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REVIEW

Biopolymer-Based Nanomedicine for Cancer Therapy: Opportunities and Challenges

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Abstract: Cancer, as the foremost challenge among human diseases, has plagued medical professionals for many years. While there have been numerous treatment approaches in clinical practice, they often cause additional harm to patients. The emergence of nanotechnology has brought new directions for cancer treatment, which can deliver anticancer drugs specifically to tumor areas. This article first introduces the application scenarios of nanotherapies and treatment strategies of nanomedicine. Then, the noteworthy characteristics exhibited by biopolymer materials were described, which make biopolymers stand out in polymeric nanomedicine delivery. Next, we focus on summarizing the state-of-art studies of five categories of proteins (Albumin, Gelatin, Silk fibroin, Zein, Ferritin), nine varieties of polysaccharides (Chitosan, Starch, Hyaluronic acid, Dextran, cellulose, Fucoidan, Carrageenan, Lignin, Pectin) and liposomes in the field of anticancer drug delivery. Finally, we also provide a summary of the advantages and limitations of these biopolymers, discuss the prevailing impediments to their application, and discuss in detail the prospective research directions. This review not only helps readers understand the current development status of nano anticancer drug delivery systems based on biopolymers, but also is helpful for readers to understand the properties of various biopolymers and find suitable solutions in this field through comparative reading.

Keywords: drug delivery, nanoformulations, polymer, proteins, polysaccharides

Introduction

Cancer is the second leading cause of death worldwide, with over 30 different types of cancer reported. Common types include breast cancer, lung cancer, liver cancer, prostate cancer, colorectal cancer, and others. Current main treatment modalities for cancer include surgery, chemotherapy, radiation therapy, and immunotherapy, among others. These treatments have shown efficacy in cancer treatment, but they often come with noticeable side effects. Surgical resection may be challenging to completely remove tumor tissue, while chemotherapy delivers anticancer drugs to tumor sites through systemic, non-selective administration, causing harm to healthy tissues and exhibiting low efficacy with the potential for drug resistance.[1] In addition, some anticancer drugs exhibit significant cytotoxic effects on cancer cells, such as curcumin,[2] doxorubicin, paclitaxel, cisplatin, and vinblastine. However, many of these drugs are hydrophobic in nature, leading to low oral bioavailability, and most of them require renal excretion. Immunotherapy, on the other hand, stimulates the body's immune system by targeting specific antigens on the surface of cancer cells through antibody binding. However, this treatment approach has limited efficacy in certain patient populations, such as those with autoimmune diseases, and repeated administration may potentially induce immune-related adverse events.[3] High dosage and repeated administration are common challenges associated with these treatment modalities, undoubtedly increasing the risk of damage to normal organ tissues. Therefore, novel targeted delivery strategies are needed to improve the treatment of cancer.

Various delivery system strategies have been developed for cancer treatment, including antibody-based delivery, polymer-based delivery, liposome-based delivery, and protein-based delivery. The antibody-based delivery strategy involves conjugating antibodies as carriers with radioactive drugs or chemotherapeutic agents for radioimmunotherapy or targeted immunotherapy. Currently, FDA-approved targeted radiotherapeutics include Lutathera, Zevalin, and Bexxar.[4] Targeted

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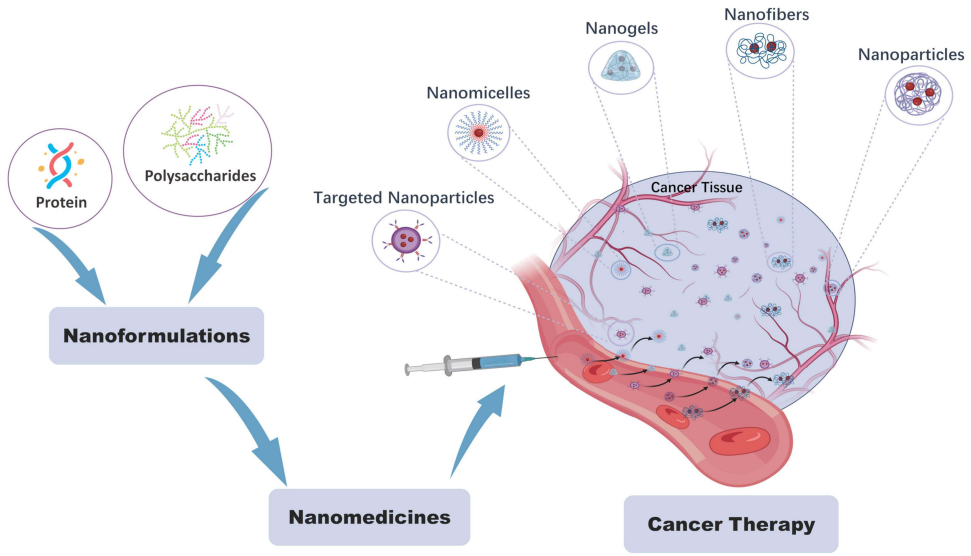
Graphical Abstract



immunotherapy offers a potential solution to reduce the adverse effects of systemic treatments like chemotherapy on patients. The FDA has approved various types of targeted therapy drugs that focus on specific aspects of cancer treatment. These include drugs targeting the tumor vasculature system, such as sorafenib, bevacizumab, and sunitinib. Additionally, there are drugs targeting the tumor immune system, such as nivolumab, pembrolizumab, and atezolizumab, which aim to enhance the body's immune response against cancer. Furthermore, drugs targeting the tumor microenvironment, including ramucirumab, axicabtagene ciloleucel, and denosumab, are designed to modify the tumor's surrounding environment.[5] The clinical application of antibody-based drug carriers relies heavily on the expression of specific antigens on the tumor surface, while resistance, off-target effects, and toxic side effects such as bone marrow suppression and venous occlusion limit their effectiveness. Polymer-based carriers come in various forms, including polymer micelles (Nanoxel® M, Genexol® PM, SP1049C), polymer-drug conjugates (Oncaspar, Asparlas), dendrimers (DEP®docetaxel, AZD0466), and polymer implants (GLIADEL Wafer). However, polymers are often non-degradable and possess high immunogenicity.[6] Liposomes, with a long history as delivery vehicles, have examples like Doxil®, an early FDA-approved liposomal formulation, and Vyxeos®, approved in 2017 for the treatment of acute myeloid leukemia. Liposome preparation is relatively straightforward, but their delivery performance is influenced by size and composition, and they lack targeting specificity.[7,8] Proteins, such as the FDA-approved Transdrug®, exhibit low immunogenicity but suffer from poor stability.

Nanotechnology has revolutionized the field of medicine,[9,10] particularly in cancer treatment, through the development of nanomedicine. Nanomedicine encompasses a wide range of applications, including prevention, monitoring, diagnosis, and treatment of cancer. Nanoscale materials possess unique properties that enable personalized design and targeted delivery of therapies.[11] This technology has overcome many limitations of traditional cancer treatments by offering numerous advantages. Nanoparticles can encapsulate poorly soluble drugs, improving their solubility and efficacy.[12] They can also enhance drug circulation time, increasing their bioavailability.[13] Through ligand modification, nanoparticles can specifically target tumor sites, overcoming drug resistance and minimizing damage to healthy tissues.[14] Additionally, nanomaterials can be engineered to exhibit temperature and pH sensitivity, allowing for controlled drug release. Furthermore, their ability to cross the blood-brain barrier opens new possibilities for treating neurological diseases.[15] The emergence of nanomedicine has brought significant advancements to cancer treatment, addressing challenges and improving outcomes for patients.

Nanomedicine predominantly relies on nanomaterials and delivery strategies. In the subsequent section of this paper, we elucidate the applications of nanomaterials, delivery strategies, and the distinctive attributes of various nanomaterials.

