Targeting Engineered Nanoparticles for Breast Cancer Therapy

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Breast cancer (BC) is the second most common cancer in women globally after lung cancer. Presently, the most important approach for BC treatment consists of surgery, followed by radiotherapy and chemotherapy. Therapeutic drugs or natural bioactive compounds generally incorporate engineered NPs of ideal sizes and shapes to enhance their solubility, circulatory half-life, and biodistribution, while reducing their side effects and immunogenicity. Furthermore, ligands such as peptides, antibodies, and nucleic acids on the surface of NPs precisely target BC cells. Engineered NPs and their ideal methodology can be validated in the next-generation platform for preventive and therapeutic effects against BC.

1. Introduction

Breast cancer (BC) is the outcome of aberrant and uncontrolled cell proliferation of cancerous cells in the breast tissue. BC is the second most common cancer in females and the third-leading cause of death globally [1]. BC therapy involves a multidisciplinary approach comprising surgery as well as radiotherapy and chemotherapy as adjuvant and neoadjuvant therapies [2]. Chemotherapy is a technique that kills cancer cells using chemical agents. Although it is the most effective approach for cancer therapy, the cytotoxic effects of these chemotherapy agents generate various side effects [3]. Radiotherapy also decreases the risk of cancer recurrence and mortality. Nevertheless, it typically involves radiation exposure to adjacent organs, increasing the risk of cardiac and lung diseases. Such therapies may increase the risk of leukemia, especially in association with certain classes of adjuvant chemotherapy [4]. Conversely, these therapeutic methods are often unsuccessful in treating BC because of their adverse effects on healthy tissues and organs [5][6].

The main reason for these adverse effects and the mortality rate is the failure of therapeutic agents, which act not only on the tumor sites but also induce severe adverse effects on healthy tissues and organs, causing toxicity to the individual. BC is a highly multifaceted and heterogeneous disease and is categorized based on histopathological types. The most predominant BC cases are those of invasive ductal carcinoma, although other less-common subtypes are noteworthy due to their ferociousness and clinical manifestations [7]. The next major concern is the stage of the tumor. During cancer development, the primary tumor occurs within the breast tissue (stage 1), and then rapidly spreads to the adjacent tissues and lymph nodes (stage 2–3) or distant organs such as the lung, bone, liver, or brain (metastasis, i.e., stage 4) [7][8]. Staging of the disease is clinically important. The death rate increases as the tumor metastasizes. Moreover, BC is also categorized based on the grade and molecular subtype, viz., luminal A and B, human epidermal growth factor receptor 2 (HER2), and triple-negative BC (TNBC) [8]. Once the cancer metastasizes, the effectiveness of most standard drugs is significantly low. Finding novel, effective, and safe forms of therapy for this fatal malicious disease is thus critical. It is necessary to discover highly efficient therapeutics (the so-called "magic bullets") which can pass through natural barriers and differentiate between benign and malignant cells in order to target malignant tissues. These agents "wisely" react to the complex tumor microenvironment for an on-demand discharge of an optimum dose range [9][10].

Tumor nanotechnology has the potential to modernize cancer diagnosis and treatment. Developments in protein engineering and material science have contributed to the development of innovative nanoscale targeting strategies, providing new optimism for BC patients. Nanoparticles (NPs), identified as pharmaceutical carriers, provide a new juncture for drug delivery to cancer cells by infiltrating tumors deeply, resulting in a high level of specificity to the targeted cancer cells [11][12][13][14][15]. Furthermore, NP treatment minimizes destructive effects on healthy tissues and organs [16][17]. Nanotechnology has been approved by the National Cancer Institute, which recognizes this technology as an outstanding paradigm-shifting approach for improving the diagnosis and treatment of BC [16].

Several therapeutic NPs, viz., Doxil®, Lipoplatin®, Onivyde®, Genexol-PM, and Abraxane®, have already been approved and are extensively employed for BC adjuvant therapy, with promising clinical outcomes [18][19][20][21]. NP-based drug

delivery systems (DDSs) include several valid designs with regard to the size, shape, and nature of the biomaterials loaded with drugs, enhancing the solubility, drug stability, circulatory half-life, biodistribution, and drug release rate and reducing side effects, toxicity, and immunogenicity [22].

