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Optimizing Cancer Treatment: A Comprehensive Review of Active and Passive Drug Delivery Strategies

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ABSTRACT

Nanocarriers as powerful tools for delivering drugs to tumors provide new strategies for cancer treatment. These delivery systems encompass a diverse variety of structures, including polymeric NPs, liposomes, dendrimers, micelles, and inorganic NPs such as gold and silica. Each type exhibits distinct physicochemical advantages that contribute to stability, drug-loading capacity, and targeting efficacy. Engineered nanocarriers can be utilized for the active targeting of tumor-specific receptors or for passive targeting of tumors via the EPR effect, a characteristic of abnormal tumor vasculature. This targeting approach enables the precise delivery of the therapeutic agents at tumor sites, increasing drug efficacy while minimizing exposure to healthy tissues. The benefits of these strategies include reduced systemic adverse effects, improved bioavailability, and an optimized therapeutic index. This review examines both active and passive drug delivery systems, with a special focus on the characteristics of the EPR effect. ***DOI: 10.61186/ibj.4960***

Keywords: Nanocarriers, Drug delivery, Active targeting, Passive targeting

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INTRODUCTION

Drug delivery refers to the administration of pharmacological agents to humans or animals to achieve beneficial effects[1]. A significant area of research in drug delivery focuses on exploring innovative substances or carrier systems that transport pharmaceuticals efficiently[2]. These methods are critical in treating various illnesses. However, the development of novel therapeutic molecules is often a costly and time-consuming process, underscoring the need to improve existing pharmaceuticals via innovative delivery systems. In this context, DDSs provide effective solutions by enhancing the pharmacological profiles of the established compounds, decreasing development costs, and accelerating clinical translation[3].

Several strategies can enhance the safety and efficacy

List of Abbreviations:
ADC: antibody-drug conjugate; **ANANAS:** avidin-nucleic-acid-nano-assemblies; **DDS:** drug delivery system; **DM1: a** cytotoxic drug used in ADC; **DOC:** docetaxel (a taxane-based anticancer drug); **DOX:** doxorubicin (a chemotherapeutic drug); **Doxil®:** PEGylated liposomal doxorubicin; **ECM:** extracellular matrix; **EPR:** enhanced permeability and retention; **LNP:** lipid nanoparticle; **mAb:** monoclonal antibody; **NE:** nanoemulsion; **NP:** nanoparticle; **PEG:** polyethylene glycol; **SELEX:** Systematic Evolution of Ligands by Exponential Enrichment; **SLN:** solid lipid nanoparticle; **T-DM1:** trastuzumab emtansine; **Tf:** transferrin; **Tf-LP-DOC:** transferrin-conjugated docetaxel-loaded liposome; **TfR:** transferrin receptor; **TME:** tumor microenvironment; **VEGF:** vascular endothelial growth factor; **HA:** hyaluronic acid; **RGD:** arginine-glycine-aspartic acid

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of outdated medications, including dose adjustment, personalized drug therapy, and therapeutic drug monitoring. Drug delivery can be steady, controlled, or targeted. Furthermore, an ideal DDS should be resilient to external influences. In other words, it must follow predictable physicochemical principles, accommodate different active agents and dosages, improve or maintain the chemical and physical stability of the active agent, and contain the active agents that provide optimal efficiency, safety, and reliability[4].

Delivering therapeutic agents to the appropriate site is one of the most complex challenges in treating various ailments. Most conventional drugs exhibit low specificity, efficacy, and biological dispersion, along with significant side effects. Regulating DDS can help overcome these limitations by ensuring that the drug reaches its intended target. DDS also prevents rapid degradation[5], increasing drug concentrations in the desired organs and reducing the required treatment dosages. Targeted drug delivery to the specific cells or tissues using specially designed carriers is a more reliable option[3]. Furthermore, biomolecules can interact uniquely with nanocarriers to enhance their long-term stability and circulation time. Nanocarriers can also effectively combine multiple medications and therapeutic approaches to treat cancer[6]. The incorporation of targeting molecules—such as antibodies, peptides, aptamers, and small molecules—alongside delivery carriers (e.g., liposomes, polymers, metal oxides, and silica) represents a significant innovation in developing various nanocarrier-based targeted DDSs[7]. Developing these targeting molecules and delivery carriers improves the precision and effectiveness of drug delivery, facilitating more effective interactions with tumor cells[8].

The combination of targeting molecules with delivery carriers has emerged as a significant breakthrough in nanocarrier-based tumor DDSs. By refining both targeting molecules and delivery systems, tumor cells can be more effectively and accurately targeted, thereby enhancing drug delivery. This advancement is crucial for precisely targeting tumor tissues while minimizing side effects, ultimately improving cancer treatment outcomes[7]. Passive and active targeting are the most advanced approaches for precisely leading the drug-loaded vehicle systems to critical diseased areas within the human body (Fig. 1). The passive EPR effect relies on the lifespan of the drug carrier in the circulatory system and its accumulation in the pathological sites with compromised vasculature. In contrast, the active targeting method involves attaching the specific ligands to the surface of pharmaceutical carriers to identify and subsequently bind to the target cells[9]. The present research specifically examines nanocarrier-based DDSs that are either in the clinical phase or have obtained FDA approval, providing a practical and translational