Following that, the core of this paper (biopolymer-based nanodelivery carriers) is discussed in detail, focusing on the current research status of biopolymer-based delivery carriers (proteins, polysaccharides and liposome), extant challenges, and potential future directions. The article aims to provide assistance and guidance to researchers in this field.

Nanomedicine for Cancer Therapy

Nanomedicines Applications

The clinical use of natural anti-tumor drugs is limited by low water solubility, rapid clearance from the circulation, lack of selectivity and low tissue permeability. Paclitaxel (PTX) and doxorubicin (DOX) are frequently prescribed anticancer medications. PTX exhibits low water solubility, and direct injection can lead to varying degrees of bodily damage, necessitating formulation with 50% ethanol and 50% Cremophor-EL (CrEL) (a polyoxyethylated castor oil derivative) in clinical settings.[16] However, CrEL poses a risk of inducing neuropathy and hypersensitivity reactions, necessitating pre-treatment with antihistamines. In contrast, directly injected PTX is highly cytotoxic, leading to side effects such as myelosuppression (neutropenia, anaemia, and thrombocytopenia) and cumulative neurotoxicity (peripheral sensory abnormalities, sensory hypersensitivity, arthralgia, and myalgia). DOX is indicated for the treatment of a wide range of solid tumors, including breast, ovarian, gastric, thyroid and liver cancers, and directly injected DOX can be rapidly distributed to all body tissues, however, DOX and its metabolite, Zoerythromycin, produce free radicals that cause cardiotoxicity, and also have side effects such as myelotoxicity, neuropathy, hypersensitivity reactions, hair loss, and gastrointestinal toxicity.[17] In addition to anticancer drugs, nucleic acid-mediated therapies are also effective tools in cancer treatment. For example, siRNA can precisely target and silence almost any gene of interest. However, nucleic acid therapeutics such as siRNA are readily cleaved by endonucleases in the serum and extracellular environment.[18]

Nanomaterials have garnered significant attention from researchers due to their excellent specific surface area and extremely small volume. When used as drug carriers, they can overcome challenges associated with low bioavailability, non-specific distribution, and poor water solubility of free drugs.[19] Abraxane and Opaxio are clinically utilized PTX nanoformulations capable of effectively limiting drug exposure to normal tissues. Particularly, Abraxane utilizes albumin as a drug carrier. The unique characteristics of albumin significantly enhance the pharmacokinetics of PTX and facilitate the drug's targeting to tumors. Furthermore, Doxil and Myocet are DOX liposome nanoformulations used clinically, which effectively reduce cardiotoxicity by encapsulating DOX in liposomes.[17]

Due to the rapid growth of tumors, there is an increased demand for oxygen and nutrients, leading to the rapid expansion of the vascular system and increased permeability of the blood vessel walls. Additionally, tumors often lack a functional lymphatic system, which allows for prolonged retention of large molecular substances within the tumor region. This enhanced permeability and retention (EPR) effect in tumors is the main working principle of current nanomedicines.[20] By utilizing the EPR effect, nano drugs larger than 8 nm can penetrate blood vessels and permeate the tumor microenvironment, thereby achieving effective drug delivery. Through appropriate modifications of nanomaterials, they can exhibit specific sensitivity to factors such as near-infrared light, pH, temperature, magnetic fields, and ultrasound, enabling responsive drug release. By combining various treatment modalities such as photothermal therapy (PTT), magnetothermal therapy, chemotherapy (CHT), radiation therapy (RT), gene therapy, immunotherapy, photodynamic therapy (PDT), chemical dynamic therapy (CDT), and starvation therapy, targeted controlled release of drugs can be achieved.[19] Furthermore, these approaches can be combined with molecular imaging techniques to enable multifunctional treatments, including localized imaging and tracking. However, there is a scarcity of clinically approved nanomedicines. Examples of such approved nanomedicines include Abraxane®, Doxil®, Ontak®, Genexol® and a few others.

Table 1 collates some of the nano-formulations currently FDA-approved for cancer treatment, encompassing those for physical therapy and chemotherapeutic drug treatment. However, clinical utilization of nano-formulations remains limited, primarily due to the low delivery efficiency of nano-administered drugs. Reports indicate that only 0.7% of the injected dose reaches solid tumors, with a concurrent risk of damage to normal tissues.[21]

Table 1 FDA-Approved Anticancer Nanomedicines

Clinical Products	Description	Treating Cancer	Clinical Effect
Abraxane®	Albumin Load PTX	Advanced non-small cell lung cancer (surgery or radiotherapy not an option), metastatic breast cancer (secondary), metastatic pancreatic cancer (primary)	No hypersensitivity
NanoTax®	PTX nanoparticles prepared by SCF technology	Malignant tumor of the peritoneum	Reduced systemic exposure and toxicity[22]
Genexol®	PTX micelles	Breast cancer, locally advanced or metastatic NSCLC	Reduced hypersensitivity and neurotoxic effects
Opaxio®	PTX polymer formulations	Glioblastoma	Avoid exposure of normal tissues to high levels of unconjugated active chemotherapy and its associated toxicity (hair loss, infections and cardiac symptoms)[23]
Paclical®	Paclitaxel micelles	Epithelial ovarian cancer	Allows for higher doses, shorter infusion times, elimination of the need for preoperative medications, and improved patient safety
MagForce NanoTherm®	Magnetic Thermal Therapy	Glioblastoma	Lower magneto-thermal conversion efficiency, severe MRI artefacts, susceptibility to tumor leakage
AuroShell®	Thermal therapy with near-infrared laser sources	Prostate cancer	Reduce side effects
NBTXR3/Hensify®	Crystalline Hafnium Oxide Nanoparticles	Locally advanced squamous cell carcinoma	To improve the anti-tumor efficacy of radiotherapy while reducing its potential side effects, such as damage to surrounding healthy tissue[24]
Pegasys®	PEG-coupled interferon	Persistent (chronic) infection with hepatitis C virus or hepatitis B virus	Longer half-life
Oncaspar®	PEG-coupled asparaginase	Paediatric acute lymphoblastic leukaemia	Hepatotoxicity, pancreatitis, thrombosis, nausea, vomiting and fatigue[25]
Neulasta®	PEG-modified recombinant methionyl human G-CSF (r-metHuG-CSF)	Non-myeloid malignant tumor	Enhanced activity compared to filgrastim[26]
Eligard®	PLGA-encapsulated leuprolide	Advanced prostate cancer	Lack of overall safety and tolerability and outbreak drug release[27]
Kadcyla®	Ado- Trastuzumab Emtansine	Recurrent HER2-positive, metastatic breast cancer	The most common side effects are nausea, fatigue, muscle or joint pain, low levels of platelets in the blood (thrombocytopenia), elevated liver enzyme levels, headache and constipation
VYXEOS®	Liposome-encapsulated cytarabine with zorubicin	Acute myeloid leukaemia	Can lead to a severe generalised rash
Patisiran/ ONPATTRO®	Liposome-encapsulated siRNA	Transthyretin (TTR)-mediated amyloidosis	Back pain, nausea, abdominal pain, dyspnoea.
Doxil/ Caelyx®	PEGylated liposome doxorubicin	Metastatic breast cancer, advanced ovarian cancer	Hand-foot syndrome, a sign of idiosyncratic non-IgE-mediated hypersensitivity reaction[28,29]
Myocet®	Liposome doxorubicin	Treatment of metastatic breast cancer (primary)	May reduce cardiotoxicity associated with doxorubicin treatment and may avoid unwanted toxicity caused by PEG or adriamycin[30]

(*Continued*)

Table 1 (Continued).

