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Tumor Discovery

REVIEW ARTICLE

Targeted drug delivery approaches for the management of tumors

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Abstract

The treatment of tumors requires specific and selective drug delivery approaches capable of efficiently eliminating the root cause of oncogenesis. In this context, targeted drug delivery strategies are the preferred choice due to their exceptional recognition of tumor cell biology and their high transfection efficacy within the tumor microenvironment. The emergence of nanoscale techniques has marked significant milestones in the successful management of various types of tumors. The development of targeted delivery approaches for tumor therapeutics has gained momentum over the past few decades. However, in contrast to the plethora of successful pre-clinical studies, only a limited number of passively targeted nanocarriers have been approved for clinical use, and none of the actively targeted nanocarriers have advanced beyond clinical trials. This review delves into the major molecular principles associated with tumorigenesis, including active targeting, passive targeting, and cell-mediated targeting. It also explores the biological barriers (systemic, biological, and cellular) encountered in tumor drug delivery. Moreover, the review examines various tumor-targeted drug delivery systems that have been developed over the past decade. These systems encompass polymeric nanoparticles (micelles, nanoparticles, dendrimers, and polyplexes), lipid-based carriers (solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsion), vesicular systems (liposomes, niosomes, aquasomes, and phytosomes), and inorganic nanocarriers (iron oxide nanoparticles, quantum dots, carbon-based nanoparticles, and mesoporous silica nanoparticles), all designed for the alleviation of tumors.

Keywords: Oncogenesis; Transfection efficacy; Microenvironment; Biological barriers; Nanocarriers

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1. Introduction

Tumors are defined as abnormal growth of cells that proliferate and differentiate more rapidly than normal cells and do not undergo programmed cell death. Tumors can be classified as benign (non-harmful) or malignant (neoplasm and cancerous). Although benign tumors can grow large and do not invade neighboring cells/tissues in other parts of the body, they can be life-threatening if they compress vital organs, including blood vessels or nerves[1]. In contrast, malignant tumors exhibit high aggressiveness, invade adjacent tissues, and have the potential to spread through the body's vascular systems

(circulatory and lymphatic systems). It is estimated that every year, approximately 10 million individuals suffer from malignant tumors, and around 1.3 million of them succumb to the disease. Advanced medical and pharmaceutical strategies, including surgical procedures, radiotherapy, chemotherapy, and targeted drug delivery systems, have contributed to a reduction in mortality rates over the past 5 years.

According to a report by the Personalized Medicine Coalition report (2017–2023), the introduction of personalized medicine has proven to be a successful approach in oncology, constituting approximately 50% of Food and Drug Administration-approved antitumor therapeutics. Malignant tumors, commonly referred to as cancers, exhibit six hallmarks, including the activation of the proliferative signaling pathway, the inhibition of growth suppressors, resistance to cell death, the acquisition of replicative immortality, the promotion of angiogenesis, and the facilitation of metastasis. These hallmarks play pivotal roles in the development of tumors and cancer[2]. In a nutshell, tumor cells exhibit highly differentiated and disordered tissue structures, along with anomalous vasculature compared to normal cells. The deprivation of essential nutrients and oxygen supply results in increased interstitial pressure within cells, leading to an acidic and hypoxic environment. Hypoxia-inducible transcription factors (hif1 and hif2) are implicated in promoting distant metastasis and mediating the progression of tumor cells[3].

Moreover, disorganized tumor cells exhibit inefficiencies in proton efflux to the extracellular environment, leading to a hypoxic environment that disrupts the regulation of glycolysis, adenosine triphosphate (ATP) generation, and lactate production. At the molecular-level, these variations and alterations in the tumor's architectural profile differentiate them from normal cells. Tumor cells exhibit remarkable efficiency in mass-producing a range of factors, such as growth factors, transferrin, interleukins, cytokines, chemokines, proteases, and sugar moieties that play crucial roles in tumor progression. Over the past three decades, numerous successful strategies have emerged for the treatment and management of tumors. These strategies are developed on a deep understanding of the processes involved in tumor genesis and the complex interplay with the tumor microenvironment. The development and formulation of efficient drug delivery systems, including polymeric nanocarriers, vesicular systems, and inorganic nanoparticles, have demonstrated their effectiveness as targeted mechanisms for delivering therapeutics into intracellular organelles. These systems undergo successful functionalization and surface modification, facilitating recognition by tumor cell receptors. These biocompatible and biodegradable nanoengineered systems enable precise release of therapeutics at cancerous sites and have found extensive applications in diagnosis and treatment. Vesicular systems have proven to be efficient vehicles for delivering natural antioxidants and phytochemicals due to their antiproliferative- and apoptosis-inducing properties. In addition, solid lipid nanoparticles are preferred due to their high payload efficiency and stability, even at elevated body temperatures, making them suitable for delivering therapeutics to treat brain tumors. Furthermore, researchers have extensively explored repetitive branched structured dendrimers for the treatment of inoperable liver cancers. A significant percentage of systemically delivered therapeutics relies on transvascular processes for permeating malignant solid tumors, although this process is very slow and requires a high concentration gradient for successful penetration. Consequently, only a small fraction of the drug reaches the target site, resulting in poor bioavailability. It is important to consider that increasing the dosage may lead to potential toxicity. Several biological barriers exist that restrict the transportation of chemotherapeutics at systemic, organ, and cellular levels.

2. Biological barriers influencing tumor-targeted drug delivery systems

The anatomy and physiology of both tumor and host cells present inherent biological barriers that restrict the entry of drug delivery systems. Therefore, to achieve effective therapeutic results at the target site, it is imperative to design drug delivery systems that are tailored to overcome the obstacles.

2.1. Systemic barriers

Biodistribution and clearance represent two prominent systemic barriers that pose challenges to nano-based drug delivery approaches, particularly in achieving efficient delivery to the target site. These barriers encompass a range of structural and chemical processes that shield ingested foreign substances from adverse pH conditions and the immune system's responses. The immune system, including macrophages, plays a critical role as a barrier to active drug-loaded particles, swiftly removing them from surrounding tissues and the circulatory system[4]. Similarly, first-pass metabolism can affect the therapeutic window of drug delivery systems, particularly when targeting lung cancer. Factors within the circulatory system, mucosal lining, basal membrane, and the intercellular gaps between endothelial cells all play roles in determining the selective localization of size-dependent drug delivery systems[5]. For instance, nanoparticles tend to accumulate more within the larger gaps between endothelial cells and in areas with a discontinuous basal membrane in blood vessels,

such as bone spaces. On the other hand, in regions with a continuous basal membrane, which includes endocrine glands, nanoparticles may have poorer localization[6].

2.2. Organ-level barriers

One of the critical barriers at the organ level is the blood-brain barrier, which is of utmost concern for effectively delivering therapeutic agents and nutrients across the blood-brain membrane. The brain capillaries that line the brain exhibit a high degree of polarization and consist of different luminal and abluminal membranes with different functional roles[7]. In addition, the presence of tight junctions in the endothelial cells of brain capillaries restricts the diffusion of small hydrophilic molecules, resulting in a low rate of transcytosis (poor movement of solutes through transcellular pathways). Several factors related to nanocarriers influence their ability to transverse the blood-brain barrier, including lipid solubility, surface area, size, polarity, and concentration gradients[8].

2.3. Cellular-level barriers

The internalization of nanocarriers, achieved through processes such as phagocytosis, pinocytosis, or receptor-mediated endocytosis, represents cellular-level barriers. Cellular endocytosis is a common occurrence in tumor cells, although it may vary from cell to cell and can be affected by extracellular conditions. The functionalization of nanocarriers with ligands plays a crucial role in enhancing internalization, cellular uptake, and achieving precise targeting with tumors[9]. In addition, the size of nanocarriers has an impact on cellular uptake and the internalization process. Smaller particles (<200 nm) can be internalized through a clathrin-mediated process, while larger particles (>200 nm) are taken up via caveolin-mediated pathways[10]. The presence of surface charges on tumor-targeted nanocarriers is also significant, as they influence cell binding, signaling, and cell responses. These surface charges determine the extent and type of protein interactions, thus governing cell adhesion.

3. Molecular principles in tumor-targeted drug delivery systems

At present, three approaches are employed in targeted drug delivery systems for the management of tumors at the molecular level. These approaches include passive targeting based on tumor vasculature, active targeting through molecular binding, and cell-mediated targeting[11].

3.1. Passive targeting

Passive targeting involves the targeting of structural features associated with the newly formed blood vessels that supply nutrition and metabolic support to the tumor site. During the initial stages of tumor growth, there is a significant release of pro-angiogenic factors that contribute to the formation of convoluted, disorganized, and immature vessels with indistinct arterioles, venules, and capillaries. These developed tumor vessels exhibit aberrant cellular organization and contain numerous factors, including vascular endothelial factor, tumor-infiltrating leucocytes, protein factor, and tumor necrosis factor. In addition, reactive ions such as reactive oxygen, carbon monoxide, nitric oxide, and hydrogen peroxide are present, along with various processes associated with hemoxigenase, matrix metalloproteinase, and inflammation[12]. All of these factors play a role in regulating vascular permeability within tumor vessels, as well as in processes related to inflammation, intravasation, and the distribution of tumor cells[13].

Tumor-targeted therapeutics aim to accumulate around the tumor and induce an enhanced permeation and retention effect (EPR), facilitating the increased accumulation of bioactive agents at the target site. The disorganized architecture of tumors, along with leaky vasculature and impaired lymphatic drainage, enables enhanced EPR efficiency. A schematic illustration of passive targeting is depicted in Figure 1. Several drug delivery approaches, such as liposomes, nanoparticles, micelles, polymeric nanoparticles, and dendrimers, achieve enhanced EPR through passive targeting, gradually releasing active ingredients within the tumor mass. Numerous passively targeted drug delivery systems from different countries have been successfully employed in clinical use. Examples of such nanocarriers include Doxil™, DaunoXome™, Marqibo™, Onivyde™ (USA), Mepact™, Myocet™ (Europe), SMANCS™ (Japan), and Genexol-PM™ (Korea).

3.2. Active targeting

Active targeting, also referred to as receptor-mediated targeting, capitalizes on the distinctive overexpression of specific receptors, such as vascular epithelial growth factors, transferrin receptors, and human epidermal growth factors within tumor masses. These receptors serve as recognition for target ligands, including tethered antibodies, linked peptides or proteins, aptamers, affisomes, and small molecules. The presence of leaky vasculature, a disrupted lymphatic system, and a hypoxic or acidic environment within tumors further facilitate the covalent or non-covalent binding between receptors and ligands, essential for the successful execution of active targeting[14]. Figure 2 illustrates the fundamental concept behind the internalization of a tumor-targeted drug delivery system through active targeting. The epidermal growth factor receptors (EGFRs) family is incessantly involved

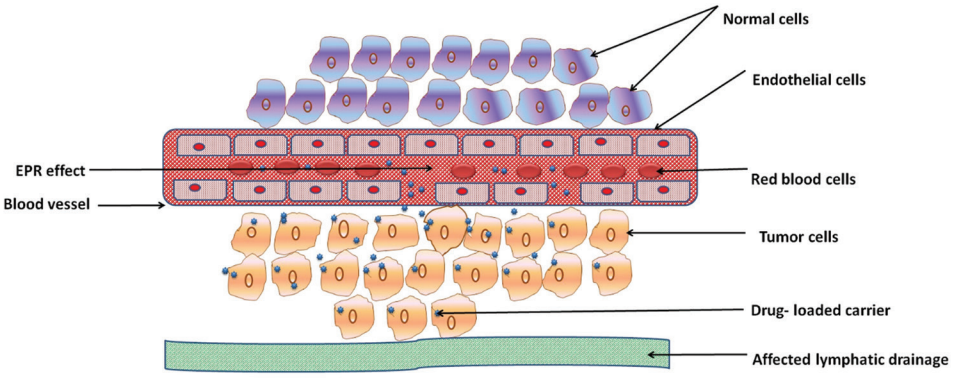


Figure 1. Schematic illustration of tumor targeting using drug-loaded nanocarriers through passive targeting approach.
Abbreviation: EPR: Enhanced permeability and retention.

