International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 2, 2023

Review Article

SOLID LIPID NANOPARTICLES: A REVIEW ON DIFFERENT TECHNIQUES AND APPROACHES TO TREAT BREAST CANCER

SHILPA A. GAJBHIYE*, MORESHWAR P. PATIL

Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nasik 422003, Maharashtra, India
Email: gajbhiye.shilpa81@gmail.com

Received: 30 Nov 2022, Revised and Accepted: 14 Jan 2023

ABSTRACT

Breast cancer, the most common malignancy among women, is also the second-leading cause of cancer deaths all over the world. As commonly used chemotherapy drugs, which are given systematically, causes toxicity not only to cancerous cells but also to proliferating normal cells. Similarly, drug resistance leads to drastic side effects and treatment failure. Thus arises the need for improving the therapeutic index of anticancer drugs. Owing to these failures, nanotechnology holds significant promises.

Using keywords like multi-drug resistance, effective targeting, therapeutics, intracellular pathways, efficacy, and breast cancer, references were looked up from specialised databases including Elsevier, Pubmed, and Cambridge from the year 1994 to 2023. This review was supplemented by a few references from Springer Nature and pertinent data from an online source. Along with online articles from Medscape, StatPearls, and The Lancet Respiratory Medicine, it was excellent.

Supported literature was used to overcome these challenges; therapeutic drugs are encapsulated in nanoparticles. Concurrently, solid lipid nanoparticles (SLN), with their few merits, like enhancing the therapeutic profile, overcoming multidrug resistance, providing a targeted approach, and serving as a controlled release, have gained the attention of researchers. SLNs confine significant promises, overcome these challenges, and help to possibly deliver the drug to a specific part of the body, particular organ, or tissue by an actively or passively targeted delivery system, which will be beneficial in the diagnosis and treatment of breast cancer. The objective of this article is to highlight the factors that influence the targeted drug delivery system and resultant bioavailability and also provide updates on recent research and various approaches used for breast drug delivery systems.

Keywords: Breast cancer, Efficacy, Multi-drug resistance, Effective Targeting, Therapeutics, Intracellular pathways

DOI: https://dx.doi.org/10.22159/ijap.2023v15i2.46970. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Drug delivery systems have started a new parade to enhance the therapeutic benefits of active compounds. Solid lipid nanoparticles (SLNs), in particular, have emerged as an advantageous nanocarrier system in the treatment of cancer [1]. With a few significant advantages such as increased bioavailability, low toxicity, the ability to incorporate both lipophilic and hydrophilic drugs, and the feasibility of large-scale production. Moreover, it has the ability to sidestep the problems that are faced during conventional cancer therapy [2]. Non-specificity and burst release, in general, cause toxicity, side effects, and the destruction of normal cells [3]. The composition and preparation process of SLN will determine its performance. The ability of SLN to go past several physiological obstacles that prevent drug delivery to tumour sites and also get beyond the primary drug resistance mechanism of cancer cells [4]. In 1999, Yang S. C. *et al.* prepared SLNs of camptothecin (CA), a specific drug targeting the brain. Among the investigated organs, the brain had the greatest CA-SLN to CA-Sol AUC ratio. *These findings suggest that SLNs are a viable sustained release and drug targeting strategy for lipophilic antitumor medications that are possible, with a potential for dosage reduction and less systemic toxicity* [5].

Drug delivery to the target site can be achieved by different mechanisms, like passive targeting while considering the tumour microenvironment and similarly active targeting by performing surface modification of solid lipid nanoparticles as well as co-delivery mechanisms [6]. Different drugs can be easily incorporated irrespective of their solubility criteria and are effective in different types of tumours like breast, colon, lung, brain, and liver, validating their potential [7]. Still, many challenges need consideration while formulating SLN's for cancer therapy, but their possibilities appear to be quite high [8]. Many therapeutic nanoparticles are used to treat cancer, which results in toxicity due to high drug accumulation or enhanced permeation and retention (EPR) effects. These significant drawbacks are due to leaky vasculature and inefficient drainage at tumour sites [9]. As we found, the response rate of these drugs is very poor, and drug resistance developed by the patient is very high [10]. Early menarche, late menopause, null parity, advanced age at first birth, reduced nursing, and postmenopausal hormone therapy are risk factors for breast cancer, according to GLOBOCAN 2020, as well as oral contraceptives. Alcohol consumption, obesity, and a lack of exercise are additional breast cancer risk factors [11]. Anticancer medications are used to treat cancer, extend life, or lessen cancer-related symptoms [12]. The majority of anticancer medications work by interfering with cell division [13]. Breast abscesses are one of the main causes of morbidity for women in developing nations, but they are less frequent in affluent nations due to improvements in maternal hygiene, nutrition, the standard of living, and early antibiotic administration. It has been demonstrated that ultrasound is effective for diagnosing breast abscesses, directing needle placement during aspiration, and enabling visibility of multiple abscess locations, all of which are necessary for needle aspiration and re-aspiration of breast abscesses [14].

Proteins belonging to the family ATP-binding cassette (ABC) have a vital role in drug resistance in multiple malignancies and high resistance to chemotherapy [15]. The major obstacle in breast cancer treatment and the prognosis is multidrug resistance (MDR) [16], which is usually due to high expression of certain proteins, namely P-glycoprotein (P-gp/ABCB1), ABCG2, and BCRP [17]. The most common malignancy and the second leading cause of cancer death among women is breast cancer [18]. The reason behind this is the potential for metastasis to obscure organs. The modulation of breast cancer and its progression to metastasis are mainly mediated by several pathways [19]. The various biological receptors responsible for breast cancer are oestrogen receptors (ERs), progesterone receptors (PRs), and human epidermal growth factor receptor 2 (HER-2) for multiple subtypes of breast cancer [20].

Breast receptors: targeted drug delivery system

Over few decades, while comparing free drugs, nanocarriers have played a vital role in various cancer therapies [21]. As nanocarrier-encapsulated drugs are target oriented and accumulate at tumor

site, across EPR effects by such means, it improves the therapeutics outcomes and selectivity, thereby decreasing the side effects and toxicity [22]. A significant amount of effort has gone into developing a novel target-oriented nanocarrier and analogous therapeutic approach. The targeted nanocarrier was prepared by conjugating various ligands like proteins, aptamers, peptides, and copolymers against various receptors so as to reach the clinical site [22, 23].

The use of a selective targeting drug delivery system can improve drug release governance and therapeutic potency [24]. This system employs ligands that precisely interact with cancer cell receptors to improve the binding and internalization of encapsulated nanoparticles [25]. Nanoparticles with targeting components like antibodies, proteins, and peptides on the external surface of the nanoparticle reveal a substantially greater affinity for tumour cells [26, 27]. The need for targeted drug delivery arises with the rise in complications, such as the physiological and molecular mechanisms induced by stress in the tumour microenvironment that lead to the establishment of treatment resistance. A cancer therapy-targeted nanocarrier having a particular receptor, Signalling pathways and intrinsic subtypes in the molecular biology of breast cancer nanoparticle delivery for metastatic breast cancer, the connection between breast cancer cell line classification and breast tumour subtyping. Multidrug resistance is caused by the increased production of proteins like P-glycoprotein (P-gp/ABCB1), ABCG2, and BCRP (MDR). Using various nanocarrier-based drug delivery techniques Gene expression profiling and histopathological evaluation of triple-negative or basal-like breast carcinomas.

Factors to be considered in the design of breast-specific drug delivery system

Before designing a breast-specific drug delivery system, it is important to analyse the many different influencing elements that will affect how well the medicine works therapeutically [28, 29]. Below are a few of the factors.

Anatomy of breast

Breast cancer is a complicated illness with well-defined clinical, morphological, and molecular characteristics [30]. Different kinds of fatty, fibrous, and glandular tissues make up the female breasts. The fatty tissue that occupies the spaces between glandular and fibrous tissue mostly determines the size of our breasts. The fibrous, so-called supporting or connective tissue, determines ligaments and scars. Parts of the glandular tissue include the breast ducts and lobes.

Fibro-glandular tissue refers to all non-fatty tissue. From the skin to the body's chest wall, there are bands of strong, flexible connective tissue known as ligaments that maintain the breast tissue in the proper position. The breast muscle is also very important. Both breasts are supported by the pectoral muscle, which is normally found against the chest wall beneath both. Additionally, blood arteries are there to carry away waste and also offer oxygen to the breast tissue [31].

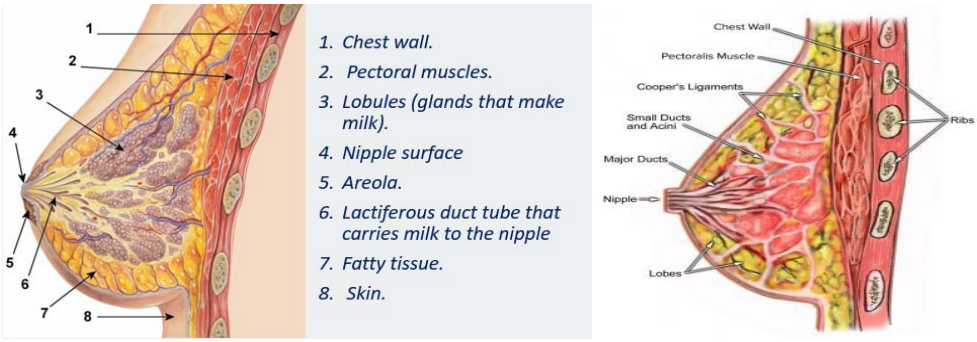

Fig. 1: Anatomy of breast [31, 32]

Hormonal receptors

Only clinical factors, such as tumour size, lymph node involvement, histological grade, and age, as well as biomarkers like the oestrogen receptor (ER), progesterone receptor (PGR), and human epidermal growth factor receptor 2 (HER2), which are primarily used in the diagnosis and treatment of cancer patients, can explain the heterogeneity of breast receptors. But we must pay close attention to the molecular biology of cancer [33]. One in five women is affected by the most prevalent type of breast cancer among them, known as HER-2-positive breast cancer, which is brought on by the overexpression of HER-2 [35].