Clinical Products	Description	Treating Cancer	Clinical Effect
Marqibo®	Liposome vincristine	Philadelphia chromosome-negative acute lymphoblastic leukaemia (tertiary)	Higher maximum tolerated dose, superior antitumor activity and delivery of more active drug to the target tissue[31]
MEPACT®	Liposomal mifamurtide	Osteosarcoma	Well tolerated, but with sequelae such as chills, fever, headache, nausea and myalgia[32]
Onivyde®	PEGylated liposome irinotecan	Metastatic pancreatic cancer (secondary)	May cause life-threatening neutropenia, diarrhoea[33,34]
Depocyt®	Liposomal adriamycin	Neoplastic meningitis	Develop serious treatment-related neurological complications[35]

Abbreviations: SCF, supercritical fluid; NSCLC, non-small cell lung cancer; MRI, magnetic resonance imaging.

Tumor Microenvironment and Biobarrier

The tumor microenvironment and biological barriers are two crucial factors that hinder the delivery of nanomedicines. Targeted delivery strategies based on nanotechnology primarily rely on several specific markers of cancer, including (1) Aberrant proliferation signaling pathways; (2) Resistance to cell death; (3) Induction of neovascularization (angiogenesis); (4) Escape from growth inhibitory factors; (5) Activation of invasion and metastasis; (6) Replicative immortality;[36] (7) Dysregulated cellular energy and metabolism;[2] (8) Evasion of immune destruction. The heterogeneous and unique physiological microenvironment of tumors, such as hypoxia, acidity (pH 6.5–6.9), and elevated glutathione levels, often serve as endogenous stimuli for responsive drug release in nanomedicine targeting. When the drug reaches the tumor site, it senses these heterogeneity-related differences and releases the drug accordingly.

Despite the advantages offered by nanotechnology, the delivery of anticancer drugs based on nanotechnology still needs to overcome various physiological barriers. Firstly, it needs to overcome systemic obstacles such as the mononuclear phagocyte system (or reticuloendothelial system), and clearance by the liver, biliary system, and urinary system, to have a chance to interact with tumor tissue. Secondly, the tumor tissue penetration of the nano delivery system is crucial, with a general requirement that its hydrodynamic size should be smaller than 100 nanometers. Tumor tissue resembles an organ, comprising tumor cells and a heterogeneous tumor stroma, which collectively give rise to a complex and dynamic tumor microenvironment. In addition to the physical barriers conferred by the dense tissue stroma and elevated intra-tumoral pressure, there are also multiple drug resistance mechanisms and immune suppression mediated by tumor-associated cells. Lastly, the uptake of nanodelivered drugs by tumor cells is essential, as the delivered drugs need to cross the cell membrane and reach specific cellular organelles to exert therapeutic effects.[37] Additionally, tumor cells exhibit variable uptake of nano-delivery drugs, and since the therapeutic targets of most therapeutic agents are located intracellularly, delivery carriers need to traverse the cell membrane to reach specific organelles for therapeutic efficacy. However, the presence of lysosomes within the cell poses a challenge as they contain various hydrolytic enzymes that may lead to drug degradation or loss of effectiveness.[38] Bypassing endosomal pathways and endosomal rupture mechanisms are currently the main strategies employed to address this issue.

Nanomedicine Delivery Strategies

Nano-formulations have been developed to overcome the limitations of free small molecule drug delivery, demonstrating significant potential in enhancing drug bioavailability and reducing drug toxicity. Strategies for delivering nanomedicines to tumors typically involve two main approaches: passive targeting and active targeting, as shown in Figure 1.

Passive targeting, primarily reliant on the Enhanced Permeation and Retention (EPR) effect, facilitates the accumulation of nanoformulations, typically ranging from 10 to several hundred nanometers in size, within tumors. This effect occurs due to leakage from the tumor vascular system and compromised lymphatic vessels. However, despite its utility, this delivery strategy presents notable drawbacks, as outlined below.[40](1) Lack of Specificity. Passive targeted therapeutic

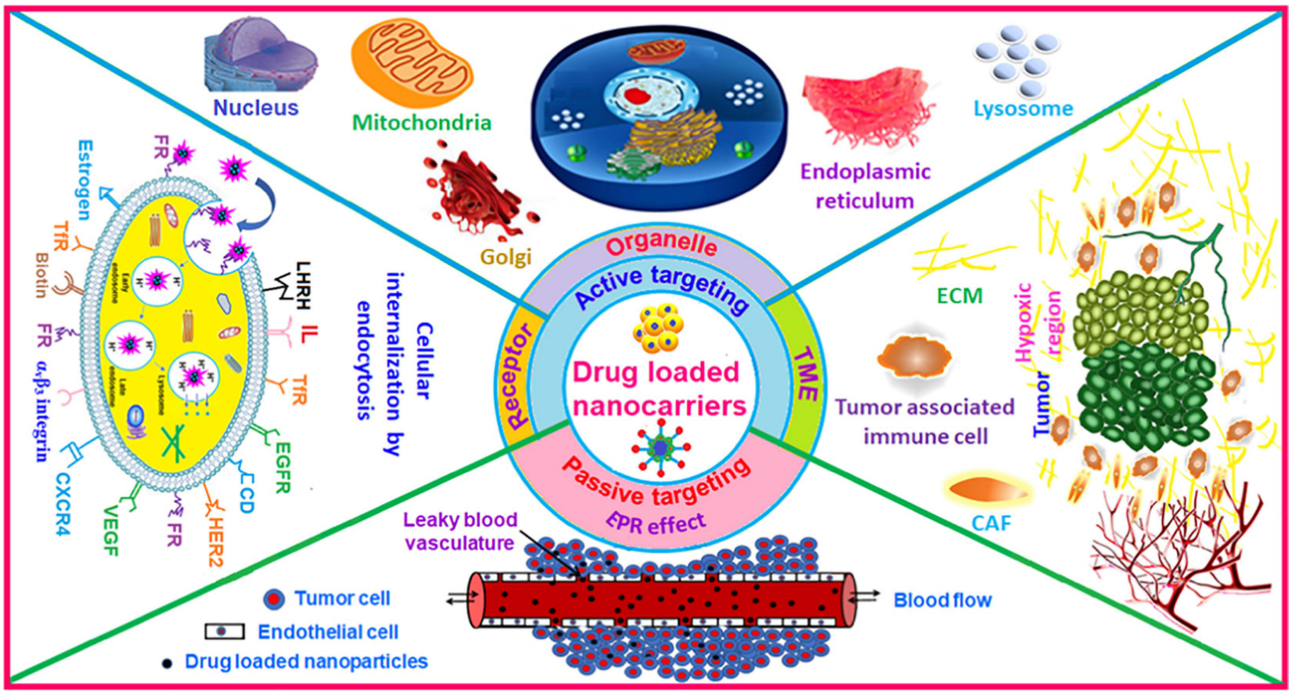


Figure 1 Tumor Targeting Strategies. Reprinted from Advances in Colloid and Interface Science, 296, Dutta B, Barick KC, Hassan PA. Recent advances in active targeting of nanomaterials for anticancer drug delivery, 102509 Copyright 2021, with permission from Elsevier.[39]

approaches to tumors often rely on the variability of tumor tissue from normal tissue. However, this variability is not always apparent, potentially resulting in adverse effects of the drug on normal tissue, such as toxicity. (2) Intra-tumor Heterogeneity. Variability, such as uneven cell density and blood vessel distribution, exists within tumor tissue, influencing the distribution and efficacy of drugs within the tumor. (3) Limited Drug Release. Upon entering tumor tissue, certain targeted drugs or carriers may be influenced by the tumor microenvironment, leading to restricted drug release and reduced therapeutic efficacy. (4) Development of Drug Resistance. Resistance exhibited by certain tumor cells against the targeted drug can diminish its therapeutic effect, thereby reducing overall efficacy. (5) Challenges in controlling drug release and distribution. Passive targeting presents difficulties in accurately controlling the release rate and distribution of drugs within tumor tissue, potentially resulting in inadequate or excessive drug concentration, thereby impacting therapeutic effectiveness and safety. (6) Influence of the Tumor Microenvironment on Therapeutic Effectiveness. Changes in the tumor microenvironment can impact the Enhanced Permeability and Retention (EPR) effect, consequently influencing drug accumulation and therapeutic efficacy.

