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REVIEW

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Surface-modified lipid-based nanocarriers as a pivotal delivery approach for cancer therapy: application and recent advances in targeted cancer treatment

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Abstract

Background Nanoparticle-mediated drug delivery aims to target specific cells, addressing the challenge that many drugs lack the necessary properties to reach their intended targets effectively. Lipid-based nanocarriers considered as a promising drug delivery due to their biocompatibility and ability to encapsulate various drugs. Surface modifications, including the attachment of polyethylene glycol for stability and the conjugation of targeting ligands (e.g., antibodies, peptides) for specific delivery, play a crucial role in enhancing the interaction of these nanocarriers with biological environments. These modifications improve cellular uptake and targeted delivery, thereby increasing therapeutic efficacy and reducing side effects. This review will explore various surface modification techniques and their impact on the performance of lipid nanocarriers in drug delivery.

Main body Lipid-based nanodelivery platforms have garnered significant interest due to their notable characteristics, including their ability to accommodate high drug loads, reduced toxicity, improved bioavailability, and compatibility with biological systems, stability within the gastrointestinal environment, controlled release capabilities, streamlined scaling up processes, and simplified validation procedures. Targeted lipid-based nanocarriers represent a significant advancement over non-targeted counterparts in cancer therapy. Unlike non-targeted systems, which distribute drugs indiscriminately throughout the body, targeted lipid-based nanocarriers can be engineered with ligands or antibodies to specifically recognize and bind to tumor-associated markers, enabling precise drug delivery to cancer cells. This targeted approach enhances therapeutic efficacy while minimizing adverse effects on healthy tissues, thereby offering a promising strategy for improving the outcomes of cancer treatment.

Conclusion The authors in this review provide an overview of preclinical research on diverse lipid-based nanocarriers, such as liposomes, solid lipid nanocarriers, and lipid polymer hybrid nanoparticles. The customization of these carriers using various surface modifiers is discussed, including folic Acid, peptides, polysaccharides, transferrin, and antibodies. Surface-modified nanocarriers offer regulated discharge, improved penetration capability, and precise drug conveyance. This work compiles recent instances of emerging surface-modified lipid-based nanocarrier systems and their applications, sourced from existing literature. Novel approaches to surface engineering of these nanocarriers, aimed at enhancing their specificity and efficacy in targeted drug delivery, were discussed. Key advancements in this field, such as improved targeting mechanisms and significant therapeutic outcomes demonstrated in preclinical studies, were highlighted. Additionally, critical gaps that require attention include long-term

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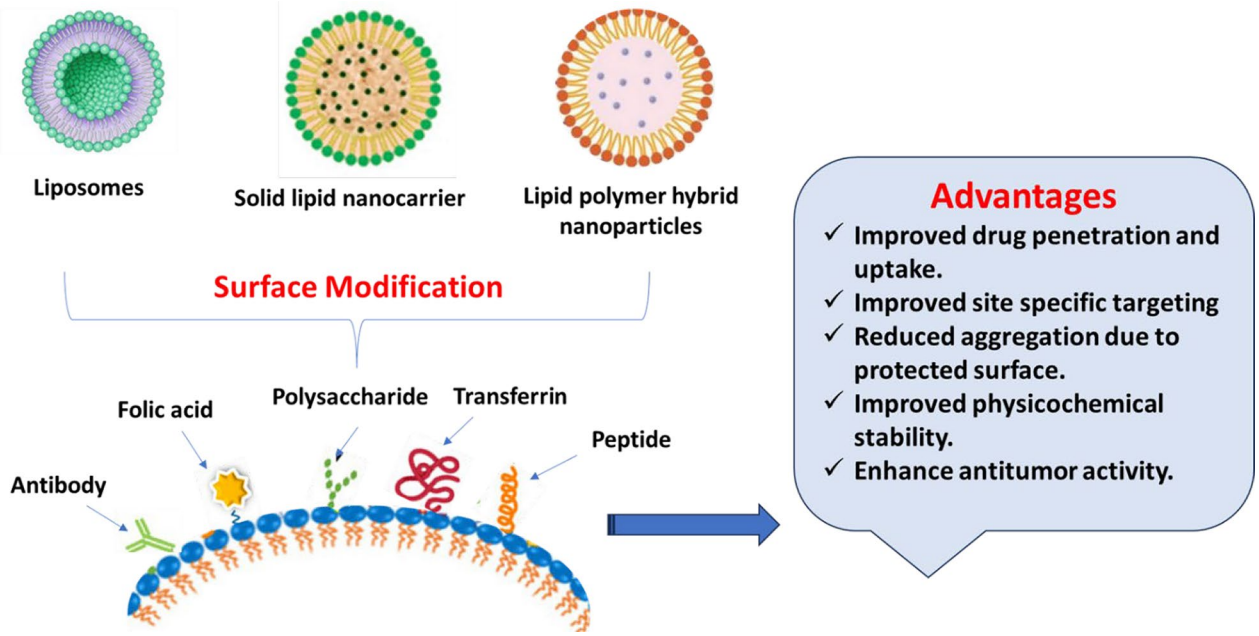
stability, biocompatibility, scalable production methods, regulatory challenges, and the necessary steps to transition from bench to bedside.

Keywords Lipid-based nanocarriers, Surface modifiers, Targeted lipid, Cancer treatment

Graphical abstract



1 Background

In recent years, progress in developing novel medications has slowed due to substantial costs and lengthy discovery periods. Additionally, the prevalence of adverse reactions and drug resistance underscores the need to enhance the safety and efficacy balance of established pharmaceuticals. One viable approach to tackle these obstacles is ensuring the precise delivery of drugs to their intended sites of action [1, 2]. This involves achieving targeted accumulation of drugs at the appropriate locations, in optimal quantities, and at the correct timing [2]. Nanocarriers, characterized by their small size, narrow size distribution, and high surface-to-volume ratio, exhibit enhanced cellular penetration and interaction with biomolecules, thereby improving absorption, bioavailability, and stability [3, 4]. They offer the advantage of precise targeting, and facile surface modification for active targeting purposes [4]. These nanocarriers are categorized into lipid-based, polymer-based, viral nanoparticles, or inorganic nanoparticles, based on their constituent materials [5]. Among these, the lipid-based nanocarrier system represents the forefront of drug delivery technology, offering advantages such as easy large-scale production, biocompatibility, and biodegradability owing to its inherent material characteristics [6]. Additionally, it boasts low toxicity, enables controlled, and tailored drug release, [7] enhances drug solubility and accommodates both hydrophilic and lipophilic drugs [8].

1.1 Objective

This review focuses on the role of surface modifications in enhancing the targeting capabilities of lipid-based nanocarriers for cancer therapy. It aims to provide a comprehensive overview of various surface modification techniques, their applications in targeted drug delivery, and recent advances in this field.

2 Lipid-based nanocarriers and surface modifications

Lipid-based nanocarriers have emerged as a versatile and promising platform for drug delivery, gene therapy, and diagnostics. Utilizing naturally occurring lipids, these nanocarriers encapsulate therapeutic agents to enhance stability, bioavailability, and targeting capabilities. Major

Table 1 Systematic comparison of the advantages, disadvantages, and specific applications of the major types of lipid-based nanocarriers

Criteria	Property	liposomes	SLNs	LPHNs
Advantages	Stability	Moderate	High	High
	Drug Encapsulation	Hydrophilic and hydrophobic drugs	Mainly hydrophobic drugs	Hydrophilic and hydrophobic drugs
	Biocompatibility	High	High	Moderate to High
	Controlled Release	Yes	Yes	Yes
Disadvantages	Production Complexity	High	Moderate	High
	Cost	High	Low to Moderate	High
	Shelf Life	Short	Longer compared to liposomes	Longer compared to liposomes
	Special issue	Quickly cleared by the mononuclear phagocyte system (MPS)	Lipids can undergo polymorphic transitions, affecting drug release profiles	Potential Toxicity
Uses	Drug deliver applications	Cancer, vaccines, gene therapy, immunotherapy	Topical, oral, ocular delivery	Cancer, gene delivery, multidrug delivery

types include liposomes, SLNs, and LPHNPs (Table 1). Surface modifications for lipid-based nanocarriers are techniques used to alter the surface properties of lipid nanocarriers to improve their performance for drug delivery applications. These modifications can enhance the stability, targeting ability, and overall efficacy of the nanocarriers.

2.1 Liposomes

Liposomes, initially introduced in 1964, are molecular assemblies created from amphiphilic components, like polar lipids, dispersed within water. These structures, resembling cell membranes in composition, and structure, form bilayer spheres [9]. With an aqueous core, liposomes feature core–shell structures, allowing the encapsulation of both hydrophilic, and hydrophobic substances [10]. They are straightforward to prepare and can be tailored for various uses by adjusting their composition, size, and lamellarity. Additionally, liposomes can be modified with different molecules, giving them specific functionalities for a wide array of applications [11]. They have found utility in diverse fields including drug delivery, vaccine development, the exploration of protocells, and the origins of life. Liposomes can also be loaded with nanocarriers of different types, and sizes, expanding their potential applications even further due to their exceptional characteristics, and properties. For all the mentioned advantages of liposomes, several commercially available formulations have been developed such as Doxil® (doxorubicin HCl liposome injection) is well known for improving the delivery of doxorubicin to cancer cells while minimizing systemic toxicity and is used in treating breast cancer, ovarian cancer, and Kaposi's sarcoma. Additionally, DepoCyt® (cytarabine liposome injection) targets lymphomatous meningitis by delivering cytarabine more effectively to the central nervous system. Similarly, Myocet® (doxorubicin liposome injection) offers similar benefits for breast cancer treatment, enhancing drug stability and reducing side effects. These formulations showcase the clinical efficacy and impact of liposomal technology in cancer therapy [12].

