-targeted gold nanoparticles penetrate deeper into BC tumors
Immune evasion and low response to immunotherapy	Nanocarriers deliver immune adjuvants and checkpoint inhibitors directly to tumor	PLGA nanoparticles delivering anti-PD-L1 and CpG oligonucleotides
Systemic toxicity and side effects	Nanocarriers protect healthy tissues by controlled release in tumor milieu	Albumin-bound paclitaxel (Abraxane®) reduces hypersensitivity reactions
Limited efficacy in TNBC (Triple Negative BC)	Allows co-delivery of chemotherapeutics and siRNA or CRISPR agents	Lipid-based nanocarriers with doxorubicin and siRNA for EGFR silencing

Frequent dosing and patient non-compliance	Sustained release reduces dosing frequency and improves compliance	PLGA-based depot injections with sustained paclitaxel release

4.1 NPs Synthetic activities

There was no secret that the NPs are of different shapes, sizes as well as structure. So there are various procedures of synthesis methods and it is easy to divide it into two or less; as; a bottom up approach or a top down approach. Where the bottom-up process is involved a pre-reduction of the raw materials to sizes/dimension smaller than the molecular dimension (which is the atomic level) is performed and then self-assembling of the raw materials occurs, or further addition of catalytic agents to facilitate their assembly to form NP. The non-materials requirements are in the top-down process synthesized of external and macroscopic raw materials and under this process, the extraction and processing of the large-scale raw materials is sufficiently regulated (Tagde *et al.,* 2022). That is, a larger molecule may be degraded or disintegrated to smaller components and consequently another transformation of the molecule to NPs can be attained.

4.2 Classification of medicine NPs

4.2.1 Liposomes

Liposomes are vesicles that are in the shape of nanospheres, and they are made up of amphiphilic molecules of lipids. These molecules of lipids possess a hydrophilic side and the other side is hydrophobic. Thus, they are in a position to form in spherical particles having inner hydrophilic core instantly on their reaction with the water owing to the property (Moreira *et al.,* 2023). They have 25-2.52 m liposomes with one and/or more bilayer membranes. This unique characteristic of liposomes renders this product very beneficial to have the hydrophobic drugs in the hydrophobic lipid shell and the hydrophilic drugs in the hydrophilic water content. Moreover, the liposomes are easy to accumulate on the cell membrane due to the same shape because of which the liposomes easily fuse with the cell membrane and consequently the drug loaded in the liposome is injected inside the cell. It is worth noting that the form of nanomedicines that was the first one treated in FDA clinical trials was the liposomes one. The normal liposomes therefore possess very short half lives because of the fact that the lipid bilayer structures of the liposomes can be elicited by the immune system and then removed by the macrophages within the circulation system (Pal, Rahul, *et al.*, 2023)
Still, this form of clearance can be reduced through PEGylation liposome surface, with respect to the liposomal NPs. Through this, the blood thickness of the liposomal NPs is more prolonged and the efficacy towards the patients is improved. Indicatively, the

functionally most general type of nanomedicine that has been introduced into clinical practice by the Food and Drug Administration (FDA) is the PEGylated liposome doxorubicin (DOX) hydrochloride or Doxil 1995 which can be applied to clinical use in metastatic BC and also has the capacity to decrease the overall systemic toxicity and has the ability to preserve the antitumor capabilities of DOX and maintains systemic circulation by the prevention of early doxorubicin elimination. Also, co-delivery system (liposomes) will be used to co-deliver, chemotherapeutic agents and the inhibitors, which will make cancer cells susceptible to anticancer agents. As Tang *et al*. board found out, not only the co-encapsulated DOX and verapamil liposome neutralized the P-gp mediated multidrug resistance of BC cells, but they were able to reduce the detrimental outcome on other key non-target organs (Moreira *et al*., 2023).