Molecular biology in breast cancer: intrinsic subtypes and signalling pathways

Over the last ten years, extensive research on cancer molecular biology has revealed links between various signalling pathways [36]. Among the most well-known platforms are the wound-response model, the rate of two genes model, the genomic grade index, and the intrinsic subtype model, as well as Mamma-Print and onco-type DX [39]. However, the useful data on tumour biology resulted in a better understanding of the signalling networks that control tumour growth and maintenance [41]. IGF1R, HER2, oestrogen receptor, IGF1R, PI3K/AKT, mTOR, AMPK, and angiogenesis pathways lead to the development of new targeted therapeutics [42].

Tumor micro-environmental stress

The specific messenger and communicator between tumour cells and other cells containing genetic material and proteins linked to cancer is called a tumor-derived exosome (TDE). And TDEs, which are also one of the crucial elements that make up the tumour microenvironment (TME), can alter the TME and interact with it to encourage the growth and metastasis of tumours [43].

According to a wealth of research, the tumour micro-environment is a well-established regulator of cancer growth, distant metastasis, and the acquired resistance of cancer cells to various therapies [44]. Despite significant improvements in radiotherapy and chemotherapy, less effective medications are produced as a result of the development of treatment resistance [45]. Surgery, radiation therapy, hormone therapy, chemotherapy, biological therapy (targeted medication therapy), and evidence-based guidelines are some of the main breast cancer treatment options [46].

Methods used for drug targeting to the breast

In this review, we talk about the many nano-drug delivery technologies for treating breast cancer, including localised and receptor-based approaches. The most desirable but exclusive goal of a medicine delivery system has become drug targeting [47]. The ability to alter pharmacokinetics and biodistribution, as well as confine drug action to treated tissue, in order to improve efficacy and reduce the toxicity of both new and existing medications [48]. Different strategies have been developed to get over these obstacles by leveraging possible drug carriers to enable site-specific targeting [49].

Drugs must get past a variety of obstacles, including pharmacological, biochemical, and physiological ones, in order to reach their intended audience [50]. These challenges can be

overcome by addressing the target organs directly or via catheterization, using the EPR effect in tumours or RES organs (unmodified surface nanosystems), bringing surface-bound active ligands together, useful for intracellular targeting, a specific release pattern, imaging, and treatment [51]. Targeted drug delivery methods not only improve the therapeutic effectiveness of medications but also reduce drug toxicity, enabling the use of lower doses of the drug during therapy [52]. Both active and passive targeting techniques were investigated as cutting-edge nanosystems for medication delivery [53].

Table 1: Drug targeting approaches

Passive targeting	References	Active targeting	References
1. Pathophysiological factors	54-56	1. Biochemical targets	115-118
• Inflammation/infection	57,58,60,61,62	• Organ	122
• EPR effect	9,,63,64,123	• Cellular	125
2. Physicochemical factors	59, 74	• Organelles	126
• Size	53, 65	• Intracellular	119
• Molecular weight	65	2. Physical/External stimuli	92,121
3. Anatomical opportunities	66	• Ultrasound	13
• Direct injection	67,68	• Magnetic field	120
• 4. Chemical approaches	63-73	3. Pre-targeting/Sandwich targeting	127
Prodrugs	124	4. Promoter/Transcriptional targeting	128
• Chemical delivery systems	74-78		

Different types of targeting approaches are

Passive targeting approaches

Because passive targeting compromises the vasculature, it results in the sustained release of pharmaceutical actives and drug accumulation in the drug-carrier system at a specific spot [54]. The passive targeting of a medication or nanocarrier system is aided by pathophysiological and anatomical research [55].

Amir Tajbakhsh, Malihe Hasanzadeh, Mehdi Rezaee, *et al.* conducted a study on the passive targeting of curcumin SLNs to breast cancer tumour tissues, exhibiting remarkably greater tissue availability. By focusing on important signalling pathways to either increase the effectiveness of the existing medication or decrease toxicity. Despite having anticancer properties, curcumin has been found in multiple clinical trials to lessen the severity of radiation dermatitis in breast cancer patients receiving irradiation. Even though it has limited bioavailability. Various methods have been used to increase its absorption rate. To increase curcumin's bioavailability, numerous adjuvants and conjugates were tested during curcumin delivery. Another strategy to improve curcumin absorption in the digestive tract is lipid-based nano-micelles, whereas polymer-based nano-formulations (such as poly D, L-lactic, co-glycolic [PLGA]) enable the release of curcumin at a sustained level. It was concluded that, however, different formulations of curcumin have now enhanced its bioavailability compared to unmodified curcumin, despite the fact that the low oral absorption of curcumin is one of the main limits of its application. Clinical investigations have looked into the medicinal application of curcumin, either as an adjuvant or alone using different formulations, with encouraging outcomes [56].

According to Guorgui J. *et al.*, passive targeting of curcumin-SLN in TPGS resulted in a 50.5% growth reduction of the Hodgkin's lymphoma (HL) xenograft in the group that received it. The *SLN-curcumin (SLN-curc)* resulted in a reduction of expressions that are responsible for cell proliferation and apoptosis (XIAP and Mcl-1) in the HL tumour extracts. HL cells in culture have the ability to reduce the expression of relevant anti-inflammatory cytokines (IL-6 and TNF-) in a concentration-dependent manner. In conclusion, SLNs seem to be a suitable and efficient method for delivering *curcumin*. It was hypothesized that *curcumin*, when properly prepared, is a promising adjuvant for the treatment of HL and merits further investigation, given the effectiveness of *SLN-curc* and the improved growth-inhibitory impact when paired with chemotherapeutic medicines [57].

Nausicaa Clemente ID, Benedetta Ferrara, Casimiro Luca Gigliotti, and colleagues created *temozolomide* (TMZ) solid lipid nanoparticles (SLN), which proved to be effective in inhibiting the growth and vascularization of B16-F10 melanoma in C57BL6 mice without causing any toxicity. They concluded that temozolomide SLN could be a promising strategy for allowing increased stability of the drug and, thereby its employment in the treatment of aggressive malignancies [58].

Mansi K. Shah, Parshotam Madan, *et al.* developed and evaluated Carvedilol SLNs to boost total bioavailability by encouraging lymphatic uptake of carvedilol-loaded SLNs; the drug release should be regulated, and first-pass metabolism might be avoided. The enteric-coated, carvedilol-loaded SLNs tablet will provide prolonged release profiles to protect carvedilol from acidic environments. In the Caco-2 cell line, carvedilol absorption was higher from SLNs than from drug solutions, suggesting a potential delayed drug release. Findings indicate that SLNs may enter the lymphatic system after cellular absorption, avoiding first-pass metabolism and increasing oral bioavailability [59].

Pathophysiological opportunities

The physiological state of sick tissue may change under different clinical circumstances, which can be used to a drug's advantage when used passively [60]. Leukocyte extravasation is made possible by the release of numerous chemotactic factors from diseased or inflamed tissues, which also improves the permeability for particulate drug carriers [61]. These pathophysiological potentials include an increase in vascular permeability caused by various inflammatory situations, which primarily permits the extravasation of nanocarrier systems and their site-specificity in inflamed tissue [62]. It is possible for the nanosystems inside the tumour to have an enhanced permeability and retention (EPR) effect due to the increased vascular permeability and the tumour's impaired lymphatic drainage [63]. In order to achieve passive tumour accumulation using the EPR effect, the targeted system must have lengthy blood circulation times, maintain drug activity while in circulation, and maintain drug carrier interaction [64].

Mi-Kyung Lee, Soo-Jeong Limc, Chong-Kook Kim, and colleagues created and tested paclitaxel solid lipid nanoparticles (SLNs) made from trimyristin (TM) as a solid lipid core and egg phosphatidylcholine and pegylated phospholipid as stabilizers. It was found that the *in vitro* drug release study shows a slow drug release in a time-dependent manner. Furthermore, *paclitaxel*-loaded SLNs produced cytotoxicity that was equivalent to those of a commercially available Cremophor EL-based *paclitaxel* formulation when used to treat the OVCAR-3 human ovarian cancer cell line and the MCF-7 breast cancer cell line. These findings collectively imply that *paclitaxel* parenteral administration with our modified SLN formulation may be an alternate delivery method [65].

Anatomical opportunities

Drugs may be injected directly or through catheters into "discrete anatomical compartments," such as the breast, lungs, knee joints, respiratory tract, and eye, using minimally invasive techniques. These techniques for site-specific localized drug administration limit

unintended systemic exposure of the drug, avoiding negative pharmacological effects in tissues that are not specifically targeted [66]. This reduces both the dose and the price of the medication. A cutting-edge method for targeting the cytotoxic activity of anticancer medicines to cancer cells and medication delivery to inaccessible organs like the heart or brain is provided by the successful strategy to overcome biological barriers [67].