2.1.1 Folic acid targeted liposomes

Phospholipid-anchored folate conjugates direct liposomes to tumors with folate receptors, offering a promising chemotherapy delivery strategy [13]. Epithelial neoplastic cells, including those found in various cancers such as kidney, lung, colon, breast, cervical, and brain, commonly exhibit overexpression of two main forms of FA receptors (FR a and FR b) on their surfaces [14]. Notably, normal tissues generally express minimal levels of FRs. Folate receptors (FRs) are glycoproteins rich in cysteine with a high affinity for binding folate. They facilitate the uptake of folate through receptor-mediated endocytosis. Once FRs ligands bind, the plasma membrane envelops the receptor-ligand complex, creating an endosome. This specific binding and uptake mechanism makes FRs an attractive target for drug delivery in cancer therapy [15]. FA stands out as a preferred targeting ligand due to its distinct advantages over other ligands, including its high specificity towards tumors, high tumor cell penetration, lack of immunogenicity, enhanced stability, and ease of functional group modification [16]. FA-modified liposomes was fabricated to deliver 5-fluorouracil (5FU) to tumor cells [17]. The liposomes were prepared using the thin-layer method with PC/cholesterol and PC/cholesterol/FA-PEG-DSPE at molar ratios of 2:1 and 2:1:0.031, respectively. Initially, FA was conjugated with amino-PEG acetic acid using EDC and NHS as coupling reagents, yielding FA-PEG-COOH.

Subsequently, FA-PEG-COOH was conjugated with 1,2-distearoyl-sn-glycero-3-phosphorylethanolamine (DSPE) in the presence of EDC and NHS to produce the FA-PEG-DSPE conjugate. Studies conducted using CT26, a murine colorectal carcinoma cell line, revealed that the targeted liposomes exhibited elevated cellular uptake and enhanced reactive oxygen species (ROS) production compared to the free drug when evaluated in colon cancer cells. Additionally, the half-maximal inhibitory concentration (IC_{50}) values, a critical metric for evaluating the inhibitory strength of a substance and determining the potency and potential efficacy of drugs, were measured and found to be very low. Hemolysis assays confirmed that the liposomes were biocompatible with blood. In vivo experiments demonstrated that the folate-targeted liposomes were more effective at inhibiting tumor growth than the free drug [17]. Moreover, in another study FA -modified liposomes were loaded with curcumin (Cur) to target and treat breast cancer. The goal was to enhance the effectiveness of Cur against breast cancer cells by specifically targeting FR that are abundant in these cells [18]. The researchers developed and tested both the folate targeted liposomes and untargeted ones using cell cultures in 2D and 3D models. Results showed that folate targeted liposomes had a significantly stronger toxic effect on the cancer cells compared to free Cur and untargeted formulation. Furthermore, cellular uptake assays indicated that modified liposomes had better penetration into the cells and spheroids compared to the other formulations, suggesting that folate targeted liposomes improved their ability to be internalized by breast cancer cells through interaction with FR [18]. Additionally, for improving the effectiveness of vincristine (Hanfang Pharmaceutical Co.) against multidrug-resistant cancers, FA-linked PEGylated liposomes were used to encapsulate vincristine for treating resistant cancers, the authors aimed to enhance its antitumor activity. Their findings showed that this delivery method had the highest toxicity against resistant cancer cells compared to naked liposomes. Additionally, it effectively inhibited tumor growth in both laboratories, animal studies, and induced cell death [19].

2.1.2 Peptide targeted liposomes

Peptides have emerged as a promising tool for targeting cancer cells due to their unique properties and versatility. Key perspectives on their use in cancer cell targeting include their high specificity, which reduces impact on healthy cells and minimizes side effects. Additionally, their versatile functionalization allows them to be tailored to enhance stability, binding affinity, and resistance to enzymatic degradation [20]. Most peptide-targeted liposomes have been created using peptides that are already known to bind to specific receptors [21]. Peptides exhibit high specificity due to their unique amino acid sequences, which determine their three-dimensional structure and receptor affinity. Upon binding, the receptor undergoes conformational changes, initiating intracellular signaling cascades and recruiting adaptor proteins. The receptor-ligand complex is often internalized through clathrin-mediated endocytosis, with clathrin proteins forming a coated pit on the plasma membrane's inner surface. This process ensures targeted delivery and minimizes off-target effects, improving therapeutic outcomes by releasing the therapeutic agent within target cells [22]. Numerous peptides possess both the structure and biological characteristics necessary to guide liposomes toward tumor tissues. Utilizing a tumor metastasis targeting (TMT) peptide to deliver liposomes containing doxorubicin (DOX, Hisun Pharmaceutical Co.) to highly metastatic cancer cells was designed specifically to highly metastatic tumors [23]. The researchers showed that these targeted nanocarriers had favorable characteristics such as drug release behavior as well as particle size when tested in laboratory settings. They are taken up more quickly by highly metastatic cancer cells through a receptor-based process, and they effectively target highly metastatic tumors both in living organisms, and in laboratory samples. Furthermore, the study indicated that the designed targeted liposomes significantly improved the effectiveness of DOX in slowing down the growth of xenograft tumors and causing cancer cell death, with minimal side effects [23]. To address the challenges posed by the acidic conditions and cancer-associated fibroblasts (CAFs) in the tumor microenvironment (TME), which can impact the stability, release profiles, and uptake of nanocarriers, Chen and colleagues developed targeted liposomes. This nanocarrier, called TR-PTX/HCQ-Lip, featured a tandem peptide targeting integrin αvβ3 and was designed to respond to the acidic conditions of tumor microenvironments. It is engineered to deliver a combination of the autophagy inhibitor hydroxychloroquine and the chemotherapy drug paclitaxel (PTX) to both tumor cells and CAFs. Their research demonstrated that these liposomes effectively target and penetrate pancreatic tumors, inhibit autophagy, and reduce stromal fibrosis, leading to improved therapeutic outcomes in various pancreatic cancer models [24]. Vakhshiteh et al. [25] developed liposomes modified with cyclic RGD peptides and PEG to deliver miR-34a, a known tumor suppressor microRNA, directly to breast cancer cells. These liposomes selectively targeted cells expressing integrin receptors, which are abundant in breast cancer. The results found that the targeted liposomes were significantly more internalized by breast carcinoma cells, leading to increased miR-34a

accumulation. Consequently, this resulted in notable inhibition of tumor cell growth, migration, and invasion, along with a reduction in the proportion of cancer stem-like cells [25]. CAFs hinder drug delivery within tumors and deteriorate the TME. Directly depleting CAFs risks tumor metastasis. This study explores reversing epithelial–mesenchymal transition (EMT) in liver cancer by using CFH peptide (CFHKHKSPALSPVGGG)-decorated liposomes containing oxymatrine (CFH/OM-L) to target Tenascin-C. CFH/OM-L upregulates E-cadherin and downregulates vimentin, N-cadherin, and snail protein, effectively reversing EMT. Combined with an icaritin-loaded lipid complex, it enhances anticancer efficacy, reduces collagen levels, and improves nanocarrier penetration in tumor models. CFH/OM-L inactivates rather than kills CAFs, reducing metastasis risk and reprogramming the TME to activate immune cells. This approach offers a promising strategy for combination therapies in hepatocellular carcinoma [26]. In a recent study cationic liposome was developed as a targeted delivery system by attaching a peptide-based ligand (THRPPMWSPVWP) that binds specifically to transferrin receptors at the blood–brain barrier (BBB). This liposome was then combined with a CRISPR/Cas9 plasmid designed to knock down P-glycoprotein (P-gp). The peptide-conjugated liposomes showed significantly higher uptake in bEND.3 cells compared to those without the peptide. Additionally, the CRISPR/Cas9 liposomes effectively knocked down P-gp, leading to increased P-gp-related ATP activities in the treated cells [27].

2.1.3 Polysaccharides targeted liposomes

Polysaccharides play an important role in the field of pharmaceutical industry, being widely utilized in various applications. Cellulose derivatives, alginate, hyaluronic acid (HA), mannans, and dextrans are commonly used to modify nanocarriers, creating targeted delivery systems for drugs, vaccines, theranostics, and immune-therapeutics [28]. The mechanism of polysaccharide-receptor interactions is influenced by the distinct arrangement of sugar residues. Receptors have carbohydrate-binding domains that identify specific glycan structures through various non-covalent interactions. For instance, receptors like C-type lectin receptors and galectins possess specialized carbohydrate-binding domains (CBDs) that enable the recognition and binding of polysaccharides. When a polysaccharide binds to the receptor, it induces conformational changes in the receptor, which can trigger intracellular signaling pathways. This understanding is crucial for optimizing the design of polysaccharide-modified nanocarriers to enhance their targeting and therapeutic efficacy [29]. A particular focus is placed on the modification of liposome surfaces with polysaccharides, representing a unique aspect of bioconjugation chemistry. A novel, and challenging approach involves the use of chemistry for the orthogonal binding of polysaccharides onto the surface of liposomes, aiming to enhance the development of drug, and vaccine targeting nanosystems [30]. Innovative method for producing sucrose-coated liposomes using a microfluidic system was developed, which improves the delivery of drugs to cancer cells. Specifically focusing on loading liposomes with berberine hydrochloride (BBH, ACEF Italy), a natural compound known for its anticancer properties, particularly against triple-negative breast cancer cells [31]. The results revealed that sucrose-coated liposomes exhibited notably stronger antiproliferative effects on MDA-MB-231 cells compared to non-coated ones. The results confirmed that the presence of sucrose on the liposome surface increased drug uptake by cancer cells, thus improving the therapeutic effectiveness of encapsulated BBH. In this research, liposome surfaces were modified with disaccharide molecules, such as sucrose or maltose, which interact with lectins (carbohydrate-binding proteins) found on the surface of many cancerous cells [32]. The study demonstrated that these decorated liposomes enhance the uptake of liposomes into different cancer cell lines through the mechanism of endocytosis. Moreover, disaccharide-modified liposomes loaded with the anticancer drug DOX exhibit increased cytotoxicity against diverse cancer cells compared to unmodified liposomes. Consequently, the authors suggest that disaccharide-modified liposomes hold promise as cancer-targeting carriers, enhancing intracellular uptake, and cytotoxicity through lectin-mediated endocytosis [32].