4.2.2 Nanoparticles- Polymeric nanoparticles

The promising ones are the new drug delivery systems, which have a lot of potentials in the diagnosis and treatment of breast cancer, and they are polymeric nanoparticles (PNPs). The common biodegradable and biocompatible polymers to form these nanoparticles are; poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), polylactic acid (PLA), chitosan or PEGylated Polymers. Solubility, stability, bioavailability and the ability to target, control and the release chemotherapeutic agents may improve through the customizability of PNPs. Another special therapeutic quality of PNPs in treatment of breast cancer is the advantage needed in beating some deficiencies of traditional chemotherapy e.g. lack specificity, systemic toxicity, and multidrug resistance. Polymeric nanoparticulate encapsulation has been effective to boost the therapeutic as well as the effects of drugs like doxorubicin, paclitaxel, tamoxifen, as well as curcumin to reduce side effects of the given drugs. Actively or passively such nanoparticles may be targeted into the tumor via the increased permeability and retention (EPR) effect or through functionalization of the nanoparticle surface with ligands such as folic acid, HER2 antibodies or aptamers, and subsequent targeting by cancer cells via recognition of a tumor specific surface receptor. Moreover, polymeric nanoparticle may be constructed to be pH-, enzyme-, redox-, or temperature-sensitive or respond to magnetic fields to the site-specific release drugs in the tumor microenvironment. Since the treatment options in triple-negative breast cancer (TNBC) are limited, PNPs could become an administrator of combination therapy, siRNA, gene editing technology (ex. CRISPR/Cas9), and increase their efficiency in the treatment (Rimawi., Schiff., & Osborne, 2015). The other new trends are polymeric nanoparticles that are under investigations as co-delivery systems to synergistically integrate chemotherapy and immunomodulators, or photothermal agents or photodynamic agents. Examples include doxorubicin and immune adjuvants conjugated to nanoparticle have had an increased effect of inducing immune stimulation and tumor regression in the

preclinical studies in the form of a co-load with nanoparticle-PLGA (Pal, Rahul, *et al.* 2025).

4.2.3 Polymeric micelles

Self assembly involves polymer micelles and hydrophobic cores that make nanocarriers such as polymer micelles. Besides this, the advantage of hydrophobic core is the fact that it retains hydrophobic drug in its core and is generally highly used to administer anti-cancer low water-soluble drugs such as PTX (Junnuthula *et al*., 2022).

4.2.4 SLN (Solid Lipid Nanoparticles)

Solid lipid nanoparticles (SLN) is comprised of solid lipid matrix and this solid lipid matrix may be clarified in regard of being in solid state at room temperature and body temperature. SLNs Long-chain fatty acids, fatty acids esters, and waxes are solid lipids. The drug delivery is carried out by embedding into the lipid core or be bonded to the surface of lipid. SLNs are the most common to improve the bioavailability of the bad oral water soluble drugs and show a lot of advantages such as the ease of manufacture, stability of the employed drugs, large number of drugs, release of the drugs passively and the long-term stability of the drugs (Michaels., Worthington., & Rusiecki, 2024).

4.2.5 Dendrimers

The three segment compositions of the dendritic nanoparticle are, its central core, again repeated unit of branches and outer surface functional group and it has dimensions of size ranging between 1 and 100 nm. The dendrimers are especially very helpful in destabilizing hydrophobic drugs due to the fact that the core portion of the dendrimers is usually hydrophobic (Ibrahim *et al*., 2024).

Possible modifications of the dendrimers structures which are branched include an ability to significantly increase the content of a drug and the specific release of the drugs. Besides this, the outer surface functional group may also be altered to a substantial degree chemically or may be complexed with medicines, ligand targets and furthermore, visualization agents (Bharali *et al*., 2009). The common dendrimers used in treatment of cancer are poly (L-lysine) (PLL), polypropylene imine (PPI), polyamidoamine (PAMAM), polyamidoamine dendrimers (PAMAMOS). Therefore, these kinds of variations of traits and features can be perceived as the advantageous aspects of dendrimers applied in the drugs delivery with references to the treatment of cancers (Zhou *et al*., 2023).