Active targeting can specifically home in on the tumor area, substantially enhancing therapeutic efficacy. This strategy typically branches into two major directions: surface receptor targeting and targeting the unique pathological environment of the tumor. Following these directions, active targeting strategies can be further classified into three approaches.[39] (1) Targeting cancer cell surface receptors. This method involves specific receptors present on the surface of cancer cells, such as the folate receptor, transferrin (Tf) receptor, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER), cluster of differentiation (CD) receptor, integrin receptor, estrogen receptor, among others.[41,42] (2) Targeting subcellular organelles. Certain biologically active molecules, such as peptides or nucleic acids, necessitate delivery to specific organelles to attain maximal therapeutic efficacy. Additionally, targeting specific organelles can enhance therapeutic effectiveness and minimize toxicity at lower doses. Currently, the primary subcellular organelles targeted include mitochondria, nucleus, lysosome, endoplasmic reticulum, and Golgi apparatus. (3) Targeting the tumor tissue and microenvironment. Depending on the specific composition of tumor tissues or cells, it is possible to prepare targeting active peptides, such as tumor-homing peptides and cell-penetrating peptides. Tumor homing peptides specifically recognize and adhere to tumor cells/tumor vascular system, and cell-penetrating peptides can target and penetrate the anatomical barrier of the tumor. The tumor

microenvironment possesses several unique features, such as low pH, hypoxia, and high glutathione levels. Capitalizing on this heterogeneity, stimulus-responsive nanomedicines with hypoxia-responsive, acid-responsive, GSH-responsive properties, among others, can be designed. Moreover, owing to enhanced angiogenesis in the tumor microenvironment, targeting the vascular endothelial growth factor (VEGF) receptor, highly expressed in this milieu, is achievable.[43] Additionally, certain inflammatory mediators are overexpressed in the tumor microenvironment, making them suitable targets for immune cells to mediate immune therapy. Active targeting is able to bind specifically to tumors, deliver drugs selectively, and circumvent the problem of drug resistance, but some of the challenges remain to be solved. Active targeting mainly relies on modifying some characteristic proteins or peptides on the carrier surface, which may be cleared by reticuloendothelial system (RES) and induce local immune responses. In addition, the preparation process is complex and difficult to industrialize.[44]

Main Parameters of Nanomedicines

The main influencing factors of nanomedicines include size, morphology, surface charge and surface chemistry. These parameters are essential to ensure the efficacy, safety and controllability of nano-formulation design, preparation and application. By regulating and optimising these relevant parameters, the biocompatibility and stability of nano-formulations in organisms can be enhanced, thereby improving the bioavailability of drugs in vivo.

Size

The Size of nano-formulations is a critical factor affecting their bioavailability, as it influences various aspects of their behavior within the body.[45] Formulations that are too large can induce inflammatory reactions and peritoneal adhesions, while those that are too small may have insufficient residence time for effective tumor penetration.[46] Typically, nanopreparations range in size from 10 to 1000 nm. Nanoparticles smaller than 20–30 nm are rapidly cleared by the excretory system, whereas larger particles (>200 nm) are taken up by the mononuclear phagocytosis system.[47] Nanoparticles in the range of 150–300 nm tend to accumulate predominantly in the liver and spleen, while colloids sized between 200 to 400 nm are quickly cleared by the liver.[48] In cancer therapy, nano-formulations often rely on the Enhanced Permeability and Retention (EPR) effect of tumors. The gap size for vascular leakage in tumors typically ranges from 100 to 780 nm. Larger particle sizes (60–200 nm) favor prolonged in vivo retention, while smaller sizes (30–50 nm) facilitate penetration into tumor tissue.[49] Previous studies have demonstrated that nanocarrier sizes around 50 nm are optimal for enhanced drug delivery and tumor specificity. Designing size-variable nano-formulations can enhance intracellular delivery, promote deep tumor penetration, and improve tumor targeting, thereby optimizing their effectiveness in cancer therapy.[48,50]

Surface Charge

Surface charge plays a critical role in protein adsorption, with the Zeta point commonly utilized to characterize the charged properties of particles. Positively charged nanocarriers exhibit strong binding to negatively charged proteins via electrostatic attraction, leading to their uptake not only by various plasma proteins but also by phagocytes, ultimately resulting in their excretion from the bloodstream.[51] This process reduces the penetration and efficacy of nanomedicines. In contrast, neutral nanoparticles or those with a slightly negative charge demonstrate significantly prolonged circulating half-life. Moreover, the surface charge of nanopreparations is pivotal for cellular internalization. Positively charged liposomes, for instance, have been shown to be more favorable for cellular internalization, albeit this depends on factors such as the growth stage of the tumor and the type of cancer cells.[52,53] Designing nanodelivery systems with triggered charge reversal, wherein stimuli such as pH, reactive oxygen species (ROS), enzymes, glutathione (GSH), adenosine triphosphate (ATP), light, and thermal responses are employed, can mitigate the toxic side effects associated with positive surface charge and effectively enhance the delivery efficiency of nanomedicines.[54]

Morphology

The Morphology of nano-formulations plays a pivotal role in various biological processes, including biological barrier crossing, cell internalization, immune escape, and protein corona formation.[55] For instance, non-spherical nanoparticles exhibit a longer circulation time compared to spherical particles, facilitating drug penetration and bioaccumulation at the tumor site.[56,57] The cellular uptake of nanoparticles can be modulated by altering the shape of the nanomaterials.[58–61] Li Ying et al discovered that the order of cellular uptake of nanoparticles was spherical > cubic > rod > disc.[62] Rod-shaped gold nanoparticles demonstrated

superior penetration compared to spherical ones.[63] Shenshen Cai et al investigated the impact of filamentous micelles versus spherical nanoparticles on drug delivery and found that filamentous micelles had longer in vivo circulation times compared to polyethylene glycolated liposomal particles.[64] Marginal dynamics, or the lateral drift of nanoparticles towards the endothelial wall, is a crucial consideration in nanoparticle design. Binding to the vessel wall facilitates particle-cell binding and receptor-ligand interactions in active targeting strategies and enables extravasation through the tumor's open-window vascular system. Disc particles experience marginalization under blood flow, significantly altering circulation time, biodistribution, and cellular interactions. Nanodiscs exhibit strong binding to the phospholipid bilayer, primarily to the cell membrane, and can be employed for cell membrane tracing.[65,66] Ning Wang et al, utilizing erythrocyte membranes coated with disc-shaped mesoporous silica nanoparticles encapsulated with DOX, demonstrated successful drug release in hypoxic environments with enhanced permeability and drug accumulation compared to spherical shapes.[67] This in vivo effect attributable to shape differences is correlated with the formation of a protein corona. It was observed that rods and spheres exhibit a shape-dependent relationship with the amount of protein adsorbed, with rods adsorbing a greater quantity of protein.[68]