2.1.4 Transferrin-targeted liposomes

Naturally occurring proteins like Tf have garnered significant interest in drug targeting due to their non-toxic, biodegradable, and non-immunogenic properties. Additionally, their high abundance of receptors on cell surfaces enables precise targeting to specific sites [33]. The high affinity of transferrin for TfRs allows nanocarriers to efficiently bind to and target overexpressed receptors on cancer cells. Following this binding, the transferrin-coated nanocarriers are internalized via clathrin-mediated endocytosis, mimicking the natural transferrin-TfR complex. Inside the cancer cells, the nanocarriers release their therapeutic payload in response to the acidic pH of the endosome, enabling controlled release of the agents and improving therapeutic efficacy while reducing off-target effects [34]. The effective cellular uptake through the Tf pathway has demonstrated promise in delivering anticancer drugs, [35] therapeutic genes, and proteins into highly proliferating malignant cells that exhibit heightened expression of Tf receptors (TfRs). A study was

conducted to create an innovative drug delivery method for glioblastoma. The researchers utilized Polyethylene glycol-coated (pegylated) liposomes to encapsulate resveratrol (RES, Sigma Aldrich (St. Louis, MO)) [36]. To target cancer cells specifically, the liposomes were modified with Tf components, taking advantage of the increased presence of TfRs in glioblastoma multiforme (GBM), Fig. 1. Results indicated that these modified liposomes, exhibited greater cytotoxicity, and prompted higher levels of apoptosis in GBM cells in comparison with free RES or RES-L. In a mouse model xenograft of GBM, Tf modified liposomes were notably more effective in impeding tumor growth, and enhancing survival rates. The authors concluded that the developed liposomes containing RES demonstrate promising efficacy both in laboratory settings and animal models [36]. Fernandes et al. [37] developed and characterized liposomes loaded with docetaxel and functionalized with Tf to precisely target prostate cancer cells. Encapsulation efficiency for docetaxel was approximately 69% for functionalized liposomes and 37% for non-functionalized ones. Functionalized liposomes demonstrated enhanced uptake by prostate cancer cells compared to non-functionalized ones. In vitro cytotoxicity assays revealed that functionalized liposomes were more effective against prostate cancer cells than the commercial formulation [37]. In another study theranostic Tf targeted liposomes intended for the treatment of brain cancer were developed. This investigation utilized D-alpha-tocopheryl PEG 1000 succinate mono-ester (TPGS) liposomes as carriers for brain theranostics [38]. These liposomes incorporate Tf as a ligand recognizing specific tumor cell markers, and were loaded with both docetaxel (Neon Laboratories Ltd) and quantum dots [39]. In vivo experimentation suggests that these liposomes show potential as vehicles for brain theranostics because of their small size for delivery and ability to penetrate and offering enhanced and prolonged brain targeting of docetaxel and quantum dots compared to non-targeted formulations [38].

2.1.5 Antibody-targeted liposomes

Antibody-targeted nanocarriers are advanced drug delivery systems designed to enhance the specificity and efficacy of therapeutic agents. These nanocarriers are engineered with antibodies or their derivatives that specifically bind to antigens or receptors overexpressed on cancer cells. The Y-shaped glycoprotein of the antibody recognizes and binds to a unique epitope on the receptor protein present on the surface of the target cells. This binding interaction is mediated by the variable regions of the antibody, which are highly specific to the antigen. The effectiveness of this interaction is often augmented by the increased surface expression of the receptor on the targeted cancer cells. Once bound, the antibody-receptor interaction can trigger various cellular responses, such as internalization of the nanocarrier and subsequent release

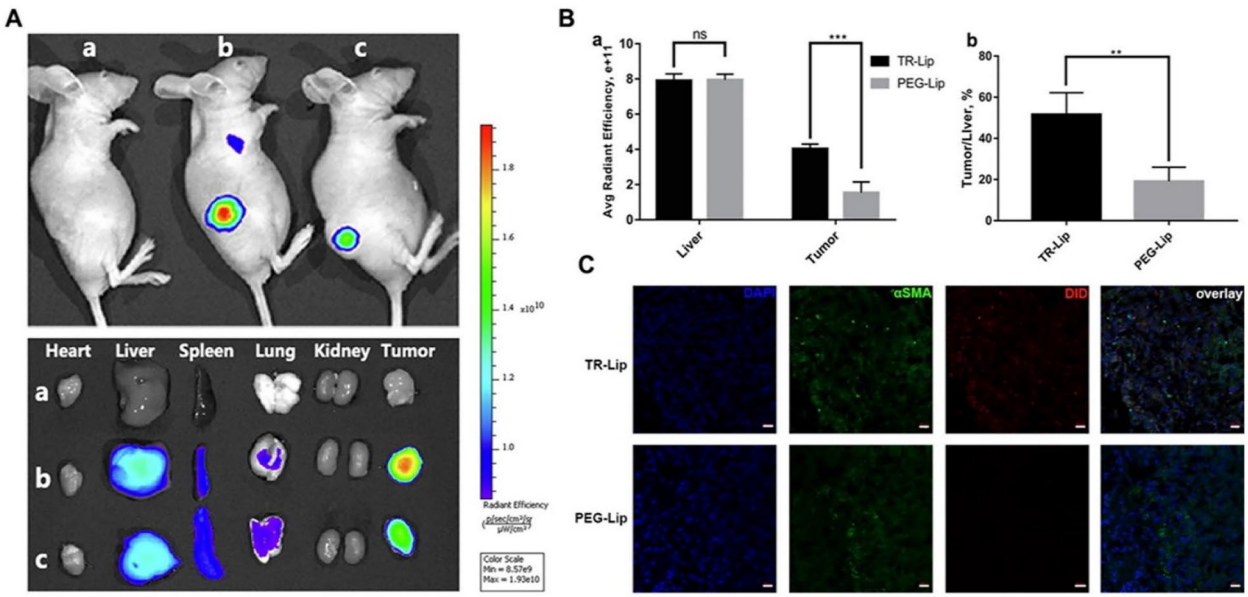


Fig. 1 Tf-directed liposomes containing RES aimed at addressing glioblastoma. These targeted formulations showed superior pharmacokinetics (PK), and brain accumulation properties as well as improved in vitro cytotoxicity, and uptake also exhibited superior effectiveness compared to the unencapsulated drug or non-targeted liposomes in both in vitro, and animal studies. Adapted with permission from ref. [24] copyright (2024) Elsevier

of the therapeutic agent, depending on the specific nature of the antibody-receptor engagement [40]. Monoclonal antibodies (mAbs) or their derived compounds frequently serve as the designated ligands within ligand-targeted liposomes (LTLs) [41]. When LTLs are enhanced with mAbs or their derivatives, they are categorized as immunoliposomes [42]. These specialized liposomes are engineered to enhance the therapeutic efficacy of conventional drugs. The advancement of immunoliposomes, combining antibody engineering with liposome technology, is a promising frontier in research [43]. A novel approach to targeted cancer therapy involves the creation of DOX-loaded liposomes with extended circulation times, modified with the monoclonal nucleosome (NS)-specific 2C5 antibody (mAb 2C5). By coating the liposomes with PEG, a hydrophilic polymer, they become adept at accumulating in solid tumors via the enhanced permeability and retention effect. In vitro experiments demonstrated that these modified liposomes, laden with DOX, exhibited superior efficacy in killing various tumor cells in comparison with the non-targeted liposomes carrying the drug [44]. Lukyanov et al. [44] investigated the potential for attaching an anticancer mAbs 2C5 to the liposomes loaded with Doxil Pharmaceutics (West Roxbury, MA). Results indicated that mAb 2C5-targeted liposomes exhibited increased accumulation in tumors, leading to significantly superior therapeutic effects in vivo compared to all Doxil control treatments. Tumor weights following mAb 2C5-Doxil treatment were reduced to only 25% to 40% of those in control groups, highlighting the effectiveness of 2C5-targeted Doxil in delivering drugs specifically to tumors and enhancing therapy efficacy. In another formulation liposomes were modified with anti-CD44 antibodies in order to improve the effectiveness of timosaponin AIII. The results showed that the anti-CD44 antibody-modified liposomes displayed significantly heightened cytotoxicity, and more potent suppression of tumor growth compared to their unmodified counterparts. This research suggests that anti-CD44 antibody-modified liposomes hold promise as a treatment option for CD44-positive cancers, offering substantial antitumor benefits [45]. Table 2 demonstrates summary for surface modified liposomes for cancer therapy. By addressing the role of TME in influencing the effectiveness of liposomes delivery, tumor-associated macrophages (TAMs) are considered one of the most aggressive barriers to effective cancer treatment. These macrophages, which are a major component of the TME, often support tumor progression by promoting angiogenesis, suppressing immune responses, and enhancing tumor cell invasion and metastasis. Chen et al. [46] devised a combined treatment strategy for TME using a co-delivery liposome system containing the mTOR inhibitor rapamycin and the antiangiogenesis drug regorafenib to simultaneously regulate tumor metabolism and angiogenesis. By dual modification with a PD-L1 antibody and mannose ligand, the liposomes targeted TAMs and cancer cells overexpressing PD-L1 and mannose receptors. This delivery system effectively reduced glycolysis, repolarized TAMs, suppressed angiogenesis, reconfigured immune cells, and consequently inhibited tumor growth. A recent study demonstrated that delivering CRISPR/Cas9 via liposomes effectively targets HPV, inducing autophagy and immune activation. In vivo, HPV-targeting guide RNA-liposomes increased CD8 + T cell infiltration, elevated proinflammatory cytokines, and reduced regulatory T cells and myeloid suppressor cells. Combining these liposomes with immune checkpoint inhibitors and anti-PD-1 antibodies enhanced antitumor effects and induced immune memory in cervical cancer models [47].