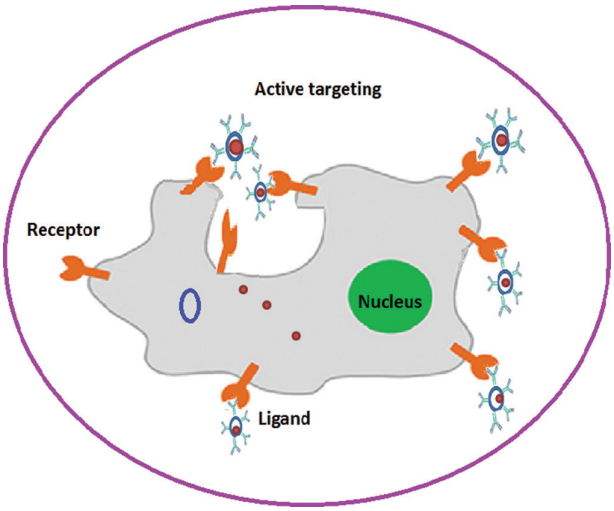


Figure 2. Ligand-bound receptor-mediated or active targeting of tumor cells.

in tumor cell metabolism and targeting suitability. The overexpression of EGRF is associated with the development of various cancers, including those affecting the breast, stomach, and lungs. Consequently, EGRF becomes the preferred active targeting site for the efficient delivery of anticancerous agents[15]. In addition, folate receptors are highly expressed on the cell surface in epithelial, cervical, ovarian, brain, lung, and colorectal cancer regions. Furthermore, myriad disorders and cancers, including the pancreas, prostate, testicles, lymphomas, and sarcomas, exhibit elevated levels of folate receptors. Hence, folate receptors are the preferred choice for active targeting using various inorganic nanoparticles.

Furthermore, tumor progression is closely associated with the angiogenesis process, which is physiologically regulated through the overexpression of vascular EGFRs and integrins found in endothelial cells[16]. This overexpression has been linked to the development of prostate cancer, leukemia, and melanoma. Both of these target sites are preferred for active targeting, as they not only restrict the supply of nutrients but also mediate the disruption of tumor cells[17]. Potential targets containing specific proteins include B-cell maturation antigen and lymphocyte antigens (relevant to hematological tumors), G-protein coupled receptors (such as lysophosphatidic acid, melanocortin, estrogen, angiotensin, vasopressin, and gastrin-releasing peptides), cluster differentiation proteins, interleukin receptors (associated with gliomas), and prostate-specific membrane antigens[18,19]. Current tumor-targeted drug delivery systems are designed to improve blood perfusion, promote internalization, and facilitate tissue infiltration by activating antitumor responses.

3.3. Cell-mediated targeting

The cell-mediated targeting approach is a highly recommended strategy for anticancer drug delivery owing to its distinct virtues, including the precise direction of drugs to the target site, prolonged retention, and controlled drug release, all while minimizing immunogenicity and cytotoxicity. This approach involves drug interactions with cell-mediated substrates, which encompass cytokines (macrophage colony-stimulating factor), chemokines (monocyte chemotactic proteins), and cellular growth factors (EGFR and vascular endothelial growth factor)[20]. Drug carriers loaded with low molecular compounds, genetic materials, proteins, and oncolytic viruses activate T-lymphocytes, neutrophils, monocytes, macrophages, and mesenchymal stem cells, all working together to target tumor cells[21]. Figure 3 depicts the process of cell-mediated antitumor activity.

Various factors, including cell adhesion molecules and regulatory T cells, amplify cancer-associated responses, while cytotoxic T cells and natural killer (NK) cells

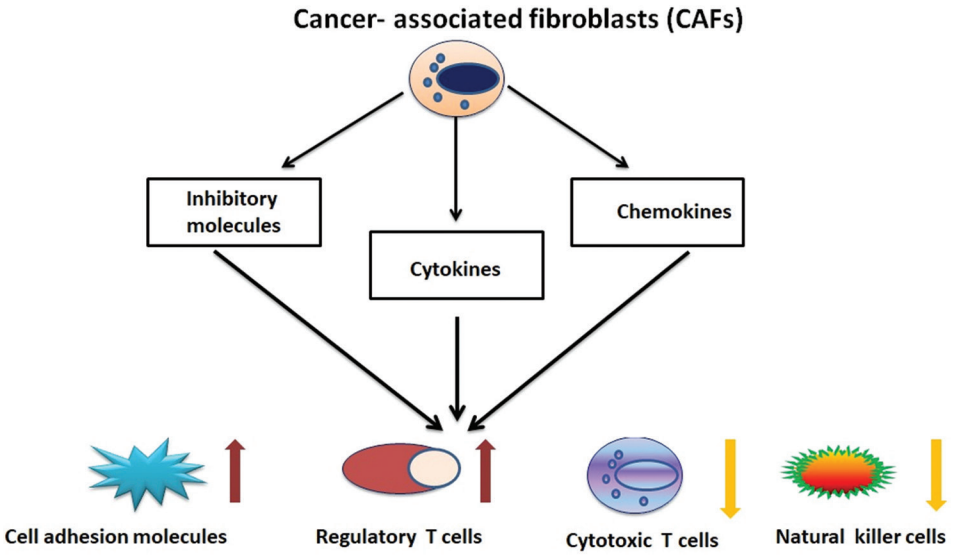


Figure 3. Stimulation of cell-mediated responses by cancerous cells.

restrict cancer progression[21]. T cells combat cancer cells through both direct and indirect mechanisms. In the context of lymphoma and bone marrow cancers, these cells themselves become cancerous. NK cells are capable of directly destroying cancerous cells through perforin- or granzyme-based mechanisms. Similarly, cytotoxic CD8+ cells are highly desirable for targeting cancer and are potent effectors often employed in chemotherapy. New-generation genetically modified cytotoxic T cells are currently being explored in clinical trials for potential cancer treatment.

4. Types of tumor-targeted drug delivery systems

4.1. Microscale tumor-targeted drug delivery system

Highly proliferative tumor cells exhibit distinct genetic and functional differences compared to normal cells, necessitating cell-specific drug treatments. Conventional approaches not only fail to deliver drugs to the target sites (abnormal cells) but also lead to severe side effects. Microspheres offer the potential to target tumor-affected cells with minimal side effects. These free-flowing colloidal microspheres (an approximate size of 200 μm) are composed of drug-entrapped biodegradable polymers capable of controlled drug release at the target organ vessels. Microspheres have found widespread application in drug delivery, particularly in contexts such as organ transplantation, surgery, and radiation treatments associated with hepatic metastases[22]. For instance, Sangi *et al.* discussed a microsphere-based chemotherapeutic system designed for lung targeting, involving the development of 5-fluorouracil-loaded gelatin microspheres with an average size of 9.6 μm[23]. After I/V (intravenous injection), the half-life of the drug significantly improved that extended from 1.23 to 18.3 h, and remained prolonged in circulatory system. These microspheres exhibited a shriveled shape, microsized (5–15 μm), biodegradability, biocompatibility, and stability under both ambient and refrigerated storage conditions. Histopathological studies revealed no changes in the stained lung tissue. In another study, Fan *et al.* explored dual drug release from nanofibrous microspheres for the targeted treatment of colon cancer[24]. They prepared polymeric nanofibrous microspheres containing docetaxel and curcumin without the use of surfactants. They utilized pluronic, a water-soluble biocompatible polymer, which exhibited an affinity for the intestinal surface and contributed to the improved solubility and stability of poor water-soluble therapeutics. This developed system demonstrated biodegradability and provided slow and controlled drug release due to its fibrous surface. In vivo studies demonstrated synergistic antitumor efficacy against colon carcinoma (CT 26) through the use of dual drugs (docetaxel and curcumin) within nanofibrous microspheres. In addition, the system held promise for the treatment of abdominal metastasis of colon cancer.

Shell *et al.* demonstrated the bright luminescence of europium chelate microspheres, which were affixed with multiple copies of cetuximab[25]. This system enabled the selective imaging of overexpressive EGRFs in A431 tumor cells. The microspheres were intravenously injected into athymic mice that had previously been treated for A431 flank tumors. The outcomes, gathered using enzyme-linked

immunoassay and fluorescence microscopy, revealed the selective accumulation of cetuximab microspheres at the targeted tumor site. Conjugated europium antibody microspheres have the potential for efficient tumor site imaging and accumulation within the tumor *in vivo*.

Another micronized delivery system, microemulsions (0.1 μm), serves as adaptable carriers that exhibit enhanced bioavailability of poorly soluble actives, improved absorption, and high permeation due to their small size distribution and low surface tension[26]. Table 1 compiles a few microscale tumor-targeted delivery approaches and their applications. These systems are thermodynamically stable and can effectively deliver both hydrophobic and hydrophilic actives across the skin[27].