Surface Chemistry

Surface chemistry is a pivotal factor influencing the interactions at the nanobio-interface, ultimately determining the pharmacokinetics and tumor targeting of the formulation. Various surface chemistries, such as peptides, natural polysaccharides, and synthetic polymers, exhibit different cellular affinities.[69] Studies have revealed that carboxylated surface chemistries exhibit a notable affinity for ovarian cancer cells. Moreover, nanoparticles encapsulated with poly-L-aspartic acid, poly-L-glutamic acid, and hyaluronic acid demonstrate superior tumor targeting compared to conventional polyethylene glycolated (PEG) nanoparticles. Jing Wang et al modified bovine serum albumin-poly(N-3-acrylamidophenylboronic acid) nanoparticles with PEI-PEG copolymer and cRGD peptide, illustrating that surface chemical modification of nanoparticles effectively enhances tumor accumulation and cellular uptake.[70] Furthermore, surface chemistry impacts the composition of the protein corona and the quantity of protein. By precisely controlling the surface chemistry of the formulation, modulation of the protein corona and cellular uptake can be achieved.[71]

Other Parameters

Dispersibility, drug loading, and drug release rate are crucial parameters in nano-formulation design. Dispersibility refers to the extent of uniform distribution of particles in a solution or matrix. Optimal dispersibility ensures stability and homogeneity of the formulation during application. Meanwhile, drug loading and release rate are vital factors affecting the administered dose and therapeutic efficacy. Adequate drug loading ensures the delivery of the intended dosage, while the release rate influences the kinetics of drug release, directly impacting the therapeutic effect. Therefore, careful consideration and optimization of dispersibility, drug loading, and drug release rate are essential for the development of effective nano-formulations.

The pharmacokinetics and pharmacodynamics of drugs are essential parameters for assessing the in vivo behavior of nanomedicines and the mechanism of drug effects. The main parameters and significance of pharmacokinetics are

Table 2 Pharmacokinetic Parameters

Parameters	Description
C_{max}	Maximum observed concentration of a drug collected from an animal or human body
$C_{through}$	Means the lowest concentration from the initial moment of administration to the next administration when multiple administrations have reached steady state, and is a reflection of the level of accumulation of the drug
T_{max}	Time to reach T_{max}
AUC	Area under the concentration curve, representing the total drug exposure experienced by the subject in the study
$T_{1/2}$	Half-life, the time for the concentration of the drug to decrease by half
MRT	Mean residence time, the average time a drug molecule spends in the body
V_d (volume of distribution)	A volume estimated as the ratio of the blood concentration (C) to the amount of drug in the body (D) when the drug is absorbed and distributed to reach a steady state blood concentration.
CL (Clearance Rate)	The number of apparent volume of distribution of a drug removed from the body per unit of time, meaning how many volumes of plasma are cleared of the drug per unit of time

summarized in Table 2. Compared to free drugs, carrier-mediated anticancer drugs or conjugated drugs can achieve optimized pharmacokinetic profiles through parameter tuning, thereby striking a better balance between efficacy and toxicity. (1) Nanomedicines can mitigate the clearance of the mononuclear phagocyte system (MPS) through surface chemical modification. (2) Functionalized nanomedicines can prolong the half-life, enhance the bioavailability, and increase the volume of distribution of the drug. (3) Nanomedicines can exploit the EPR effect or active targeting to access the tumor microenvironment, thereby enhancing drug specificity and reducing toxicity. (4) Encapsulating more therapeutic drugs within nanomedicines can decrease the frequency of required drug dosing intervals and enhance the anticipated pharmacological effects. This leads to a reduction in systemic adverse side effects and an improvement in treatment compliance.[72–74]

Biopolymer-Based Nanosystems for Cancer Drug Delivery

Cancer nanomedical technology primarily relies on its delivery carriers. The ideal delivery carrier should exhibit good biocompatibility, biodegradability, excellent drug-loading capacity, ease of acquisition, low production costs, and low or no toxicity. Nanomaterials can be primarily categorized into inorganic materials (including metal nanomaterials, carbon nanomaterials, and mesoporous silica nanomaterials) and polymer materials (synthetic polymers and biopolymers).

Inorganic nanomaterials exhibit unique photonic and electromagnetic properties, coupled with their diminutive size. However, there in vivo circulation time is short. Polymers, as macromolecular materials, fulfill the fundamental requirements for serving as delivery carriers. They not only possess exceptional stability but also offer adjustable dimensions. Polymers can be further are subdivided into two categories based on their sources: synthetic polymers and biopolymers. Artificially synthesized polymers, such as polyethyleneimine (PEI), N-(2-hydroxypropyl) methacrylamide (HPMA),[75] and polyethylene glycol (PEG), possess high stability. The manufacturing process of these polymers is conducive to commercialization. However, these synthetic polymers often exhibit poor biodegradability and low bioactivity.

Biopolymers derived from animal, plant, or microbial sources offer advantages as drug delivery carriers in tumor therapy. These biopolymers, such as proteins, polysaccharides, and liposomes, exhibit good biocompatibility, ease of degradation, low toxicity, and easy modifiability. Biopolymers used as delivery carriers can be broadly classified into three categories: proteins (such as albumin, silk fibroin, ferritin, zein, and gelatin), natural polysaccharides (including chitosan, dextran, alginate, hyaluronic acid, pectin, gum, and carrageenan) and liposomes. Based on our research, common forms of biopolymer-based nanocarriers for anticancer drug delivery include nanoparticles, nanogels, nanofibers, nanomicelles, nanocapsules, and nanospheres.[76] Current research on biopolymer-based nanocarrier systems for anticancer drug delivery primarily focuses on (1) optimizing preparation processes to improve drug loading efficiency, (2) chemical modification or surface functionalization to enhance targeting and controlled release properties, and (3) combination with chemotherapy or other treatment modalities to enhance therapeutic efficacy. We have provided an overview of the current research status of biopolymer-based nanosystems for cancer drug delivery and prospect future research directions in this field.

Protein

Proteins, as a type of natural biopolymer, are abundantly present in the human body and play a crucial role in the field of medicine. Their exceptional properties, including excellent biocompatibility, biodegradability, and low immunogenicity, make them highly valuable for various medical applications such as drug delivery, imaging, and protein-based therapies.[77] The wide availability of proteins in the human body, combined with their favorable characteristics, has positioned them as essential components for advancing medical interventions and improving patient outcomes in diverse medical domains. Several proteins have been extensively studied and applied for drug delivery purposes, including serum albumin, silk fibroin, gelatin, zein, and ferritin (Figure 2).

Albumin

Albumin, the most abundant protein in human blood, exhibits unique physiological characteristics that make it a valuable member of the drug delivery carrier family, especially in the context of cancer treatment. Albumin carries a net negative charge, which gives it excellent water solubility and a relatively long half-life. Its negative charge also allows it to evade

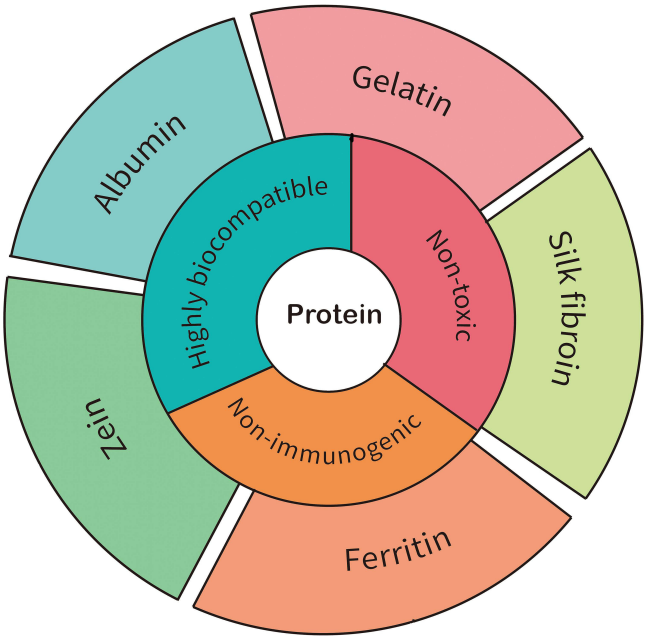


Figure 2 Schematic representation of various members involved in Protein-based nano drug delivery carrier for cancer treatment.