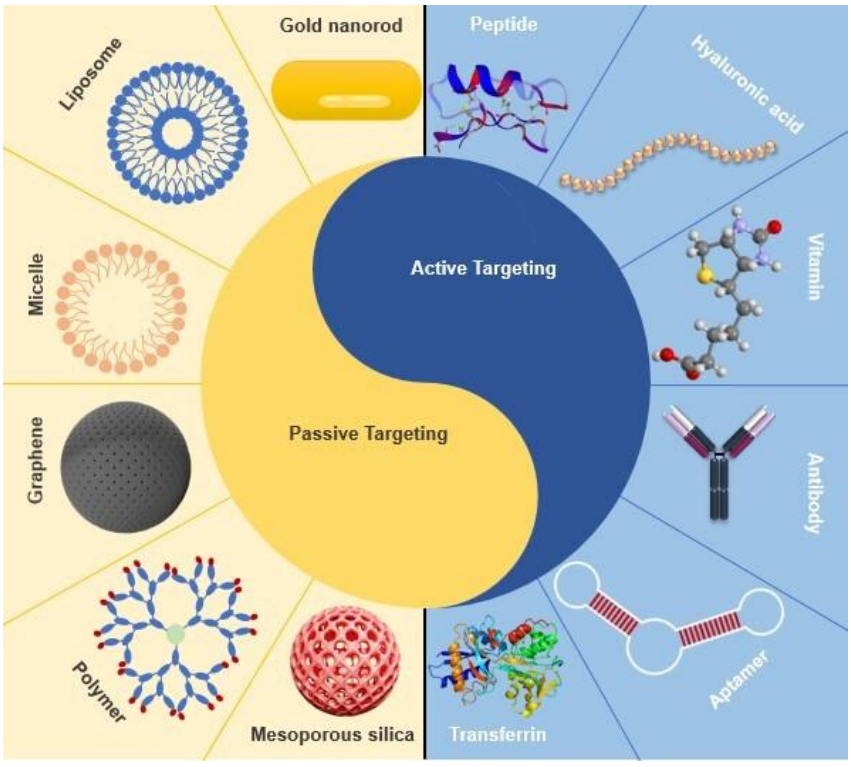

Fig. 1. Passive and active targeting ligands and delivery carriers.

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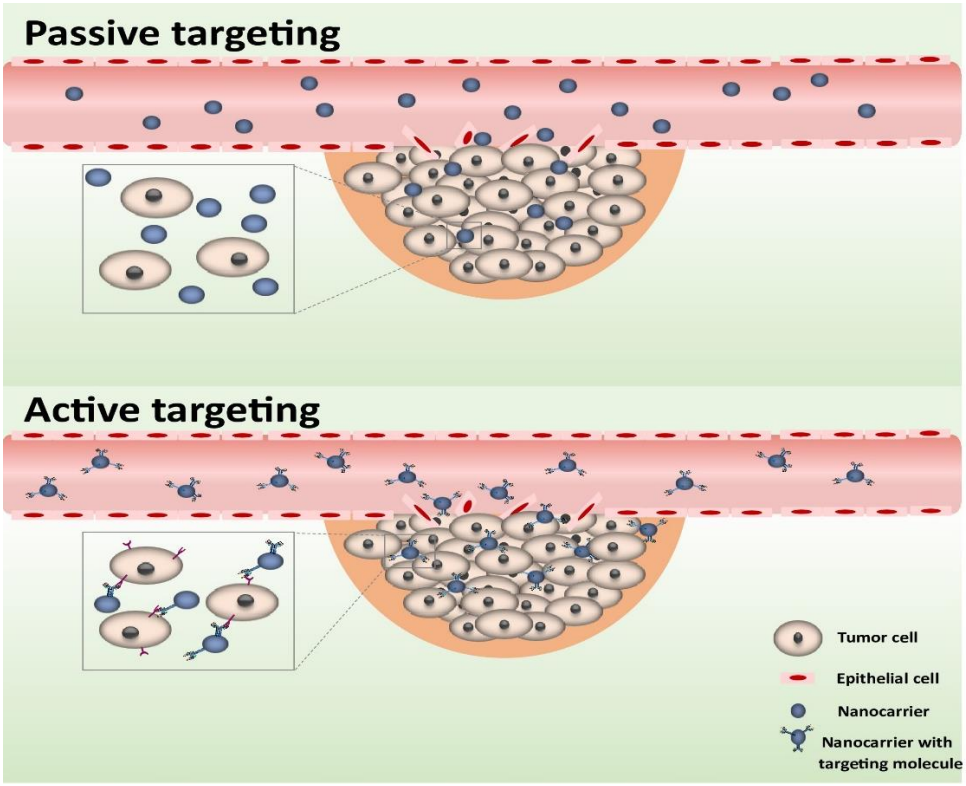

Fig. 2. A schematic representation of the passive and active targeting nanodelivery system used in cancer treatment.

perspective on targeted cancer therapy, which differs from previous reviews. The current analysis provides a detailed understanding of systems likely to influence current and future cancer therapies, with a focus on clinically validated or patent-protected approaches. Likewise, the study will explore key concepts and applications of targeted drug delivery (Fig. 2), highlighting how medications can be delivered using a variety of carriers that have both passive and active targeting effects.

Passive targeting

To achieve a controlled release of chemotherapeutic agents, it is essential to determine an appropriate drug dosage and therapy duration, in combination with a well-defined DDS, to obtain optimal results. The DDS aims to deliver safe and effective amounts of drugs compared to the existing treatment methods[10]. Tumor targeting is a valuable strategy for accessing tumors while minimizing penetration of drugs into normal tissues. This approach can be categorized into passive and active targeting, in which active targeting occurs only after passive aggregation within tumors[11]. The passive targeting mechanism utilizes nanocarriers to deliver drugs to tumor cells via passive diffusion or convection across the spaces in tumor capillary pores. Primary components of passive targeted DDSs include liposomes, silicon dioxide, metal oxide, and polymeric NPs[12]. Passive NP targeting has gained popularity due to its ease of use and significant advantages over active targeting methods[10]. However, there are some drawbacks to passive targeted drug delivery. A major concern is the heterogeneity of tumors among individuals, which complicates the ability to distinguish between healthy and diseased tissues[13]. The concept of passive tumor targeting through the EPR effect was first introduced by Maeda and Matsumura in 1986, establishing a basis for improving drug delivery, specifically for cancer. The EPR effect is a feature of tumor blood vessels that facilitates the transport of macromolecules into tumor tissues due to the increased leakiness and high permeability of the vasculature[14]. Since the discovery of the EPR effect, many efforts have been made to understand its importance in tumor targeting and the development of suitable DDS[15]. Despite its advantages, passive targeting through the EPR effect faces significant challenges, mainly due to the variability and heterogeneity of the TME[16]. Passive targeting uses the EPR effect to rapidly create hyper-permeable tumor vasculature, which arises from the reduced lymphatic drainage of the damaged tissue. NPs ≥100 nm are extravasated into the TME, by which their clearance will be inhibited. Drug carriers with lipid-based products enhance drug bioavailability through

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both passive and active targeting strategies. Advanced DDS can also simplify gene therapy, chemotherapy, or their combination for theranostic applications, overcoming the limitations of passive, active, or combined targeted strategies[17].