Yuan Zhao1, Meng-lei Huan, and colleagues looked into how combination therapy could be used to overcome medication resistance. Resistance to drugs like doxorubicin (DOX) has emerged as one of the major obstacles to treating breast cancer. To circumvent DOX resistance, resveratrol (RES) and DOX were co-encapsulated in PLGA to create nanoparticles (NPS). The Confocal Laser Scanning Microscopy (CLSM) outcomes demonstrate that DOX/RES-loaded NPS simultaneously transported DOX and RES into the nuclei of DOX-resistant human breast cancer cells. As a result, MDA-MB-231/ADR and MCF-7/ADR cells showed considerable cytotoxicity when exposed to DOX/RES-loaded NPS. Additionally, by preventing the expression of drug resistance-related proteins such as P-gp, MRP-1, and BCRP, as well as by inducing apoptosis by suppressing the expression of NF-B and BCL-2, DOX/RES-loaded NPS may overcome DOX resistance. They demonstrate that DOX/RES-loaded NPS primarily transport DOX and RES to tumour tissue in tumor-bearing mice. In contrast to free DOX, DOX/RES-loaded NPS greatly reduced the growth of DOX-resistant tumours in tumor-bearing mice without significantly increasing systemic toxicity. As a result, DOX/RES-loaded NPS is effective in treating DOX-resistant breast cancer and can overcome DOX resistance. It was concluded that, in comparison to traditional medications, NP-based DDS is associated with improved pharmacokinetics, biocompatibility, tumour targeting, and stability. Additionally, NPs offer a fantastic framework for combination therapy, which aids in overcoming MDR. Numerous NP forms, including metallic, polymeric, and hybrid NPs, have demonstrated increased drug delivery efficacy as a result of growing research [68].

Physicochemical factors

The size, surface hydrophobicity, and surface charge of nanosystems, which can be controlled for passive targeting, are physicochemical parameters that influence their *in vivo* biodistribution and clearance kinetics [63]. After being opsonized by blood-stream proteins, the reticuloendothelial system (RES), primarily fixed macrophages in the spleen and liver, typically absorbs a significant portion (about 90%) of the nanosystems administered intravenously [69]. The best opportunity for passive drug targeting to the macrophages present in the liver and spleen is promoted by the fact that particles smaller than 100 nm easily pass through the liver endothelium and sinusoidal sieve plates localise in the spleen and bone marrow [70]. This is a natural tendency for any nanosystems to localise in the RES. Antibiotics and antiviral medicines are typically targeted for intracellular infections [71].

Stolnik, B. Daudali, and colleagues investigated the impact of Poloxamer 407 adsorbed on colloidal drug carrier polystyrene nanoparticles, as well as the effect of different degrees of surface coverage and polyethylene oxide (PEO) chain confirmation on biological fate. The adsorbed layer of Poloxamer 407 was characterized in terms of percentage surface coverage, the thickness of the adsorbed layer, and average surface area per PEO chain by computer modelling of the adsorbed layer. The *in vitro* interactions of the nanoparticles with different degrees of Poloxamer 407 surface coverage with serum components and the *in vivo* biodistribution in the rat model were assessed. The results state that an increase in the surface coverage by Poloxamer 407 shows an increase in the volume fraction of the PEO in the adsorbed layer. Further increases in the PEO chains from the surface result in closer packing of the chains at the surface. Increased surface coverage results in a reduction in the amount of serum proteins adsorbed and, more importantly, affects the type of proteins adsorbed. Because surface coverage was greater than 25%, high molecular weight proteins resist absorption. They found that nanoparticles with 5% surface coverage resulted in improved circulation times as compared to the uncoated nanoparticles. Despite the fact that it was concluded that a relatively low degree of surface coverage with PEO chains could result in a long *in vivo* blood circulation time, Even the nanoparticles with the smallest amount of surface coverage (around 5%) had superior circulatory patterns after intravenous delivery to rats compared to the uncoated nanoparticles. For the 40 nm nanoparticles, the effect was more noticeable. In comparison to uncoated and 5% coated systems, a further increase in the surface coverage to around 25% led to a noticeably longer period of circulation time for all sizes of nanoparticles. Importantly, it was shown that PEO chains allowed nanoparticles with a relatively modest degree of surface coverage to attain a lengthy *in vivo* blood circulation period [72].

Chemical approaches

Anand Kumar Kushwaha *et al.* used *raloxifene hydrochloride*, a selective oestrogen receptor modulator (SERM), to create and test solid lipid nanoparticles via solvent emulsification/evaporation. There were only 2% estrogenic effects on bone and anti-estrogenic effects on endometrium and breast. Following the oral treatment of Wistar rats, RL-HCL-loaded SLN had a bioavailability that was nearly five times higher than pure RL-HCL. One of the interesting drug delivery candidates is lipid-based drug carriers, which have numerous applications for improving bioavailability. The attempt to create RL-HCL SLN using a straightforward conventional technique was interesting in that it showed that employing SLN as a carrier boosted the RL-bioavailability of HCL and was shown to be five times better than its suspension. Current research shows that SLN carriers may aid in improving *raloxifene's* bioavailability. However, more research is required to fully understand the mechanisms underlying SLN lymphatic absorption [73].

Active targeting approaches

Active targeting approaches enable the precise tailoring of medication or drug carrier nanosystems with "active" molecules that have a specific affinity to recognise and interact with a particular cell, tissue, or organ in the body [75]. One receptor-targeted ligand approach allows thousands of active drug molecules to be imported through the formation of a couple with the active agent while limiting the coupling capacity to a small number of drug molecules [76].

Yukiko Nishioka, Hiroyuki Yoshino, *et al.* worked on lymphatic drug targeting by using a colloidal drug carrier for efficient anticancer chemotherapy using lymphatic targeting in order to prevent metastasis of tumour cells by accumulating the amount of drug in the lymphatic region like a lymph node by subcutaneous administration. Before surgery, the primary goal of lymphatic targeting is to make sure that the medicine is targeted to lymphatic regions such as nodes and arteries. As a result, it increases the pre-oral bioavailability of macromolecule drugs like proteins and polypeptides. Unlike previous formulations, the *in vivo* study shows that poly-iso-butyl-cyanoacrylate (PIBCA) nanoparticles increased drug accumulation in lymph nodes. According to our preliminary research, nanocapsules is one of the most promising methods for lymphatic targeting due to its ability to be produced using a simple manufacturing procedure. The surface modification of nanocapsules appears to benefit from the interfacial deposition approach. The *in vivo* investigation demonstrated that following intramuscular delivery, PIBCA nanocapsules had the potential to retain medication in the local lymph node [77].

Geeta S. Bhagwat, Rajani B. Athawale, and colleagues investigated the efficacy of *Tamoxifen citrate*, a selective oestrogen receptor modification activity, in the treatment of cancer. Tamoxifen citrate has uterine toxicity and an anti-estrogenic impact on breast and uterine cells. This work effectively created transferrin-conjugated solid lipid nanoparticles (SLNs) to improve the active targeting of tamoxifen citrate in breast cancer. The proposed formulation was more cytotoxic than pure *Tamoxifen citrate* in a concentration-dependent manner on human breast cancer MCF-7 cells. MCF-7 human breast cancer cells' qualitative uptake of produced D-SLN and SMD-SLN was verified by cell uptake and flow cytometry experiments. It was concluded that transferrin-engineered nano-carriers have increased therapeutic response for the treatment of breast cancer [78].

Targets

Receptors

The presence of receptors on cell membranes enhances active targeting by enabling receptor-induced endocytosis, which facilitates the uptake of the drug carrier system by allowing selective interactions with cells [79].

Bin Lua,b Su-Bin Xiong *et al.* conducted an experiment to improve the therapeutic effect of mitoxantrone (MTO) for the treatment of breast cancer as well as to treat metastases of breast cancer lymph nodes. They performed the characterization and manufactured solid lipid nanoparticles for testing on animals by employing the film dispersion-ultra sonication technology. An *in vitro* investigation of the MTO-SLN revealed sustained MTO release with no burst release impact. The Q24 h = 25.86 0.82%, t50 = 5.25 1.10, and t90 = 28.38 4.50 d values are displayed in the release profile. It was determined that the concentration of MTO-SLN in lymph nodes was significantly higher than that in other tissues and that the concentration of MTO solution was likewise lower. The P388 lymph node and human MCF-7 breast cancer mouse models were chosen to study the therapeutic impact. MTO-SLN was administered locally, and the primary tissues showed no toxicity. According to MTO-solution, the liver and lungs suffer the majority of the medium-to-severe toxicity. This investigation of active anti-tumor drug delivery with better therapeutic benefit and minimal side effects against breast cancer and its lymph node metastases provided fresh insight [80].

Folic acid receptor

Folic acid is a vitamin that is taken up by cells by receptor-mediated endocytosis using membrane-associated folate receptors because it is necessary for the *in vivo* nucleotide synthesis [81]. Folate receptors, which are selectively overexpressed in cells of malignancies with epithelial origin, but are only expressed on specific epithelial cells in individuals [82]. It has mostly been utilised for tumor-specific drug delivery in a variety of tumours, including those of the breast, ovary, brain, and lung [83].