2. Designing of Engineered NP Carriers

Nanomedicine has the potential to evade various issues in the treatment of traditional formulations. Noteworthy strides have been made towards the application of engineered NPs for BC therapy with high sensitivity, specificity, and efficiency. The engineering of NPs primarily requires various classes of chemicals with extensive structures, sizes, and compositions [23][24]. In recent years, many techniques in nanotechnology have been developed using novel biomaterials and ligands to achieve treatments with little or no toxicity. For instance, physicochemical properties of NPs such as size, geometry or shape, composition, physical and chemical structure, charges on the surface, ligand binding, and mechanical effects can be engineered to advance their performance in vivo [25]. One fascinating example was established through the use of PEGylation, conjugation, and NP-loaded liposomes for BC diagnostics and therapeutics [26]. These techniques are feasible for reducing their deposition and toxicity in major organs to a satisfactory level by elevating their half-life in the circulation [27].

2.1. Organic/Inorganic Nanocarriers

Based on chemical requirements, NPs are classified as organic or inorganic. Organic NPs (macromolecular and lipid-based nanocarriers) are characterized by higher biocompatibility and biodegradability, with manifold activation and function of the drug on their surface. Inorganic nanoparticles (carbon, silica, quantum dots, and metallic NPs) exhibit high stability, with intrinsic and visual properties appropriate for theranostics. The most investigated types are metallic NPs (gold, silver, and iron oxide) that show distinctive properties (optical and electronic), and aid in cancer imaging [28]. Based on the stability pattern, therapeutic BC drugs are mostly conjugated on their surface. They can be degraded and exchange dynamics rapidly in vivo. Hybrid NPs occupy both organic and inorganic classes, improving the biocompatibility, biodegradability, and stability of the NPs (**Figure 1**). The application of inorganic NPs in therapy is inadequate due to their low biodegradability. Mesoporous inorganic NPs are typically biodegradable, and silica-based NPs enable us to preserve drugs within a porous morphology with physicochemical properties [29].
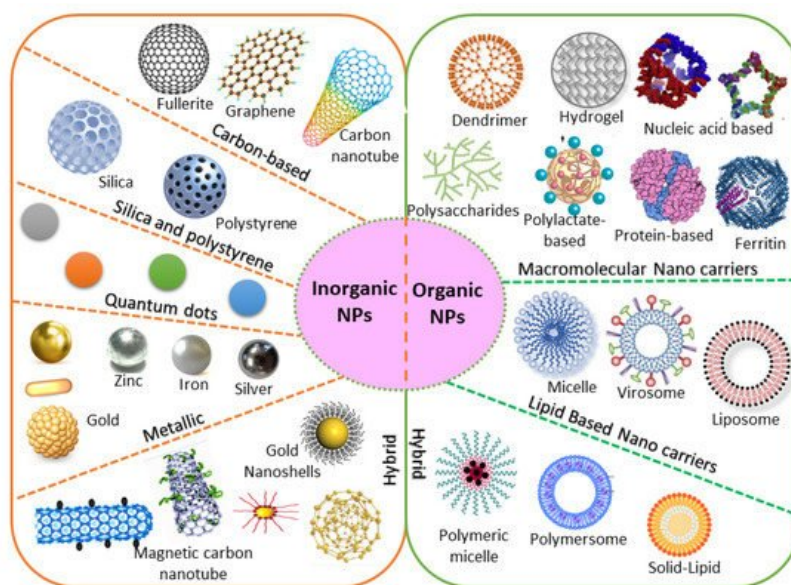
Figure 1. Chemical requirements for engineered NPs in BC therapy.

The large organic subfamily comprises macromolecular nanocarriers, both synthetic (polylactate derivatives, dendrimers, fluorescent organic NPs) and natural (protein, nucleic acid, ferritin, and polysaccharide-based NPs), with greater stability and several free functional groups, resulting in greater drug-loading capability [23]. Due to these functional characteristics, increasing attention is being paid to nanocarriers in BC therapy. Lipid-based NPs are also an important class in clinical investigation due to their noteworthy biocompatibility [30]. Lipid-based NPs comprise monolayer (micelles) or bilayer (liposomes) nanocarriers that can carry a wide range of materials with diverse physicochemical functions. The lipid bilayer of liposomes can be implanted with hydrophobic drugs, while hydrophilic drugs can be captured either in the aqueous core of liposomes or are exhibited on the surface [31]. Nevertheless, lipid-based NPs still have numerous issues, including instability and poor loading capacity, which lead to drug leakage. Novel hybrid NPs have been established to conjugate with subclasses. Examples include solid–lipid, hybrid polymer–lipid, and hybrid organic–inorganic NPs [32][33].