clearance by the kidneys through tubular reabsorption. Additionally, albumin possesses inherent binding sites and can accumulate at sites of vascular leakage. The active and passive drug delivery mechanisms for albumin are shown in Figure 3A. Albumin can bind to Gp60 on endothelial cells and thus enter and exit the vasculature by transcytosis. In addition, albumin can bind to SPARC receptors overexpressed in tumor tissues, thereby targeting the tumor tissue. Albumin drug-loaded nanomicrospheres can also enter the tumor microenvironment through the EPR effect. Based on these properties, albumin has been utilized as a carrier for anticancer drug formulations that have found clinical use. One notable example is Abraxane (albumin-bound paclitaxel), which has received FDA approval for the treatment of metastatic breast cancer.[78]

The successful clinical application of the albumin-bound paclitaxel strategy has inspired researchers to explore additional functionalities of albumin-based drug delivery systems. Some researchers have investigated the surface loading of nitric oxide (NO) donors onto albumin-paclitaxel nanoparticles and incorporated a glutathione-responsive mechanism. This approach aims to achieve tumor vascular normalization while inhibiting tumor cell growth (Figure 3B).[80]

Albumin itself has the ability to encapsulate drugs within its hydrophobic interior. However, the encapsulation of certain drugs, such as curcumin and camptothecin, is challenging due to their polarity and planar structure. These drugs are often loaded onto albumin through covalent conjugation. To expand the range of anticancer drugs that can be loaded onto albumin and to achieve multifunctionality, researchers have utilized boronic ester functionalization to covalently link albumin with nucleotides, enabling drug release under acidic conditions (Figure 3C).[81] In addition to chemical functionalization, albumin can also be radiolabeled to facilitate targeted diagnostic and therapeutic imaging, integrating multiple functionalities into one system.[82]

Although albumin has gained clinical applications, there are still some aspects that need to be improved. Firstly, although albumin can interact with tumor cells through specific receptors or proteins, its targeting and specificity are still limited. When designing albumin nanocarriers, it is necessary to consider how to improve its specific binding to tumor cells to enhance drug targeting and anti-tumor effects. Secondly, despite its good biocompatibility, albumin may still be cleaved or broken down by enzymes in vivo, leading to drug failure or unstable release rates. Therefore, stable albumin nanocarriers need to be designed to ensure drug stability and long-term sustained release. Finally, albumin has limited

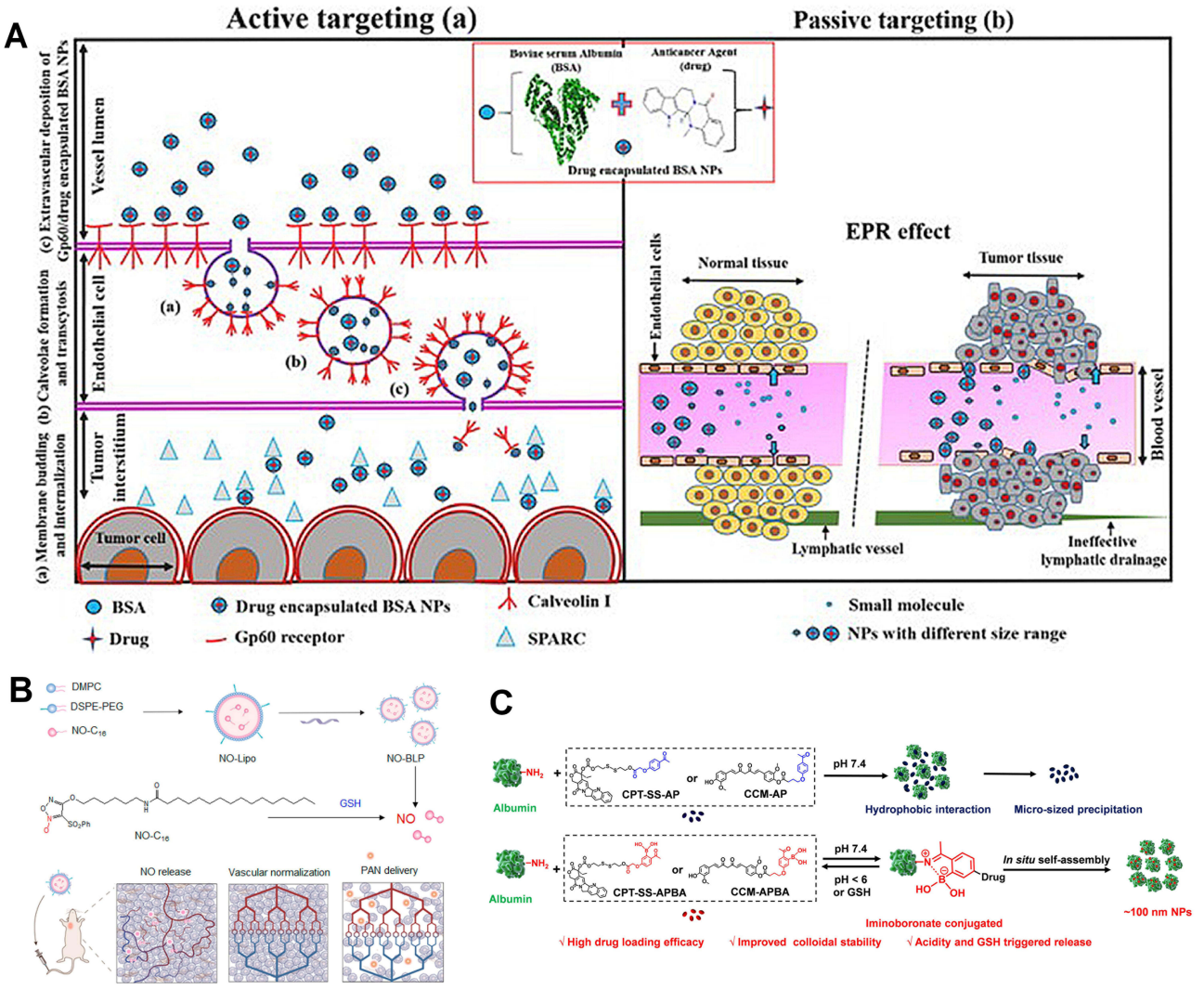


Figure 3 The delivery mechanisms and applications of albumin. (**A**) Mechanisms of albumin accumulation, in which (a) and (b) represent active and passive drug delivery strategies, respectively. Reprinted from International Journal of Biological Macromolecules, 193, Solanki R, Rostamabadi H, Patel S, Jafari SM. Anticancer nano-delivery systems based on bovine serum albumin nanoparticles: a critical review, 528–540, Copyright 2021, with permission from Elsevier.[79] (**B**) Illustration of Designing GSH-responsive nitric oxide-loaded bioinspired lipoprotein system (NO-BLP) to normalize tumor vessels for improving intratumor delivery and chemotherapy of albumin-bound paclitaxel nanoparticles (PAN). Adapted with permission from Wu Y, Xie H, Li Y, et al. Nitric Oxide-Loaded Bioinspired Lipoprotein Normalizes Tumor Vessels To Improve Intratumor Delivery and Chemotherapy of Albumin-Bound Paclitaxel Nanoparticles. Nano Lett. 2023;23(3):939–947. Copyright© 2023 American Chemical Society. [80] (**C**) Preparation principle of albumin-based nanomedicine. Reprinted from Journal of Controlled Release, 330, Hao L, Zhou Q, Piao Y, Zhou Z, Tang J, Shen Y. Albumin-binding prodrugs via reversible iminoboronate forming nanoparticles for cancer drug delivery, 362-371, Copyright 2021, with permission from Elsevier.[81]

loading capacity as a drug carrier, and drug release is affected by temperature, pH value and other factors, which requires precise control of its safety.