2.2 Solid lipid nanoparticles

Solid lipid-based nanoparticles exhibit considerable promise for transporting pharmaceuticals, and genetic material. These lipidic system offer an encouraging avenue for advancing new therapies, primarily due to their simplicity of formulation, and distinct size-related characteristics [48]. Their capacity to encase drugs, and nucleic acids, alongside their facile surface modification, renders them appealing nanosystems for precise drug, and gene delivery. These nanocarriers can be given through different methods such as through the skin, oral, parenteral, and pulmonary, expanding their applicability. In comparison with alternative delivery systems, lipidic nanocarriers amalgamate several benefits such as minimal toxicity, controlled release of enclosed substances, and high biocompatibility. They have demonstrated effectiveness in delivering drugs that are poorly water-soluble or insoluble, reducing unintended side effects, and enhancing the targeted delivery of active agents [49].

2.2.1 Folic acid-targeted SLNs

Utilizing FA ligands for targeting SLNs presents a promising approach to address the issue of non-selectivity in cancer therapy. Consequently, FA has been widely employed for nanocarriers modification to enhance endocytosis via FRs. Yassemi et al. [50] discussed the development of SLNs to serve as carrier SLNs s for letrozole (LTZ, Tofigh Daru Co. (I. R. Iran)) and modified with FA. Scanning electron microscopy (SEM) revealed the uniform, and spherical morphology of both SLNs-LTZ, and FA-SLNs-LTZ. Results from cell culture experiments demonstrated that FA-SLNs-LTZ exhibited significantly higher cytotoxicity against MCF-7 cancer cells compared to SLNs-LTZ, and free

Table 2 Surface modified targeted liposomes for cancer therapy

Target agents	Drugs	Cancer type	Main outcome	References
Liposomes				
Folic acid	5-fluorouracil	Colon cancer	FA-modified liposomes present a promising, effective, and safe strategy for targeted chemotherapy in colon cancer	[17]
	Curcumin	Breast cancer	The liposomes markedly increased cytotoxicity and cellular internalization in breast cancer cells compared to free Cur and unmodified liposomes, indicating enhanced targeting and therapeutic potential against breast cancer	[18]
	Vincristine	Multidrug-resistant cancer	Demonstrating significant potential in targeting and treating multidrug-resistant cancers, the approach exhibited enhanced cytotoxicity and inhibition of tumor growth both in vitro and in vivo	[19]
Peptide	Doxorubicin	Highly metastatic cancer cells and tumors	Significantly enhancing the delivery of DOX to highly metastatic cancer cells via endocytosis mechanisms, this approach leads to enhanced tumor inhibition and regression of side effects compared to unmodified liposomes	[23]
	Paclitaxel and irinotecan	Pancreas cancer	These liposomes exhibited superior targeting and penetration abilities, effectively suppressing autophagy in both pancreatic cells and cancer-related fibroblasts, while enhancing therapeutic effects in pancreatic cancer models	[24]
	Microrna-34a	Breast cancer	Significantly inhibiting tumor cell growth, migration, and invasion, these interventions effectively reduced the cancer stem-like population in breast carcinoma cells	[25]
	P-gp CRISPR/Cas9	Brain cancer	CRISPR/Cas9 liposomes effectively knocked down P-gp, leading to increased P-gp-related ATP activities in the treated cells	[29]
Polysaccharide	Berberine hydrochloride	Breast cancer	Liposome formulations decorated with sugar showed significantly higher antiproliferative effects on triple-negative breast cancer cells	[30]
	Doxorubicin, and irinotecan	Breast, non-small cell lung, and colon cancers	Demonstrated potent antitumor efficacy in mammary carcinoma xenografts, significantly enhancing tumor distribution and therapeutic outcomes compared to single drug-loaded formulations	[31]
	Doxorubicin	Liver, breast lung, and cervical cancers	Enhancing intracellular cytotoxicity and the uptake of DOX in cancer cells via lectin-mediated endocytosis, these findings suggest their potential as promising cancer-targeting carriers	[32]

Table 2 (continued)

Target agents	Drugs	Cancer type	Main outcome	References
Transferrin	Resveratrol	Glioblastoma cancer	Demonstrated favorable in vitro and in vivo efficacies, significantly enhancing drug delivery and therapeutic outcomes in glioblastoma models compared to non-targeted treatments	[36]
	Docetaxel	Prostate cancer	Showing higher uptake by prostate cancer cells and increased cytotoxicity compared to non-functionalized liposomes, these formulations suggest promising potential for targeted cancer therapy	[37]
	Docetaxel	Brain cancer	Enhancing the delivery of docetaxel and quantum dots across the blood–brain barrier for improved brain cancer therapy, these carriers demonstrate promising potential for brain theragnostics	[38]
Antibody	Doxorubicin	Metastatic, ovarian breast cancer, and AIDS-related Kaposi's sarcoma,	Exhibited increased binding to various tumor cells and more efficient killing in vitro compared to non-targeted liposomes	[43]
	Doxorubicin	Breast, colon, and prostate cancer	Demonstrated increased tumor accumulation and reduced tumor weights in various tumor models compared to controls	[44]
	Timosaponin AIII	Breast, lung, ovarian, and liver cancer	Significantly enhancing the targeted delivery and antitumor activity of timosaponin against CD44-positive cancer cells, without detectable toxicity	[45]
	CRISPR/Cas9	Cervical cancer	Enhanced antitumor effects and induced immune memory in cervical cancer models	[49]

LTZ, with an IC_{50} value of 81 ± 0.89 nM. Overall, this study suggests that FA-SLNs-LTZ holds potential to trigger programmed cell death in a precise target-oriented fashion while minimizing adverse effects on the entire system [50]. Another study aimed to enhance the therapeutic potential of Chrysin (CHY) by loading it onto SLNs and then decorating these nanocarriers with folate-bound chitosan. The targeted SLNs loaded with CHY exhibited scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) (IC_{50}: 108.7 µg/mL), and 2,2-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid (ABTS) (IC_{50}: 123.73 µg/mL) free radicals, as well as suppressing angiogenesis. The observed up-regulation of Bax, and caspase 9 genes, along with findings from fluorescence staining, and cell cycle analysis, provided further evidence of the pro-apoptotic properties of CHY-SCF-NPs. These findings suggest that the targeted SLNs loaded with CHY hold promise as a further exploration in preclinical, and clinical studies, particularly for pancreatic cancer treatment [51]. Chitosan-coated SLNs were fabricated to co-load trans-resveratrol (RSV) and ferulic acid (FER), and they were conjugated with folic acid (FA) for targeting colon cancer, utilizing Sulfo-NHS and EDC as coupling reagents. In vitro studies indicated that FA targeted RSV-FER-SLNs effectively heightened cytotoxicity against cancer cells, leading to apoptosis induction compared to free RSV-FER. Consequently, the robust stability of the optimized formulation under acidic conditions suggests their promise as a prospective candidate for innovative nano drug formulations in colon cancer treatment [52].

2.2.2 Peptide-targeted SLNs

Modifying the surface of SLNs by attaching different ligands such as cell-penetrating peptides and homing peptides aims to address issues of non-specificity, reduce adverse effects, and enhance the effectiveness of anticancer treatments. This approach increases drug concentration at the tumor site due to their small size, allowing them to penetrate tumors more effectively compared to larger molecules like antibodies [53]. For treating GBM were developed with surface modification using a cyclic cell-penetrating peptide sequence (cRGD; Gly-Asp-Arg) to enhance the targeting of the drugs to GBM tumor cells. The research aimed to address the challenges associated with current GBM treatments, such as poor drug permeability into the brain, and tumor metastasis. The optimized SLNs exhibited a particle size of 129 nm, a surface charge of 23 mV, and drug loading efficiency exceeding 7%. In vitro drug release studies showed that over

70% of the drug was released within an 8 h period. Pharmacokinetic evaluation in vivo demonstrated that there have been notable enhancements in drug absorption metrics in contrast to the free drug suspension. The study concluded that the targeted dual drug-loaded SLNs provided enhanced chemoprotective effects compared to the non-targeted SLNs, and plain drug solution [54]. Luteinizing-hormone-releasing-hormone (LHRH) receptors are excessively expressed in prostate cancer cells. One of the most obstacles for the treatment of cancer is the presence of various immune cells in the TME that can lead to the uptake and clearance of nanocarriers before they reach cancer cells, so strategies like surface modification with PEG to evade immune detection was reported. PEG conjugated lipids demonstrate enhanced retention, and circulation within biological systems. PEGylated dipalmitoylphosphatedylethanolamine (DPPE-PEG) was conjugated with new LHRH-receptor positive peptide analog. This novel peptide analog positive for LHRH receptors was utilized to target the delivery of DOX into prostate cancer cells, a surface-modified SLNs loaded with DOX was formulated through a solvent emulsification/evaporation technique. Modification of SLNs resulted in a homogeneous surface morphology, as confirmed by dynamic light scattering. Cellular uptake, and in vitro efficacy against LHRH-positive PC3/SKBR3 prostate, and breast cancer cell lines, respectively indicated higher internalization, and cytotoxicity. Dye staining, and flow cytometry illustrated increased apoptosis in cancer cells. They concluded that these receptor-specific drug delivery systems hold significant potential for prostate cancer therapy [55]. One of the most promising aspects of using peptides for cancer cell targeting is their potential to be labeled with radioactive isotopes or fluorescent dyes. This capability allows for imaging and diagnostic purposes, aiding in the early detection and monitoring of tumors [20].