2.2. Natural/Synthetic Nanocarriers

Natural products are often attractive due to their abundance and higher biocompatibility, as well as the capacity adapt through biochemical mechanisms [34]. Naturally occurring substances offer many benefits over their synthetic counterparts. Natural bioactive compounds encapsulated in nanocarriers can result in increased in vivo stability and water solubility, a longer circulation time of the natural product in the blood, improved biodistribution and targeting of BC cells, and controlled and sustained drug release. They are considered potent antioxidants with closer proximity and positive effects on cancer-specific pathways, with reduced side effects [35]. Natural therapeutic drugs accumulate more appropriately for longer at the tumor site through active or passive targeting of the breast tumor tissue [36]. Several in vitro and in vivo BC model studies were established and validated the antitumor functions of nano-encapsulated phytochemicals (**Table 1**). Furthermore, experimental studies were established using liposomes, polymers, magnetic NPs, lipid-based NPs, and protein-based NPs, confirming the potential effects of plant-based natural products for BC therapy. The association of NPs with recognized plant-based antitumor compounds has been considered a promising method to reduce tumor growth and their adverse effects [37].

Natural materials can be rapidly metabolized and removed by the body system through hydrolytic or enzymatic degradation [36]. The most common issue with natural products is that of the immune response, which can readily occur upon administration into the body. This issue is due to the protein-derived materials; however, the response is often less severe with the administration of polysaccharide (chitosan)-derived NPs [38]. This immunogenic effect can be minimized by either chemical alteration or purification to eliminate the immunogenic constituents [39].

Presently, drug delivery takes place using NP-based-synthetic substances, as they allow an appropriate control over the physicochemical nature of the nanoproducts. NP-based synthetic substances are stable, safe, biologically inert, and are in circulation for a longer time, improving the distribution of therapeutic BC drugs to the tumor sites. The NPs can stimulate the generation of a corona of plasma proteins near the surface. Thus, extremely charged NPs are engulfed more rapidly by the mononuclear phagocyte system than neutrally charged NPs [40][41]. Hence, using synthetic nanocarriers, the hydrophobicity and surface charges of NPs can be suitably adjusted, improving their half-life in the circulation. Furthermore, their surface functions can be quickly engineered to improve their conjugation to the targeted receptors.

Table 1. Anti-BC effects of natural product-based nano-formulations.

Drug	Nanocarriers	Natural Compound	Size	The Outcome of the Study	BC Types	References
Doxorubicin	Poly-glycerol-malic acid-dodecanedioic acid	Curcumin	~110–218 nm	Significantly increased cytotoxicity, apoptotic cell death, and cellular intake compared to free drug in MCF-7 and MDA-MB-231	Luminal BC and TNBC	[42]
Doxorubicin	Silver NPs	Andrographolide	~450 nm	Significantly increased cytotoxicity, apoptotic cell death, and cellular intake compared to free drug in MDA-MB-453	TNBC	[36]
Adriamycin	Silver NPs	*Camellia sinensis*	~220 nm	Significantly increased cytotoxicity, apoptotic cell death, and cellular intake compared to free drug in MCF-7	Luminal BC	[43]
Doxorubicin	Folate and chitosan	Ursolic acid	~420 nm	Anticancer effects in an MCF-7 xenograft mouse model	Luminal BC	[38]
Doxorubicin	Lipid carriers (precirol® ATO 5, vitamin E, poloxamer 188, Tween 80)	Sulforaphane/Isothiocyanate	145 nm	Anticancer effects in an MCF-7 xenograft mouse model	Luminal BC	[37]