The EPR effect is a cornerstone of the nanodrug delivery system, utilizing the leaky blood vessels and impaired lymphatic drainage characteristic of tumors to facilitate the accumulation of therapeutic agents. However, the variability of the EPR effect across different tumor types and individuals presents a significant challenge to the consistent efficacy of nanodrugs. To address these limitations, inventive strategies targeting the TME have been established. These strategies include molecular targeting of specific TME markers, employing external physical methods, and physiological modifications of the TME to enhance drug delivery and therapeutic outcomes. Furthermore, significant differences between human and animal models in tumor architecture and immune responses make clinical translation of therapeutic strategies complex. These biological variations result in discrepancies in the accumulation and functionality of NPs among different individuals. Numerous approaches have been proposed to enhance the EPR effect in cancer treatment. Some methods involve the use of nitric oxide donors to improve blood flow, while others employ enzyme-based strategies, such as matrix metallo-proteinases to facilitate NP penetration through tumor stroma. Furthermore, functionalized NPs that target specific tumor receptors and respond to external triggers—like hyperthermia and ultrasound—have the potential to enhance drug delivery and therapeutic efficacy. In spite of these advancements, the clinical translation of these technologies has remained unpredictable. Variability in immune system infiltration, tumor vasculature, and ECM composition significantly influences NP accumulation within tumors. Therefore, therapeutic effectiveness can be inconsistent, even under appropriate suboptimal EPR conditions. Factors such as surface properties, NP size, and circulation time can affect biodistribution and clearance of NPs, leading to challenges such as off-target delivery and rapid clearance by the immune system. In conclusion, although the EPR effect serves as a basis for cancer nanomedicine, its clinical application is limited by tumor heterogeneity and variations in therapeutic responses. Recent approaches, such as TME modulation and the use of external physical stimuli—including high temperature, light, magnetic field, electric field, ultrasound, pH, and enzymes—are increasingly being applied in chemotherapy and radiotherapy (Table S1). Additionally, ligand-targeted NPs show potential to improve therapeutic outcomes. However, continuous refinement and careful patient stratification are essential for the successful clinical translation of EPR-based therapies[18]. The EPR effect not only promotes drug accumulation in tumors but also faces significant challenges from interstitial pressure and the structural irregularities of tumor vasculature. The elevated interstitial pressure and permeable blood vessels hinder drug delivery, thereby diminishing the advantages of the EPR effect. As previously discussed, while the EPR effect facilitates the passive delivery of therapeutic agents, the complex structure of tumor blood vessels—particularly under hypoxic conditions—increases interstitial pressure, which can further diminish this effect[19]. In certain situations, such as inflammation or hypoxia within cancerous tissues, blood vessels exhibit heightened permeability. The gap between these vessels can exceed 100 nm, and, in some cases, reach up to 800 nm, as shown in Figure 3[20]. Under hypoxic conditions, the rapid growth of tumors stimulates the proliferation of new blood vessels by altering and extending pre-existing vessels, giving rise to newly formed and leaky vessels. This vascular dysfunction selectively enhances the penetration of macromolecules larger than 40 kDa and nanosystems into the tumor stroma[21].

The leakiness of the newly formed tumor vessels significantly impacts nanomedicine permeation. This enhanced leakiness causes an increase in the interstitial pressure, which can prevent the accumulation of drug carriers within the tumor. Furthermore, due to the varying pro- and anti-angiogenic signals across different tumor regions, the blood vessels often exhibit abnormalities characterized by tortuous, saccular, and dilated channels, as well as disorganized branching and interconnections[15]. Tumor cells do not consistently proliferate in response to a heterogeneous blood supply; hence, cells located near blood vessels tend to proliferate more rapidly and receive less oxygen and nutrients compared to those situated in the tumor core. These data highlight the presence of hypoxic/necrotic regions within the cores of large tumors, where nanomedicines struggle to deliver the molecule to the heterogeneous region effectively. This phenomenon has been documented in numerous human and murine tumors. The elevated interstitial pressure inhibits drug delivery through convection and compresses newly formed blood vessels, redirecting blood flow from the center of the tumor to its periphery[19]. To improve tumor perfusion, certain molecules can promote vascular normalization or induce hypertension. Other techniques, including radiation, ultrasound, photo-immunotherapy, and hyperthermia, can moderate tumor vasculature and enhance the permeation of nanosystems. However, all of these methods have

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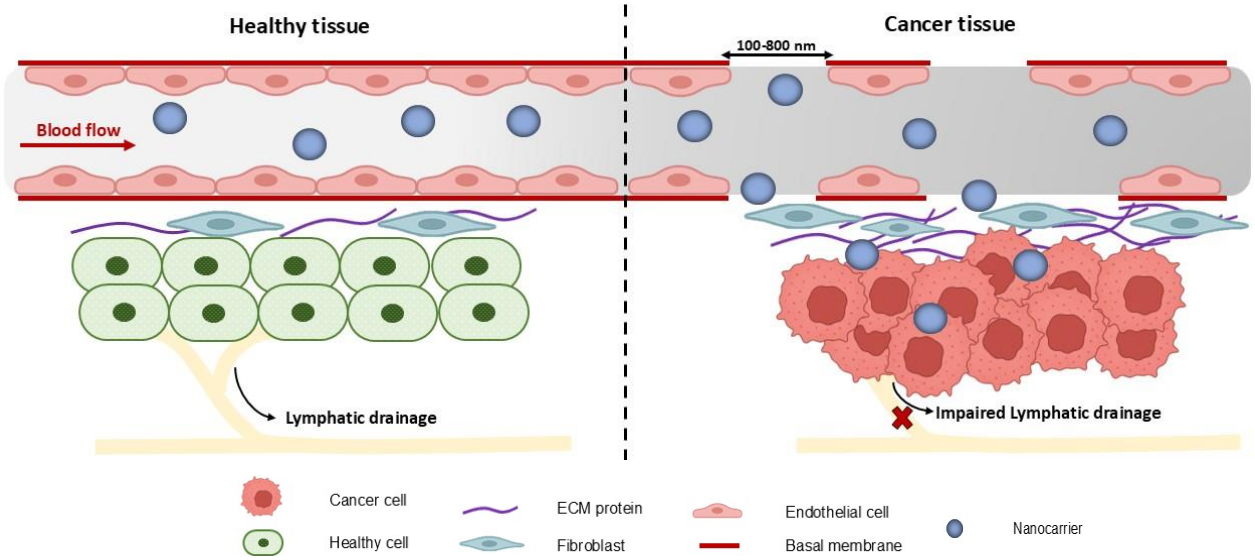

Fig. 3. Principle of the EPR phenomenon. Healthy tissues possess intact blood vasculature, which inhibits the extravasation of NPs. Cancerous tissues exhibit compromised blood vasculature and deficient lymphatic drainage, facilitating the extravasation and accumulation of NPs.

contraindications and limitations that must be taken into account carefully[19,22]. Active targeting strategies complement passive methods, facilitating the administration of therapeutic agents that face challenges in traversing cell membranes, which may harm healthy tissues. These strategies involve modifying the surfaces of nanocarriers with ligands that specifically target cancer cell surface receptors; however, this process can introduce complexities regarding chemistry and bioavailability. Ultimately, NPs must navigate the complexities of the TME to ensure effective drug delivery. This form of passive targeted drug delivery exemplifies a significant application of medicinal nanotechnology[20].