Folic acid receptors constitute tumor-specific targeted drug delivery was studied by Yingjuan Lu, Philip S. Low, *et al.* In many types of human malignancies, it is typically unregulated. Myeloid cells, breast, lungs, renal, brain, ovary, and other cancers. Only a small portion of a specific region on the epical membrane of polarised epithelia has folate receptors that are accessible to normal tissues. As the cancer progresses or worsens, the density of foliate receptors increases. They used folate-linked medicines to work on the therapy of cancer; as a result, folic acid is linked to both macromolecular complexes and low molecular weight medications. Folic acid is readily delivered to cancer cells that express the folate receptor and its conjugation to macromolecules. Due of macromolecule's ability to penetrate solid tumours, *in vivo* targeting of folate-mediated macromolecules has, however, only yielded inconsistent outcomes. However, it was concluded that the idea of folate targeting has considerably increased the likelihood that a macromolecule-based therapy will be effective in treating advanced cancer [84].

LDL receptors

A family of nine endocytic receptors called low-density lipoprotein (LDL) receptors carries cholesterol-rich lipoproteins (LDL) into cells by receptor-mediated endocytosis [85]. It has been suggested that several medications and some lipid-based substances, including SLNs, liposomes, and cholesterol-rich emulsions, can interact with these receptors [86].

The 14 single-transmembrane receptors of the low-density lipoprotein receptor (LDLR) family were studied by Oceane Campion, Tesnim Al Khalifa, *et al.* They contain structural similarities and shared repeats. These receptors can function independently or in complexes with membrane-spanning co-receptors that are in charge of lysosomal degradation or cell-surface recovery. They recognise and internalise a variety of external ligands. As multifunctional endocytic receptors, LDLRs are active in pleiotropic processes that influence both tumour cells and the microenvironment around them, including growth factor signalling, chemo-attraction, multicellular proteins, and cell-matrix adhesion turnover. These receptors play a contentious role and are affected by the presence of cancer. So it came to the conclusion if we better understand the activity of this receptor, it will be important to develop more sophisticated *in vitro* multicellular and 3D tumor-based systems (tumorous) utilising patient-derived cells. The strategy should be focused on the endocytic features of overexpressed LRP1 rather than on the modulation (e. g., inhibition or reduction) of LRP1 expression in the next years and in order to consider LRP1 as an innovative vectorization tool [87].

The LDLR members' specific contributions to the development of breast cancer are as follows: Due to particular expression patterns, these receptors are beneficial in primary tumours or distant metastases. New mechanisms and signalling pathways make potential diagnoses and treatment approaches possible.

Peptide receptors

Many peptide receptors that are often expressed in certain tumour cells. In tumour cells, there are receptors for peptides like somatostatin analogues, vasoactive intestinal peptide, gastrin-related peptides, cholecystokinin, and luteinizing hormone-releasing hormone [88].

To get the required therapeutic response, Nina Svensen, Jeffrey G. A., *et al.* worked on targeting particular cell types. Focusing on homing peptides (HPs) and cell penetrating homing peptides (CPHPs), they examined peptidic tissue-specific indicators that allow peptides to operate as homing devices for certain tissues and organs (CPHPs). HPs are in charge of cellular uptake and are capable of delivering a wide range of cargos into tissues and cells, including medicines, oligonucleotides, and nanoparticles. It was concluded that targeted administration using CPHP improves the therapeutic compounds' efficacy and reduces their side effects while providing molecules that are commercially feasible and often immune-suppressive. Additionally, the combination of CPHPs and active pharmacophores can effectively increase tissue penetration and cell permeability because their size decreases clearance rates, lengthening the half-lives of unmodified peptides that would otherwise be brief [89].

Lipid components of cell membranes

New targets for anti-cancer medications are developed in the form of the lipid components of cellular membranes [90]. Synthetic lipid analogues interact with biological membranes to alter their lipid content, permeability, and fluidity, which affects signal transduction pathways and causes apoptotic cell death [91].

Giulio Preta created an efficient therapeutic approach against the worst cancer with only a few adjustments to the structure and composition of lipid membranes. All eukaryotic cells' membrane micro-domains, also known as lipid rafts, are recognised as the primary platform for protein receptors that control intracellular signalling, apoptosis, redox balance, and immune responses. The lipid content of malignant cells' and healthy cells' cellular membranes aids in the development of innovative medicines. By focusing on the membrane lipids of cancer cells, chemotherapeutic drugs can be more effective at increasing sensitivity and overcoming multidrug resistance. A future area of research in MLT may be the examination of how variations in the structural makeup of raft proteins affect the organisation of lipid microdomains. Rafts proteins also play a crucial role in controlling lipid characteristics. It is surprising that targeting these proteins as an MLT strategy has received so little attention. This is because these membrane proteins are viewed as mere visitors rather than active members of lipid rafts. Additional research on these protein-lipid interactions may help us comprehend the molecular basis of the architecture of the raft domains and reveal novel approaches for controlling them. The ultimate goal of this modulation in cancer therapy is to boost chemotherapeutic drug efficacy overall, overcoming MDR and producing a synergistic effect. A promising and creative method for creating novel therapeutic techniques is to research and test membrane-lipid-targeting medicines in combination with chemotherapeutic drugs [92].

Surface antigens/proteins

Monoclonal antibodies against these proteins can be used to read the biochemical writing on the cells, which is composed of several

proteins expressed on the surface of the majority of cells [93]. The sick cells may express variable amounts (under/over) of the proteins seen on normal cells or they may express novel proteins [94]. With the development of proteomics technology, tumor-specific antigens are now much easier to identify and validate. An ideal tumor-specific antigen that may be used to target drugs is one that is solely expressed by tumour cells and similarly by all tumor-associated cells [95].

According to a study by Myriam Santos *et al.*, the surface of simian virus 40-transformed mouse cells contains a molecular complex comprising the major tumour antigen (T-Ag) and the cellular protein p53. The stability of the two proteins' connection with the cell surface was identified. Cells were either metabolically labelled with 35S methionine or had their surfaces iodinated using the lactoperoxidase method. Surface antigens were then identified by differential immune precipitation using certain antibodies either right away after labelling or after incubation at 37 °C. T-Ag and p53 were seen to rapidly and concurrently disappear from the cell surface. Researchers have failed to detect any association between T-Ag and the H-2 antigens on the surface of SV40-transformed mouse cells, although the effect of NP40 on the stability of such a putative molecular interaction is unknown. Studies are in progress to further analyse this point [96].

Targeting ligands

The use of active agents or ligands, which typically interact to some extent with the specific targets/receptors found in specific cell types, can be used to actively target medications [97]. For actively targeted medication delivery, simple compounds, including sugars, proteins, folic acid, peptides, and specially tailored antibodies, are used as targeting ligands [98].

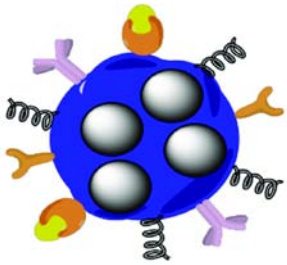

Fig. 2: Representation of a smart multifunctional drug-loaded nanoparticle decorated with various moieties for targeting, imaging and stealth properties [99]

Manasi Das *et al.*, stated in her review that the limited access of the drug to tumor cite, non-adequate availability of the drug to the site of action, cytotoxicity, high drug resistance and non-specific targeting. With the development of drug-loaded nanocarrier conjugates with various targeting moieties for the delivery and targeting of anticancer drugs serves the purpose. Hopefully, the discovery of cancer cell-targeting ligands and the creation of ligand-targeted therapy will help us increase therapeutic efficacy and lessen adverse effects. While successfully combating the cancer cells. It suggests that ligands are crucial for targeting cancer cells. It was concluded that researchers will be able to increase therapeutic efficacy and lessen adverse effects with the development of ligand-targeted therapy and the discovery of how to target ligand to cancer cells. Unlike previous types of therapy, it will enable us to effectively combat the cancer tissue while preserving the patient's quality of life. It suggests that ligands are essential for targeting cancer cells [100].

Folic acid

Folic acid can be targeted by employing it as a targeting moiety since different folate receptors are significantly overexpressed in a variety of malignant cells [101]. Folate has been coupled to radiolabelled dendrimers and liposomes to promote the accumulation of therapeutic drugs in tumour cells and their preferential absorption [102].

In two randomized controlled studies, Marta Ebbing *et al.* evaluated the effects of treatment with folic acid and vitamins B on cancer outcomes and all-cause death. Patients with ischemic heart disease who received treatment with folic acid and vitamin B12 had higher cancer survival rates and all-cause death. So it concluded that in Norway, where there is no folic acid food fortification, treatment with folic acid and vitamin B12 was linked to higher cancer outcomes and all-cause mortality in patients with ischemic heart disease [103].

Sugars

Endogenous lectins are present in the epithelial cells of several gastrointestinal areas, and they can be exploited to target drugs by attaching sugars to them [104]. While fructose binds to the distal sites, galactose interacts more with the proximal parts of the stomach. Another example of an endogenous lectin is the asialoglycoprotein receptor, which is often expressed on the surface of hepatocytes and is beneficial for drug targeting by galactose-containing drug carrier systems [105].

The prospective pharmacological interactions between medications currently used in anticancer therapy and its expression or function of facilitating sugar transporters were revealed by Moises Blanco Calvo *et al.* Finally, researchers discuss new information regarding how treatments will be developed in the future to combat the use of sugar by cancer cells. The most important information on the biochemical and biological characteristics of sugar transporters in healthy tissues is compiled in this work, and they also evaluate the data about sugar carrier expression in various cancer types. They also discuss potential relationships between the expressions or operation of facilitative sugar transporters and medications currently utilised in anticancer therapy. They also discuss future therapeutic designs that will be aimed at preventing cancer cells from utilising sugar [106].