2.2.3 Polysaccharides -targeted SLNs

Coating nanocarriers with polysaccharides presents an opportunity to alter both the physical, and chemical characteristics as well as the targetability behavior of the SLNs [56]. Researches developed SLNs that have been modified on their surface with galactose, and contain the chemotherapy drug DOX [57]. The authors emphasize that the galactosylation of SLNs resulted in the creation of promising delivery vehicles, especially for targeted drug administration to enhance therapeutic efficacy. The galactosylated SLNs loaded with DOX exhibited increased cellular uptake, cytotoxicity, and localization within the cell nucleus when tested against A549 cells, suggesting their potential for enhancing DOX delivery in cancer treatment [57]. Furthermore, in another research SLNs were decorated with fucose for enhancing delivery of methotrexate. The results indicated that the fucose-decorated SLNs exhibited improvement in the cytotoxicity, and cellular uptake, with a lower IC_{50} of methotrexate in breast cancer cells, leading to increased apoptosis, and altered lysosomal membrane permeability. Also In vivo assessments demonstrated maximal bioavailability, and tumor targeting efficiency, while minimizing secondary drug distribution in organs compared to free drug administration. The authors concluded that fucose-decorated SLNs hold promise for developing targeted therapies for breast cancer [58]. Wang et al. [59] formulated SLNs loaded with PTX (Zhejiang Hisun Pharmaceutical Co., Ltd (Zhejiang, China)) and decorated with HA and pluronic 85 (P85) to address drug resistance and enhance antitumor effectiveness in mice with cervical and breast tumors. Results indicated that the HA decorated P85-PTX- SLNs had an average size of 160.3 nm, an entrapment efficiency (EE) of 88.2%, and a drug loading capacity (LC) of 4.9%. The release of PTX from HA-PTX-P85- SLNs demonstrated a more prolonged and sustained profile compared to free PTX. Additionally, biodistribution analysis showed higher concentrations of the drug in tumors with HA decorated SLNs than with free PTX [59]. Additionally, in another study HA was tagged to SLNs, and loaded with docetaxel (DTX) to effectively target, and combat drug-resistant tumor cells. The particle sizes of the SLNs and HA-SLNs measured 109.5 ± 8.2 nm and 224.3 ± 15.9 nm, respectively. It was observed that HA-SLNs exhibited increased cellular uptake and cytotoxicity in MCF7/ADR cells compared to other cell types, indicating their ability to effectively target and address tumor resistance. Consequently, the researchers concluded that HA-SLNs represent a promising targeted drug delivery system for delivering DTX to overcome drug-resistant tumors [60].

2.2.4 Transferrin-targeted SLNs

Transferrin-conjugated SLNs were successfully developed for enhancing the active targeting of anticancer drugs to cancer cells. Jain et al. [61] investigated effectiveness of Tf-anchored SLNs loaded with DOX for specifically targeting brain cancer. The study aimed to overcome the challenge of delivering chemotherapy agents across the blood-tumor barrier (BTB) by leveraging TfRs abundantly present on brain cancer cells. The modified SLNs had an average particle size of 210.3 nm. In vitro experiments conducted on U87 MG brain cancer cell lines demonstrated that the cytotoxicity of D- SLNs-T was significantly enhanced upon anchoring Tf to the nanocarriers, leading to increased cellular uptake of the drug. These findings suggest that D-SLNs-T holds promise for enhancing the treatment

of brain cancer by effectively targeting, and delivering DOX to cancerous cells [61]. SLNs loaded with Cur were bioconjugated with Tf using EDC as coupling reagent to target prostate cancer cells, aiming to enhance Cur's clinical efficacy despite its poor bioavailability. The researchers aimed to improve the clinical effectiveness of Cur, which is limited by its poor bioavailability. The results showed that Tf-SLNs exhibited notably higher cellular uptake, and induced greater apoptotic effects compared to non-conjugated SLNs. In vivo models with prostate cancer showed that the use of Tf- SLNs led to significant tumor regression. These findings suggest that bioconjugated SLNs represent a promising strategy for targeted cancer therapy [62]. In breast cancer treatment, tamoxifen citrate was loaded in SLNs that conjugated with Tf in an attempt to improve the targeted delivery of tamoxifen citrate. The findings indicated that the developed formulations showed increased toxicity against MCF-7 human breast cancer cells compared to pure tamoxifen citrate solution. Consequently, the study suggests that Tf-engineered nanocarriers hold potential for enhancing the therapeutic efficacy of nanomedicines in breast cancer treatment [63].

2.2.5 Antibody-targeted SLNs

The creation of positively charged SLNs modified with specific mAbs targeted for the epidermal growth factor receptor (EGFR) marked the initial advancement in utilizing antibody-driven approaches with SLNs loaded with drugs for cancer treatment [64]. A research investigated the conjugation of SLNs with Death receptor-5 antibodies (DR5 mAb) to deliver γ-secretase inhibitor effectively into cancer cells Fig. 2. The DR5 monoclonal antibody (mAb) was covalently attached through its amino (NH_2) group to the exposed carboxylic (COOH) group of the

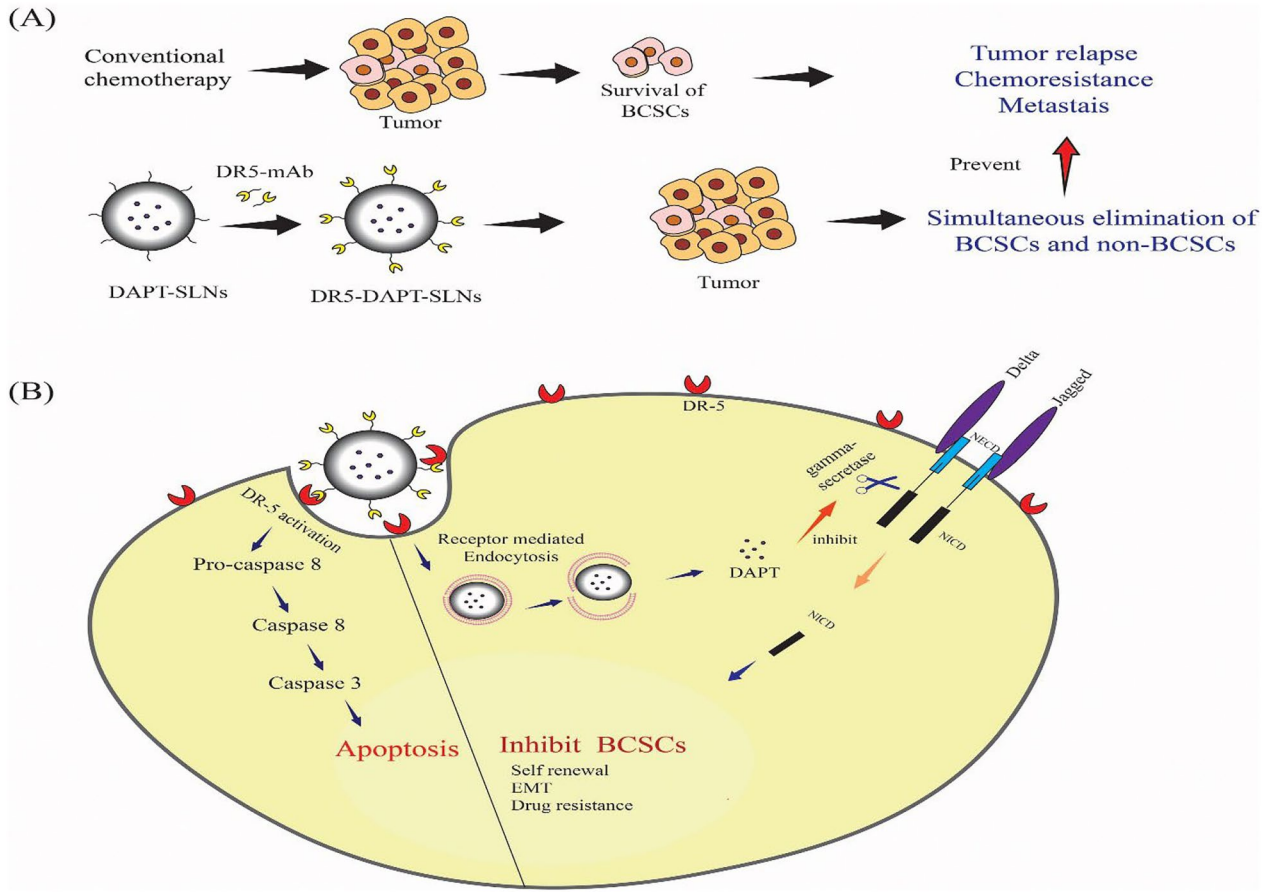


Fig. 2 The process by which BCSCs contribute to the recurrence of tumors, their spread to other parts of the body, and their resistance to chemotherapy is explained. In the case of DAPT-DR5-SLNs, the way it works involves the DR5-mediated intake of DAPT. This intake stops γ-secretase activity, thus halting the splitting of the Notch intracellular domain (NICD). Consequently, the shutdown of downstream Notch signaling inhibits various functions such as cell growth, blood vessel formation, resistance to cell death, and the ability of BCSCs to renew themselves by blocking the expression of genes targeted by Notch. In addition to its role in actively seeking out targets, DR5mAb triggers the extrinsic apoptotic pathway, potentially leading to improved reduction of tumors. Adapted with permission from ref. [65] copyright (2024) Elsevier