Nanocarriers have been developed as a promising DDS, providing numerous advantages over conventional passive delivery methods. Different nanocarrier systems include nanolipid delivery systems such as NEs, protein, polymeric, and lipid NPs carriers, to enhance drug delivery efficiency[23]. Table 1 compares these carriers in drug delivery in terms of their advantages and limitations[24]. Table 2 compares their key characteristics. Nanocarriers are colloidal-sized particles with diameters ranging from 1 to 1000 nm, transporting drug molecules either encapsulated, adsorbed, or dispersed within them. They enhance the stability of the hydrophobic drugs, facilitate administration, and improve biodistribution and pharmacokinetics, thereby increasing efficacy. Despite the many advantages over conventional therapy, NPs can pose risks of tissue and organ toxicity due to their diverse biodistribution profiles. Several physical and chemical properties, such as size, charge, and surface chemistry, influence the toxicity and pharmacokinetic profiles of NPs[25].

Nanocarrier systems

NE carriers

Many researchers are investigating NEs due to their application in pharmaceutics, cosmetics, and the food industry. In the pharmaceutical industry, NEs have been proposed as DDS due to their ability to solubilize non-polar active compounds for targeted delivery and controlled release of substances. They are utilized in the treatment of cancer and fungal infections. Moreover, NEs are employed for ocular drug delivery in ophthalmic formulations[26]. One study developed an NE-based system as a topical ocular therapy to enhance the efficacy of moxifloxacin in ophthalmic drug delivery[27].

Protein NP carriers

Protein NPs show significant promise for drug delivery. Ligand-decorated nanocarriers transport pharmaceuticals to their target sites, such as the cytoplasm or nucleus, through receptor-mediated endocytosis. This process helps reduce toxicity and off-target effects. An innovative theragnostic system can monitor disease progression and treatment efficacy in real-time by using either an active or passive drug carrier alongside a diagnostic or imaging agent. These systems have been developed based on tumor biology and novel drug carriers. To date, only 15 passively targeted nanocarriers have received approval for clinical

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Table 1. A comparative analysis of drug delivery carriers: advantages, disadvantages, and relative therapeutic effectiveness[24]

Carrier	Advantages	Disadvantages	Relative effectiveness
NE	Efficient transport of active compounds across a semipermeable membrane, enhanced absorption owing to the extensive surface area	Constraints related to stability, temperature, and pH pose challenges for compounds with elevated melting points due to their inadequate solubility	
Protein NP	Elevated drug loading capacity, favorable for in vivo tolerance	Variations between batches	
Polymeric NP	Enhanced drug delivery versatility through the encapsulation of various therapeutic agents, facilitating modification of size, surface characteristics, and drug release kinetics, rendering them highly customizable for targeted drug delivery applications	Potential for toxicity and immunogenicity, difficulty in achieving precise control over drug release kinetics, and the variability in degradation factors such as pH, temperature, and enzymatic activity	This method of targeted drug delivery reduces off-target effects and enhances therapeutic efficacy
Lipid NP	Biocompatibility, controlled release, and degradation protection	Inconsistent mechanisms of action, labor-intensive and costly engineering and manufacturing processes, restricted feasibility for extensive clinical application, potential toxicity and difficulty in eliminating substances from the body for clinical applications, pertinent stability and prolonged storage as their degradation or efficacy diminishes over time, difficulties in scaling up owing to the necessity for meticulous regulation of particle size and distribution	The intricate interactions between different drugs within the NPs likely influence their effectiveness and overall therapeutic results, restricted effectiveness in targeting multidrug-resistant tumor cells results in minimal impact on the cells and suboptimal treatment outcomes

use, and none of the actively targeted nanocarriers have completed clinical trials, despite numerous preclinical studies. The low success rate is attributed to physiological challenges, including hypoxia, tumor infiltration, tumor heterogeneity, and difficulties with endosomal escape[28]. Free drug molecules enter the bloodstream through oral administration or injection. Owing to their small particle sizes, they can pass through the spaces between the endothelial cells of blood vessels and disperse throughout the body. In contrast, nanodrugs have larger particle sizes, which contribute to the prolonged circulation within the bloodstream, particularly in the form of PEG-coated. As a result, the likelihood of delivering drugs to the diseased areas using nanocarriers would be significantly higher compared to free drugs[20]. Some of these nanocarriers, such as the commercially available Caelyx© and Doxil©, have become the gold standard in passive tumor targeting design, as they demonstrate effective clinical applications of the EPR impact[16]. Unlike normal organs, the EPR effect increases tumor specificity by 20-30% during drug delivery. This effect is highly dependent on several intrinsic tumor biological factors, specifically: (1) intratumoral pressure; (2) the degree of perivascular tumor growth and stromal response density; and (3) the extent of lymphangiogenesis and angiogenesis. These physicochemical properties of nanocarriers will influence the drug delivery efficacy[13], as illustrated in Table 3.

Polymeric NPs carriers

Conjugated polymer drugs are emerging as a prominent class of nanoscale anticancer therapies, especially as passive targeting systems that include platinum-based anticancer agents. Polymer-based DDS typically utilizes the differences between healthy and cancerous tissues to improve drug selectivity and efficacy for targeted treatments. As innovative and practical solutions, they effectively address the limitations of traditional chemotherapy[29]. In this context, both synthetic and natural polymers have

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Table 2. Comparison of the key properties of NE, protein NP, polymeric NP, and lipid NP carriers in DDSs