Lectins

Different cell types, and sick cells, in particular, different express glycan's on their surfaces compared to healthy cells. Therefore, choosing the right locations enables medications to enter particular cells [107].

Tammy Yau and others, the locations of animal and plant origin discussed in this article have the potential to be turned into anticancer medicines because they cause cancer cells to undergo apoptosis and autophagy. Galectins, C-type lectins, annexins, *Haliotis discus discus* lectin, and Polygonatum odoratum lectin are examples of lectins that cause apoptosis. Although preliminary results from *in vitro* laboratory and *in vivo* animal studies are encouraging, it is evident that clinical trials are required to progress the field of cancer research and the use of lectins as chemotherapeutic agents. Low dosages of lectin-containing mistletoe extract have been used therapeutically to treat a variety of malignancies without causing major side effects, and the activity sometimes appears to be advantageous [108].

Modified albumins

A promising targeting ligand-based injury-targeting and metastasis-targeting properties of platelets, a photo-thermal therapy strategy with activated platelet-targeting albumin-based nanoparticles specifically for site-specific cancer treatment [109].

According to Leen Van De Sande, albumin has great potential for intraperitoneal administration of chemotherapy in patients with peritoneal metastases (PM). According to data from recent (pre) clinical trials, IP albumin-bound chemotherapy may be more effective than conventional chemotherapy formulations for treating PM. The field of intraperitoneal treatment for PM is expanding quickly. Results from recent preclinical and clinical trials have demonstrated that IP distribution of albumin-bound chemotherapy is more effective than conventional chemotherapy formulations in the treatment of PM. The natural transport abilities of albumins make it possible to deliver chemotherapy to specific areas. Similar to transendothelial transport, transcytosis is used to move albumin-bound complexes through the mesothelium. It is still unclear exactly

how albumin transcytosis occurs in mesothelial cells. The existence of albumin-binding receptors, the mechanisms of albumin transcytosis, and the creation of transcytosis vesicles in mesothelial cells should therefore be the main areas of future study. The processes and kinetics of IP albumin-drug dissociation should be identified, and they should be correlated with pharmacokinetic and pharmacodynamics models, *in vivo* toxicity, and anti-cancer efficacy. Knowing these pathways may help researchers design well-informed early-phase clinical trials that use IP albumin-based medication delivery in PM patients [110].

Peptides

Drugs are targeted to specific receptors that are abundantly expressed in various disease states using peptides like vascular endothelial growth factor (VEGF) [111], vasoactive intestinal peptide (VIP), luteinizing hormone-releasing hormone (LHRH), somatization, etc. [112]. Successful protein transport to the brain has been accomplished after protein-to-TAT peptide conjugation [113].

According to Susan Marquis, therapeutic peptides are a novel and potentially effective way to treat a variety of disorders, including cancer. They are superior to proteins and antibodies in a number of ways, including (a) ease of synthesis, (b) high target specificity and selectivity, and (c) minimal toxicity. The stability and short half-life of therapeutic peptides do have some notable disadvantages. It was found that the possibility of curing cancer with therapeutic peptides. Due to their ease of synthesis and excellent target specificity and selectivity, therapeutic peptides can be created to target virtually any protein of interest. Different therapeutic peptides have been specifically created to target transcription factors, tumour suppressor proteins, cell cycle, and signal transduction pathways. These medicinal peptides bind precisely to the target proteins that they are intended to attach to. Both *in vitro* and *in vivo*, they cause cell death in different cancer cells. They target cancer cells with precision, sparing healthy cells from damage. Using peptide-based cancer therapy has advantages, but it also has drawbacks. The limitations of peptides have been solved in a number of ways, including by utilising CPP to effectively deliver these anti-cancer peptides to their targets in tumour cells. The use of therapeutic peptides in cancer treatment is a novel and intriguing strategy [114].

Antibodies

When utilising antibodies as targeting moieties in hybridoma technology, antibodies against particular antigens or proteins are typically produced on the cell surface [115]. As highly specialised targeting agents with a high affinity for their targets, whole antibodies have been used [116]. To achieve drug targeting, they can be coupled either directly to the pharmaceuticals (immunotherapeutic) or to nano-sized delivery systems [117].

According to Ruei-Min Lu *et al.*, the humanization of monoclonal antibodies, phage display, the human antibody mouse, single B cell antibody technology, and affinity maturation are some of the most important antibody engineering techniques employed in the creation of therapeutic antibody therapeutics. Lastly, potential applications and outlooks are also examined. Researchers conclude ultimately; we discovered a number of new peptides, such as SP90, that can attach precisely to the cell surface of breast cancer cells both *in vitro* and *in vivo*. Through improved tumour apoptosis and reduced tumour angiogenesis, linking SP90 to liposomes containing doxorubicin improved the therapeutic efficacy in mice bearing human breast cancer xenograft. Doxorubicin levels were quantified and visualised, and the results showed higher drug concentrations in the liposome-targeted tumour tissues, demonstrating improved drug delivery and tumour penetration. Our findings suggest that the SP90 peptide may be employed to facilitate the diagnosis of breast cancer as well as enable targeted treatment of malignant cells. [118].

CONCLUSION

Different strategies for improving the therapeutic effects or efficacy of compounds that are already effective have been created via advanced drug delivery systems. Particularly, the growing trend of Solid Lipid Nanoparticles (SLNs) has shown promise as a nanocarrier in the treatment of cancer. Because it demonstrates minimal toxicity, good efficacy, simplicity in incorporating hydrophilic and lipophilic medications, and viability of large-scale manufacture.

Moreover, cost-effective methods overcoming many physiological obstacles preventing the medication from reaching the targeted spot. SLNs make it simple to get through the cancer cells' inherent multidrug resistance mechanisms. By actively and passively targeting the molecules, SLNs can enhance drug delivery to the target region. While active processes involve surface alteration of SLNs and co-delivery mechanisms, passive techniques exploit the tumour microenvironment. The ability to combine multiple medications at once with SLNs, which have been shown to be most successful in a variety of malignancies (including breast, brain, lung, liver, and colon), confirms their promise. The implementation of SLNs in anticancer treatments still faces significant hurdles, although the likelihood of success is still relatively high.

ACKNOWLEDGEMENT

The authors are thankful to Trustees, MET's Institute of Pharmacy, Bhujbal Knowledge City, Nasik for making available the resources to complete this review.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Nounou MI, Elamrawy F, Ahmed N, Abdelraouf K, Goda S. Syed-Sha-Qhattal H. Breast cancer: conventional diagnosis and treatment modalities and recent patents and technologies supplementary issue: targeted therapies in breast cancer treatment. Breast Cancer Basic Clin Res. 2015;9(2):17-34.
2. Wong HL, Bendayan R, Rauth AM, Li Y, Wu XY. Chemotherapy with anticancer drugs encapsulated in solid lipid nanoparticles. Adv Drug Deliv Rev. 2007;59(6):491-504. doi: 10.1016/j.addr.2007.04.008, PMID 17532091.
3. Din FU, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int J Nanomedicine. 2017;12:7291-309. doi: 10.2147/IJN.S146315, PMID 29042776.
4. Gavas S, Quazi S, Karpiński TM. Nanoparticles for cancer therapy: current progress and challenges. Nanoscale Res Lett. 2021;16(1):173. doi: 10.1186/s11671-021-03628-6, PMID 34866166.
5. Yang SC, Lu LF, Cai Y, Zhu JB, Liang BW, Yang CZ. Body distribution in mice of intravenously injected camptothecin solid lipid nanoparticles and targeting effect on the brain. J Control Release. 1999;59(3):299-307. doi: 10.1016/s0168-3659(99)00007-3, PMID 10332062.
6. Güney G, Kutlu HM. Importance of solid lipid nanoparticles in cancer therapy. Technical. 2011;3:400-3.
7. Hanahan D, Weinberg R. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.
8. Bayon Cordero L, Alkorta I, Arana L. Application of solid lipid nanoparticles to improve the efficiency of anticancer drugs. Nanomaterials (Basel). 2019;9(3):474. doi: 10.3390/nano9030474, PMID 30909401.
9. Nakamura Y, Mochida A, Peter L, Choyke HK. Nano-drug delivery: is the enhanced permeability and retention (EPR) effect sufficient for curing cancer? Physiol Behav. 2016;27(10):2225-38.
10. Makki J. Diversity of breast carcinoma: histological subtypes and clinical relevance. Clin Med Insights Pathol. 2015;8(1):23-31. doi: 10.4137/CPath.S31563, PMID 26740749.
11. Das P, Das S, Jana A, Das TK. Demograph ic, clinicopathological profile, and immunohistochemistry study in female breast

cancer in eastern India: a hospital-based retrospective study. Journal of Pharmaceutical and Clinical Research 2022;15(12):1-4.