4.2. Nanoscale tumor-targeted drug delivery systems

4.2.1. Polymeric nanocarriers

Polymeric nanocarriers are considered a promising approach for drug delivery to alleviate various disorders, including tumors. Their remarkable pharmacokinetic properties, namely, solubility, stability, significant distribution, and accumulation at tumor cells, have garnered attention for developing new chemotherapy regimens[36]. Polymers utilized include polyethylene glycols, polysaccharides, and polyvinyl alcohol, which not only enhance solubility but also extend the circulation half-life of the active drug and bypass the opsonization process. Improved stability, prolonged retention time, and reduced clearance of polymeric nanoparticles offer notable applications in oncology. These cargos are actively taken up by the cell-mediated active transport system[37]. Moreover, these systems are protected from the unfavorable environment of the gastrointestinal tract and bypass first-pass metabolism, resulting in increased bioavailability and reduced metabolic clearance. Furthermore, the polymeric integrity enables a high payload and controlled release of the actives at the target site[38]. Polymeric nanocarriers entail the use of polymeric nanoparticles, polymeric micelles, dendrimers, and polyplexes for specific drug delivery at the tumor target site, as illustrated in Figure 4, and they are further elaborated as follows:

(a) Polymeric nanoparticles

Nanodimensional particles serve as excellent carriers for site-specific drug release and effective antitumor management by virtue of their biocompatibility and prolonged circulation efficiency. Numerous nanocarriers (below 1000 nm), including liposomes, polymeric

Table 1. Microscale tumor-targeted delivery systems and their applications

Therapeutic agent and formulation	Targeted site	Research Objective	Application	References
Yttrium-90 microspheres	Liver	Development of microspheres to provide prolonged patient survival through precisely nourishing vasculature related to hepatic tumors	Local radiotherapy for liver tumors	[28]
MDHJ (Methyl dihydrojasmonate) containing microemulsion	Breast	Phytochemical MDHJ microemulsion has the capability to reduce tumor volume and necrotic effects in MCF-7 cell lines	Targeting solid tumor (transdermally)	[29]
Magnetic iron oxide bovine serum albumin microspheres	Skin	Prolonged delivery of sulforaphane through iron oxide magnetic microspheres	Promising drug carrier for anticancer drug	[30]
Mitoxantrone (MXN)-albumin microspheres	Breast	Preparation of MXN microspheres to reduced toxicity and improved moderate survival in murine mammary adenocarcinoma	Localized breast cancer chemotherapy	[31]
5-fluorouracil microspheres	Brain	Formulation of biodegradable microspheres for sustain release of 5-fluorouracil and impressive management of neoplastic cells present in brain tissues	Prolonged local delivery of 5-fluorouracil in malignant brain tumor	[32]
CA125-poly(lactic-co-glycolic acid) (PLGA) microspheres	Ovary	Preparation of antigen CA125-loaded PLGA microspheres for induction of T lymphocytes	Immunotherapy of ovarian cancer	[33]
Pancreatin microspheres	Pancreas	Development of enteric-coated pancreatin microspheres for the direct release in the pancreatic duct	Unresectable pancreatic cancer	[34]
Paclitaxel microspheres	Urinary bladder	Development of bioadhesive paclitaxel microspheres for the controlled release at the urothelium	Intracavitary treatment for superficial carcinoma of the urinary bladder	[35]

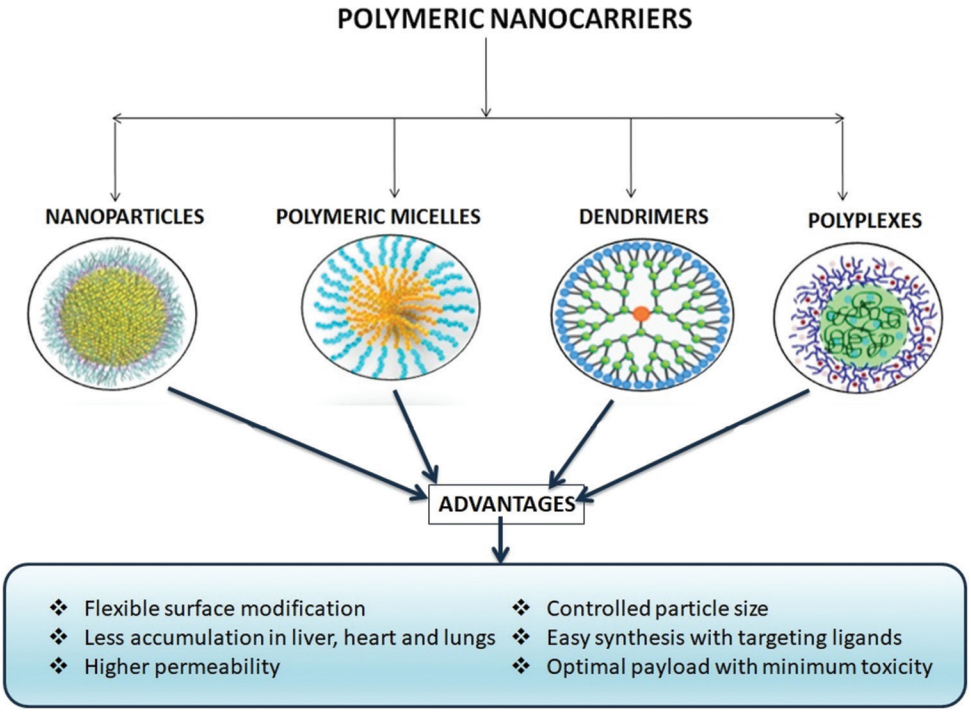


Figure 4. Polymeric nanocarriers involved in tumor management.

nanoparticles, solid lipid nanoparticles, dendrimers, and inorganic nanoparticles, have been reported for their effectiveness in the treatment of various types of tumors[39]. Their unique size, shape, and surface architecture allow for active targeting (binding to specific cell receptors), passive targeting (enhanced EPR and dysfunctional lymph vessels), and cell-mediated targeting (stimulated cytokines and chemokines). The size of nanoparticles significantly influences various factors, including circulation time, biodistribution, accumulation, penetration, and cellular uptake within tumor cells or tissues. Circulation time and particle size serve as pivotal determinants of the drug delivery system's efficacy. Notably, particle size greatly affects clearance through the mononuclear phagocytic system (MPS), with smaller nanodimensional particles undergoing reduced uptake by this system. In addition, nanoparticle size plays a critical role in biodistribution, renal filtration, and vascular infusion within the liver. The literature describes that nanoparticles below 50 nm can easily penetrate endothelial cells and infiltrate liver cells, while smaller particle sizes (approximately 5 nm) are excreted through renal filtration. The variable pore size (ranging from 200 nm to 1.2 μm) is influenced by leaky vasculature and the rapid growth of tumor cells[40].

However, larger particles are inefficient at entering tumor cells; they are retained in the surrounding of tumor cells but struggle to penetrate dense tumor cells[41]. In contrast, smaller particles (below the pore diameter of tumor cells) can easily penetrate tumor cells and exhibit passive targeting but are swiftly pushed back into the circulatory system due to the high interstitial pressure within tumor cells[42]. Therefore, optimizing particle size can enhance intratumor distribution, cell penetration, retention, and, consequently, the effectiveness of antitumor treatment. Yu *et al.* have demonstrated an intelligent, size-tunable approach for proficient antitumor action[43]. The size-tunable approach overcomes the limitations associated with nanoparticles, as their sizes can be adjusted (shrunk or enlarged) in response to physiological stimuli. This adjustment significantly improves the retention and penetration of the tuned particles within tumor cells. Both internal (pH, enzyme, and redox reactions) and external stimuli (temperature and light) modulate the morphology (shape and size) of nanoparticles through the processes such as protonation, π-π stacking, and hydrogen bonding. As a result, sized-tuned particle drug delivery systems are utilized for efficient therapy, diagnostics, and bioimaging of cancers. Figure 4 illustrates smart polymeric nanocarriers that exhibit a controlled release of actives within tumor cells, thereby boosting drug efficiency by modifying the tumor microenvironment[44]. Table 2 compiles certain polymeric nanoparticles and their applications for the management of various tumor cells.

Table 2. Polymers employed in the development of tumor-targeted drug delivery systems

Polymers	Approaches	Research highlights	References
Polyethylene glycol (PEG)-functionalized poly(lactic-co-glycolic) acid	CD133 aptamer-decorated salinomycin nanoparticles (AP-SAL-NP)	The nanocarrier AP-SAL-NP exhibited comparative specific and selective cytotoxicity for CD133(+) osteosarcoma cancer stem cells than bare SAL-NP.	[45]
Hyaluronic acid, nonsulfated glycosaminoglycan	Hyaluronan-paclitaxel bioconjugate (ONCOFID-P) for ovarian cancer	After intraperitoneal administration, the developed polymeric conjugate ONCOFID-P interacted with CD44 via an active transport mechanism and exhibited a higher therapeutic concentration at target sites, that is, human ovarian cancer, when compared to paclitaxel.	[46]
Polyethylene glycol	Utilizing gelatinase nanoparticles for the delivery of miR200c-docetaxel in augmented elimination of cancer stem cells	The developed miR-200c/DOC nanoparticles significantly suppressed the growth of the tumor. Furthermore, these polymeric nanocarriers demonstrate a promising approach for nucleic acid delivery in the management of tumor disorders.	[47]
Biodegradable polylactic acid	Docetaxel-loaded polylactic acid nanoparticles for anti-metastatic remedy	Developed nano-cargos were effective against lung cancer stem-like cells (CSLCs) and proved an effective strategy for lung cancer metastatic treatment.	[48]
Chitosan	Cisplatin-encapsulated chitosan (CS) nanoparticles for improved cellular cytotoxicity in tumor cells	PEG-epidermal growth factor peptide-grafted cisplatin-encapsulated CS nanoparticles were effective against lung cancer cells.	[49]

(b) Polymeric micelles

Polymeric micelles are colloidal particulate systems with particle size approximately 5–100 nm. FDA-approved Genexol-PM (an advanced form of paclitaxel) has found application in the management of breast cancer. These systems have the potential to incorporate ligands (such as antibodies) and form chelate complexes for site-specific drug delivery[50]. Polymeric micelles have demonstrated their competence in delivering hydrophobic drugs effectively, thanks to their exclusive self-assembled morphology that enhances solubility and bioavailability. Amphiphilic di- and tri-block copolymers can self-assemble to create spherical micelles with a hydrophobic core (for the encapsulation of bioactive agent) and a hydrophilic shell (for the provision of stealth properties to the system). This exclusive morphology of polymeric micelles extends circulation time and reduces the likelihood of clearance by the reticuloendothelial system. These particles ensure enhanced permeability across tumor cells and higher drug accumulation. These systems are more efficacious and possess superior stability at lower concentrations compared to micelles derived from surfactants. Recent clinical studies have suggested the potential applications of polymeric micelles in oncotherapy. In addition, the block polymers in polymeric micelles are stimuli-sensitive, responding to factors such as pH, ultrasound, light, heat, and more, enabling controlled delivery of bioactive agents on activation, whether by active or passive means[51].

Kanamala *et al*. discussed the chemical design and vital applications of pH-sensitive polymeric micelles for tumor-targeted drug delivery[52]. Among various stimuli, pH-triggered systems are particularly significant due to their direct influence on the extracellular and intracellular microenvironment of solid tumors. Various mechanisms, including protonation, the breakdown of chemical bonds, and charge reversal, facilitate cellular uptake and drug delivery from polymeric micelles. Optimized stimuli-responsive polymeric micelle assemblies can undergo alterations or rearrange their chemical structure into unimers when exposed to different stimuli. These polymeric micelles effectively recognize the abnormal microenvironment of tumor cells (weak acidity, hypoxic conditions, abnormal temperatures, elevation of metabolites, and overexpression of receptors), enabling active targeting. Table 3 compiles various polymeric micelles that have been investigated for their antitumor efficacy. On cellular uptake, these nanocarriers enhance therapeutic efficacy, imaging sensitivity, and the delivery of antineoplastic agents under various extracellular and intracellular stimuli, including reductive or oxidative microenvironments, anomalous bioactive substances, and the presence of enzymes such as beta-glucuronidase and matrix metalloproteinase[53].

(c) Dendrimers

Nanosized globular dendrimers consist of three distinct sites: A central core, a branched mantle, and a corona adorned with peripheral functional groups. The unique architecture and characteristic features of dendrimers enable high payload capacity and site-specific drug delivery.