Gelatin

Gelatin is derived from the degradation of collagen and consists of residues of glycine, proline, and hydroxyproline. However, the safety limitations of its material source have hindered its clinical applications. Gelatin exhibits excellent biocompatibility, possesses abundant reactive functional groups, and can be easily prepared at a low cost, making it a promising drug delivery carrier. Researchers are still exploring ways to improve its performance through modifications or co-formulation with other polymers.[15,83] Mi Zhou et al have developed a size-adjustable and charge-conversion dual-responsive nanocluster called FA-GelDMA@DOX-HMON-NH by combining gelatin with mesoporous silica. It involves the self-assembly of positively charged DOX-HMON-NH within the FA-GelDMA framework. When the nanocluster

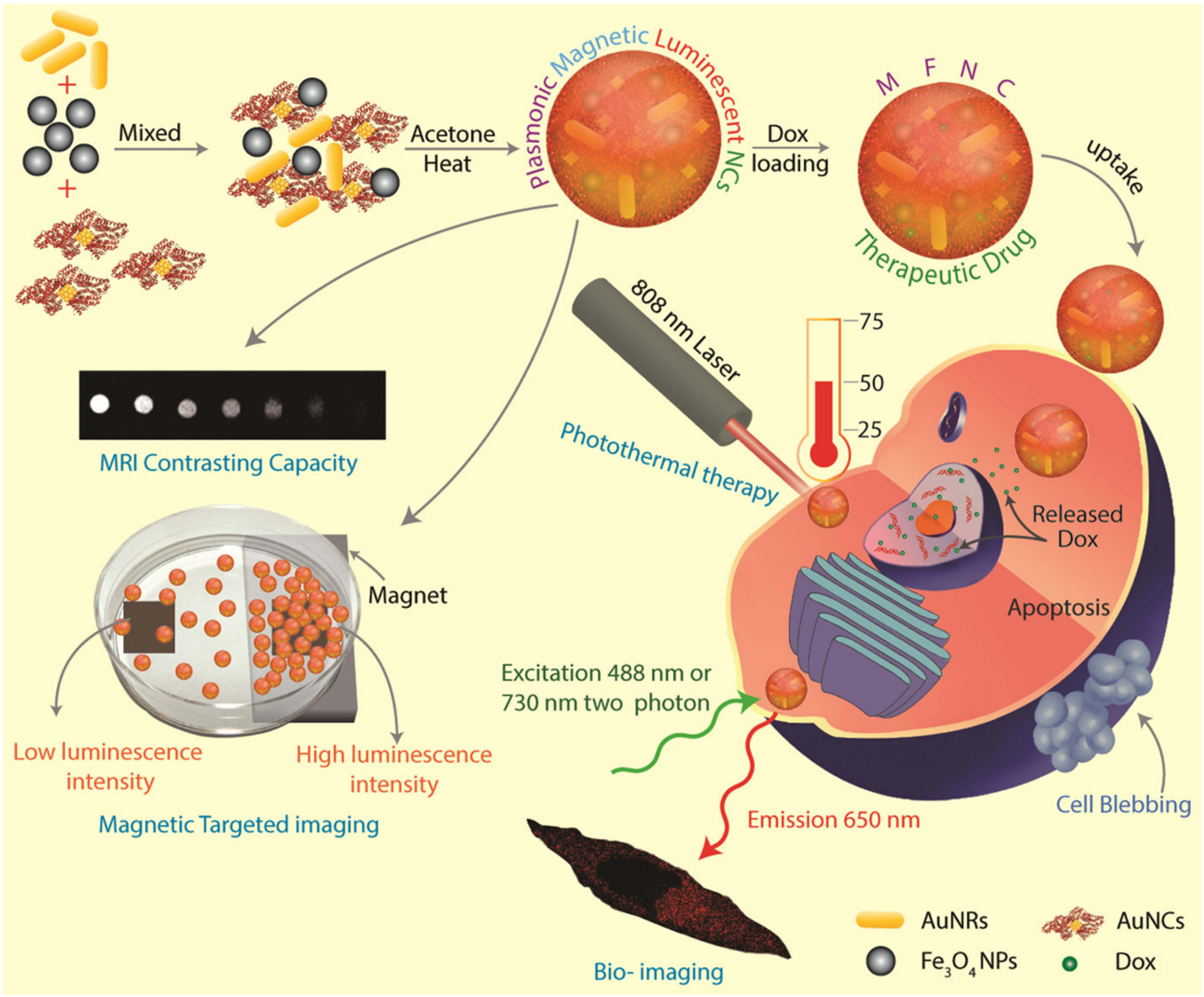


Figure 4 Schematic depiction of preparing MFNCs, their capacity for in vitro MRI contrasting and magnetic targeting, two-photon imaging, plasmonic photothermal therapy, and inducing cell death in cancer cells (Hela), following successful loading and delivery of anticancer drug DOX. Adapted with permission from Pan UN, Khandelia R, Sanpui P, Das S, Paul A, Chattopadhyay A. Protein-Based Multifunctional Nanocarriers for Imaging, Photothermal Therapy, and Anticancer Drug Delivery. ACS Appl. Mater. Interfaces. 2017;9(23):19495–19501. Copyright© 2017 American Chemical Society.[85]

enters the tumor environment, it responds to acidic conditions and enzymatic degradation. This triggers the release of DOX-HMON-NH, leading to the inhibition of cancer cells.[84]

In addition, gelatin exhibits stable physical properties and can serve as a versatile matrix for loading various particles, enabling the construction of multifunctional nanoplatforms. Exploiting this characteristic, researchers have employed gelatin as a matrix to develop a novel nano-therapeutic strategy with photo-responsive and magnetic-responsive properties.[85] In this system, respectively as shown in Figure 4, iron oxide nanoparticles, gold nanoclusters, and an anticancer drug, DOX, are loaded into the gelatin matrix, enabling integrated photothermal therapy, chemotherapy, and imaging tracking. The loaded magnetic nanoparticles facilitate targeted delivery of the drug to the tumor site through external magnetic fields, minimizing accumulation in normal tissues. The involvement of gold nanoclusters imparts photo-responsive characteristics, generating heat under near-infrared light irradiation, which further triggers the release of chemotherapy drugs and enables targeted eradication of tumor cells. Successful implementation of photo-responsive and magnetic-responsive properties has been demonstrated in Hela cells, highlighting the versatility and potential of the gelatin-based nano-anticancer delivery system.