4.2.6 Nanostructured lipid carriers (NLCs)

The above are the merits of SLNs but low drug loading, crystallization leakage during storage and uncharacteristic polymorphic transformation ought to be improved upon. Fortunately, these demerits of SLNs can be avoided by exploiting the other type of lipid NPs that is nanostructured lipid carriers (NLCs) (Schettini & Prat, 2021). NLCs are made

of solid lipid liquid mixes. Given that NLCs are the second variant of lipid based nanocarriers, they have unstructured plot owing to presence of divergent constituents of NLCs. NLCs retain a solid state character despite their being lower in melting points compared to SLNs even at body heat levels. In addition to that, liquid NLCs possess extra volume of drugs to dissolve and payload since they possess unarranged nature and crystallization defect (Soni *et al*., 2020).

4.2.7 Carbons nanotubes

The diameter of the carbon nanotubes is in nanometers and it is shaped like a cylinder with one more than one coaxial layer of graphite. Their ability to handle high payload content is enabled by a high surface area while they also present exclusive optical, electronic emission and mechanical properties, which can be attributed to carbon nanotubes (Dizaji *et al*., 2020). In such a way, carbon nanotubes can be used as distribution catalysts and can be relieved of targeting and balancing drugs, diagnosis and identification of breast tumors contrast materials, biosensors, etc (Srivastava *et al*., 2023).

4.2.8 Nanoparticles of gold (AuNPs)

The advantages of gold nanoparticle (AuNPs) include among others, the properties of biocompatibility, multifunctionality, high photothermal conversion ability, imaging contrast ratio and allergies on their surface which can be easily modified. Therefore, AuNPs can be excellent materials to perform photothermal therapy (PTT). Due to a high level of the photothermal conversion efficiency, besides the ability to transform the energy of the light in the near-infrared range (NIR) into heating energy, AuNPs can also result into the death of cancer cells (Lee *et al*., 2014).

4.2.9 Mesoporous silica nanoparticles (MSNs)

High surface area, tunable pore size and release profile, high drug-loading capacity and absence of premature drug release, and high flexibility were the features that enabled mesoporous silica nanoparticle (MSN) to be used as drug carrier. Thus, MSNs may be deemed as one of the most powerful drug carriers since they have enhanced pharmacokinetic features (Tsai *et al*., 2009).

4.2.10 Quantum dots (QDs)

Quantum dots (QDs) are of nanometer scale (2-10nm) in size; they are diameters of the nanometer scale; they are made of the shell and the core of crystalline metalloids. Optical properties and high spectral excitation range and a sharp symmetric intense distribution allow QDs to be used in bioimaging, bio-labeling and biosensi (Wang *et al*., 2015). The stiffness flexibility of Dong and co-workers fabricated an ultra-small Ag2Te QDs to

suggest a high-performance computer tomography (CT) imaging mediated photonic tumor hyperthermia. Furthermore, photo-thermal conversion (50.5) was highly efficient whereby these non-toxic and highly biocompatible Ag2Te QDs had large inhibition rate (94.3) on 4T1 tumor cells on xenograft animals (Kunachowicz *et al*., 2024).

5. Nanomedicine-based therapeutic approach of BC

The approaches of nanomedicine that have been used to provide therapeutic effects on tumour may be generally classified as passive targeting, active targeting and stimuli responsive tumour targeting.

5.1 Extrinsic targeting

Passive targeting is achieved because of increased permeability and retention (EPR) effect which results in accumulation of NPs in the tumor tissues, as a result of the leakage of the vasculature in tumor microenvironment (Tagde *et al*., 2022). In uncomplicated circumstances, the rate is addressed when the tumor cells with a massive growth rate encounter an occasion of hypoxia because of a neovascularization response system. These replacement blood vessels tend to have massive pores in comparison to the normal ones hence leading to the fact that the tumor vessels are not selective of the permeability. Further, the extracellular fluid of the normal tissues is retained in the normal drainage and replacement by lymphatics. This growth of tumor leads to lymph malfunctioning and hence, to an extent, the interstitial fluid is withdrawn to minimum levels. This is another quality of EPR which assists in the retention of NPs in the tumor. It is the effect which is potentially helpful to facilitate selected collection of the chemotherapy drugs in tumor with BC. Nonetheless, the human tumor heterogeneity encompasses the parameters of pore availability, hypoxia region, pericellular space coverage, basement membrane and extra cellular matrix, which will reduce the effectiveness of EPR in cancer-celling targeting (Li *et al*., 2023).