Table 3. Polymeric micelles and their antitumor importance

Components	Purpose	Outcomes	References
Thioridazine (THZ), doxorubicin (DOX), urea-functionalized diblock copolymers of polycarbonate and polyethylene glycol	Co-delivery of THZ-DOX using polymeric micelles for the management of breast cancer	Nanodimensional THZ- and DOX-embedded polymeric micelles (100 nm) exhibited synergistic action via inhibiting cancer stem cells. Developed micelles were efficient in lowering the side population of sorted cancer stem cells.	[54]
Curcumin,N-isopropylacryamide, N-vinyl-2-pyrrolidone, polyethylene glycol monoacrylate	Nanocurcumin polymeric micelles for cancer therapy	Developed nanocurcumin micelles (50 nm) were efficient against pancreatic cancer. Readily dispersed nanocurcumin exposed to advanced physicochemical parameters. Moreover, induced cellular apoptosis, inhibition of nuclear factor kappa B, and associated cytokines/interleukins stepped toward remarked control of tumor growth.	[55]
Amphiphilic block polymer N-octyl-O-sulphate chitosan and paclitaxel	Paclitaxel-embedded polymeric micelles for treatment of multidrug-resistant cancer	Formulated micelles (PTX-M) showed two-fold higher cellular uptake and lesser paclitaxel efflux compared to bare paclitaxel. The outcomes suggested efficient activity (75%) both for hepatocellular carcinoma and multidrug-resistant HepG2 cells.	[56]
Phenformin, diblock polymers (PEG-urea functionalized polycarbonate and acid functionalized polycarbonate)	Phenformin polymeric micelles for prevention of metastasis associated with lung carcinoma	Phenformin, an antidiabetic drug, has the efficiency to kill cancerous cells. Phenformin-diblock polymers composed of micelles (102 nm) were stable and compatible with non-cancerous cells. More than 90% of the drug was delivered for 96 h, predicted its prolonged efficacy. *In vivo*, results on H460 human lung carcinoma exhibited superior antitumor action in affected tissues.	[57]
Pluronic P123/F127 and curcumin	Ultrasound triggered pluronic-curcumin micelles for improved chemotherapy	Developed curcumin-loaded pluronic P123/F127 polymeric micelles can be readily permeabilized and well uptaken through cellular mode on ultrasound stimulation. After intratumoral injection, polymeric micelles exhibited prolonged circulation time and exhibited spatial-temporal delivery of curcumin.	[58]

The periphery of these nanocarriers supports the conjugation of targeting ligands, imaging agents, and bioactive substances, while the inner core facilitates the incorporation of inorganic metal nanoparticles, commonly employed in a myriad of biomedical applications[58]. Dendrimers (measuring 10–20 nm in size) easily extravasate and selectively accumulate within tumor cells through the EPR effect, a form of passive targeting. This accumulation results in a high concentration of actives within the tumor. Moreover, these nanocarriers bind to high molecular weight plasma proteins, facilitating prolonged circulation time and reduced renal clearance. However, passive targeting encounters certain anatomical and pathophysiological barriers that can impede drug delivery to the target site and potentially lead to multidrug-resistant tumors. In contrast, active targeting facilitates selective conjugation between overexpressed receptors and ligand-functionalized dendrimers. The peripheral structure of dendrimers is enriched with reactive functional moieties, enabling successful binding to various ligands, including antibodies, genes, amino acids, biotin, aptamers, and folic acid. This characteristic allows for efficient targeting of tumor tissues[59].

Several classes of dendrimers, such as polyamidoamine (PAMAM), poly-L-lysine (PLL), polypropyleneimine (PPI), polyethylene glycol (PEG), citric acid-polyethylene glycol-citric acid (CPEGC), and carbohydrate-based dendrimer (glycodendrimer), are extensively utilized in chemotherapy[60,61]. Among these, clinically proven PAMAM dendrimers, which consist of an ethylenediamine core and methyl acrylate-linked ethylenediamine branches, have been extensively explored for antitumor drug delivery. They are valued for their hydrophilicity, biocompatibility, and non-immunogenicity. The permeation efficacy of PAMAM dendrimers depends on their generation, which determines their morphology[62]. Higher-generation dendrimers are spherical and compact, offering a larger surface area than their smaller-generation counterparts[63]. However, the presence of terminal cationic groups in PAMAM dendrimers may interact with negatively charged healthy cells, causing the disruption of cell membranes and leading to cell death. Therefore, surface modification with shielding moieties is employed to control cytotoxicity and enhance cellular uptake within tumor-specific cells. Table 4 summarizes a selection of dendrimers and their applications in antitumor therapies. Liu *et al.* designed phospholipid-decorated PAMAM (PL-dendriplexes) to encapsulate siMDR1 for mitigating multidrug resistance in breast cancer cells (MCF-7/

Table 4. Types of dendrimers and their associated ligands formulated for antitumor applications

Dendrimers type	Generation	Ligand/therapeutic agent	Application	References
Poly(amidoamine) dendrimers with polyethylene glycol and lactobionic acid (PAMAM-PEG-Gal)	-	Astrocyte elevated gene-1 (AEG-1) and all-trans-retinoic acid (ATRA)	Hepatocellular carcinoma	[68]
Poly(amidoamine) dendrimers (PAMAM)	Fifth-generation	siRNA, cisplatin, and selenium	Lung cancer	[69]
	Fourth-generation	Gallic acid	Breast cancer	[70]
	Third-generation	Methotrexate	Folic receptor-expressing tumor cells	[71]
	Second-, third-, and fourth-generations	Arginine	Suppress TEL/AML1 protein in gene therapy	[72]
Polypropylene imine (PPI)	Fifth-generation	Retinoic acid, dexamethasone, ATRA	Breast cancer	[73]
	Fourth-generation	Melphalan	Folic receptor-expressing tumor cells	[74]
	Fluorinated third-, fourth-, and fifth-generations	Lipofectamine 2000	Human embryonic kidney cells and HeLa cells	[75]
Poly-L-lysine (PLL)	Sixth-generation	Doxorubicin	Chemotherapy	[76]
	Fifth-generation	Doxorubicin	Lung metastases	[77]
	Third-generation	Porphyrin	Gene transfection	[78]
	First-, second-, and third-generations	Fluorescein isothiocyanate and 5-fluorouracil	Multidrug-resistant tumors	[79]

ADR cells)[62]. The developed polymeric nanocarriers demonstrated superior gene silencing efficacy and reduced p-glycoprotein (p-gp) expression. Furthermore, PL-dendriplexes exhibited a synergistic effect with paclitaxel, enhancing apoptosis, regulating the cell cycle, and effectively managing multidrug-resistant cancers. In a study by Jiang *et al.*, a nanodimensional miR-150 encapsulated dendriplex containing FLT3L-G7 PAMAM was developed for the treatment of acute myeloid leukemia (AML). These dendriplexes were designed to target the tumor suppressor through the overexpressed FMS-like tyrosine kinase 3 (FLT3 receptors). The FLT3L-grafted miR-170 nanocarriers selectively targeted overexpressed receptors in AML cells, promoting apoptosis[63]. These designed dendriplexes tend to accumulate in the bone marrow, inhibiting the progression of FLT3 without disrupting normal hematopoiesis. In addition, maltose-derived polypropylene imine glycodendrimers (PPI-mOS, 4th generation) have been explored for anticancer therapy. These cationic nanocarriers efficiently interact with negatively charged nucleoside analogs (cytarabine), overcoming their metabolic limitations (inefficient cellular uptake and drug resistance). The studies conducted on leukemic cell lines (1301 and HL-60) revealed significant cytotoxicity and apoptosis due to the augmented cellular uptake. Furthermore, the system demonstrated the ability to inhibit the human equilibrative nucleoside transporter (hENT1), which plays an important role in the oncogenesis of leukemia[64]. Another advanced carbosilane dendrimer has been successfully employed for nucleic acid delivery. Their termination sites are rendered with anionic or cationic functional groups, which participate in electrostatic interactions between cell membrane and phosphate groups of nucleic acids. These dendrimers exhibit distinct morphologies based on their generation number and display excellent biocompatibility[65]. Similarly, positively charged phosphorous dendrimers have been explored as carriers for anticancer applications. Their functionalization with triethylammonium and cyclic ammonium groups has shown potential for transporting therapeutics to target sites for the management of several fatal disorders, including bovine spongiform encephalopathy (BSE), Alzheimer's disease, and Prion disease[66].

The development of polycationic phosphorous dendrimers (G1–G3) for the transportation of DNA plasmids in tumor management has been reported. These designed dendrimers were functionalized with piperidine-derived moieties and complexed with negatively charged plasmid DNA (pDNA), encoding p53 and enhanced green fluorescence protein. Viability assay using the CCK-8 method exhibited a 50% cell viability rate for human cervical carcinoma (HeLa cells) at an N/P ratio (the molar ratio of the positive charge of the dendrimers to phosphates

in the pDNA backbone) of 20. Furthermore, cell viability was found to decrease in a dose-dependent manner. The results revealed that fabricated polyplexes (composed of polycationic phosphorous dendrimers and plasmid) had reduced positive charge in the system, resulting in minimal cytotoxicity. These outcomes suggested that the fabricated phosphorus dendrimers hold promise as an effective carrier system for gene delivery in cancer treatment[67].

(d) Polyplexes

These polymeric nanocarriers are formulated by conjugating siRNA/DNA or genes via electrostatic interactions between cationic polymers and anionic nucleic acid components. These systems serve the dual proposes of protecting sensitive genes from enzyme degradation and facilitating controlled release at the tumor site. Polycationic polyplexes show great promise as a drug delivery approach for the specific delivery of anticancer agents due to their ability to enhance transfection efficiency. DNA polyplexes (polymeric-based) and DNA lipoplexes (lipid-based) are systemic gene delivery systems necessary for cases of tumor metastases, where cancerous cells spread throughout the organism. Polyethyleneimine polyplexes, functionalized with PEG, have been developed and conjugated with transferrin or epidermal growth factor to facilitate effective DNA (or gene) transfer within tumor cells. This modification masks the surface charge of polyplexes to prevent interactions with systemically present circulatory components, including erythrocytes, plasma, and the reticuloendothelial system[80]. Table 5 enlists surface-modified cationic and anionic polyplexes designed to efficiently deliver nucleic acid in tumors.

Lee *et al.* explored the successful delivery of branched peptide (GE11) for cancer cells overexpressing EGFR. They investigated the use of low molecular weight disulfide cross-linked polyethylenimine and PEG to develop GE11-tethered polyplexes and evaluated their transfection efficiency in EGFR-overexpressed tumor cells. The formulated polyplexes demonstrated efficient gene condensing capacity, improved transfection efficiency, and specific targeting capabilities[81]. Polyplexes are generally designed for receptor-mediated gene delivery through systemic routes, facilitating efficient internalization due to their augmented transfection efficiency. In this context, Taschauer *et al.* evaluated the significance of the overexpression of CD49f in both benign and malignant tumors[82]. CD49f molecules are associated with the phosphatidylinositol 3-kinase and the serine/threonine protein kinase (Akt signaling pathway), which play a crucial role in the regulation and development of bone mesenchymal stem cells and contribute to tumor metastasis in solid cancers such as hemangioma, breast cancer, prostate cancer, and gastric cancer. A nanodimensional molecular conjugate (200 nm) consisting of the CD49f peptide (CYESIKVAVS) and linear polyethyleneimine (LPEI) was synthesized for the purpose of targeting breast tumor lesions. The fabricated polyplexes could be aerosolized without particle aggregation. When delivered through intratracheal aerosolization, the system was well-tolerated and demonstrated measurable transgene efficacy. Hattori compiled various cationic and anionic polyplexes with genes to enable their delivery to tumor-targeted sites without aggregation with blood components[83]. Surface modification of cationic polyplexes with anionic polymers led to the development of a stable drug delivery approach that effectively delivered pDNA and siRNA to the target site[84].