Carriers	Size (nm)	Targeting ability	Half-life	Clinical status	Ref.
NE	20-200	Moderate to high targeting ability, modified for targeted delivery (e.g., active targeting through ligands)	Varies widely (hours to days) based on polymer type and biological interaction	Numerous present in clinical trials; a few are approved for specific applications	[26]
Protein NP	50-300	High targeting ability, ability to be engineered for specific binding to cells or tissues	Generally, a short half-life (minutes to hours) due to rapid metabolism	Some in clinical trials, limited FDA-approved products	[86]
Polymeric NP	10-1000	High targeting potential; programmable for site-specific delivery with functionalization	Generally longer half-life (hours to days) due to stability in circulation	Increasing number of clinical trials, some approved for drug delivery	[30]
Lipid NP	50-500	Good targeting ability, commonly used in mRNA and vaccine delivery systems	Short to moderate half-life (minutes to hours) depending on formulation	Widely used in clinical applications (e.g., vaccines and gene therapies), with multiple FDA approvals	[87]

demonstrated potential in facilitating the delivery of platinum-based medications. PVP, PEO, poly(N-(2-hydroxypropyl) methacrylamide), and PEG are the commonly used polymers[30]. Compared to small-molecule chemotherapeutic drugs, DDSs have the potential to reduce the limitations of conventional formulations, such as (i) controlled drug release and extended blood circulation, (ii) enhanced solubility via the encapsulation of insoluble drugs, and (iii) the ability to combine multiple drugs. Drug targeting and delivery carriers are designed to be biodegradable and biocompatible, and by incorporating functional groups, the selectivity and solubility will be increased. Polymeric nano-carriers are categorized into five main types: dendrimers, nanogels, micelles, capsules (comprising vesicles), and hybrid NPs with porous cores[31,32]. Passive tumor targeting, facilitated by the EPR effect, is recognized as an effective strategy for promoting the accumulation of small, long-circulating NPs in solid tumors. Factors such as tumor growth rate, presence of growth factors, and hypoxia stimulate the rapid development of tumor vasculature, resulting in the formation of immature vessels that are characterized by fenestrations. These structural abnormalities allow the extravasation of relatively large particles into the tumor microenvironment. The maximum size of particles that can extravasate into the tumor interstitium is determined by the cutoff size of these fenestrations[14].

Lipid NPs carriers

LNPs have demonstrated passive targeting capabilities. Sclareol-SLNs, with an average size of 88 ± 5 nm, showed a significantly higher inhibitory effect on the expression of human lung epithelial cancer cells A549 after 48 hours compared to the drug alone. These SLNs also facilitated a prolonged release of the medication[33]. Additionally, passive tumor targeting with curcumin-conjugated SLNs exhibited remarkably higher tissue availability in breast cancer models[34]. Furthermore, a growth inhibition of 50.5% was observed in Hodgkin's lymphoma xenografts treated with curcumin-SLNs[35]. In a study focused on passive targeting for glioblastoma and melanoma, temozolomide-conjugated SLNs indicated greater inhibition of cancer tissue proliferation with less cytotoxicity to healthy cells compared to temozolomide without the SLN[36].

FDA-approved drugs utilizing passive targeting mechanisms

Most FDA-approved nanomedicines have been developed based on passive targeting through the EPR effect[37]. Nanocarriers should be stable in the bloodstream until they reach the TME to evade clearance by the reticuloendothelial system and avoid being captured by the mononuclear phagocyte system. While active targeting ligands can enhance the therapeutic specificity and efficacy of nanomedicines, they may also be recognized and cleared by the immune system. Passive targeting is applied in various pathologies and has significantly improved Bioavailability and biodistribution[38]. Currently, at least 15 cancer nanomedicines that utilize EPR-mediated passive tumor targeting has received clinical approval. Among these, PEGylated liposomal DOX (Doxil®) was the first FDA-approved nanomedicine, whereas paclitaxel micellar (Apealea®)[39] is among the most recently approved

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Table 3. Some passive targeted nanocarriers used for diagnostic therapeutic purposes

Carrier	Ligand (coating shell)	Imaging or therapeutic agents	Application	Ref.
NE	PEGylated hydrophilic molecules (Kolliphore ELP)	Iodinated mono glyceride and iodinated castor oil, contrast agents	Blood pool imaging agents, accumulated particularly in the liver or spleen, and imaged by X-ray CT	[88]
Albumin NP	–	TAC	TAC-loaded HSA-NPs target inflamed joints in rheumatoid arthritis tissues	[89]
Polymeric NP	C18PMH-PEG	Fe_3O_4 contrast agent and the DOX drug	Magnetically controlling drug delivery and serving as a contrast agent in T2-weighted MR imaging (theranostics)	[90]
LNC	Polysaccharides, Lipochitosan, lipodextran	DiD fluorescent dye	Selective for mice bearing HEK293(β3) tumors, detected by fluorescent imaging	[91]

ELP: extra low peroxide; TAC: tacrolimus; LNC: lipid nanocapsules

formulations. Nanomedicines employ NPs ranging from 1 to 100 nm to reduce toxicity, improve targeting, or boost the efficacy of therapeutic or imaging agents in vivo. In addition to intravenous or oral administration, transdermal delivery methods, such as Estrasorb™, are also available. These advancements are achieved by conjugating NPs with existing medications to modify their PD and PK properties. Most NP/drug conjugates are passively targeted by non-specific accumulation in the diseased tissues, particularly solid tumors. They enhance the concentration of nanomedicines in the TME through the EPR effect[37]. Liposomes were the first nanomedicines to enter FDA clinical trials. Classical liposomes used for intravenous delivery exhibit short half-lives due to the rapid clearance from circulation, as their lipid bilayer structure leads to immune system recognition and subsequent clearance by macrophages; however, surface PEGylation has reduced this clearance. The number of trials and approvals involving liposomal delivery has increased since the mid-1990s, starting with the approval of liposomal formulations of DOX and amphotericin B[40]. PEGylated liposomal DOX (Doxil®) is notable for effectively reducing the cardiotoxic effects of doxorubicin. Doxil® has been approved for metastatic breast cancer, ovarian cancer, multiple myeloma, and Kaposi's sarcoma. Compared to free doxorubicin, the PEGylated liposome demonstrated a 4- to 16-fold increase in drug concentration in malignancies[41]. The PEGylated liposomal carrier was later modified for the delivery of other drugs, such as amphotericin B (Ambisome®) for fungal infections and verteporfin (Visudyne®) for wet macular degeneration. Many approved liposomal formulations use passive targeting to effectively improve drug delivery to diseased tissue. Liposomal irinotecan (Onivyde®), a topoisomerase I inhibitor, is the most recently approved liposomal drug carrier used as a second-line treatment for metastatic pancreatic cancer, which relies on passive targeting[42]. Albumin-bound paclitaxel (Abraxane®), approved by the FDA in 2005, is an example of protein-drug conjugation, designed in the form of a particle to eliminate the need for the toxic solvent Cremophor in paclitaxel delivery. Abraxane® is a type of protein-drug NP that excels in refining toxicity and passive delivery to specific targets, and accumulates in tumors via the EPR effect[43]. Incorporation of active and passive targeting in DDSs is a hypothesis that could increase drug uptake and therapeutic efficacy while preventing clearance by the reticuloendothelial system. Living systems are complex and rely on both active and passive transport mechanisms, necessitating a detailed investigation of these processes, either separately or in combination. Combining actively and passively targeted DDS will extend circulation time, allowing the targeting agent enough time to interact with its targets. The PK parameters of these delivery systems should be thoroughly investigated to better understand these processes[44]. In vitro and in vivo studies performed by Kudgus and colleagues on ACG44 nanoconjugates have indicated high tumor growth inhibition in an orthotopic preclinical model of pancreatic cancer. They investigated the pharmacokinetics of ACG44 and AIG44 PKs, as well as the impacts of passive targeting to moderate circulation time for improving gold NP activity[45]. Prior reports have shown that a long plasma half-life can enhance the uptake of therapeutic agents,