Drug	Nanocarriers	Natural Compound	Size	The Outcome of the Study	BC Types	References
Doxorubicin	Hydrophobically modified glycol chitosan with 5 beta-cholanic acid	Camptothecin	280–330 nm	Anticancer effects in an MDA-MB-231 xenograft mousemodel	TNBC	[44]
Doxorubicin	Phytosome	Quercetin	~85 nm	Anticancer effects in an MCF-7 xenograft mouse model	Luminal BC	[39]
Doxorubicin	PEGylated liposome	Gambogic acid	~107 nm	Anticancer effects in an MDA-MB-231 orthotopic xenograft mouse model	TNBC	[45]

2.3. Geometric Morphometry

Nanomedicine, as a discipline that involves the fields of chemistry, engineering, and material science, utilizes the unique features of NPs to design improved therapeutic BC interventions. Size, shape, density, and consistency are the key factors to be considered for not only DDSs but also for the engineering of NPs, as these factors regulate in vivo drug loading, stability, circulation, targeting capability, drug release, biodegradability, and toxicity [46]. For instance, particles that are smaller in size have a higher likelihood of accumulation during incubation and storage in vitro, and characteristically have a longer half-life in circulation in vivo [47]. Several investigations have confirmed that NPs display more benefits over micrometer-sized fragments in the range of 0.1–100 μm for DDSs [48]. The biodegradation of polymer NPs can be potentially affected by their size due to rapid degradation products.

The shape of NPs is also equally significant in the use of DDSs. Spherical NPs are generally a worthy candidate for DDSs. In addition, the morphology of anisotropy can also offer greater productivity due to their higher ratios between surface area and volume. They permit the nanocarrier to assume an encouraging shape for attachment to the cell through sharp ends and corners. Through these mechanisms NPs can cross cell membranes, and have been subjected to a wide range of investigations [49][50].

2.4. Surface Properties

The surface of the NPs represents another key factor determining the drug-loading efficacy, release profile, half-life in circulation, tumor targeting, and drug clearance. In fact, NPs generally have a hydrophilic surface to prevent protein adsorption and hence avoid uptake by the immune system [51]. This mechanism is generally achieved by coating the surface of NPs with a hydrophilic polymer (PEG), impacting toxicity, immunogenicity, and biodistribution [52].

The surface charge of NPs is often employed based on the zeta potential. It is determined according to the electrostatic potential of NPs, composition, and the medium used. Charged NPs with a zeta potential greater than 30 mV are indicated to be stable in suspensions, and these surface charges can generally avert the particles from aggregation. Furthermore, the surfaces of cells and blood vessels include several negatively charged ions, which resist negatively charged NPs. When the surface charge of NPs is higher, they can be hunted by the immune system, resulting in a higher clearance of NPs. Thus, the surface charge has a crucial role in minimizing the generic interactions between NPs and the immune system, averting NP loss in undesired settings. Surface hydrophilic PEG chains capsulated with NPs are frequently used to minimize generic interactions. PEGylation is considered to shield NPs such as liposomes, polymer NPs, and micelles from premature clearance during circulation. Various studies have suggested that PEGylated liposomal doxorubicin shows a prolonged half-life in the circulation and elevated stability, which is suggested to be linked to improved BC treatment efficacy [53][54][55][56][57].

Polysaccharides represent another natural surface polymer and are frequently used with NPs. They have been extensively employed in several DDSs and in tissue engineering due to their improved biocompatibility and accessibility, as well as their simple changeability. Dextran, chitosan, hyaluronic acid, fucoidan, and heparin have been employed as standard stealth-coating materials in NPs for BC therapy [58][59]. NPs coated with polysaccharides have more competent cellular uptake than other NPs due to their specific attachment with various receptors on the surface of the BC cells [60]. Hence, polysaccharides have received much attention in the field of nanomedicine.

2.5. Ligands

Several methods and tools are presently accessible to shield NPs for the active targeting of BC cells. Previously, monoclonal antibodies were employed to target epitopes on the cell surface; however, the widespread screening of peptide and aptamer archives has significantly extended the number of ligands available for targeted BC therapy [61]. Various ligands are presently employed, viz., antibodies, peptides, aptamers, oligosaccharides, and small molecules, and can precisely identify and attach to an overexpressed target on the surface of the cell [62][59][60][63]. This novel targeting mode involves a type of molecular recognition that initiates the binding of the ligand receptor. This conjugation allows the NPs to fix to the surface of the tumor cell selectively. Earlier studies have also confirmed this potential binding and validated these NPs as being effective in vitro and in vivo [64][65][66][67][68]. For instance, when attaching to a targeting ligand, the NPs generally demonstrate advanced internalization and are subjected to receptor-mediated endocytosis [16] [69]. Based on strong conjugation with ligand, the binding affinity increases and thus promotes more effective receptor-mediated endocytosis.