lipid in DAPT-SLNs, with EDC serving as the coupling agent for the covalent linkage. Results indicated that the targeted SLNs exhibited increased cytotoxicity in MDA-MB231 triple-negative breast cancer (TNBC) cells compared to non-targeted SLNs [65]. In animal studies, targeted SLNs demonstrated superior tumor regression compared to non-targeted SLNs, indicating selective targeting of cancer cells, and enhanced anticancer efficacy against TNBC cells [65]. In another research they focused on enhancing the delivery of the anticancer drug etoposide to treat GBM, by developing SLNs combined with melanotransferrin antibody (MA) and tamoxifen to traverse the blood–brain barrier. Etoposide-SLNs were preactivated with EDC and NHS and then conjugated with tamoxifen. Results indicated that a higher concentration of MA on the particle surface led to elevation in the permeability coefficient for etoposide across the blood–brain barrier, this study concluded that MA-conjugated etoposide-loaded SLNs represent a promising approach for delivering pharmacotherapy for GBM [66]. Souto et al. [67] developed a new method of drug delivery for breast cancer treatment using SLNs modified on the surface with a antibody targeting human epithelial growth receptor called CAB51. Scientists connected CAB51 to cationic SLNs to target breast cancer cells. The findings indicated that the antibody showed increased uptake in negative MCF-7 breast cancer cell lines. At lower concentrations, the antibody- conjugated SLNs displayed a synergistic impact on cell viability, surpassing the effects of SLNs or antibody alone. They concluded that these MA surface- modified SLNs have the potential to offer targeted delivery, thereby minimizing systemic side effects [67]. Table 3 demonstrates summary for surface modified SLNs for cancer therapy.

2.3 Lipid-polymer hybrid nanoparticles

The lipid polymer hybrid nanoparticles is an innovative formulation that merges polymeric nanoparticles, and liposomes, effectively overcoming the drawbacks associated with each component when used alone [68]. Liposomes, characterized by spherical vesicles comprising a lipid bilayer membrane, offer the advantage of delivering both hydrophilic, and hydrophobic drugs. However, they encounter various limitations such as lipid peroxidation, oxidation, hydrolysis of phospholipids, and unintended leakage [69]. Conversely, polymeric nanocarriers demonstrate excellent controlled release capabilities in comparison with liposomes, and are recognized as a cost-efficient approach. Nonetheless, they suffer from the drawback of having a moderate circulation half-life [70].

2.3.1 Folic acid—targeted LPHNPs

Folic acid, a commonly utilized ligand, targets the FR present on different cancer cells. In their research, Gu et al. [71] employed FA as a targeting tool, showcasing its effectiveness in directing delivery via folate modification. Their investigation displayed distinct monodispersity, and stability for indocyanine green (ICG) compared to free ICG, shielding ICG from degradation, and offering superior near-infrared (NIR) penetration during in vitro experimentation [71]. Additionally, in vivo trials of β-amino ester-prepared nanocarriers for targeted delivery of docetaxel exhibited heightened intracellular uptake, and cytotoxicity Fig. 3. These particles, sized at 100 nm with a narrow distribution, demonstrated superior tumor targeting ability in mice bearing tumors [72]. Tang and his colleagues fabricated FA-conjugated lipid-coated chitosan/chondroitin sulfate (CT/CS) nanocarriers loaded with sorafenib, demonstrated significantly enhanced uptake by cancer cells compared to the non-targeted nanocarriers. This heightened internalization was primarily due to its specific interaction with FR, which are overexpressed in liver cancer cells. FA targeted lipid polymer hybrid NPs displayed potent cytotoxicity across all tested concentrations, as evidenced by a notably lower IC_{50} value of 0.78 μg/mL compared to 3.92 μg/mL. These findings underscore the promising potential of folate-conjugated LPHNPs for delivering anticancer drugs in liver cancer treatment [73]. Additionally, LPHNPs targeted with FA were loaded with gefitinib (GEF, European Pharmacopoeia Reference Standard) and yttrium-90 (Y90, PerkinElmer, Waltham, MA) [74]. FA-targeted-LPHNPs, sized approximately 150 nm, showed increased accumulation in nasopharyngeal carcinoma cells and demonstrated superior cytotoxicity. In vivo experiments revealed remarkable tumor inhibition with a tumor volume of 221.2 ± 13.5 mm [3] by day 21 post-treatment, alongside minimal changes in body weight, indicating low systemic toxicity. These findings suggest that FA-GEF-Y90-LPHNPs could serve as a safe therapeutic system for nasopharyngeal Cancer treatment.

2.3.2 Peptides—targeted LPHNPs

Peptides employed for active targeting in different cancer types have demonstrated impressive efficacy in delivering anticancer drugs [75]. Research on RGD-targeted delivery has shown its exceptional targeting precision, and therapeutic impact across various in vivo investigations. One such study utilized docetaxel-loaded RGD-L-P nanocarriers with a size of 110 nm, revealing enhanced targeting capability, and treatment effectiveness. In experiments on rats with GBM, administration of these nanocarriers led to a median survival duration of 57 days, highlighting their promising therapeutic potential [76].

Table 3 Surface modified targeted SLNs for cancer therapy

Target	Drug	Cancer	Main outcomes	References
SLNs				
Folic acid	Letrozole	Breast cancer	FA-SLNs-LTZ exhibited significantly higher cytotoxicity against MCF-7 cancer cells compared to SLNs-LTZ with minimal systemic side effects	[50]
	Chrysin	Pancreatic cancer	The targeted SLNs loaded with CHY exhibited scavenging activity against DPPH (IC_{50}: 108.7 µg/mL), and ABTS (IC_{50}: 123.73 µg/mL) free radicals	[51]
	Ttrans-resveratrol, and ferulic acid	Colon cancer	FA targeted RSV-FER-SLNs effectively heightened cytotoxicity against cancer cells, leading to apoptosis induction compared to free RSV-FER	[52]
Peptide	Paclitaxel, and naringenin	Brain cancer	The developed modified liposomes showed enhancement in oral bioavailability, and anticancer activity of PTX, and naringenin, with improved drug absorption parameters, and cytotoxicity against U87 glioma cells	[54]
	Doxorubicin	Prostate cancer	Cellular uptake, and in vitro efficacy against LHRH-positive PC3/SKBR3 cancer cell lines indicated higher internalization, and cytotoxicity	[55]
Carbohydrate	Doxorubicin	Breast cancer	For targeted delivery of DOX, which demonstrated higher cellular uptake, cytotoxicity, and nuclear localization against A549 cells, indicating an efficient formulation for cancer therapy	[57]
	Methotrexate	Breast cancer	Improved internalization by cells, and increased toxicity against breast cancer cells, along with improved bioavailability, and tumor targeting efficiency, leading to a significant reduction in tumor volume	[58]
	Paclitaxel	Cervical and breast cancer	Potential to overcome drug resistance and increase antitumor efficacy in mice-bearing cervical and breast tumors, with a significant enhancement in drug accumulation in tumor tissues and improved pharmacokinetics	[59]
	Docetaxel	Breast cancer	Effectively target and overcome drug-resistant tumor cells by enhancing cellular uptake and cytotoxicity in CD44-expressing cancer cells, particularly in drug-resistant MCF7/ADR cells	[60]
Transferrin	Doxorubicin	Brain cancer	Demonstrated increased cytotoxicity and enhanced cellular uptake in U87 MG brain cancer cell lines, indicating potential for improved brain cancer treatment	[61]
	Curcumin	Prostate cancer	The development of Tf bioconjugated SLNs loaded with Cur for active targeting of prostate cancer cells, demonstrating significant tumor regression in mice bearing prostate cancer after 4 weeks	[62]
	Tamoxifen citrate	Breast cancer	Enhance the active targeting of tamoxifen citrate in breast cancer therapy, demonstrating increased cytotoxicity and therapeutic response in human breast cancer MCF-7 cells compared to pure tamoxifen citrate solution	[63]
Antibody (DAPT)	γ-secretase inhibitor	Triple-negative breast cancer	These nanocarriers selectively target cancer cells, enhancing the anticancer efficacy of the γ-secretase inhibitor, DAPT, while minimizing off-target effects	[65]
	etoposide	Brain cancer	Mediate targeting and managing GBM by enhancing the delivery of anticancer drug etoposide across the blood–brain barrier	[66]
	Streptavidinbiotin	Breast cancer	Fabricated nanocarriers showed increased internalization, and a synergistic effect on cell viability in HER2 overexpressing BT-474 breast cancer cells compared to non-targeted SLNs	[67]