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diagnostic tools, or imaging materials, which is a crucial objective in these fields[46]. Passive targeting through the EPR effect has been employed to support this goal[19]. It has been hypothesized that nanoconjugates acting through both active and passive targeting mechanisms could further improve therapeutic effectiveness. Combining 2 kDa dithiol PEG with ACG44 nanoconjugates to create ACG44p2k demonstrated that PEGylation caused significant differences in pharmacokinetics and plasma clearance compared to unPEGylated conjugates. PEGylation is expected to decrease clearance rates and increase the exposure of the nanoconjugate to target cells[47]. Likewise, advanced polymeric NPs, such as peptide vaccines, are being developed for cancer immunotherapy. Notably, a phase I clinical trial (NCT00199849) has been completed using the NY-ESO-1 DNA vaccine (pPJV7611, plasmid) for tumor vaccination[48] (Tables S1 and S2).

Active targeting

Active targeting has revolutionized the field of drug delivery by delivering therapeutic agents specifically to the abnormal cells while minimizing side effects on healthy tissues[49]. This innovative approach is achieved by attaching drug carriers to the specialized molecules (targeting moieties), such as antibodies or peptides. These moieties selectively bind to the receptors that are overexpressed on the surface of abnormal cells. Compared to traditional drug delivery methods, active targeting offers several advantages. It increases drug concentration at the target site, reduces side effects and exposure to healthy tissues, and enhances overall therapeutic efficacy. This strategy holds significant promise for advancing the treatment of conditions such as inflammation, infections, and cancer[49].

Active targeting moieties

Antibody

Antibodies are glycoproteins that belong to the immunoglobulin superfamily. They can specifically recognize and bind to their target antigens. The antigen-binding fragment of an antibody is responsible for recognizing these antigens, while the Fc region mediates interactions with components of the immune system[45]. Antibodies can trigger cancer cell death through different mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, ligand blocking, and receptor blocking[50]. Several formats of mAbs, such as full-length structures, antigen-binding fragments, and single-chain variable fragments, have enhanced targeted therapies[51]. While mAbs have demonstrated efficacy as single agents for cancer treatment, their effectiveness is often not as much as traditional chemotherapy. This limitation has led to the development of combination therapies and DDSs[50]. For effective active drug delivery, the target antigen must be widely distributed, readily available, and uniformly generated on the surface of cancer cells[52]. Various antibodies are utilized in drug delivery due to their unique ability to recognize specific targets. The most common targets in cancer-targeted therapies include *HER2*, *EGFR*, *CEA*, *VEGF*, and *PSMA*[53]. Roncato et al. have designed a targeted therapy for breast cancer using cetuximab, an antibody that specifically binds to EGFR, a protein that is frequently overexpressed in various cancers. They modified ANANAS NPs with PEG-cetuximab for targeting *EGFR* and attached them to the hydrazone-linked DOX to exert cytotoxic effects. Cetuximab enhanced the ability of the NPs to be accumulated in tumor cells and internalized by *EGFR*-expressing cancer cells. Moreover, MDA-MB-231 cells absorbed cetuximab-conjugated ANANAS more efficiently than untargeted NPs, suggesting the potential of this platform for cancer treatment[54]. ADCs represent a novel and efficient method for cancer treatment that combines the targeting capabilities of mAbs with the potency of cytotoxic drugs. This strategy enables the selective destruction of tumor cells while minimizing damage to healthy tissues. To date, 14 ADCs have received FDA approval for treating different blood and solid tumors, with many others in clinical development[55]. ADCs consist of mAbs linked to cytotoxic drugs, often via a chemical linker. The mAb component of ADC specifically binds to a tumor-specific antigen, facilitating the targeted delivery of the cytotoxic payload directly to the cancer cells. Once internalized by the cancer cell, the linker releases the cytotoxic drug, triggering the destruction of tumor cells[56]. Ado-T-DM1, marketed as Kadcyla, was developed by Roch and it was the first FDA-approved ADC for treating solid tumors, specifically *HER2*-positive breast cancer[57]. Ado-trastuzumab emtansine (T-DM1) targets *HER2*, which is overexpressed in 15-20% of breast cancer patients. The T-DM1 combines trastuzumab, a *HER2*-binding mAb, with the cytotoxic drug DM1. Non-cleavable linker, (Succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate), holds them together[58]. T-DM1 has been compared to lapatinib and capecitabine for *HER2*-positive breast cancer in the EMILIA study. The trial found that T-DM1 was more effective than lapatinib plus capecitabine. T-DM1 had 43.6% ORR, while lapatinib-capecitabine had 30.8%[59]. The T-DM1 arm had a median PFS of 9.6 months, while lapatinib plus capecitabine had 6.4 months. Lapatinib plus capecitabine had a median OS of 25.9 months, while T-DM1 had 30.9 months[55].