Monoclonal antibodies are extensively employed as targeting ligands due to their high attaching affinity and specificity for targeting BC cells, as well as their easy accessibility. Numerous investigations have been performed using monoclonal antibodies that conjugate with all families of NPs, such as superparamagnetic iron oxide nanoparticles [70], quantum dots [71], liposomes [3], and silver nanocages [36], to contribute BC-specific targeting capacity. Using bioengineering, the monoclonal antibodies edit the redundant parts of the single-chain variable fragments, reducing the size with respect to the original antibody as well as the immunogenicity [72]. This chimeric antigen receptor-engineered T-cell is a promising tool and has extended to the treatment of other cancers, including B-cell leukemia and lymphoma [72].

Other noteworthy ligands are aptamers and peptides, which are characterized by feasible targeting methods with numerous advantages. The use of peptides shows numerous advantages, including lower molecular weight, tissue diffusion potential, loss of immunogenicity, ease of construction, and relative flexibility in chemical conjugation methods [73]. Similarly, aptamers are synthetic nucleic acid oligomers that can provide multifaceted three-dimensional structures that firmly bind to surface markers with high specificity [74]. Recently, a double aptamer–NP conjugate-based complex and adenosine triphosphate aptamer-conjugated CdTe quantum dots showed high potency for the efficient detection, monitoring, and treatment of BC [74].

Ligands such as folic acid, epidermal growth factor, and transferrin are presently more attractive for BC targeting due to their better attachment to their respective receptors with greater affinity and less immunogenicity [75][76][77]. Targeting ligands are nowadays receiving great attention due to their accessibility, assortment, high affinity, ease of attachment, and cost-effectiveness. Several ligands have been reported to conjugate with various receptors and NP families, as described in **Table 2**.

Table 2. Targeting ligands employed for BC therapy.

Type of Nps	Therapeutic BC Drug	Size of the Nps	Ligands Used for Engineering	The Outcome of the Study	BC Types	Reference
Albumin-bound NPs	2-methoxy-estradiol	~240 nm	Bovine serum albumin	Significantly enhanced cytotoxicity and cellular uptake when compared with the free drug examined in the SK-BR-3 and MCF-7 cell lines and tumor-bearing mice	HER2 + BC	[73]
Chitosan	Doxorubicin	~50 nm	Anti-HER2 peptide (5–10%) and O-succinyl chitosan graft Pluronic® F127	Significantly enhanced cytotoxicity and cellular uptake when compared with the free drug in the MCF-7 cell line	HER2 + BC	[78]

Type of Nps	Therapeutic BC Drug	Size of the Nps	Ligands Used for Engineering	The Outcome of the Study	BC Types	Reference
Iron oxide	siRNA	130 nm	Caffeic acid, calcium phosphate, iron oxide, PEG-polyanion block copolymer	Significantly enhanced cytotoxicity and cellular uptake when compared with free drug on HCC1954. mRNA expression was decreased by 38% when compared with naked siRNA	HER2 + BC	[79]
Iron oxide	Baicalein	100 nm	PEG-coated iron oxide magnetic NPs	Significantly increased anti-apoptotic activity	TNBC	[80]
Liposome	Doxorubicin	~80 nm	1,2-Distearoyl-sn-glycero-3-phosphorylethanolamine, Distearoylphosphatidylcholine, HER2pep-K3-palmitic acid conjugate, mPEG2000	Significantly enhanced cytotoxicity and cellular uptake and reduced systemic toxicity when compared with the free drug in BT-474, SK-BR-3, and MCF-7 cell lines.	HER2 + BC	[63]
Liposome	Anti-IL6R antibody, doxorubicin	~100 nm	1,2-dioleoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine, cholesterol	Significantly increased tumor-targeting efficacy with anti-tumor metastasis effects in BALB/c mice bearing 4T1 cells	Luminal BC	[81]
Liposome	Doxorubicin	194 nm	1,2-distearoyl-sn-glycero-3-phosphoryl ethanolamine, estrone conjugated dipalmitoyl phosphatidylcholine- PEG2000-NH_2 liposomes	Significantly increased uptake in MCF-7 BC cell lines and decreased uptake in MDA-MB-231 BC cell lines	Luminal BC	[82]
PolymericNPs	Curcumin	~10 nm	Chitosan NPs with an apoptosis-inducing ligand (TRAIL)	Significantly reduced tumor volume when compared to control when tested in BALB/c mice	TNBC	[83]
Polymeric NPs	Trastuzumab	~125 nm	Antigen-binding fragments cut from trastuzumab)-modified NPs (Fab'-NPs) with curcumin	Significantly increased cytotoxicity and cellular uptake when compared with the free drug in the MDA-MB-453 cell lines and a xenograft mice model.	HER2 + BC	[84]
Polymeric NPs	Paclitaxel	~225 nm	Poly(lactic-*co*-glycolic acid) NP coated with hyaluronic acid	Significantly increased cytotoxicity and cellular uptake when compared with the free drug in MDA-MB-231.	TNBC	[85]