4.2.2. Lipid carriers

Lipid-based nanosystems are extensively utilized for targeting and regulating the tumor microenvironment

Table 5. Surface-modified polyplexes and their conjugates for nucleic acid delivery in tumor management

Polyplexes	Nucleic acid	Conjugate	References
Cationic polymers			
Lipofectamine 2000	Plasmid DNA	Hyaluronic acid (HA)	[84]
Chitosan	Plasmid DNA	Hyaluronic acid	[85]
Polyamidoamine	Plasmid DNA	Hyaluronic acid	[86]
Protamine	Antisense DNA	HA-antisense DNA	[87]
Dendrigraft poly-L-lysine	Plasmid DNA	Chondroitin sulfate	[88]
Anionic polymers			
Poly-ɣ-glutamic acid	Plasmid DNA	Chitosan	[89]
Poly-ɣ-glutamic acid	siRNA	Dendrigraft poly-L-lysine	[90]
Heparin	Plasmid DNA	Cationic glycopolymer (Tr4)	[91]
Poly-ɣ-glutamic acid	siRNA	Polyethylenimine	[92]

in solid tumors. Through the use of lipid carriers, chemical modification, solubility enhancement, pH responsiveness, and ligand (antibody) targeting can be effectively achieved. These systems not only shield the therapeutic agents from the immune system (gangliosides) but also facilitate drug delivery in the acidic and hypoxic environments of tumor cells. Among various nanoparticle delivery systems such as polymeric nanoparticles, micelles, dendrimers, and liposomes, lipid carriers are considered the least toxic and are widely utilized for gene, DNA, and RNA delivery at the target sites[93]. Lipid carriers, such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), are capable of transporting both hydrophilic and hydrophobic agents. They prolong the retention time of these agents (by increasing their half-lives) and provide controlled release of therapeutic agents from the delivery depot[94]. Moreover, lipid-based systems can effectively deliver dual drugs, enhancing the outcomes of chemotherapy (Figure 5). Despite their shared lipid-based formulations, there are distinct features that set SLNs and NLCs apart: (i) SLNs have lower drug encapsulation efficiency compared to NLCs; (ii) polymeric transitions occur during the preparation of SLNs, leading to a shorter storage shelf-life compared to NLCs; and (iii) SLNs, being crystalline, exhibit a slower release of therapeutics.

Lipid carriers employed for tumor management are further elaborated as follows:

(a) Solid lipid nanoparticles

SLNs or lipospheres have emerged as a rapid and promising approach for the safe and effective delivery of drugs to the target sites. This first-generation lipid-based sub-micron colloidal carrier contains dispersed lipids in an aqueous surfactant solution. SLNs offer several advantages, including ease of preparation, stability, biocompatibility, controlled release, the feasibility of incorporating both hydrophilic and hydrophobic drugs, lyophilization capability, non-toxicity, high payload capacity, cost-effectiveness, and the potential for site-specific drug release. These attributes make them a particularly appealing choice for designing systems aimed at delivering drugs specifically to tumor sites[95]. Various types of lipids, such as triglycerides esters of hydrogenated fatty acids (Lubritab™, Dynasan™, cutina™, and sterotex™) and waxes (cetyl palmitate), in combination with biocompatible surfactants and emulsifiers, are utilized to prepare SLNs through various methods[96,97].

SLNs excel in bolstering membrane stability, extending residence time at the target site, and minimizing issues associated with drug leaching, polymer degradation, and toxicity, as seen in conventional approaches. Cholesterol, a major component of SLNs, is also highly demanded

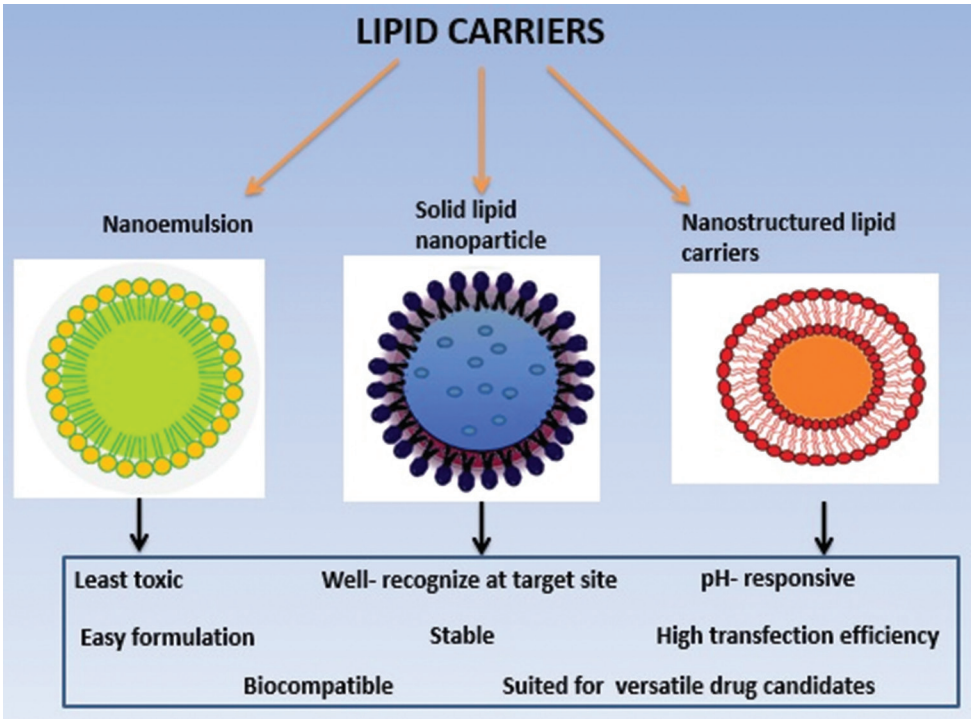


Figure 5. Lipid carriers employed for tumor management.

by tumor cells. Therefore, these lipid nanocarriers show promise for both therapeutic applications and tumor monitoring through modified uptake of low-density lipoproteins.

Bhagwat *et al*. developed transferrin-decorated SLNs containing tamoxifen citrate for improved breast tumor targeting with minimal toxicity[98]. Tamoxifen citrate, a selective estrogen receptor modulator, blocks the passage of estrogen to breast tissues, inhibiting tumor cell growth. However, the associated uterine toxicity associated with tamoxifen limits its broader application in solid tumor management. The developed transferrin-modified tamoxifen citrate-conjugated SLNs exhibited preferential accumulation at the target site (in MCF-7 cells), were qualitatively taken up at the M2 level of the cell cycle, and significantly alleviated human breast cancer in a concentration-dependent manner. The solubility and bioavailability of the poorly water-soluble candidate efavirenz can be modified through the use of SLNs. Efavirenz, a non-nucleoside reverse transcriptase inhibitor, is widely used to treat HIV-positive patients and for antineoplastic management.

Metastasis represents a critical stage in the progression of malignant tumors, such as breast cancer, and is associated with high mortality rates. To address this challenge, docetaxel-loaded SLNs (SLN-DTX) were prepared using Compritol 888 ATO. These SLN-DTX nanoparticles exhibited remarkable stability with a nanodimensional size of 128 nm, resulting in enhanced entrapment efficiency (86%) and controlled *in vitro* release of docetaxel. Notably, the developed SLN-DTX demonstrated significantly greater cellular uptake and accumulation in the G2–M phase (73%) when compared to the free drug (23%), ultimately leading to the induction of apoptosis in tumor cells. Histological investigations confirmed the antitumor activity of SLN-DTX and its potential for spontaneously preventing metastasis in a murine mammary cancer model (4T1)[99,100]. Table 6 summarizes a comprehensive overview of various SLNs and their chemopreventive potential.

(b) Nanostructured lipid carriers

Biocompatible NLCs are second-generation lipid-based drug carriers that effectively shield drugs from degradation, extending their stability and bioavailability. NLCs offer compelling advantages over traditional lipid carriers, including increased storage permanency, improved solubility, enhanced permeability, and minimal adverse effects on associated cells. These formulations are biocompatible and hold great promise for targeted cancer

Table 6. Developed solid lipid nanoparticles and their associated antitumor usages

Drug candidate	Purpose	Research highlights	Application	References
5-fluorouracil (5-FU)	Develop a biocompatible and therapeutically effective 5-FU/SLNs.	Developed 5-FU/SLNs that exhibited a 3.6-fold area under the curve, demonstrating superior inhibition of tumor cells compared to bare 5-FU. In addition, the extent of HER2 receptors and HCT116 cells was markedly reduced in liver and kidney tissues	Colorectal cancer	[101]
Alpha(v)beta(3) integrin cyclic arginyl-glycyl-aspartic acid (RGD)	Preparation of novel receptor targeting (overexpressive alpha(v) beta(3) integrin receptors) and near-infrared light-emitting SLNs for enhanced biodistribution and accumulation.	Developed RGD-SLNs exhibited active tumor targeting on intravenous administration in mice bearing xenograft human breast tumor. The system was specifically distributed in the liver, spleen, and tumor blood vessels	Chemotherapy and chemoimaging	[102]
Camptothecin (CPT)	Development of pH-sensitive SLN system for prolonged accumulation in different tumor sites.	CPT-embedded PEGylated SLNs were spherical, small (53 nm), and exhibited excellent entrapment efficiency (99%). The *in vitro* drug release profile displayed a pH-dependent pattern of drug release. Developed CPT–PEG–SLNs were effective against diverse carcinoma, including lungs (CRL5802, NCL-H358, and CL1-5), colon (HCT-116), and liver (HCC36).	Chemotherapy	[103]
Resveratrol	Inhibition of breast tumor proliferation through resveratrol-SLNs	The developed system was spherical, negatively charged, and smaller compared to bare resveratrol. Western blot analysis suggested superior inhibition efficiency against the proliferation of MDA-MB-231 cells and minimized expression of cyclin D1/c-Myc that explored potential usage for the management of breast tumors	Breast cancer treatment	[104]

therapy. Surface modification or functionalization is recommended to combat drug resistance in chemotherapy.

Thus, augmented drug performance becomes apparent at the delivery site. These novel systems are composed of both solid and liquid lipids, offering increased capacity for hydrophobic antineoplastic drug candidates. Their unordered surface lends itself to straightforward functionalization or modification with various functional moieties (stealthy polymers and ligands) to enhance transfection efficiency at the tumor site. The nanodimensional particles can readily transform into aqueous solutions, resulting in improved pharmaceutical and pharmacokinetic properties, including enhanced solubility, absorption, and bioavailability[105].

Varshosaz *et al*. have developed a lipid-based spherical nanosystem (20–100 nm) containing efavirenz. This system shows great promise for oral administration due to its high solubility, entrapment efficiency, and improved bioavailability[106]. *Ex vivo* investigations conducted on rat intestines revealed enhanced gut permeation of the developed efavirenz NLCs when compared to the efavirenz suspension. This suggests that oral administration of efavirenz through NLCs could be a viable strategy.