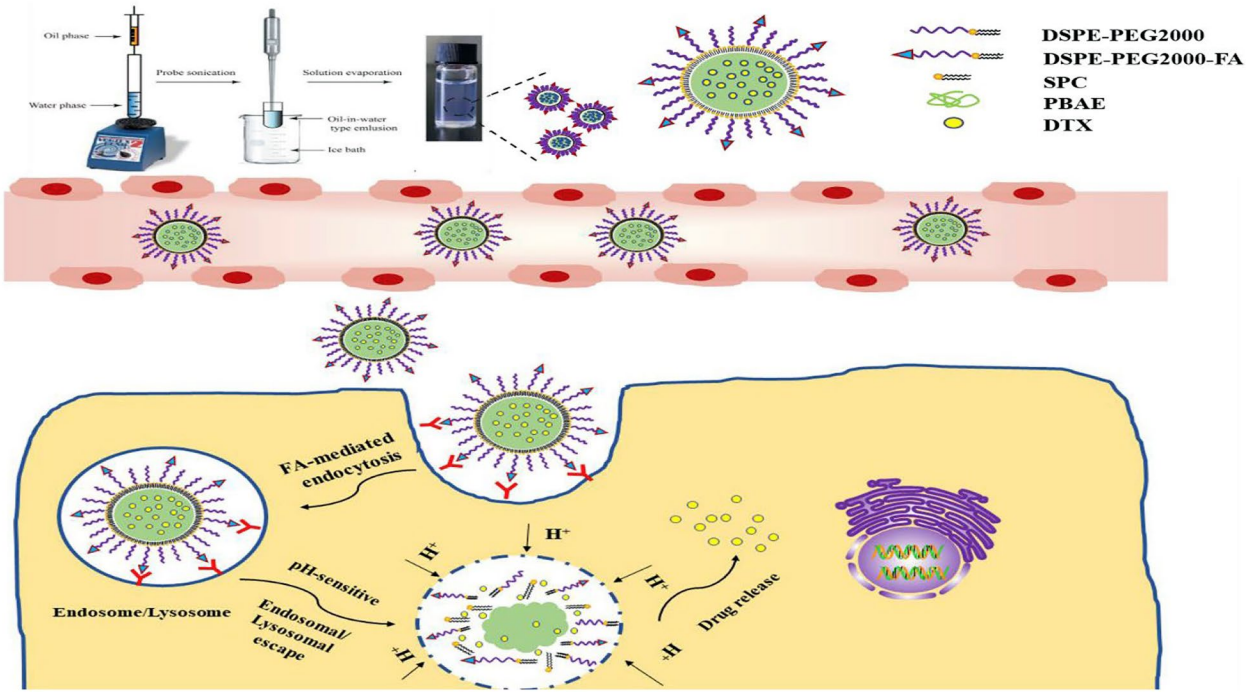


Fig. 3 A diagram illustrates the delivery process of FA/PBAE/DTX-NPs for medication transport. Tumor cells will take up FA/PBAE/DTX-NPs internally through FA-mediated endocytosis. Once the inclusion bodies are absorbed by tumor cells, the acidic conditions within the cells cause PBAE to become protonated, transitioning from hydrophobic to hydrophilic states. This alteration enables the nanocarrier to escape from lysosomes/endosomes, and promptly release the drug. Adapted with permission from ref. [72] copyright (2024) Elsevier

Gao et al. [77] conducted a study using, a hybrid nanoparticle (NP) system to enhance the therapeutic efficacy of Isoliquiritigenin (ISL). Incorporating internalized Arg-Gly-Asp (iRGD) peptides onto their surface using a post-insertion approach resulted in the formation of ISL iRGD NPs. In comparison with free ISL, and non-iRGD modified counterparts, ISL-iRGD NPs exhibit elevated cytotoxicity, and induce greater levels of cell apoptosis across various breast cancer cell types. This enhanced effect is attributed to heightened cellular accumulation facilitated by iRGD-integrin recognition, and the nanoscale properties of the particles. Crucially, owing to the active tumor-targeting ability of iRGD peptides, and prolonged circulation in vivo, ISL-iRGD NPs demonstrate superior efficacy in inhibiting tumor growth in mouse models bearing 4T1 breast tumors [77]. Furthermore, researchers developed hybrid nanoparticles comprising a lipid shell and a polymer core (lpNPs) that loaded with Cur and were modified with RGD peptide. The optimized RGD-lpNPs, exhibited high entrapment efficiency, submicron size, and a core–shell structure. Cytotoxicity demonstrated that Cur encapsulated within RGD–lpNPs maintained potent antitumor effects. Cellular uptake revealed increased uptake of Cur when encapsulated in RGD–lpNPs. Additionally, Cur-loaded RGD–lpNPs exhibited superior efficacy by impeding the growth of tumors in a subcutaneous B16 melanoma tumor model [78].

2.3.3 Polysaccharide—targeted LPHNPs

Shao et al. [79] created LPHNs with a core–shell configuration, loading DOX, and gallic acid together, and targeted with HA. This strategy combined the biomimetic properties of lipids with the structural benefits of polymer cores, resulting in an exceptional delivery system. The HA-modified LPHNs had dimensions approximately measuring 160 nm. Among these, the dual drugs loaded HA-modified LPHNs exhibited the highest cytotoxicity, with optimal synergy observed at a DOX/GA ratio of 2/1. In animal studies, the dual drugs loaded HA-modified LPHNs significantly reduced tumor volume from 956 mm [3] to 213 mm [3], achieving a remarkable inhibition rate of 77.7% [79]. Furthermore, within the insertion of HA on the surface of the co-loaded LPNs incorporating irinotecan, and a gene, there was an observed improvement in cytotoxic effects, resulting in heightened efficacy against SW480 cells. This enhancement was accompanied by peak plasma concentrations of 41.31 ± 1.58 μg/mL, and half-lives of 12.56 ± 0.67 h [80]. Additionally, in the realm of vaccine distribution, hybrid nanoparticles

comprising cationic lipid–poly(lactide-co-glycolide) acid (PLGA), adorned with HA, proved to be efficient conveyors. Interestingly, trials conducted within living organisms showcased that vaccination using HA-targeted nanocarrier triggered notably stronger immune reactions when contrasted with cationic lipid-PLGA nanocarrier, and unbound ovalbumin. This method has emerged as a powerful framework for fostering potent immune responses [81].

2.3.4 Transferrin—targeted LPHNPs

Iron is crucial for the proliferation of cancer cells and can be efficiently transported to tumors via Tf, which is known to have heightened expression on numerous cancer cells. Many authors have therefore attached Tf to LPHNPs to enhance the targeted delivery of anticancer agents to tumor cells. Alpha-mangostin was incorporated into an LPHNPs delivery system conjugated with Tf. The conjugation of Tf to the LPHNPs was done by utilizing the thiol–maleimide "click" reaction. The results demonstrated a sustained release of alpha-mangostin following an initial burst release, contrasting with the rapid release observed with the drug solution. Decoration of alpha-mangostin-LPHNPs with TF enhanced its uptake by cancer cells, consequently augmenting its antiproliferative activity compared to the free drug solution. Moreover, it represents a promising therapeutic approach warranting further optimization as a cancer treatment modality [82]. Nevertheless, for enhancing targeting to non-small cell lung cancer, a protein- LPHNPs equipped with Tf was formulated to encapsulate both DTX, and cisplatin (CIS). The analysis revealed a particle size of approximately 189.5 ± 5.9 nm, with a surface charge measured at around − 16.9 ± 2.1 mV. When compared with CIS/DTX-LN, which lacked Tf, and other singly loaded formulation, and free drugs, Tf-targeted LPHNPs demonstrated significantly superior efficacy against tumors both in laboratory cell studies, and in vivo [83].

2.3.5 Antibody—targeted LPHNPs

Antibodies have been employed to regulate the dispersion of functional nanoparticles toward specific tissues. Conjugating antibodies to nanoparticles enables precise cancer targeting. Yang et al. [84] employed a site-specific anticlaudin 3 (CLDN3) antibody conjugation to LPHNPs. The targeted LPHNPs showed high colloidal stability, and xenograft mouse model resulted in remarkable tumor ablation compared to non-targeted LPHNPs. This study establishes a precise antibody-linking technique for enhancing breast cancer treatment. In an attempt to modulate hepatocellular carcinoma (HCC), LPHNPs loaded with adriamycin and linked to an anti-EGF receptor antibody have been developed. For the conjugation of antibodies, the formulated system was coupled with thiolated anti-EGFR Fab´ to form LPHNPs anti-EGFR Fab´ conjugate. Anti-EGF-targeted LPHNPs demonstrated markedly increased cellular cytotoxicity against HCC cells with elevated EGFR expression compared to non-targeted system. In vivo results demonstrated that the accumulation of targeted LPHNPs was notably higher than that of non-targeted LPHNPs with high antitumor efficacy [85]. Table 4 demonstrates summary for surface modified LPHNPs for cancer therapy.

3 Summary

Different targeting agents exhibit distinct properties that make them suitable for specific applications. A systematic comparison facilitates the selection of the most suitable agent tailored to the specific requirements of a given application, such as targeted drug delivery to specific types of cancer [86, 87]. Table 5 provides a comprehensive overview, highlighting both advantages and disadvantages, thereby ensuring a balanced evaluation across different targeting agents. This approach promotes impartial assessment and aids in selecting the most appropriate agent for specific applications. Moreover, it identifies gaps in current knowledge and outlines opportunities for further research [53].

4 Conclusion

In conclusion, the review on targeted lipid-based nanocarriers highlights their immense potential in revolutionizing drug delivery systems. Through meticulous examination, it becomes evident that these nanocarriers offer precise targeting, enhanced drug efficacy, and minimized adverse effects. Their ability to encapsulate therapeutic agents and navigate biological barriers underscores their significance in overcoming challenges associated with traditional drug delivery methods. Furthermore, the versatility of lipid-based nanocarriers allows for customization to meet specific therapeutic needs, promising advancements in machine learning models that can analyze patient-specific data to design personalized lipid-based nanocarriers that cater to individual therapeutic needs. This ensures that treatments are tailored to the unique genetic and molecular profiles of patients. As research in this field continues to evolve, targeted lipid-based nanocarriers are poised to play a pivotal role in shaping the future of health care by delivering treatments with unprecedented precision and efficacy.