Type of Nps	Therapeutic BC Drug	Size of the Nps	Ligands Used for Engineering	The Outcome of the Study	BC Types	Reference
Polymeric NPs	Paclitaxel	131.7 nm	Hyaluronic acid-coated polyethylenimine-poly(*d*,*l*-lactide-*co*-glycolide) NPs with miR-542-3p	Significantly increased cytotoxicity and cellular uptake when compared with the free drug in MDA-MB-231.	TNBC	[86]
Polymeric NPs	Gambogic acid	121.5 nm	Hyaluronic acid-coated polyethylenimine-poly(d,l-lactide-co-glycolide) NPs with RAIL plasmid (pTRAIL) and gambogic acid	Significantly increased cytotoxicity, apoptotic cell death, and cellular uptake when compared with the free drug in MDA-MB-231.	TNBC	[87]
Polymeric NPs	Thymoquinone	~22 nm	Pluronic® F127 NPs, hyaluronic acid-conjugated Pluronic® P123.	Significantly reduced cell growth and migration of MDA-MB-231 cell lines and xenograft Balb/c mice	TNBC	[88]
Solid–lipid NPs	Di-allyl-disulfide	~116 nm	Pluronic F-68, solid–lipid NPs engineered with palmitic acid and soya lecithin and surface-modified with glycation end product antibodies	Significantly enhanced cytotoxicity and cellular uptake, augmented activity at the tumor site, and reduced systemic toxicity when compared with the free drug in MDA-MB231	TNBC	[89]

2.6. Polymeric Nanocarriers

Earlier, NPs carriers were developed and examined using a variety of materials, including monosaccharides, polysaccharides, proteins, synthetic polymers, metals, lipids, and organic/inorganic compounds. As the main prerequisite for designing NP carriers, the size, shape, composition, surface properties, and biodegradability are characteristics which must be accurately engineered and improved to achieve site-specific drug discharge with therapeutically dose-dependent optimum effects [90]. Engineered NPs activated with precise ligands can target BC cells using an appropriate method and can transport encapsulated payloads efficiently. Furthermore, advanced drug loading, enhanced half-life in the circulation, organized release, and selective delivery of NPs can also achieved by adapting the size, structure, composition, and surface properties. In the design of the engineered NPs, polymers (proteins, lipids, liposomes, dendrimers, hydrogels, organic/inorganic materials) and ligands (nucleic acids, peptides, oligosaccharides, small molecules, and antibody fragments) have been included on the surface of NPs to improve their targeting efficacy (**Figure 2**).
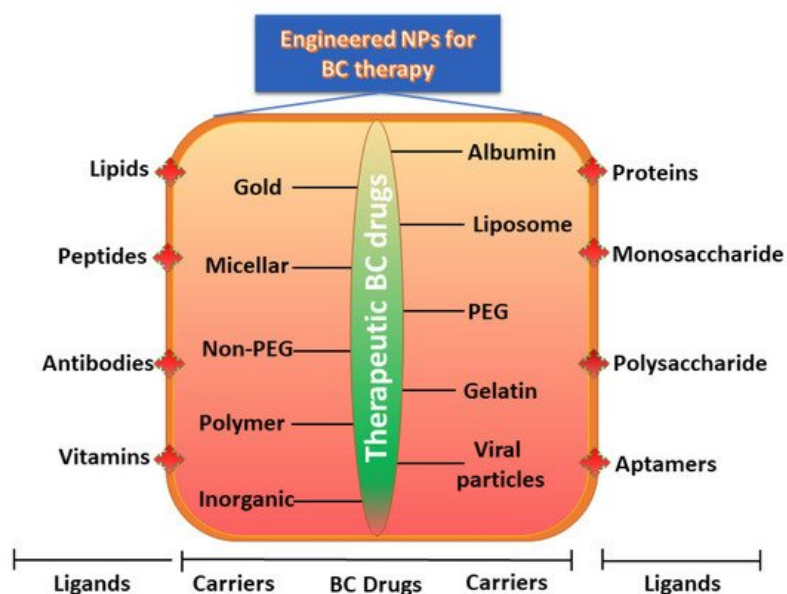
Figure 2. Engineered NPs for BC therapy.