5.2 Targeted activity

Innovative therapy involves the use of nanomedicine to facilitate breast cancer (BC) treatment due to its ability to target and perform the specified activity within the body hence defeating traditional challenges of the conventional therapy which includes systemic toxicity, poor bioavailability, and multidrug resistance. Targeted nanomedicine refers to the employment of engineered nanotransporters such as liposomes, dendrimers, polymeric nanoparticle, solid lipid nanoparticles, and micelles that gets functionalized with ligands, antibodies or peptides designed to target tumor-associated receptors of these, the human epidermal growth factor receptor 2 (HER2) is one of the most researched ones, being overexpressed in around 2025 percent of BC; the conjugation of nanocarriers to anti-HER2 antibodies trastuzumab allows receptor-mediated endocytosis

and selective drug delivery to effect in HER2-positive cells, minimizing off-target effect (Alibakhshi *et al*., 2017). Focus similarly to the process of treating estrogen receptor-positive (ER+) breast cancers, one can use estradiol-bound nanoparticle which will propensity to tamoxifen sensibility and ingestion into the cells. In case of triple-negative breast cancer (TNBC), ER, PR, and HER2 are not expressed, nanomedicine offers new approaches by targeting either folate receptor or epidermal growth factor receptor (EGFR), which are overexpressed by TNBC cells. PLGA nanoparticles functionalized with folate and EGFR-aptamer-functionalized liposomes have increased TNBC tumor accumulation and superior chemotherapeutic or siRNA delivery. In addition, another potential of integrins like alpha V beta 3 which is involved in angiogenesis and metastasis of the tumor can be blocked with RGD peptide-functionalized nanoparticles to gain enhanced insertion of the tumor mass as well as therapeutic index (Toss & Cristofanilli, 2015). The next essential nanomedicine innovation contains the use of the tumor microenvironment (TME) that consists of an acidic pH and elevated glutathione levels and enzymes. Smart, stimuli-responsive nano-carriers would liberate the drugs upon those TME indicators, thus gaining regional work and reducing their systemic depression. To take an example, doxorubicin loaded pH sensitive liposomes can release cargo in acidic tumor sites selectively. It is also reported that CD44 as a surface marker, which is overexpressed in breast cancer stem-like cells, is targeted using hyaluronic acid-modified nanoparticles in reducing tumor recurrence and drug resistance. These nanocarriers can both provide greater solubility and bioavailability of poorly soluble drugs, as well as co-delivery of two or more agents; e.g. chemotherapeutics with MDR inhibitors, or siRNA with small-molecule drugs, conferring synergistic effects and potential to dose-reduction **(**Burguin., Diorio., & Durocher, 2021). Nanotechnology translations into clinical formulations of novel BC drugs (Doxil is a product name in which the active ingredient is doxorubicin loaded into liposomes (liposomal doxorubicin) such as Doxil/liposomal doxorubicin and Abraxane/albumin-bound paclitaxel have already occurred, even though difficulties such as scale-up and replication of production and regulatory approval must be overcome. Regardless of these obstacles, nanomedicine platforms have tremendous potential in the precision, flexibility, and adaptability of personalized cure of breast cancer, by delivering cancer systems with the molecular characteristics of tumors (Alibakhshi *et al*., 2017). The next-generation technology can combine imaging substances with therapeutics to monitor in real-time, which can allow theranostic and adaptable therapies. Table 1.4 represented targeted activity of drugs in breast cancer are as follows:

Table 1.4: Therapeutic strategies of breast cancer with the help of nanomedicine by specific activity (Burguin., Diorio., & Durocher, 2021).