NLCs have garnered significant attention in the pharmaceutical and cosmeceutical sectors due to their ease of preparation, biocompatibility, high transfection efficiency, scalability, and the potential for site-specific drug delivery through various administration routes[103]. Multidrug resistance is a prominent issue with antitumor drugs (paclitaxel and doxorubicin), and NLCs offer a promising avenue for mitigation. In the formulation of NLCs, monostearin and oleic acid were utilized as the solid and liquid lipid matrix, respectively, employing the solvent diffusion method. Furthermore, drug-loaded NLCs were functionalized with a folate conjugate containing stearic acid to enhance sensitivity at the target site. Cytotoxicity and the impact on multidrug resistance were assessed for the modified NLCs in human breast cancer (MCF-7) and ovarian cancer (SKOV3) cell lines. Both NLCs, respectively, loaded with paclitaxel and doxorubicin, exhibited superior cytotoxicity against the selected cancerous cell lines, with a remarkable reversal activity of the loaded drugs[107]. Wang *et al*. also explored NLCs by coadministering paclitaxel and doxorubicin to achieve a synergistic effect and site-specific delivery for tumors without influencing normal cells[108]. They utilized the melt emulsification technique for NLC formulation. *In vitro* cytotoxicity studies targeting non-small cell lung carcinoma (NSCLC) and *in vivo* experiments using a mice model (NCL-H460 cells) both exhibited enhanced tumor-targeting efficiency.

The issue of drug resistance during chemotherapy has been addressed by Mussi *et al*., who developed a lipoidal carrier coloaded with docosahexaenoic acid and doxorubicin to enhance the antitumor efficacy[109]. The cellular uptake efficiency was evaluated in MCF-7 cells and MCF-7ADR cells, and the study was conducted using a monolayer model. Higher drug encapsulation and entrapment resulted in improved cellular uptake in MCF-7/ADR cells, signifying the circumvention of P-glycoprotein (P-gp) efflux. Wang *et al*. designed NLCs for the codelivery of doxorubicin and sorafenib (NLC/D-S) to effectively manage esophagus cancer[110]. Sorafenib, a multi-kinase inhibitor, plays a crucial role in regulating the tumor microenvironment, while doxorubicin is a potent inducer of immunogenic cell death. The highly stable and biocompatible NLC/D-S system exhibited an enhanced transfection and retention effect when evaluated against drug-resistant esophageal cancer cells. Therefore, combined therapy using NLC/D-S holds promise as an effective anticancer remedy, thanks to the significant roles of its component. Table 7 compiles several examples of NLCs and their significant importance in the mitigation of various types of tumors.

(c) Nanoemulsion

A nanoemulsion represents a heterogeneous colloidal dispersion system, consisting of nanoscaled droplets in a stable phase. These systems possess a notable capacity for encapsulating poorly soluble drug candidates due to their hydrophobic core. In the context of chemotherapy, researchers have extensively explored ligand-functionalized nanoemulsions designed to target specific components of tumor cells, facilitating efficient internalization within these cells and, consequently, curbing further tumor proliferation[117]. For instance, folate- and gadolinium-functionalized nanoemulsions of docetaxel were formulated using a high-shear micro-fluidization technique, showcasing impressive efficacy in testing on a human ovarian cancer cell line (SKOV3/SKOV3TR). The folate-targeted nanoemulsions (<150 nm) not only served as a theranostic system, efficiently delivering docetaxel through folate receptor-mediated endocytosis, but also outperformed the clinically approved Magnevist® (an MRI contrast agent) in diagnosing the affected tumor site. Moreover, this system demonstrated thermodynamical stability and prolonged residence time within tumor cells while sparing surrounded healthy cells[118].

Zheng *et al*. developed Vitamin E-decorated paclitaxel nanoemulsions for the treatment of human ovarian cancers[119]. The nanoemulsion system exhibited a significantly higher level of antiproliferation action compared to free drug administration of paclitaxel when

Table 7. Nanostructured lipid carriers, their purpose, and antitumor applications

Nanostructured lipid carriers (NLCs)	Purpose	Methodology	Application	References
β-lapachone (Lapa) and doxorubicin (DOX)	Facilitate the catalysis of NAD(P)H quinone oxidoreductase-1 (NQO1) enzyme and enhance intracellular uptake	Melted ultrasonic dispersion method	Overcome multidrug resistance in DOX-resistant breast cancer	[111]
Baicalein (BCL) and doxorubicin (DOX)	Hyaluronic acid (HA)-functionalized NLC for binding with HA receptors	Emulsion evaporation-solidification	Exerting cytotoxicity and synergistic effect against breast cancer, verified on DOX drug-resistant MCF-7 breast cancer cell line (MCF-7/ADR cells)	[112]
Gemcitabine (GEM) and Baicalein (BCL)	HA decorated prodrug NLC for effective binding with HA-overexpressing pancreatic receptors	Nanoprecipitation technique	Prodrug-based tumor-targeted drug delivery on pancreatic cancer	[113]
Doxorubicin (DOX), gemcitabine (GEM), and vincristine (VCR)	Combined prodrug delivery	Solvent diffusion	Stable and high drug-entrapped NLCs used as an antilymph cancer agent against B-cell lymphoma	[114]
Paclitaxel (PTX) and indocyanine green	Significantly enhanced the stability of drugs, produced sufficient local reactive oxygen species, and triggered accelerated drug release on laser irradiation, and also increased intracellular uptake of drugs and induced increased cytotoxicity in cancer cells through synergistic effects	Solvent diffusion	Chemo and photodynamic therapy	[115]
Cisplatin (DDP) plus paclitaxel (PTX)	Folate (FA) decorated nanostructured lipid carriers (NLCs) as nanocarriers for DDP and PTX delivery	Melted dispersion method	Folate-decorated NLCs for enhanced *in vitro* cytotoxicity and *in vivo* penetration efficacy against head-and-neck cancer cells (FaDu cells)	[116]

tested on the targeted cells (A2780/Taxol). Notably, there was a marked reduction in mitochondrial potential, increased intracellular accumulation, and an elevation in the Bax protein level, all suggesting potential applications for nanoemulsions in addressing multi-drug resistance tumors. Ahmad *et al*. developed an oil-in-water (o/w)-based nanoemulsion that contained an omega-3 fatty acid-modified taxoid prodrug (DHA/SBT/1214) for the management of prostate cancer. The nanoemulsion system exhibited enhanced cytotoxicity against PPT2 tumor xenograft compared to the commercially available Abraxane®[120]. Furthermore, *in vivo* treatment with the developed system resulted in higher cell viability with minimal induction of floating spheroids or holoclones, in contrast to the large numbers observed with Abraxane®.

4.2.3. Vesicular carriers

Vesicular nanosystems offer a means to deliver chemotherapeutic drugs precisely to target sites while sparing normal cells from harm. These drug delivery strategies excel as carriers due to their ability to control the active release of therapeutics, enabling localized action and maintaining desirable storage stability. A diverse range of lipids and amphiphilic building blocks (surfactants) has been explored for the creation of vesicular systems, which are characterized by highly ordered, concentric layers. Due to their exclusive morphology and small dimensions, these vesicular systems disperse effectively within the affected organ. Figure 6 displays various vesicular drug carriers, such as liposomes, niosomes, phytosomes, and aquasomes, developed for chemopreventive applications. The vesicular approach not only protects drugs from degradation but also extends the circulation time of bioactive agents. These vesicles offer numerous advantages, including biocompatibility, non-toxicity, flexible preparation, non-immunogenicity, and effective cellular uptake by virtue of their significant interactions with cancerous cells. These attributes make vesicles ideal nanocarriers for addressing tumor-related issues[121]. Table 8 compiles different vesicular carriers explored for their antitumor action.

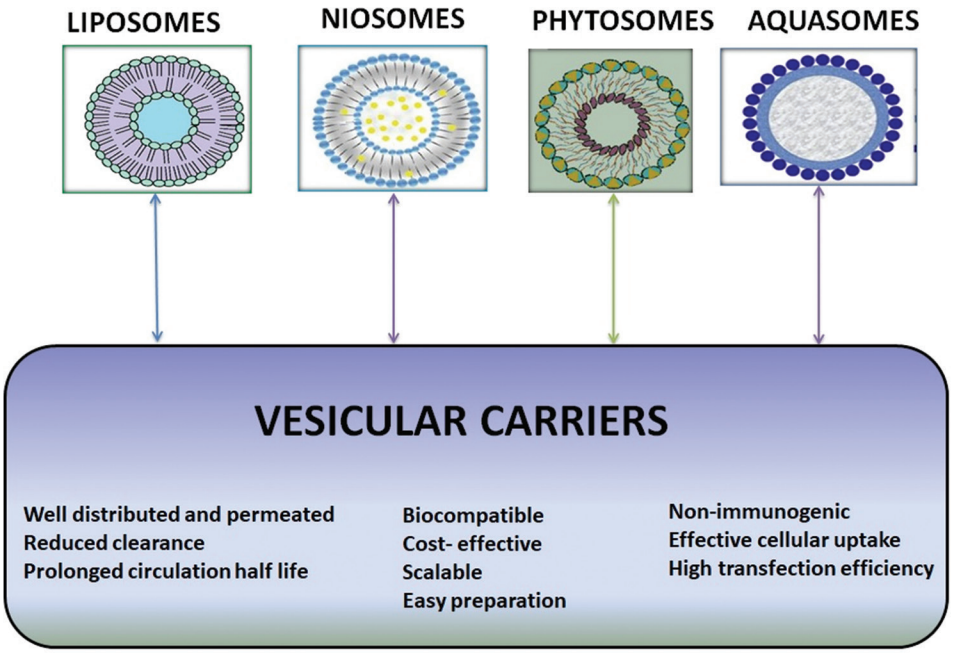


Figure 6. Types of vesicular carriers extensively employed for antitumor therapy.

Table 8. Different types of vesicular carriers for tumor management

Vesicular system	Therapeutic agent	Research highlights	Study model	Application	References
Liposomes	Mitoxantrone (MTO)	(i) Minimum MTO toxicity (ii) Improved cellular uptake (iii) Suppressed and delayed tumor growth	MDAMB-231 breast carcinoma model	Orthotopic breast carcinoma	[31]
	B16-ovalalbumin (B16-OVA), vaccine adjuvants	(i) Induced robust CD^8 T lymphocytes (ii) Impaired cell toxicity (iii) Increased programmed cell death of tumor cells (iv) Significantly improved survival rate	B16-ovalbumin (B16-OVA) solid tumor melanoma mouse model	Melanoma and immunotherapy	[135]
	anti-EGFR-9Arg-lipoplexes	(i) Remarked siRNA transfection in lung cancer cells (ii) Suppressed transcription of the targeted gene (iii) Efficiently inhibited tumor growth	LS174T-Luc cancer cells	RNA interference chemotherapy	[136]
	Thermosensitive NGRpeptide-siRNA	(i) Developed glutathione-sensitive carrier (ii) Predicted 86% encapsulation efficiency and thermal stability (iii) 3 times high *in vivo* performance of cell-penetrating peptides embedded in liposomes	HT-1080 murine model (xenograft)	Fibrosarcoma and cancer therapy	[137]
	Paclitaxel and vinorelbine	(i) High cellular uptake by both active and passive targeting mode (ii) Lessened cell toxicity compared to free drug (iii) Restricted lung metastasis	Non-small-cell lung cancer (NSCLC)-tumor-bearing C57BL/6 mice	Lung cancer	[138]

(Cont'd...)