2.6.1. Conjugation with Polymeric Protein

Successful DDSs are based on the attachment of the therapeutic BC drug to proteins for targeted drug delivery. These nanocarriers are directed to the BC through conjugation with the so-called antibody-conjugated NPs. These systems can protect the chemical structure of therapeutic drugs and deliver them to the BC site using a well-controlled method. Upon stimulation, the attachment of antibody to the drug is readily degradable, reducing toxicity [91]. Therapeutic choices may be limited for certain BC subtypes, and hence nanomedicine offers hope for patients with difficult-to-treat BC [92].

A major benefit arises from the smaller size (<10 nm) of such conjugates, which leads to a comparatively longer half-life in the circulation, and makes their extravasation into the BC region more successful when compared to NPs of greater sizes [93][94]. Studies have indicated that protease-cleavable conjugates are more stable than disulfides, although all of them can be engineered.

Standard chemotherapy shows low response rates and short progression-free survival among patients with pretreated metastatic TNBC. However, recent clinical studies showed that sacituzumab govitecan (an antibody–drug conjugate) is well engineered. This conjugate was heavily pre-administered to patients with metastatic TNBC. The outcomes showed improved primary endpoints with fewer complications. The secondary endpoints were progression-free and overall survival, which were found to be improved [95][96].

2.6.2. Liposomes

Liposomes are spherical vesicles (ranging from 50 to 500 nm in size) with a lipid bilayer, and are generated while the lipid connects with the aqueous solution. The most commonly employed lipids are phosphatidylcholine-enriched phospholipids, which produce liposomes. They can be potentially stabilized by strengthening the bilayer with an amphiphilic, long-chain polymer holding PEG at one end, which can simultaneously decrease opsonization and lengthen the circulation time in the blood [82]. Polymeric compounds with appropriate end groups for attachments with antibodies or ligands can also be implanted into the liposome bilayer; therefore, construction-targeted delivery is conceivable. As liposomes bilayers likely mimic those of cells, they can rapidly merge with the plasma membrane [81]. When they are internalized by cells through endocytosis or passive diffusion, the lipid bilayer undergoes rapid degradation due to the acidic environment generated by the endosomes and lysosomes [63].

As shown in the illustration in **Figure 2**, several engineered polymeric liposomes loaded with therapeutic drugs have used for BC [97][54][98]. Passive tissue targeting is achieved by the extravasation of NPs due to the increased vascular permeability of the BC [99]. Active cellular targeting can also be achieved using the engineered liposomes of NPs with ligands that promote cell-specific recognition and binding. Based on cellular penetration, NPs can release their contents close to the BC cells [53]. Cyclic octapeptide LXY (Cys-Asp-Gly-Phe (3,5-DiF)-Gly-Hyp-Asn-Cys)-attached liposomes carrying the therapeutic drugs doxorubicin and rapamycin targeted over-expressing integrin-α3 in a TNBC-bearing mouse model [100]. These outcomes strongly indicate that targeted combinational therapy can provide a rational approach to improve the therapeutic outcomes of TNBC. Similarly, increased antitumor activity in a TNBC xenograft mouse model has

also been revealed with doxorubicin and sorafenib-loaded liposomes [101]. Taken together, research on engineered polymeric liposomes suggests the potential efficacy of the drug-loaded polymer-link liposomes platform in BC therapy.