Target Type	Nanocarrier System	Targeting Strategy	Mechanism of Action	Example/Drug

HER2 receptor (overexpressed in HER2+ BC)	Liposomes, gold nanoparticles, dendrimers	Active targeting using anti-HER2 antibody (Trastuzumab)	Binds HER2 to deliver drug specifically to cancer cells	HER2-targeted liposomal doxorubicin
Estrogen receptor (ER+ BC)	Polymeric nanoparticles	Ligand-based targeting with estradiol or estrogen analogs	Targeting ER-positive cells to improve selectivity	Estradiol-conjugated nanoparticles loaded with tamoxifen
Folate receptor (overexpressed in TNBC)	PLGA nanoparticles, micelles	Folic acid-functionalization	Folate-mediated uptake by TNBC cells	FA-PEG-PLGA delivering paclitaxel
Integrins (αvβ3 overexpressed in invasive BC)	Liposomes, nanogels	RGD peptide targeting	Enhances binding to tumor endothelium and BC cells	RGD-functionalized nanoliposomes with docetaxel
EGFR (upregulated in TNBC)	Solid lipid nanoparticles, liposomes	Antibody or aptamer targeting EGFR	Receptor-mediated endocytosis and internalization	EGFR-aptamer liposomes carrying siRNA
Tumor microenvironment (TME)	Stimuli-responsive nanoparticles (pH, redox, enzymes)	Passive + TME-triggered release	pH/redox-sensitive drug release in acidic or hypoxic TME	pH-sensitive liposomes with doxorubicin
CD44 receptor (on BC stem-like cells)	Hyaluronic acid-modified nanoparticles	CD44-targeted delivery via HA binding	Targets cancer stem cells and inhibits recurrence	HA-PEG-PLGA nanoparticles with curcumin

5.3 Targeting of tumors with stimuli responsive therapeutics

Stimuli responsive targeted tumor refers to stimuli-responsive delivery of the load of the NP in the cancer tissues thereby forming the amplification of the therapy and the systemic toxicity due to its selective relinquishment of medicine at the tumor locations (Oshiro *et al*., 2020). Redox potential changes, enzymes and pH make up the internal stimuli. In the meantime, the factors that are outside are temperature, photodynamic therapy, those based on ultrasound, an electric field, etc. Li *et al*. (2021) have come up with an immediate pH-responsive reduction size drug orderliness system named self-aggregated DOX@HA-CD (SA-DOX@HA-CD) that was filled with drug DOX and

tributaries carbon (HA-CD) transformed with small size as monomers. SA-DOX@HA-CD could not only self-aggregate as raspberry-like structure within normal pH, but also offered preferable blood compatibility and stability (Qiao *et al*., 2019). Still, in the simulated tumor microenvironment (at pH 6.5), it would consist of shotgun-like CD monomer loaded with DOX, which might degrade very quickly due to modification of charge, hydrophilicity, and hydrophobicity, thus enhancing uptake and permeation of the breast cancer model, which would extend the efficacy of the chemotherapy (Alibakhshi *et al*., 2017).

6. Nanoparticle plays an important role in the therapies or the combination therapies of BC

To date, the monotherapy in the aim of obtaining a satisfying anti-cancer effect is usually impossible. The multiple methods of therapy possess combinatory effect and ability to have synergistic anti-cancer effect compared to the monotherapy method, which results in few side effects that are linked to the use of single drugs when using the monotherapy approach. A summary of the chemotherapy and other treatment approaches along with the nanoparticle in the treatment of BC was hence not only an experience but also elaborated in the present section (Li *et al*., 2024).

6.1 Chemotherapy regimen combined with PDT in BC

Photodynamic therapy (PDT combined with chemotherapy) is a promising area of appraisal in the treatment of breast cancer (BC) and superior to the conventional mode of therapy in treating the disease. Non-invasive PDT relies on the energy-regulated activation (depending on a specific operating wavelength light) of photosensitive molecules called photosensitizers that are used to produce reactive oxygen species (ROS). Such ROS cause local destruction in a cancerous cell killing those (Khadir *et al*., 2009). Therapeutic effects may also be achieved when PDT is combined with chemotherapy and they include; the increased sensitivity of cancer cell to drugs, drug resistance inhibition processes and decrease in the side effects of drugs Boyages, (2017). In breast cancer especially using triple negative breast cancer (TNBC), single modality chemotherapy is not effective due to the induction of multidrug resistance and destruction of healthy cells. PDT can have a chance of improving these pitfalls since the treatment is localised and hence do not come in contact with normal tissues. Moreover, PDT can moderate tumor microenvironment and make cancer cells more receptive to chemotherapy. One such situation would be that, permeability of the blood vessels growing with cancer would increase due to PDT, and this would allow the drugs of chemotherapy to permeate. It also helps in stimulation of immune cells that help in killing of the remaining tumor cells (Chakraborty *et al*., 2025). This combination technique has also been improved by the nano-technology through co-delivery of picturesensitizers with the chemotherapeutic drug using the assistance of nanoparticles.