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Aptamers

Aptamers are small, synthesized single-stranded oligonucleotides that can selectively bind to a wide range of targeted molecules, including proteins, nucleic acids, tiny compounds, and even cells and tissues[60], which offer several advantages over mAbs. Aptamers have a simpler and more reproducible production process and do not induce immunogenic reactions[61]. Their ability to adopt distinct secondary and tertiary structures enables them to create precise three-dimensional conformations, allowing for highly specific binding to their targets. The selection of high-affinity aptamers is achieved through the SELEX method. This process begins with a large pool of random oligonucleotide sequences. Through several rounds of binding, aptamers with higher target affinity are amplified and selected. The resulting aptamers exhibit exceptional sensitivity and specificity, making them highly suitable for various applications in biosensors, therapies, and diagnostics[61]. Due to their high affinity and structural versatility, aptamers are powerful tools for drug delivery. Scientists can design targeted therapies that focus on overexpressed receptors on cancer cells by creating bioconjugates, such as aptamer-drug or aptamer-NP conjugates. This approach allows for efficient drug delivery with minimal off-target effects[62]. A notable example is AS1411, a DNA-based aptamer developed by Bates and colleagues. This aptamer adopts a G-quadruplex structure and exhibits strong affinity for nucleolin, a protein expressed on the cell surface and in the cytoplasm of cancer cells, but not found in healthy cells. This selective expression makes the AS1411, a DNA-based aptamer, ideal for targeting tumors and facilitating drug delivery[62].

Hyaluronic acid

HA is a water-soluble polysaccharide known for its high viscoelasticity, biodegradability, and negative charge. Structurally, HA is made up of continuously connected disaccharide units consisting of glucuronic acid and N-acetylglucosamine. HA is a major component of ECM and belongs to the glycosaminoglycan family. One notable feature of HA is its wide range of molecular weights, which can vary from 100 to 5000 kDa. High molecular weight HA has anti-inflammatory properties, as it can suppress pro-inflammatory mediators, whereas low molecular weight HA promotes angiogenesis and cell proliferation[63]. AHA plays essential roles in various biological processes by interacting with and influencing cell surface receptors. Among these receptors, CD44 is the primary mediator of HA effects. CD44 is typically expressed at low levels in normal cells but is overexpressed in many types of cancers, including breast, melanoma, lymphoma, colorectal, and lung. This differential expression makes CD44 an attractive target for HA-based therapies. The unique properties of HA and its ability to bind only to the overexpressed CD44 receptors have shown promise for usage as a natural ligand in active targeted therapy[64]. Researchers have developed a CD44-targeted nanophotodynamic agent known as HANP/Ce6, which consists of NPs coated with HA and delivers the photosensitizer Ce6 to CD44-expressing cells. To assess its therapeutic efficacy, researchers administered HANP/Ce6 to the mice bearing human colon cancer tumors. The combination of HANP/Ce6 and laser irradiation resulted in a 10-fold reduction in tumor growth compared to the untreated mice. In addition to its therapeutic effect, HANP/Ce6 has demonstrated theranostic capabilities by combining targeted treatment and imaging potential, highlighting its promise for clinical translation in CD44-targeted cancer therapy[65].

Peptide

The specific arrangement and composition of amino acids in peptide structures contribute to the diversity of peptide classes, each exhibiting distinct properties and biological functions[12]. A key feature of peptides is their capacity to specifically recognize and bind to target molecules. This capability paves the way for developing targeted cancer therapies that utilize peptides to target the overexpressed tumor receptors. Peptides can enter tumors and pass through cell membranes due to their high sensitivity and selectivity[66]. Additionally, peptides are recognized for their low immunogenicity, indicating that they do not trigger harmful immune responses. Peptides offer various advantages for targeted therapy applications, including high specificity for targets, ease of production, simplified conjugation processes, biodegradability, biocompatibility, and the possibility of modifying peptide sequences and conjugation sites[67]. The phage display is a powerful technique for identifying peptides with high specificity toward a target molecule. In cancer therapy, peptides are valuable ligands as they can address multiple aspects of cancer, including cellular organelle-targeted peptides (plasma membrane, nucleus, and mitochondria), tumor-targeted peptides (different tumor cellular surface receptor targeting), and TME-targeted peptides (tumor vascular system targets, tumor ECM targets, and tumor-associated cell targets)[12]. Integrins are cell surface receptors composed of α and β subunits and play a key role in regulating various cellular functions, such as cell growth, cell morphology, interaction with the ECM, cell movement, and apoptosis. Integrins are also implicated in cancer metastasis and angiogenesis[51]. Research has

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indicated that several cancer types, including breast, prostate, melanoma, and ovarian cancers, increase integrin expression in their vascular endothelial cells. This behavior makes the integrin superfamily an interesting target for cancer-specific therapies. The RGD domain has a high affinity for integrins and promotes cell adhesion by linking ECM proteins (e.g., vitronectin and collagen) to integrins on the cell surface[51]. In 2018, Lu et al. utilized NPs to deliver RGD peptide for targeted cancer therapy[68]. In this context, the RGD domain was used to modify the NPs. New NPs are linked to a large gelatin NP that can be degraded by matrix metalloproteinases-2. On the other hand, metformin can stop cancer progression by blocking NF-κB nuclear translocation and preventing inflammation. However, its non-targeted action and short plasma half-life limit its accumulation at tumor sites. In combination therapy, studies have shown that a lower dose of DOX, a chemotherapy drug, is effective when combined with MET. MET or DOX NPs are formed through acid-labile imino bonding with the NPs. These larger NPs remain in circulation longer and accumulate at tumor sites. After reaching the tumor, the gelatin core of NPs breaks down due to the elevated levels of matrix metalloproteinases-2 in the TME. This degradation allows smaller NPs linked to the RGD peptide and leads to deeper penetration of DOX or MET into the tumor. DOX and MET are released when TME breaks the imino bond due to its acidity. In other words, the imino bond is broken down quickly in lysosomes, releasing MET and DOX, which reduces inflammation by inhibiting NF-κB and exerting direct cytotoxic effects on cancer cells. Animal studies have shown that intravenous administration of NPs can precisely target tumors and inhibit tumor growth and metastasis. In the CT26 and 4T1 xenograft tumor models, co-administration of RDDG and RDMG NPs is more effective in cancer treatment by targeting tumors and cancer-related inflammation[68].

Folate

Vitamins are essential micronutrients that are necessary for cell survival and maintenance of optimal physiological functions. Due to rapid growth and proliferation, cancer cells require high levels of certain vitamins, particularly folate and biotin[69]. In response to this elevated requirement, cancer cells upregulate the expression of vitamin receptors on their surface, making these receptors attractive targets for targeted cancer therapies[70]. The water-soluble vitamin B9, known as folate, is essential for cell growth and DNA biosynthesis. Its low molecular weight (441.4 g/mol) and favorable physicochemical properties make it highly suitable for application in drug delivery and gene therapy[71]. Folate is highly water-soluble, which allows it to conjugate with various carriers without losing target specificity. It is stable under both high and low pH levels and elevated temperatures. Furthermore, folate is non-toxic and non-immunogenic, with reduced side effects. These features of folate make it a good candidate to develop specific therapies with limited side effects[51].