12. Alfarouk KO, Stock CM, Taylor S, Walsh M, Muddathir AK, Verduzco D. Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp. Cancer Cell Int. 2015;15(1):71. doi: 10.1186/s12935-015-0221-1, PMID 26180516.
13. Chorma A, Pargi AK, Yadav R. A comparative study of drainage of breast abscess by conventional incision and drainage versus suction drainage versus ultrasound-guided needle aspiration. Asian J Pharm Clin Res. 2022;15(11):29-31. doi: 10.22159/ajpcr.2022.v15i11.45696.
14. Nair SS, Varkey J. Isolation of phytoconstituent, *in vitro* anticancer study in Hela and Mcf-7 cell lines and molecular docking studies of Pothos scandens Linn. Int J Curr Pharm Sci. 2021;13(5):42-51. doi: 10.22159/ijcpr.2021v13i5.1882.
15. Callaghan R, Luk F, Bebawy M. Inhibition of the multidrug resistance P-glycoprotein: time for a change of strategy? Drug Metab Dispos. 2014;42(4):623-31. doi: 10.1124/dmd.113.056176, PMID 24492893.
16. Al-Akra L, Bae DH, Leck LYW, Richardson DR, Jansson PJ. The biochemical and molecular mechanisms involved in the role of tumor micro-environment stress in the development of drug resistance. Biochim Biophys Acta Gen Subj. 2019;1863(9):1390-7. doi: 10.1016/j.bbagen.2019.06.007. PMID 31202693.
17. Abraham J, Edgerly M, Wilson R, Chen C, Rutt A, Bakke S. A phase I study of the P-glycoprotein antagonist tariquidar in combination with vinorelbine. Clin Cancer Res. 2009;15(10):3574-82. doi: 10.1158/1078-0432.CCR-08-0938, PMID 19417029.
18. Nagai H, Kim YH. Cancer prevention from the perspective of global cancer burden patterns. J Thorac Dis. 2017;9(3):448-51. doi: 10.21037/jtd.2017.02.75, PMID 28449441.
19. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana Hulin M. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23(19):4265-74. doi: 10.1200/JCO.2005.04.173, PMID 15911866.
20. Guan SKY, JL. Breast cancer: multiple subtypes within a tumor? Syn Physiol Behav. 2017;3(11):753-60.
21. Kreike B, Van Kouwenhove M, Horlings H, Weigelt B, Peterse H, Bartelink H. Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. Breast Cancer Res. 2007;9(5):R65. doi: 10.1186/bcr1771, PMID 17910759.
22. Wu J. The enhanced permeability and retention (Epr) effect: the significance of the concept and methods to enhance its application. J Pers Med. 2021;11(8):771-5. doi: 10.3390/jpm11080771, PMID 34442415.
23. Lu RM, Chen MS, Chang DK, Chiu CY, Lin WC, Yan SL. Targeted drug delivery systems mediated by a novel peptide in breast cancer therapy and imaging. PLOS ONE. 2013;8(6):e66128. doi: 10.1371/journal.pone.0066128, PMID 23776619.
24. Zhao Z, Ukidve A, Kim J, Mitragotri S. Targeting strategies for tissue-specific drug delivery. Cell. 2020;181(1):151-67. doi: 10.1016/j.cell.2020.02.001, PMID 32243788.
25. Jahan S, Karim ME, Chowdhury EH. Nanoparticles targeting receptors on breast cancer for efficient delivery of chemotherapeutics. Biomedicines. 2021;9(2):1-30. doi: 10.3390/biomedicines9020114, PMID 33530291.
26. De Jong WH, Borm PJA. Drug delivery and nanoparticles: applications and hazards. Int J Nanomedicine. 2008;3(2):133-49. doi: 10.2147/ijn.s596, PMID 18686775.
27. Attia MF, Anton N, Wallyn J, Omran Z, Vandamme TF. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. J Pharm Pharmacol. 2019;71(8):1185-98. doi: 10.1111/jphp.13098, PMID 31049986.
28. Tajbakhsh A, Hasanzadeh M, Rezaee M, Khedri M, Khazaei M, ShahidSales S. Therapeutic potential of novel formulated forms of curcumin in the treatment of breast cancer by the targeting of cellular and physiological dysregulated pathways. J Cell Physiol. 2018;233(3):2183-92. doi: 10.1002/jcp.25961, PMID 28419458.
29. Yu B, Tai HC, Xue W, Lee LJ, Lee RJ. Receptor-targeted nanocarriers for therapeutic delivery to cancer. Mol Membr Biol. 2010;27(7):286-98. doi: 10.3109/09687688.2010.521200, PMID 21028937.
30. Chang JM, Leung JWT, Moy L, Ha SM, Moon WK. Axillary nodal evaluation in breast cancer: state of the art. Radiology. 2020;295(3):500-15. doi: 10.1148/radiol.2020192534, PMID 32315268.
31. Anatomy of the breast. Available from: https://www.mskcc.org/cancer-care/types/breast/anatomy-breast.
32. Gabriel A. Breast anatomy: overview, vascular anatomy and innervation of the breast, breast parenchyma and support structures; 2016. Available from: https://reference.medscape.com/article/1273133-overview#showall. [Last accessed on 28 Jan 2023]
33. Koo MM, von Wagner C, Abel GA, McPhail S, Rubin GP, Lyratzopoulos G. Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic intervals: evidence from a national audit of a cancer diagnosis. Cancer Epidemiol. 2017;48:140-6. doi: 10.1016/j.canep.2017.04.010, PMID 28549339.
34. Kontermann RE. Immunoliposomes for cancer therapy. Curr Opin Mol Ther. 2006;8(1):39-45. PMID 16506524.
35. Sever R, Brugge JS. Signal transduction in cancer. Cold Spring Harb Perspect Med. 2015;5(4):a006098. doi: 10.1101/cshperspect.a006098, PMID 25833940.
36. Li X, Zhou J, Xiao M, Zhao L, Zhao Y, Wang S. Uncovering the subtype-specific molecular characteristics of breast cancer by multi-omics analysis of prognosis-associated genes, driver genes, signaling pathways, and immune activity. Front Cell Dev Biol. 2021;9:689028. doi: 10.3389/fcell.2021.689028, PMID 34277633.
37. Wesolowski R, Ramaswamy B. Gene expression profiling: changing face of breast cancer classification and management. Gene Expr. 2011;15(3):105-15. doi: 10.3727/105221611x13176664479241, PMID 22268293.
38. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen HP. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001;98(19):10869-74. doi: 10.1073/pnas.191367098, PMID 11553815.
39. Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J. Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res. 2015;5(10):2929-43. PMID 26693050.
40. Strehl JD, Wachter DL, Fasching PA, Beckmann MW, Hartmann A. Invasive breast cancer: recognition of molecular subtypes. Breast Care (Basel). 2011;6(4):258-64. doi: 10.1159/000331339, PMID 22135623.
41. Yersal O, Barutca S. Biological subtypes of breast cancer: prognostic and therapeutic implications. World J Clin Oncol. 2014;5(3):412-24. doi: 10.5306/wjco.v5.i3.412, PMID 25114856.
42. Luo X, Lia Y, Hua Zhenglai, Xiaoxia Xue X, Wang MP, Xiao C. Exosomes-mediated tumor metastasis through reshaping tumor microenvironment and distant niche. ScienceDirect; 2023. p. 327-36.
43. Ekyalongo RC, Yee D. Revisiting the IGF-1R as a breast cancer target. NPJ Precis Oncol. 2017;1(1):1-6. doi: 10.1038/s41698-017-0017-y, PMID 29152592.
44. Mbeunkui F, Johann DJ. Cancer and the tumor microenvironment: a review of an essential relationship. Cancer Chemother Pharmacol. 2009;63(4):571-82. doi: 10.1007/s00280-008-0881-9, PMID 19083000.
45. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The different mechanisms of cancer drug resistance: A brief review. Adv Pharm Bull. 2017;7(3):339-48. doi: 10.15171/apb.2017.041, PMID 29071215.
46. Moo TA, Sanford R, Dang C, Morrow M. Overview of breast cancer therapy. PET Clin. 2018;13(3):339-54. doi: 10.1016/j.cpet.2018.02.006, PMID 30100074.