These nano-carriers even ensure that the two therapies can reach their target destination (i.e. the site of the tumor) with precision and reduce toxicity that leads to improved drug accretion. Even others are programmed to release the chemotherapy drugs when they react with light so as to coordinate with each other. Research studies have reported that combination therapy involving combination of these, such as doxorubicin (a chemotherapeutic agent that is widely used) and photosensors, such as chlorine 6 or porphyrins create more tumor shrinkage and less side effects as compared to the use of either one of either. It is noteworthy that PDT could access the cancer stem cells, which are typically non-responsive to chemotherapy and induce recurrence (Candido *et al*., 2018). It also assists in activating the immune cells which assist in annihilation of the left over tumor cells. This is another combination method that has been enhanced by the nano-technology and this is by co-delivery of the picturesensitizers with the chemotherapeutic drug with the help of nanoparticles. The said nano-carriers even go a step further to make sure that the two therapies can not only target their area of destination (i.e. the location of the tumor) with precision and minimize toxicity resulting in better drug accumulation. Even others are pre-programmed to discharge chemotherapy drugs whenever they react with the light in order to synchronize with others. In research studies conducted, a combination therapy with a combination of these together, like the one that consists of doxorubicin (which is used widely as a chemotherapeutic agent) and the photosensors, like the chlorine 6 or porphyrins produces more tumor shrinkage with fewer side effects than the use of any one of each. It is impressive that PDT was able to target the cancer stem cells that are naturally not sensitive to chemotherapy and that causes recurrence (Lee *et al*., 2018).

6.2 Photothermal therapy (PTT) chemotherapy-BC

The interest in photothermal therapy (PTT) is caused by the fact that this type of therapy is highly non-invasive, with precise temporal and spatial selectivity. PTT and chemotherapy have been a beneficial treatment of BC. Shen *et al*. (2019) synthesized a similar therapeutic platform, PLGA-based (IDPNs), to co-administer an Intensely-doped close-infrared dye (indocyanine green (ICG) that is prevalent compared to a chemotherapeutic drug (DOX)). The IDPNs proved to be highly stable, photothermal effect, biocompatible and on-demand drug-releasing property. The chemo-photothermal therapy combination therapy elicited the favored chemical-photothermal combination therapy effect in vitro and effectively suppressed the development of tumors that harbor BC cells in nude mice with no apparent systemic toxicity (Sun *et al*., 2022).

6.3 Chemodynamic therapy (CDT) in addition to chemotherapy in the treatment of BC

A powerful treatment against cancer is the chemodynamic therapy (CDT) that produces highly active hydroxyl radical with significant oxidative cell damage and hence death.

The CDT did not require oxygen and introduction of any external source of energy, but rather relied upon the Fenton catalysts. The possible advantages of CDT are high tumor specificity and selectivity, minimal system toxicity and reduced side-effects. Other than this, the side effects associated with the drugs put in use when doing a chemotherapy can be prevented by a combination chemotherapy, including CDT and CDT, and the therapeutic outcomes can be improved (Li *et al*., 2021).

Conclusion and prospect

The nanomedicine treatment of BC in the past decades has become a big boost. The nanomedicine can reduce the toxicity and chemo resistance of the conventional chemotherapy through passively targeting, active targeting and stimuli responsive tumor targeting nanocarriers to tumor cells. There are other common forms of NP namely; liposomes, polymeric NP-polymericmicelles, dendrimers, carbon nanotubes, etc. which have also been cited and have been used against directed drug administration. This chapter has viewed the obstructive nature of the conventional treatments at the current stage and the role of nanotherapeutics in the therapy ofBC in the future. Although nanomedicineshave revealed potential application in treatment of the BC disease, medical issues, which need to be overcome before the nanomedicine is implemented into clinical practice.

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