Transferrin

Tf is a widely distributed iron-binding glycoprotein with a molecular weight of ~80 kDa. This protein is composed of 679 amino acids and two carbohydrate chains, which are essential for binding and transporting iron throughout the bloodstream. It has a very high affinity for Fe^{3+} and can bind to two iron ions at the same time[72]. TfR is a specific receptor for Tf and has two main types: TfR1 and TfR2. TfR1, also known as CD71, is the primary form of TfR and is responsible for transporting iron-loaded Tf into cells[73]. While TfR1 and TfR2 have similar structures, their affinities for holo-Tf differ significantly. TfR2 has an affinity approximately 27 times lower than that of TfR1[74]. In normal cells, the expression of TfR is relatively low; however, it is notably elevated in the vascular endothelium of brain capillaries and in fast-reproducing cells, such as cancer cells, where it contributes to cancer progression[75]. Tf binds to TfR1 and TfR2 and enters cells through receptor-mediated endocytosis. This strategy facilitates the transport of iron-loaded Tf into cells. The unique features of Tf, such as its high specificity for TfR, the ability of the receptor to internalize the Tf-TfR complex, and its elevated expression in cancer cells and brain capillaries compared to normal cells, make it an excellent candidate for targeted cancer therapy and brain-related treatments[76]. Researchers have designed TF-LP-DOC for targeted therapy in ovarian cancer[77]. DOC, a taxane-based anticancer drug, kills cells by preventing microtubule depolymerization and reducing the expression of the *bcl-2* and *bcl-xL* genes[78]. The presence of Tf on the liposomes enhances receptor-mediated endocytosis of the complex into cancer cells. As a targeting agent, Tf increases tumor drug accumulation and cancer cell uptake. In the studies, TF-LP-DOC demonstrated higher anticancer activity relative to free DOC and LP-DOC, mainly due to the docetaxel-loaded liposomes. Additionally, it showed less toxicity to normal cells when compared to LP-DOC and free DOC. In vivo studies have also revealed that TF-LP-DOC has the highest survival rate among the three groups, suggesting the Tf-loaded DOC liposomes as promising candidates for targeted ovarian cancer treatment[77] (Table S3).

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DISCUSSION

Drug carriers have exhibited a remarkable capacity to protect macromolecules during dissolution. In recent decades, the development of scientifically advanced, nanovectors, functionalized with active targeting ligands, has significantly improved the performance of these carriers. A main feature of modern nanocarriers is the integration of targeting ligands, which facilitate the precise delivery of therapeutic agents to specific tissues and cells. This strategy, known as active targeting, involves engineering ligands that selectively bind to endothelial or cancer cells, thereby enhancing the efficacy of targeted drug delivery. Advancements in drug delivery techniques could improve treatment outcomes, enable precise disease targeting, and reduce overall therapeutic costs. This comprehensive review explores recent advancements in targeted drug administration, focusing on the pharmacokinetics of delivery systems and the selection of carriers for both active and passive targeting methodologies. Active targeting is expected to revolutionize the pharmaceutical landscape by increasing the market size of the drugs that were previously difficult to sell. Clinical evidence demonstrates that technological advancements and innovations have facilitated the treatments that were previously considered unachievable. The effectiveness of DDSs is anticipated to improve substantially through targeted methodologies. Active targeting offers distinct advantages, including localized drug delivery, controlled release, and maintained biocompatibility. Moreover, active targeting often demonstrates modified pharmacokinetics and diminished systemic toxicity—key factors in the development of safer and more effective therapeutics. Notwithstanding these promising advancements, several clinical obstacles inhibit the wider clinical implementation of DDSs. These limitations include drug instability, premature release, limited bioavailability, off-target effects, and intricate regulatory challenges[79]. Recent clinical observations—such as the stability concerns associated with specific mRNA-based vaccines and the restricted tissue penetration of NP drugs such as Doxil—highlight the need for more effective delivery systems. To overcome these challenges, researchers have designed stimuli-responsive nanocarriers (such as pH- or redox-sensitive systems) capable of releasing therapeutic agents in response to specific microenvironments. Moreover, surface modification techniques—e.g., PEGylation and zwitterionic coatings—have displayed potential in extending circulation times and improving immune evasion[80,81]. This review emphasizes the significance of both active and passive drug delivery techniques in cancer therapy. Future research should focus on developing multifunctional nanocarriers that combine diagnostic, therapeutic, and monitoring capabilities ("theranostics") within a singular platform[82]. By incorporating technologies such as CRISPR/Cas9 for gene editing, RNA-based treatments, and immune-modulating therapies, scientists are opening the door to exciting new possibilities for treating diseases[83]. LNP, an effective tool for delivering siRNA and mRNA in clinical trials, has shown a significant advancement in nucleic acid-based therapies. These clinical achievements establish a basis for forthcoming DDS formulations aimed at treating not only cancer but also genetic and infectious diseases[84].

Cooperative initiatives among bioengineers, oncologists, and data scientists will be crucial for managing artificial intelligence and machine learning to optimize drug formulations and predict patient-specific responses[85]. These innovative approaches are changing the way we think about cancer treatment, enabling real-time treatment adjustments for improved patient outcomes. Combining personalized medicine with advanced imaging could enhance DDS, resulting in customized and effective treatment strategies that meet individual patient needs.

CONCLUSION

Optimizing cancer DDSs is essential for improving therapeutic outcomes and addressing the urgent need for patient-centered, compassionate care. Future research is required to concentrate on overcoming challenges posed by TME and the biological barriers that inhibit effective therapeutic delivery. Addressing these obstacles will facilitate innovative progress in cancer treatment, ultimately enhancing the lives of patients affected by the disease. The ongoing enhancement of DDSs, supported by targeted and personalized approaches, holds promise for the future of cancer treatment. A clear vision for future research entails combining advanced nanotechnologies with personalized medicine, designing intelligent nanocarriers capable of real-time responsiveness, and developing standardized guidelines for clinical implementation and regulatory validation. The primary objective is to enhance not only survival but also the quality of life for cancer patients via safer, more effective, and widely accessible therapeutic interventions.

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Authors' contributions

PT: study conception and design, and draft manuscript preparation; SMME: analysis and interpretation of results and draft manuscript preparation; AE: data collection; SZM: study conception and design and data collection; PM: study conception and design, analysis and interpretation of results, and writing and editing.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests

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