Table 8. (*Continued*)

Vesicular system	Therapeutic agent	Research highlights	Study model	Application	References
Niosomes	Doxorubicin and curcumin	(i) Prolonged blood circulation (ii) Exhibited both active and passive targeting (iii) Improved cellular uptake due to folic acid functionalization (iv) High stability, biocompatibility, and controlled release drug delivery	MCF-7 and MDA-MB-231 cancerous cells	Breast cancer	[139]
	Paclitaxel and doxorubicin	(i) Enhanced dissolution rate of poorly soluble paclitaxel (ii) Improved antiproliferative and cell penetration action (iii) Synergistic action of both drugs to overcome drug resistance	MCF-7 and PC3-MM2 malignant cells	Multidrug resistance in chemotherapy	[140]
	Tamoxifen	(i) Distinct nanoshapherical with high entrapment efficiency (92%) (ii) 2.8-fold increase in cellular uptake (iii) Reduced tumor volume (iv) Significantly prolonged release through a diffusion process	MCF-7 cell lines	Breast cancer	[141]
	Tocotrienols T3	(i) 1.5 times higher antitumor activity compared to free drug T3 (ii) 12 times lowered tumor volume than treated with free drug T3 (iii) Significantly downregulation of genes associated with metastasis	MDA-MB-231 cells	Breast cancer	[142]
Phytosomes	Mitomycin C- soybean phosphatidylcholine conjugate	(i) Restricted rapid elimination (ii) Increased cellular uptake in HeLa cells (iii) Higher accumulation in H22 hepatoma-induced mice (iv) Enhanced cytotoxicity and advanced antitumor effect	HeLa cells and H22 hepatoma cells	Cancer management	[143]
	Icariin (flavonol glycoside)	(i) Interfered pre-G1 and G2/M phase of cell cycle (ii) Induced apoptosis and cell death (iii) Reduced mitochondrial membrane potential (iv) Enhanced icariin cell permeation and cytotoxicity	OVCAR-3 cells	Ovarian cancer cells	[144]
	Methanolic extract of Allium sativum	(i) Enriched with antioxidants (ii) Exhibited chemopreventive action due to diallyl-disulfide functional groups (iii) Presented active targeting with 100% targeting efficiency	MCF-7 cells	Cancer management	[145]

Vesicular drug carriers, including liposomes, niosomes, phytosomes, and aquasomes, are further elaborated as follows:

(a) Liposomes

Liposomes have been extensively explored for their applications in chemoprevention. The functionalization of liposomes has the potential to enhance their circulation longevity by shielding nanocarriers from phagocyte recognition (opsonization) and preventing rapid removal from blood vessels. In addition, liposomes' variability in size facilitates effective extravasation, both within the hyperpermeable microenvironment of tumors (murine colon adenocarcinoma) and within poorly permeable tumor cells (pancreatic adenocarcinoma). The presence of surface charge can facilitate passive targeting and influence

opsonization by MPS. Neutral or anionic liposomes may evade clearance mechanisms, thereby prolonging their residence time in the circulatory system. In contrast, cationic liposomes tend to form non-specific interactions with negatively charged blood components, leading to their rapid clearance through the reticuloendothelial system (RES)[122].

Eloy *et al.* developed dual drug delivery immunoliposomes for the management of human epithelial growth factor receptor 2 (HER2) carcinoma[123]. These liposomes contained both paclitaxel (an anticancer drug) and rapamycin (an mTOR inhibitor) and were surface-coated with trastuzumab, an anti-HER2 monoclonal antibody, for efficient active targeting. The developed system had a particle size of 140 nm, with a higher entrapment efficiency (56 % for paclitaxel and 69 % for rapamycin) and improved stability (−9.85 mV). The trastuzumab-decorated liposome exhibited more than 70% affinity for HER 2, indicating their potential for the targeted delivery of paclitaxel and rapamycin in breast cancer.

Prasad *et al.* developed a liposome-based nano-theranostic system to improve the image resolution of solid tumors[124]. The multifunctional liposomes loaded with doxorubicin, gold nanoparticles, and quantum dots exhibited photo-triggered antitumor efficacy. In vivo antitumor diagnostics revealed bimodal imaging capabilities and tumor suppression, facilitated by the release of heat and oxygen-reactive groups. This novel vesicular formulation has opened new avenues for targeting tumors and improving tumor imaging.

Tumor-associated macrophages are important targets for chemotherapy, as they play a crucial role in regulating tumor proliferation within the tumor microenvironment. Yin *et al.* developed a dual-target vesicular system functionalized with anti-programmed death ligand 1 (anti-PD-L1) for the co-delivery of simvastatin and gefitinib, aimed at managing brain metastasis and lung cancer[125]. These liposomes demonstrated the ability to bind with transferrin receptors, efficiently penetrate the blood-brain barrier, and minimize drug resistance by suppressing the EGFR-Akt-Erk signaling pathway.

(b) Niosomes

Niosomes are self-assembled lipoidal bilayer vesicular drug carriers consisting of non-ionic surfactants and cholesterol. These systems can accommodate a wide range of therapeutically active agents with varying solubility, making them a promising strategy for multidrug applications. Unlike liposomes, niosomes are preferentially chosen for designing nanoscaled chemotherapeutic carriers due to their cost-effectiveness, scalability, stability (they are non-leakage vesicles), lack of special storage requirements, and resistance to degradation through hydrolysis and oxidation processes[126]. Mohamad Saimi *et al.* designed and optimized an aerosol delivery system for the treatment of lung cancer. They sonicated gemcitabine and cisplatin in sodium chloride solution and amalgamated them into niosomes composed of Tween 65 and Span 60 (at a 1:2 ratio) and cholesterol[127]. The optimized dual drug embedded niosomes were nanoscale (approximately 166 nm in size), had a low polydispersity index of 0.16, a zeta potential of around 15 mV, and exhibited controlled drug release for 24 h. The cytotoxicity of the aerosolized niosomal system was tested against both MRC5 normal lung cells and A549 cancerous cells, demonstrating reduced toxicity to the normal cells and high toxicity to the cancerous cells after 72 h. These results suggest a novel application for aerosolized niosomes in the management of lung cancer.

Kulkarni and Rawtani developed self-assembled niosomes to customize the solubilities of tamoxifen and doxorubicin for an effective response against breast cancer[128]. These codelivery niosomes were spherical, displayed high entrapment efficiencies, and sustained drug release for 3 days. Achieving a 15-fold increase in antitumor efficacy, through the synergistic action, compared to a free drug combination, was demonstrated in MCF-7 cell lines. The developed niosomes also exhibited significantly enhanced biodistribution and improved cellular uptake, suggesting their potential for breast cancer management. Niosomes coupled with ligands are widely explored in chemotherapy due to their ability to engage receptor-mediated endocytosis[129]. Both PEG-functionalized niosomes and ligand (peptide)-coupled niosomes are actively internalized via endocytosis, with PEG functionalization providing immunoprotection and promoting drug accumulation within tumor cells. Coupling a tumor-homing peptide (tLip-1) to the niosome surface demonstrated high penetration through active targeting in human glioblastoma (U87) cells[130].

(c) Aquasomes and phytosomes

Aquasomes and phytosomes are vesicular drug carriers resembling the properties of water, with sizes typically ranging from 60–300 nm. Aquasomes are self-assembled architecture held together by ionic, van der Waals, or non-covalent bonds. These systems consist of three major components: a central ceramic core material (providing structural stability), a carbohydrate coating substance (protecting drug), and entrapped drugs (for therapeutic action). They are primarily designed to deliver acid-labile drugs (protein and peptides) in both a sustained and targeted manner. Aquasomes have found successful applications in the delivery of various substances, including antigens, enzymes, hemoglobin, and insulin[131].

Aquasomes and phytosomes exhibit distinct morphological and functional differences. Aquasomes consist of a carbohydrate coating over a ceramic core (for stability) and are often adorned with absorbed bioactives or proteins. The cores of aquasomes are typically prepared using methods such as self-precipitation, coprecipitation, and sonication. In contrast, phytosomes are complex vesicular structures that contain phospholipids and herbal extracts (curcumin and polyphenols). They are typically prepared using the solvent evaporation method.

Etoposide is used in the treatment of drug-resistant testicular cancer, small-cell lung cancer, lymphoma, and leukemia. Its utilization is hindered by limitations such as poor bioavailability, lipophilicity, and adverse effects such as hematological toxicity, hypotension, and bronchospasm. To overcome these pharmaceutical limitations, etoposide-embedded aquasomes were designed using the lyophilization technique. The formulated aquasomes were smooth and stable and exhibited a preference for targeting lung cells, the liver, the spleen, and the kidney. When compared to free drug administration, the embedded aquasomes showed a significantly higher accumulation and localization within the targeted tumor cells[132].

Another class of vesicular systems is the phytosomes or phytophospholipid drug delivery system, designed to encapsulate bioactive agents derived from plants and facilitate their delivery across cell membranes. These systems typically have a size of approximately 40 kDa (100–1200 nm). They are capable of encapsulating various plant extracts (polyphenols, flavonoids, tannins, and terpenoids) within their core. In addition, they can be conjugated with targeted proteins at the outer periphery, enabling both active and passive targeting[133,134].

4.2.4. Inorganic nanocarriers

Inorganic nanocarriers are primarily explored for their roles in tumor imaging, facilitating the tracking of drug location, release pattern, and the evaluation of therapeutic effects. In addition, these nanocarriers are employed as theranostics to address issues related to drug resistance in chemotherapy. Commonly used inorganic carriers include iron oxide nanoparticles, quantum dots, carbon-based nanoparticles, and mesoporous silica nanoparticles. These carriers are favored for their large surface area and tunable size and structure. As depicted in Figure 7, various inorganic nanocarriers are utilized for chemotherapy. They demonstrated stimuli-responsive behaviors (temperature, magnetic field, and light), enabling the targeted release of antitumor agents, including genes and DNA, in a manner often likened to a "Trojan horse" pattern of drug release[146]. Table 9 compiles a selection of inorganic-based nanocarriers and outlines their biomedical significance in tumor management.