47. Tiwari G, Tiwari R, Bannerjee S, Sriwastawa B, Bhati L, Pandey S, Pandey P. Drug delivery systems: an updated review. Int J Pharm Investig. 2012;2(1):2-11. doi: 10.4103/2230-973X.96920, PMID 23071954.
48. Glassman PM, Muzykantov VR. Pharmacokinetic and pharmacodynamic properties of drug delivery systems. J Pharmacol Exp Ther. 2019;370(3):570-80. doi: 10.1124/jpet.119.257113, PMID 30837281.
49. Khalid A, Persano S, Shen H, Zhao Y, Blanco E, Ferrari M. Strategies for improving drug delivery: nanocarriers and microenvironmental priming. Expert Opin Drug Deliv. 2017;14(7):865-77. doi: 10.1080/17425247.2017.1243527. PMID 27690153.
50. Rong Yang R, Tuo Wei T, Hannah Goldberg H, Weiping Wang W, Kathleen Cullion K, P Kohane DS. Getting drugs across biological barriers. Adv Mater. 2017;29(37):1-54. doi: 10.1002/adma.201606596, PMID 28752600.
51. Kiptoo P, Calcagno AM, Siahaan TJ. Physiological, biochemical, and chemical barriers to oral drug delivery. Drug delivery: principles and applications. 2nd ed; 2016. p. 19-34.
52. Golombek SK, May JN, Theek B, Appold L, Drude N, Kiessling F. Tumor targeting via EPR: strategies to enhance patient responses. Adv Drug Deliv Rev. 2018;130:17-38. doi: 10.1016/j.addr.2018.07.007, PMID 30009886.
53. Vasir J, Reddy M, Labhasetwar V. Nanosystems in drug targeting: opportunities and challenges. Curr Nanosci. 2006;1(1):47-64. doi: 10.2174/1573413052953110.
54. Tewabe A, Abate A, Tamrie M, Seyfu A, Abdela Siraj EA. Targeted drug delivery-from magic bullet to nanomedicine: principles, challenges, and future perspectives. J Multidiscip Healthc. 2021;14:1711-24. doi: 10.2147/JMDH.S313968, PMID 34267523.
55. Bazak R, Houri M, Achy SEL, Hussein W, Refaat T. Passive targeting of nanoparticles to cancer: A comprehensive review of the literature. Mol Clin Oncol. 2014;2(6):904-8. doi: 10.3892/mco.2014.356.
56. Tajbakhsh A, Hasanzadeh M, Rezaee M, Khedri M, Khazaei M, ShahidSales S. Therapeutic potential of novel formulated forms of curcumin in the treatment of breast cancer by the targeting of cellular and physiological dysregulated pathways. J Cell Physiol. 2018;233(3):2183-92. doi: 10.1002/jcp.25961, PMID 28419458.
57. Guorgui J, Wang R, Mattheolabakis G, Mackenzie GG. Curcumin formulated in solid lipid nanoparticles has enhanced efficacy in Hodgkin's lymphoma in mice. Archives of Biochemistry and Biophysics. 2018;648:12-9. doi: 10.1016/j.abb.2018.04.012, PMID 29679536.
58. Clemente N, Ferrara B, Gigliotti CL, Boggio E, Capucchio MT, Biasibetti E. Solid lipid nanoparticles carrying temozolomide for melanoma treatment. Preliminary *in vitro* and *in vivo* studies. Int J Mol Sci. 2018;19(2):255. doi: 10.3390/ijms19020255, PMID 29364157.
59. Shah MK, Madan P, Lin S. Preparation, *in vitro* evaluation and statistical optimization of carvedilol-loaded solid lipid nanoparticles for lymphatic absorption via oral administration. Pharm Dev Technol. 2014;19(4):475-85. doi: 10.3109/10837450.2013.795169, PMID 23697916.
60. Sinha R. Chronic stress, drug use, and vulnerability to addiction ajita. Bone. Ann NY Acad Sci. 2008;1141:105-30. doi: 10.1196/annals.1441.030, PMID 18991954.
61. Muller WA. Getting leukocytes to the site of inflammation. Bone Vet Pathol. 2013;50(1):7-22. doi: 10.1177/0300985812469883, PMID 23345459.
62. Maeda H. Vascular permeability in cancer and infection as related to macromolecular drug delivery, with emphasis on the EPR effect for tumor-selective drug targeting. Proc Japapn Acad Ser B Phys Biol Sci. 2012;88(3):53-71. doi: 10.2183/pjab.88.53, PMID 22450535.
63. Rosenblum D, Joshi N, Tao W, Karp JM, Peer D. Progress and challenges towards targeted delivery of cancer therapeutics. Nat Commun. 2018;9(1):1410. doi: 10.1038/s41467-018-03705-y, PMID 29650952.
64. Subhan MA, Yalamarty SSK, Filipczak N, Parveen F, Torchilin VP. Recent advances in tumor targeting via epr effect for cancer treatment. J Pers Med. 2021;11 (6):571. doi: 10.3390/jpm11060571, PMID 34207137.
65. Lee MK, Lim SJ, Kim CK. Preparation, characterization and *in vitro* cytotoxicity of paclitaxel-loaded sterically stabilized solid lipid nanoparticles. Biomaterials. 2007;28(12):2137-46. doi: 10.1016/j.biomaterials.2007.01.014, PMID 17257668.
66. Ficai A, Grumezescu AM. Nanostructures for cancer therapy. Nanostruct Cancer Ther. 2017:1-882.
67. Yingchoncharoen P, Kalinowski DS, Richardson DR. Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come. Pharmacol Rev. 2016;68(3):701-87. doi: 10.1124/pr.115.012070, PMID 27363439.
68. Zhao Y, Huan ML, Liu M, Cheng Y, Sun Y, Cui H. Doxorubicin and resveratrol co-delivery nanoparticle to overcome doxorubicin resistance. Sci Rep. 2016;6:1–1535267. doi: 10.1038/srep35267, PMID 27731405.
69. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science. 2004;303(5665):1818-22. doi: 10.1126/science.1095833, PMID 15031496.
70. Baas J, Senninger N, Elser H. The reticuloendothelial system. An overview of the function, pathology and recent methods of measurement. Z Gastroenterol. 1994;32(2):117-23. PMID 8165827.
71. Colino CI, Lanao JM, Gutierrez Millan C. Targeting of hepatic macrophages by therapeutic nanoparticles. Front Immunol. 2020;11:218. doi: 10.3389/fimmu.2020.00218, PMID 32194546.
72. Wang L, Hu C, Shao L. The-antimicrobial-activity-of-nanoparticles-present-situation. Int J Nanomedicin. 2017;12:1227-49.
73. Stolnik S, Daudali B, Arien A, Whetstone J, Heald CR, Garnett MC. The effect of surface coverage and conformation of poly(ethylene oxide) (PEO) chains of poloxamer 407 on the biological fate of model colloidal drug carriers. Biochim Biophys Acta Biomembr. 2001;1514(2):261-79. doi: 10.1016/s0005-2736(01)00376-5, PMID 11557026.
74. Singh S, Kushwaha AK, Vuddanda PR, Karunanidhi P, Singh SK Kushwaha AK, Vuddanda PR, Karunanidhi P, Singh SK, Singh S. Development and evaluation of solid lipid nanoparticles of raloxifene hydrochloride for enhanced bioavailability. BiomMed Res Int. 2013;584549. doi: 10.1155/2013/584549, PMID 24228255.
75. Preta G. New insights into targeting membrane lipids for cancer therapy. Front Cell Dev Biol. 2020;8:1–1057-237. doi: 10.3389/fcell.2020.571237, PMID 32984352.
76. Gocheva G, Ivanova A. A look at receptor-ligand pairs for active-targeting drug delivery from crystallographic and molecular dynamics perspectives. Mol Pharm. 2019;16(8):3293-321. doi: 10.1021/acs.molpharmaceut.9b00250, PMID 31274322.
77. Nishioka Y, Yoshino H. Lymphatic targeting with the nanoparticulate system. Adv Drug Deliv Rev. 2001;47(1):55-64. doi: 10.1016/s0169-409x(00)00121-6, PMID 11251245.
78. Bhagwat GS, Athawale RB, Gude RP S, Alhakamy NA, Fahmy UA. Formulation and development of transferrin-targeted solid lipid nanoparticles for breast cancer therapy. Front Pharmacol. 2020;111–12.
79. Xu S, Olenyuk BZ, Okamoto CT, Hamm-Alvarez SF. Targeting receptor-mediated endocytotic pathways with nanoparticles: rationale and advances. Advanced Drug Delivery Reviews. 2013;65(1):121-38. doi: 10.1016/j.addr.2012.09.041, PMID 23026636.
80. Lu B, Xiong S BinXiong SB, Yang H, Yin XD, Chao RB. Solid lipid nanoparticles of mitoxantrone for local injection against breast cancer and its lymph node metastases. Eur J Pharm Sci. 2006;28(1-2):86-95. doi: 10.1016/j.ejps.2006.01.001, PMID 16472996.
81. Shulpekova Y, Nechaev V, Kardasheva S, Sedova A, Kurbatova A, Bueverova E. The concept of folic acid in health and disease. Molecules. 2021;26(12):1-29. doi: 10.3390/molecules26123731, PMID 34207319.
82. Cheung A, Bax HJ, Josephs DH, Ilieva KM, Pellizzari G, Opzoomer J. Targeting folate receptor alpha for cancer treatment. Oncotarget. 2016;7(32):52553-74. doi: 10.18632/oncotarget.9651, PMID 27248175.