Table 4 Surface modified targeted LPHNPs for cancer therapy

Active targeting	Drug used	Cancer type	Main outcome	References
LPHNPs				
Folic acid	Indocyanine green, and Cisplatin	breast cancer	FCINPs combined with 808 nm NIR laser treatment induced significant apoptosis, and necrosis in MCF-7 cells	[71]
	Docetaxel	Breast cancer	FA/PBAE/DTX-NPs show promise as tumor drug delivery carriers for improved breast cancer treatment	[72]
	Sorafenib	Liver Cancer	Notable cancer cell apoptosis with distorted nucleus, and apoptotic body formation	[73]
	Gefitinib (GEF), and yttrium 90 (Y90)	Nasopharyngeal cancer	Low systemic toxicity, and potential for safe treatment of nasopharyngeal carcinoma	[74]
Peptide	Docetaxel	Glioblastoma Multiforme	Strongest drug delivery intensity, indicating enhanced delivery to GBM	[76]
	Isoliquiritigenin	Breast cancer	Higher tumor growth inhibition in breast tumor mouse models	[77]
	Curcumin	–	Enhanced cytotoxicity, and apoptosis induction in melanoma cells	[78]
Polysaccharide	Goxorubicin (DOX), and gallic acid (GA)	Leukemia	Significantly inhibited tumor growth with an inhibition rate of 77.7%	[79]
	Irinotecan	Colorectal cancer	Remarkable tumor inhibition efficacy, and gene transfection efficiency	[80]
	HA-DOTAP	OVA (ovalbumin)	High potential as vaccine delivery vehicles for elevated immune responses	[81]
Transferrin	Alpha-mangostin	Breast, melanoma, and lung cancer	Alpha-mangostin-LPHNPs with TF enhanced its uptake by cancer cells, and augmenting its antiproliferative activity compared to the free drug solution	[82]
	Docetaxel, and cisplatin	Non-small cell lung cancer	Tf-targeted LPHNPs demonstrated significantly superior efficacy against tumors both in laboratory cell studies, and in vivo	[83]
Antibody	h4G3cys	Breast cancer	Xenograft mouse model resulted in remarkable tumor ablation compared to non-targeted LPHNPs	[84]
	Adriamycin	hepatocellular carcinoma	In vivo results demonstrated that the accumulation of targeted LzPHNPs was notably higher than that of non-targeted nanoparticles with high antitumor efficacy	[85]

5 Challenges and future prospective

Presently, targeted lipid-based nanocarriers present both challenges, and promising future prospects in drug delivery. Challenges include ensuring precise targeting to specific tissues or cells, overcoming biological barriers such as the reticuloendothelial system, and maintaining stability, and biocompatibility [88]. Additionally, issues related to scalability, and reproducibility need to be

Table 5 The advantages and disadvantages of FA, peptides, polysaccharides, Tf, and antibodies for targeting lipid nanocarriers

Targeting agent	Advantages	Disadvantages
Folic acid (interacts with folate receptors)	Small-size facilitates easy conjugation with minimal impact on carrier properties Low cost and well-characterized chemistry	Limited to cancers with high FR expression Potential for competition with endogenous folate Possible off-target effects on normal cells expressing folate receptors
Peptides (Interacts with specific receptors or enzymes)	Versatile and easily modifiable High specificity and affinity for a wide range of targets Small size allows for enhanced tumor penetration Lower immunogenicity compared to larger molecules	Susceptible to enzymatic degradation due to their nature Short circulation half-life Involves complex synthesis with several steps and optimization
Polysaccharides (binds to cell surface receptors)	Biodegradable and biocompatible Abundant and cost-effective Low toxicity and immunogenicity Enhances stability and circulation time of nanocarriers	Lower targeting specificity compared to other agents May require chemical modification for effective conjugation
Transferrin (binds to transferrin receptors)	Naturally occurring protein with an established safety profile Facilitates receptor-mediated endocytosis	Large size may impact nanocarrier properties and tumor penetration Potential for immunogenicity and allergic reactions Competition with endogenous Tf
Antibodies (Specific interaction with antigens)	High specificity and affinity for a broad range of antigens Versatile, available in various formats (e.g., full antibodies, fragments) Capable of eliciting the immune system to attack cancer cells	Large size may hinder tumor penetration High cost and complex production process Potential for immunogenicity Issues with stability and storage

addressed for widespread adoption. However, the future holds exciting potential for targeted lipid-based nanocarriers e.g. AI (Artificial Intelligence) can forecast the ideal composition and properties of lipid-based nanocarriers, such as size, charge, and encapsulation efficiency, based on experimental data. This facilitates the development of more potent compounds [89]. Advances in nanotechnology, and lipid chemistry offer opportunities to enhance targeting efficiency, improve payload delivery, and minimize off-target effects. Furthermore, the versatility of lipid-based carriers allows for the incorporation of various therapeutic agents, including small molecules, nucleic acids, and proteins. In order to find possible medication candidates that can be encapsulated in lipid-based nanocarriers, AI an emerging technology, may scan massive datasets. In doing so, the process of finding new drugs is sped up and compounds with the best characteristics for creating nanocarriers are found [90]. Continued research and innovation in this field are poised to revolutionize drug delivery, offering tailored solutions for diverse medical challenges.

CRISPR (clustered regularly interspaced short palindromic repeats) is one of the most exciting emerging technologies. It can also be used to alter the genetic expression of cells, enhancing their interaction with lipid-based nanocarriers and enhancing their uptake and therapeutic efficacy [91]. CRISPR technology offers a powerful tool for modifying genes that regulate receptor expression or for creating new antibodies to enhance lipid nanocarrier surfaces. Using CRISPR/Cas9, researchers can accurately alter the genetic code that governs the production of cell surface receptors, thereby improving or modifying their expression to boost the targeting efficiency of lipid nanocarriers. Furthermore, CRISPR can be employed to design cells that generate novel antibodies with specific binding properties. These engineered antibodies can be attached to lipid nanocarriers, facilitating precise delivery of therapeutic agents to targeted cell types or tissues. This method supports the creation of highly tailored nanocarriers with enhanced targeting and therapeutic effectiveness [92]. In this context, personalized medicine involves customizing lipid nanocarriers based on genetic, proteomic, and clinical data unique to each patient. By analyzing specific biomarkers and disease characteristics, researchers can modify the surface of lipid nanocarriers with targeted ligands, such as antibodies or peptides, that precisely interact with the patient's unique cellular markers. This personalized targeting improves the efficiency of drug delivery and minimizes off-target effects, leading to more effective and safer treatments. The integration of personalized medicine into lipid nanocarrier design ensures that therapies

are optimized for each patient's individual needs and disease profile [93].

The examples highlighted in this review showcase the significant potential of surface modifications in these nanocarriers. However, there are a number of important issues that need to be addressed in subsequent studies. It has been observed that the efficiency of functionalization is influenced by the selection of ligand density, type, and excipients. Depending on the precise lipid surface chemistry required for the intended biomedical applications, choosing the right surface modification techniques for lipid-based nanocarriers is essential. For all lipid-based nanocarriers, there is not a single best coating method that can be applied to increase selectivity. To accurately characterize these functionalized carriers, lipid-based nanocarriers must be purified after surface functionalization. Additionally, to demonstrate the safe and effective clinical application of fabricated surface-modified lipid-based nanocarriers, toxicity issues must be investigated [86].

Due to their significant affinity for the negatively charged cell membrane, positively modified nanocarriers tend to accumulate excessively on the surface of the cell. In order to improve therapeutic efficacy, future options involve developing nanocarriers with the ideal size, shape, and charge density. Additionally, studies should concentrate on thoroughly analyzing the interactions between particular proteins and these nanocarriers utilizing in vitro and in vivo models [94].

Targeting lipid nanocarriers presents several significant regulatory challenges, particularly concerning complex safety assessments required to determine their toxicity, especially for those combining multiple ligands to achieve advanced multifunctionality. Additionally, scaling up the synthesis from laboratory scale to large-scale manufacturing without compromising the quality and performance of the nanocarriers is a major hurdle. Ensuring batch-to-batch consistency and designing reliable clinical trials that meet regulatory standards for demonstrating safety and efficacy further complicate the development process [95]. However, with the advent of machine learning, it is now possible to identify patterns and connections by processing and analyzing large, complex datasets from clinical and preclinical research. This technology helps in understanding the factors that influence the effectiveness and safety of lipid-based nanocarriers [96].

Abbreviations

SLNs	Solid lipid nanoparticles
FR	Folate receptor
5FU	5-Fluorouracil
ROS	Reactive oxygen species
PTX	Paclitaxel
TR-PTX/HCQ-Lip	Tandem peptide paclitaxel/hydroxychloroquine-liposomes
PEG	Polyethylene glycol
RGD	Arginine-glycine-aspartic acid peptides
BBH	Berberine hydrochloride
DOX	Doxorubicin
Tf	Transferrin
RES	Resveratrol
TfRs	Transferrin receptors
TPGS	glioblastoma, D-alpha-tocopheryl polyethylene glycol 1000 succinate mono-ester
mAbs	Monoclonal antibodies
LTLs	Ligand-targeted liposomes
mAb 2C5	Monoclonal nucleosome-specific 2C5 antibody
CD44	Cluster of differentiation 44
PK	Pharmacokinetics
FA	Folic acid
LTZ	Letrozole
SEM	Scanning electron microscopy
CHY	Chrysin
DPPH	2,2-Diphenyl-1-picrylhydrazyl
ABTS	2,2-Azino-bis-3-ethylbenzothiazoline-6-sulphonic acid
FER	Ferulic acid
LHRH	Luteinizing-hormone-releasing-hormone
HA	Hyaluronic acid
P85	Pluronic 85
EE	Entrapment efficiency
DTX	Docetaxel
BTB	Blood-tumor barrier
EGFR	Epidermal growth factor receptor
TNBC	Triple-negative breast cancer
MA	Melanotransferrin antibody
CAB51	Antibody targeting human epithelial growth receptor
LPHNPs	Lipid polymer hybrid nanoparticles
ICG	Indocyanine green
NIR	Near-infrared
CT/CS	Chitosan/chondroitin sulfate
GEF	Gefitinib
Y90	Yttrium 90
ISL	Isoliquiritigenin
Cur	Curcumin
GA	Gallic acid
CIS	Cisplatin
CLDN3	Anticlaudin 3 antibody
HCC	Hepatocellular carcinoma
CRISPR	Clustered regularly interspaced short palindromic repeats
AI	Artificial intelligence
TME	Tumor microenvironment
TAMs	Tumor-associated macrophages

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