2.6.3. Lipid–Hybrid Polymer

Polymer NPs are perhaps the most widely studied carrier systems targeting drug delivery. Various synthetic polymers have been employed and investigated based on the potential effects of their hydrophobic and biodegradable nature. Furthermore, many natural polymers (such as chitosan, poly (lactic acid), poly (glycolic acid), poly (lactic-*co*-glycolic acid), gelatin, poly (alkyl cyanoacrylates), and poly (*ε*-caprolactone)) have also been employed for drug delivery in BC treatment [102][103]. When liposomes and polymeric NPs were developed, a new class of lipid-hybrid NPs providing the characteristics of both systems was also established. These lipid-hybrid NP incorporate high drug-encapsulation materials and show precise drug release, with outstanding targeting capabilities. Non-targeted drug delivery of platinum–mitaplatin using poly-D, L-lactic-*co*-glycolic-acid–block-PEG NPs resulted a higher degree of tumor inhibition in the TNBC xenograft mouse model [104].

Recently, anastrozole-loaded PEGylated polymer–lipid hybrid NPs showed high entrapment efficacy (80%), size consistency, and relatively low zeta-potential values (−0.50 to 6.01), and were found to induce apoptosis in ER-positive BC cells [105]. Similarly, another study showed that nanocarriers of a polymer–lipid hybrid encapsulating psoralen optimized its hydrophilic nature and bioavailability, which improved systemic delivery [106]. Li et al. [107] developed salinomycin-loaded polymer–lipid hybrid anti-HER2 NPs and investigated the anti-tumor activity. The outcome showed that the polymer–lipid hybrid was a promising candidate targeting both HER2 + breast CSCs and BC cells.

2.6.4. Dendrimers

Dendrimers are another important type of synthetic nanocarrier (with size ranges from 10 nm to 100 nm) generated by branched monomers of divergent or convergent synthesis. They appear as liposomes, showing a cavity-enriched spherical shape with a hydrophobic core and hydrophilic periphery, and are a distinctive carrier for the delivery of siRNA [108]. Wang et al. [109] established an antisense oligo attached to poly (amidoamine) dendrimers with links to the receptors of vascular endothelial growth factor, and showed a significant decrease in tumor vascularization in the TNBC xenograft mouse model. Another study reported the novel dendrimer G4PAMAM conjugated with GdDOTA and DL680, administered in TNBC xenograft mice as a model for tumor imaging and drug delivery. The outcome of MRI scan and infra-red fluorescence imaging showed the emission of NPs and a significant fluorescence signal in the tumor, demonstrating the selective delivery of a small-sized (GdDOTA)42-G4-DL680 dendrimeric agent to TNBC tumors that circumvented other adjacent primary organs [110]. Hence, the dendrimer is a potential nanocarrier and targeted diagnostic and therapeutic agent in the TNBC tumor mouse model.

3. Engineered NPs Increases the Circulation Half-Life

In principle, an NP-based delivery system should integrate high drug loading capability, a long circulation half-life, effective targeting capacity, discharge programmability, stimuli receptiveness, and diagnostic features. Negatively or neutrally charged NPs generally have a longer blood half-life than positively charged NPs. Using synthetic materials, the surface charges and hydrophobicity of NPs can be suitably tuned to elevate their blood half-life. Based on a longer circulation half-life, NPs can pass the lesion multiple times, with a greater chance of accruing on the lesion site [111][112]. NPs larger than 200 nm are favorably excreted by the spleen. Hence, by selecting a suitable size, surface modifications in the form of PEGylation or the use of rigid NPs will result in the longest blood half-life (2–100 folds), allowing accrual in the spleen with a high percentage and thus the improvement of overall pharmacokinetic parameters [113]. For instance, PEGylated liposomal doxorubicin exhibited a prolonged circulation half-life, which is alleged to be associated with enhanced therapeutic efficacy in BC. Studies revealed that about 50% of polystyrene NPs with the size of 250 nm and coated with poloxamine 908 accrued in the spleen almost 24 h after injection [114]. To avoid clearance by the spleen or MPS, the surface of NPs should to be cautiously engineered to avoid or at least alleviate opsonization [115].

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