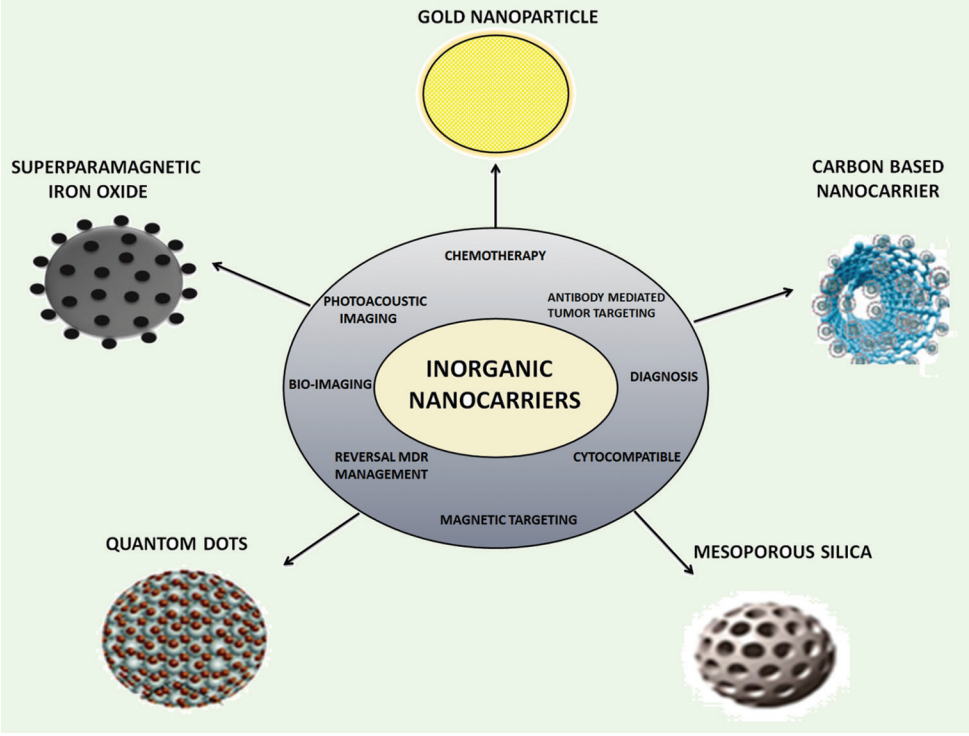


Figure 7. Various inorganic nanocarriers employed for tumor management.

Table 9. Inorganic nanocarriers utilized in tumor management

Type of nanocarrier	Inorganic compound	Research highlights	Applications	References
Inorganic nanocarriers oxide	Superparamagnetic iron oxide	Powerful noninvasive tool for bioimaging	Magnetic resonance imaging in chemotherapy	[152]
	Glutathione-induced 6-mercaptopurine and 6-thioguanine-gold nanoparticles	(i) Controlled nanomolar release of anticancer drugs at target site (ii) Effective live cell imaging technique	Monitoring and controlling Raman spectroscopic tool for tumor	[153]
	siRNA/iron oxide composite	(i) Coating of polyethyleneimine prevented the degradation of composite (ii) Reduced the expression of P-glycoprotein through siRNA transfection	MCF-7/ADR breast cancer	[154]
	Monodisperse gold-loaded iron oxide (GdIO)	Synergized enhancement of T1 and T2 contrast agents	Liver tumor diagnosis	[155]
	Doxorubicin-embedded polymeric gold nanoparticles	(i) Required a smaller dose of doxorubicin (ii) Greatly reduced tumor rate/growth (iii) Provided high therapeutic efficacy and less toxicity	Chemophotothermal therapy	[156]
	Superparamagnetic iron oxide	(i) Controlled clustering structure (ii) Internalized within mesenchymal stem cells (MSCs)	Mesenchymal stem cell (MSC) tracking and magnetic resonance imaging	[157]
	Daunorubicin and 5-bromotetrandrine-loaded iron oxide nanoparticles	(i) Increased tumor temperature (ii) Reduced p-gp and BCL-2 expression (iii) Increased caspase-3 and Bax expression	Reversal of multiple drug resistance (MDR) in leukemia	[158]
Quantum dots (QD)	Beta-cyclodextrin functionalized (CdSe/ZnSe) QDs for co-delivery of doxorubicin and siRNA	(i) Down-regulation of P-gp and mdr1 mRNA (ii) Enabled tracking through laser confocal microscopy	Real-time tracking and chemotherapeutic agent	[159]
	Dual receptor (EGRF and integrin αvβ3) targeted QD/AS-ODN/GE11-c(RGDfK)	(i) Enhanced gene silencing efficiency (ii) Augmented cellular uptake	Non-viral gene carrier for tumor management	[160]
	Manganese doped-zinc selenide quantum dots	(i) High gene transfection efficiency (ii) Biocompatible, and stable	Delivery of siRNA to pancreatic cancer	[161]
Carbon-based nanocarriers	Paclitaxel-C6 ceramide	(i) No toxicity in cell viability (ii) Improved aqueous solubility of paclitaxel (iii) Required 100 times less drug	MDR-pancreatic cancer	[162]
	Single-walled and multiwalled carbon nanotubes (SWNTs and MWNTs)	(i) Enhanced tissue penetration (ii) Provided spatial resolution (iii) Served as T2 contrast agent	Imaging probes (photoacoustic imaging)	[163]
	PEGylated MWNTs	(i) Promped drug efflux in MDR cells (ii) Stimulated ATPase activity of p-gp	Drug conjugate carrier for chemotherapy	[164]
Mesoporous silica	Trimethylammonium mesoporous silica	(i) High-efficient optical imaging of organs (ii) Stable composite within a wide range of pH	*In vivo* optical imaging	[165]
	Doxorubicin-loaded hollow mesoporous silica	(i) Displayed pore size-dependent antitumor activity (ii) Enhanced intracellular action with high MDR reversal effect	MDR reversion	[166]
	TPGS (D-tocopheryl poly ethylene glycol 1000 succinate) modified DOX- MSN	(i) Internalization through clathrin-mediated endocytosis (ii) 10-fold higher killing potency	Reversal MDR in tumor management	[167]
	Magnetic silica nanospheres	Efficient cellular uptake	Magnetic resonance imaging	[168]

The exploration of paramagnetic iron oxide and mesoporous silica nanoparticles loaded with doxorubicin and conjugated with human serum albumin has resulted in a specific focus on targeting and retention. The developed system exhibits biocompatibility and sustained release characteristics, especially in the hypoxic and acidic microenvironment of glioma tumor cells[147]. These nanocarriers have been investigated as versatile tools for encapsulating drugs, genes, and contrast agents, facilitating not only therapeutic actions but also serving as multifunctional probes for imaging tumor cells[148]. For instance, Tang *et al*. designed a magnetic targeting strategy that utilizes an antitumor nanoplatform that efficiently synergizes transfection action with magnetic guidance. Similarly, Reczyńska *et al*. modified superparamagnetic iron oxide nanoparticles (SPIONs) with a combination of non-porous and mesoporous silica coating (@SiO2@mSiO2) and non-porous silica coating (@SiO2), significantly altering the surface properties and sustaining iron release[149]. These modified systems displayed cytocompatibility and exhibited antiproliferative effects against lung cancer cells (A549 cells). Another widely employed nanocarrier, mesoporous silica, has attracted attention due to its theranostic application, attributed to its high pore volume, specific surface area, and well-structured surface properties.

Iron oxide nanoparticles and SPIONs have been explored for a myriad of biomedical applications, including the biosensing of tumor-influenced regions. These nanoparticles efficiently reduced tissue T2 relaxation time, promoting better internalization through the endocytosis pathway[150]. They are versatile carriers capable of loading a range of candidates, such as nucleic acids, antineoplastic agents, and chemical inhibitors. SPIONs that are conjugated with transferrin, aptamers, peptides, antibodies, or hyaluronic acid serve as efficient tumor-targeted drug delivery systems. They are easily recognized by overexpressed receptors and feature bioimaging capabilities while minimizing off-target effects[151]. Moreover, these nanoparticles hold the potential to reverse multidrug resistance effects in chemotherapy and are ideal candidates for diagnostic purposes to monitor therapeutic performances.

Semiconductor quantum dots represent a novel class of fluorescent molecular imaging agents known for their exclusive photophysical properties, including dual imaging capabilities, enhanced signal brightness, size-dependent light emission, and the ability to excite various fluorescent colors simultaneously. Moreover, these agents can effectively bind metal ions to their surfaces due to their high sensitivity and selectivity for metal ions. Over the past two decades, these fluorescent particles have found applications in diagnosis and drug delivery at tumor-targeted sites[169]. For instance, Nifontova *et al*. investigated the cytotoxicity of quantum dots-loaded microcapsules that were functionalized with trastuzumab, a monoclonal antibody[170]. This system specifically targeted the overexpressed HER2 in breast cancer, demonstrating sensitive and promising antibody-mediated tumor targeting with quantum dots. AbdElhamid *et al*. formulated highly fluorescent theranostic nanocapsules based on mercaptopropionic acid-coated cadmium telluride quantum dots, incorporating dual drugs — honokiol and celecoxib[171]. These nanocapsules were further modified with anionic chondroitin sulfate (for CD44 targeting) and cationic lactoferrin (low-density lipoprotein targeting). These multifunctional theranostics exhibited efficient internalization and were easily traceable due to their fluorescence behavior. Furthermore, they demonstrated enhanced cytotoxicity and improved antitumor efficacy against breast cancer cells.

Gold nanoparticles have been intensively engineered as nanocarriers for managing tumor-associated issues due to their biocompatibility, colloidal stability, size tunability, feasible surface modification, and enhanced tissue permeability. These nanocarriers find applications in bioimaging and photoacoustic imaging, due to their high electron density, enhanced optical scattering performance, and non-bleaching fluorescence in tumor cell imaging[172]. Albertini *et al*. developed peptide (arginine-glycine-aspartic acid)-decorated gold nanoparticles for the treatment and diagnosis of tumors[173]. They reported approximately a 4-fold increase in accumulation following subcutaneous administration and a 1.5-fold increase through the intracranial route in mice tumors.

5. Conclusion

This review summarizes a wide range of nanotechnology-based targeted drug delivery strategies that are commonly employed in tumor management. These drug delivery approaches exhibit cell specificity and selectivity while minimizing systemic toxicity. Advancements in nanotechnology have enabled the precise recognition of tumor sites, offering hope for successful drug delivery to tumor sites. Various versatile nanocarriers, including polymeric nanoparticles, lipid-based carriers, vesicular systems, and inorganic nanocarriers, have undergone extensive investigation for tumor management. These systems not only facilitate precise target site identification but also demonstrate a high capacity for tissue internalization. Targeting tumor sites through the application of magnetic fields and ultrasound radiation represents an emerging

concept with significant potential for the precise recognition of molecular addresses, bioimaging, and disease tracking at the tumor sites. These exclusive attributes have enabled researchers to develop novel approaches, including monotherapy and combination therapy (through ligand conjugation), aimed at improving tumor management. Polymeric-targeted approaches exhibit the efficiency to specifically enter the tumor vasculature without affecting neighbor cells and tissues. While these nanosystems offer promising alternatives for tumor management, they are not without challenges. These challenges include addressing the altered tumor microenvironment, improving uptake and internalization, overcoming the narrow therapeutic window for therapeutics, and navigating the regulatory processes required for approval. Moreover, achieving a vehicle with an extended biological half-life and enhanced targeting efficiency is crucial for site-specific actions. Current targeted approaches primarily emphasize safety and efficiency at the cancerous site. However, they also require careful consideration of potential long-term side effects, the determination of optimal dosage strength, and the establishment of suitable conditions. Recent advancements have introduced precise treatment methods, such as siRNA delivery, stem cell therapy, immune-based treatments, gene therapies, and ablation therapies. These approaches hold promise as alternatives to surgical procedures. Furthermore, newly introduced fields such as pathomics and radiomics are highly favored for collecting extensive clinical data and designing novel strategies to predict well-defined responses and advancements in cancer management.

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Conflict of interest

The authors declare no conflict of interest.

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