83. Dharap SS, Wang Y, Chandna P, Khandare JJ, Qiu B, Gunaseelan S. Tumor-specific targeting of an anticancer drug delivery system by LHRH peptide. Proc Natl Acad Sci USA. 2005;102(36):12962-7. doi: 10.1073/pnas.0504274102, PMID 16123131.
84. Lu Y, Low PS. Folate-mediated delivery of macromolecular anticancer therapeutic agents. Adv Drug Deliv Rev. 2002;54(5):675-93. doi: 10.1016/s0169-409x(02)00042-x, PMID 12204598.
85. Goldstein JL, Anderson RG, Brown MS. Receptor-mediated endocytosis and the cellular uptake of low-density lipoprotein. Ciba Foundation Symposium. 1982;(92):77-95. doi: 10.1002/9780470720745.ch5, PMID 6129958.
86. Yingchoncharoen P, Kalinowski DS, Richardson DR. Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come. Pharmacol Rev. 2016;68(3):701-87. doi: 10.1124/pr.115.012070, PMID 27363439.
87. Campion O, Al Khalifa T, Langlois B, Thevenard Devy J, Salesse S, Savary K. Contribution of the low-density lipoprotein receptor family to breast cancer progression. Front Oncol. 2020;10:1–9882. doi: 10.3389/fonc.2020.00882, PMID 32850302.
88. Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr Rev. 2003;24(4):389-427. doi: 10.1210/er.2002-0007, PMID 12920149.
89. Svensen N, Walton JGA, Bradley M. Peptides for cell-selective drug delivery. Trends Pharmacol Sci. 2012;33(4):186-92. doi: 10.1016/j.tips.2012.02.002, PMID 22424670.
90. Tan LTH, Chan KG, Pusparajah P, Lee WL, Chuah LH, Khan TM. Targeting membrane lipid a potential cancer cure? Front Pharmacol. 2017;8(12):1–612. doi: 10.3389/fphar.2017.00012, PMID 28167913.
91. Casares D, Escriba PV, Rossello CA. Membrane lipid composition: effect on membrane and organelle structure, function and compartmentalization and therapeutic avenues. Int J Mol Sci. 2019;20(9):2167. doi: 10.3390/ijms20092167, PMID 31052427.
92. Zalba S, Ten Hagen TL. Cell membrane modulation as adjuvant in cancer therapy. Cancer Treat Rev. 2017;52:48-57. doi: 10.1016/j.ctrv.2016.10.008, PMID 27889637.
93. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. B cells and antibodies-molecular biology of the cell-NCBI bookshelf. Mol Biol Cell. 2002.
94. Leth Larsen R, Lund RR, Ditzel HJ. Plasma membrane proteomics and its application in clinical cancer biomarker discovery. Mol Cell Proteomics. 2010;9(7):1369-82. doi: 10.1074/mcp.R900006-MCP200, PMID 20382631.
95. Kirpotin DB, Drummond DC, Shao Y, Shalaby MR, Hong K, Nielsen UB. Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models. Cancer Res. 2006;66(13):6732-40. doi: 10.1158/0008-5472.CAN-05-4199, PMID 16818648.
96. Santos M, Butel JS. Detection of a complex of SV40 large tumor antigen and 53K cellular protein on the surface of SV40-transformed mouse cells. J Cell Biochem. 1982;19(2):127-44. doi: 10.1002/jcb.240190204, PMID 6294133.
97. Yu B, Tai HC, Xue W, Lee LJ, Lee RJ. Receptor-targeted nanocarriers for therapeutic delivery to cancer. Mol Membr Biol. 2010;27(7):286-98. doi: 10.3109/09687688.2010.521200, PMID 21028937.
98. Yu MK, Park J, Jon S. Targeting strategies for multifunctional nanoparticles in cancer imaging and therapy. Theranostics. 2012;2(1):3-44. doi: 10.7150/thno.3463, PMID 22272217.
99. Rizvi SAA, Saleh AM. Applications of nanoparticle systems in drug delivery technology. Saudi Pharm J. 2018; 26(1):64-70. doi: 10.1016/j.jsps.2017.10.012, PMID 29379334.
100. Manasi D, Chandana M, Sanjeeb K, Das M, Mohanty C, Sahoo SK. Ligand-based targeted therapy for cancer tissue. Expert Opin Drug Deliv. 2009;6(3):285-304. doi: 10.1517/17425240902780166, PMID 19327045.
101. Zwicke GL, Mansoori GA, Jeffery CJ. Utilizing the folate receptor for active targeting of cancer nanotherapeutics. Nano Rev. 2012;3. doi: 10.3402/nano.v3i0.18496. PMID 23240070.
102. Christensen E, Henriksen JR, Jørgensen JT, Amitay Y, Shmeeda H, Gabizon AA. Folate receptor targeting of radiolabeled liposomes reduces intratumoral liposome accumulation in human KB carcinoma xenografts. Int J Nanomedicine. 2018;13:7647-56. doi: 10.2147/IJN.S182579, PMID 30538449.
103. Ebbing M, Bønaa KH, Nygard O, Arnesen E, Ueland PM, Nordrehaug JE. Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA-J Am Med Assoc. 2009;302(19):2119-26. doi: 10.1001/jama.2009.1622, PMID 19920236.
104. Ghazarian H, Idoni B, Oppenheimer SB. A glycobiology review: Ccarbohydrates, lectins and implications in cancer therapeutics. Acta Histochem. 2011;113(3):236-47. doi: 10.1016/j.acthis.2010.02.004, PMID 20199800.
105. Sicard JF, Le Bihan G Le, Vogeleer P, Jacques M, Harel J. Interactions of intestinal bacteria with components of the intestinal mucus. Front Cell Infect Microbiol. 2017;7:387. doi: 10.3389/fcimb.2017.00387, PMID 28929087.
106. Calvo MB, Figueroa A, Pulido EG, Campelo RG, Aparicio LA. Potential role of sugar transporters in cancer and their relationship with anticancer therapy. Int J Endocrinol. 2010;2010. doi: 10.1155/2010/205357. PMID 20706540.
107. Varki A. Biological roles of glycans. Glycobiology. 2017;27(1):3-49. doi: 10.1093/glycob/cww086, PMID 27558841.
108. Yau T, Dan X, Ng CCW, Ng TB. Lectins with potential for anti-cancer therapy. Molecules. 2015;20(3):3791-810. doi: 10.3390/molecules20033791, PMID 25730388.
109. Jiang Z, Li T, Cheng H, Zhang F, Yang X, Wang S. Nanomedicine potentiates mild photothermal therapy for tumor ablation. Asian J Pharm Sci. 2021;16(6):738-61. doi: 10.1016/j.ajps.2021.10.001, PMID 35027951.
110. Van de Sande L, Cosyns S, Willaert W, Ceelen W. Albumin-based cancer therapeutics for intraperitoneal drug delivery: a review. Drug Deliv. 2020;27(1):40-53. doi: 10.1080/10717544.2019.1704945, PMID 31858848.
111. Shibuya M. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: A crucial target for anti- and pro-angiogenic therapies. Genes and Cancer. 2011;2(12):1097-105. doi: 10.1177/1947601911423031, PMID 22866201.
112. Christian CA, Moenter SM. Vasoactive intestinal polypeptide can excite gonadotropin-releasing hormone neurons in a manner dependent on estradiol and gated by time of day. Endocrinology. 2008;149(6):3130-6. doi: 10.1210/en.2007-1098, PMID 18326000.
113. Lichtenstein M, Zabit S, Hauser N, Farouz S, Melloul O, Hirbawi J. Tat for enzyme/protein delivery to restore or destroy cell activity in human diseases. Life (Basel). 2021;11(9):924. doi: 10.3390/life11090924, PMID 34575072.
114. Marqus S, Pirogova E, Piva TJ. Evaluation of the use of therapeutic peptides for cancer treatment. J Biomed Sci. 2017;24(1):1–1521. doi: 10.1186/s12929-017-0328-x, PMID 28320393.
115. Parray HA, Shukla S, Samal S, Shrivastava T, Ahmed S. Elsevier has created a COVID-19 resource center with free information in English and mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information; 2020.
116. Manis JP. Overview of therapeutic monoclonal antibodies; 2022:1-18.
117. Rajesh S, Singh R, Lillard JW. Nanoparticle-based targeted drug delivery. Exp Mol Pathol. 2009;86(3):215-23. doi: 10.1016/j.yexmp.2008.12.004, PMID 19186176.
118. Lu RM, Hwang YC, Liu IJ, Lee CC, Tsai HZ, Li HJ. Development of therapeutic antibodies for the treatment of diseases. J Biomed Sci. 2020;27(1):1–31. doi: 10.1186/s12929-019-0592-z, PMID 31894001.
119. Songara NS, Bhargava AK, Chaudhary A, Sharma A. Assessment of magnesium (Mg) and zinc (Zn) in carcinoma breast patients. Asian J Pharm Clin Res. 2022;15(10):159-62. doi: 10.22159/ajpcr.2022.v15i10.45486.
120. Price PM, Mahmoud WE, Al-Ghamdi AA, Bronstein LM. Magnetic drug delivery: where the field is going. Front Chem. 2018;6:1–7619. doi: 10.3389/fchem.2018.00619, PMID 30619827.

121. Yao J, Feng J, Chen J. External-stimuli responsive systems for cancer theranostic. Asian J Pharm Sci. 2016;11(5):585-95. doi: 10.1016/j.ajps.2016.06.001.
122. Wang X, Liu S, Sun Y, Yu X, Lee SM, Cheng Q. Preparation of selective organ-targeting (SORT) lipid nanoparticles (LNPs) using multiple technical methods for tissue-specific mRNA delivery. Nat Protoc. 2023;18(1):265-91. doi: 10.1038/s41596-022-00755-x. PMID 36316378.
123. Maeda H. Enhanced permeability and retention effect; 2021. Available from: https://en.wikipedia.org/wiki/Enhanced_permeability_and_retention_effect. [Last accessed on 28 Jan 2023]
124. Giang I, Boland EL, Poon GMK. Prodrug applications for targeted cancer therapy. AAPS J. 2014;16(5):899-913. doi: 10.1208/s12248-014-9638-z, PMID 25004822.
125. Uprety B, Abrahamse H. Targeting breast cancer and their stem cell population through AMPK activation: novel insights. Cells. 2022;11(3). doi: 10.3390/cells11030576, PMID 35159385.
126. Yang J, Griffin A, Qiang Z, Ren J. Organelle-targeted therapies: a comprehensive review on system design for enabling precision oncology. Signal Transduct Target Ther. 2022;7(1):379. doi: 10.1038/s41392-022-01243-0, PMID 36402753.
127. Parker CL, Mcsweeney MD, Lucas AT, Jacobs TM, Wadsworth D, Zamboni WC. Pretargeted delivery of PEG-coated drug carriers to breast tumors using the multivalent, bispecific antibody against polyethylene glycol and HER2. Nanomedicine. 2019;21:(102076.). doi: 10.1016/j.nano.2019.102076, PMID 31394261.
128. Hye JY, Cho YH, Moon Y, Young WP, Yoon HK, Kim YJ, Yun HJ, Cho YH, Moon Y, Park YW, Yoon HK, Kim YJ. Transcriptional targeting of gene expression in breast cancer by the promoters of protein regulator of cytokinesis 1 and ribonuclease reductase 2. Exp Mol Med. 2008;40(3):345-53. doi: 10.3858/emm.2008.40.3.345, PMID 18587273.