Gelatin has good biocompatibility and degradability, and is used clinically as a biological scaffold, filler and repair material. In the realm of anticancer drug delivery, gelatin-based nanodelivery systems offer substantial advantages in

terms of drug loading and delivery efficiency. The mechanical properties of gelatin can be tailored based on its concentration, fabrication strategy, and cross-linking density, allowing for personalized pharmacokinetics as per specific requirements. However, the use of cross-linking agents introduces potential toxicity concerns, and gelatin sourced from animals may elicit an immune response, posing challenges that must be addressed before clinical translation.[86]

Silk Fibroin

Silk fibroin is the main component of silk produced by silkworms. It possesses excellent biocompatibility, biodegradability, and mechanical properties. Due to these characteristics, silk fibroin has been approved by the FDA as a medical material and is commonly used for sutures in wound closure. However, there are currently no clinically approved drug products based on silk fibroin.[87] Currently, most of the research on silk fibroin-based drug delivery for cancer treatment focuses on the forms of nanospheres[88] or nanofibers. Cao et al[89] developed a nano-particle for combined sonodynamic therapy and chemodynamic therapy in the treatment of colon cancer. The nano-particle consisted of mesoporous silica loaded with indocyanine green derivative (ID) as the internal component and was enveloped by chondroitin sulfate and regenerated silk fibroin on the outside. Chondroitin sulfate targeted tumor cells, while ID targeted the mitochondria within the tumor cells. Upon entering the tumor microenvironment, the particles were internalized by the tumor cells and targeted the mitochondria. Subsequently, they released Mn^{2+} which catalyzed the conversion of endogenous hydrogen peroxide into hydroxyl radicals and oxygen, with the oxygen further promoting sonodynamic therapy. In vitro and in vivo experiments confirmed the successful delivery of the constructed nano-delivery system to intestinal epithelial cells in the small intestine. Additionally, the researchers loaded anti-PD-L1 in the nano-particles to enhance their cytotoxic effect on tumor cells. In a mouse model of colon cancer and a subcutaneous colon tumor model, the orally administered nano-delivery system demonstrated superior tumor inhibition under ultrasound irradiation.

Silk proteins serve as carriers in various delivery systems, including sponges, gels, microparticles, and microneedles. However, they suffer from poor mechanical properties and are prone to sudden drug release. In tumor therapy, enhancing efficacy and minimizing off-target effects are primary goals. Unfortunately, silk proteins lack targeting properties, which perpetuates the challenge of off-target effects. Efforts to address these limitations may involve incorporating targeting ligands or modifying the formulation to achieve controlled drug release and improve targeting specificity.[90,91]

Zein

Zein mays albumin is an amphiphilic protein derived from maize cell membranes. It has been approved by the US FDA as a Generally Recognized as Safe (GRAS) excipient and is commonly used as a coating agent for pharmaceuticals. Utilizing Zea mays albumin as a drug delivery carrier for anticancer agents offers high drug loading capacity and low toxicity. However, Zein mays albumin lacks tumor-targeting specificity, and its delivery mainly relies on the enhanced permeability and retention (EPR) effect of tumors, making it susceptible to recognition by macrophages and resulting in short circulation time in the body. Many researchers have attempted to enhance the bioavailability of Zein mays albumin-based delivery systems by combining it with other delivery carriers or targeting ligands.[92,93] For instance,[94] Figure 5A shows a co-delivered the anticancer drug paclitaxel using a combination of chondroitin sulfate and Zein mays albumin. By utilizing chondroitin sulfate's ability to target the CD44 receptor, they achieved tumor cell targeting. Furthermore, the association with chondroitin sulfate also enhanced the stability of Zein mays albumin as a drug carrier (Figure 5B and C).

Ferritin

Ferritin is an iron storage protein composed of 24 subunits, and it is found in cells of animals, plants, bacteria, and algae. Depending on the source, ferritin can be categorized as horse spleen ferritin (HoSF), human ferritin (HFt), rat heavy-chain ferritin, Archaeoglobus fulgidus ferritin (AfFtn), and Pyrococcus furiosus ferritin (PfFt), among others. Iron ferritin, as a drug delivery carrier, is derived from its excellent biocompatibility and specific targeting properties. The cage-like structure of ferritin allows for the encapsulation of various small molecules, including metals, drugs, fluorescent molecules, contrast agents,[95] etc., with uniform shape. Ferritin can target the transferrin receptor 1 (TfR1) in tumors. Additionally, it can be modified with other targeting ligands or growth factors to enhance its targeting specificity.[96] Liu et al[97] developed a multi-responsive nano delivery system (Tf-Mn-MOF@Nira@CDDP; MNCT) for the co-delivery of cisplatin (CDDP) and

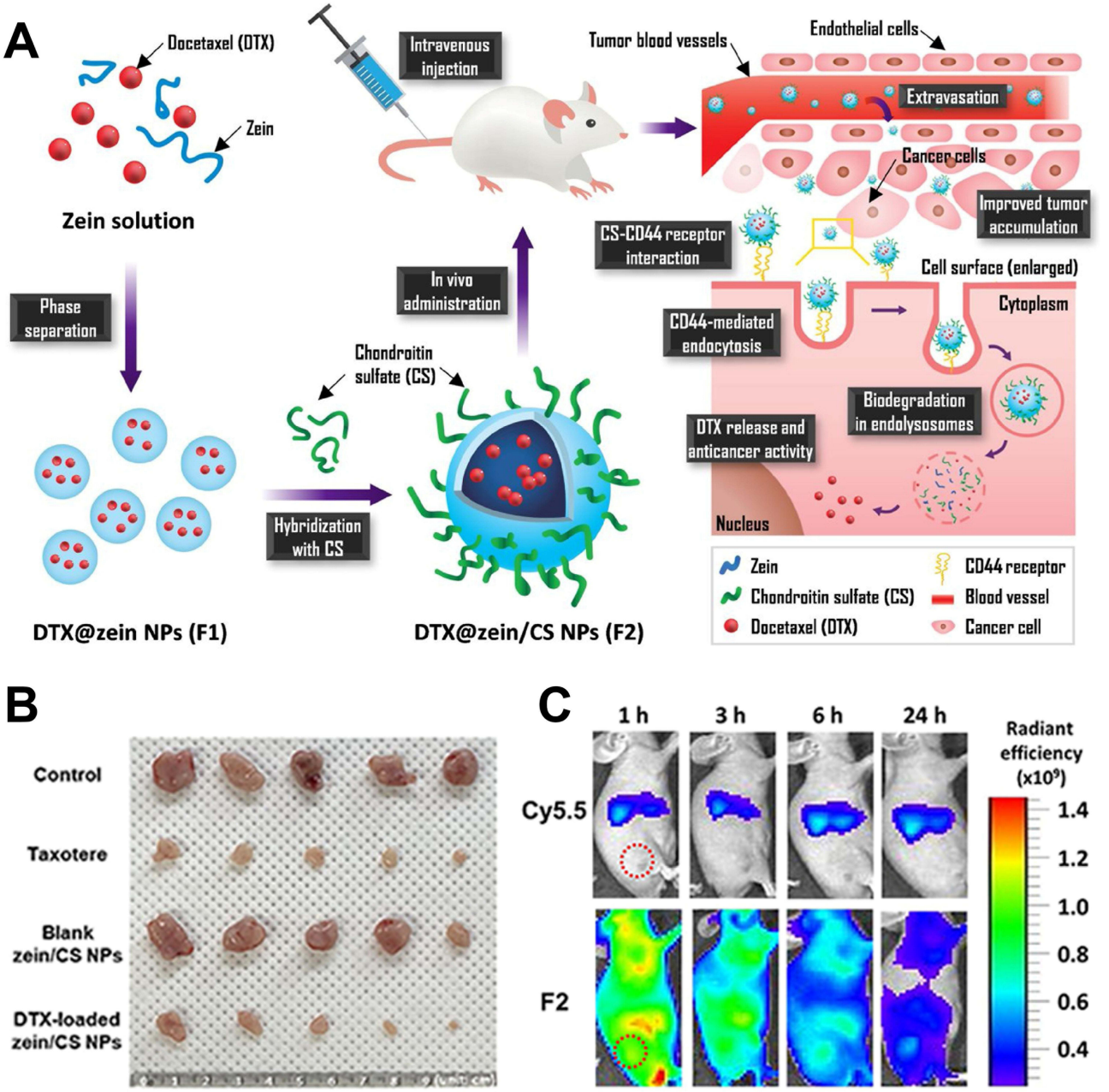


Figure 5 Mechanisms and therapeutic effects of zein-based nanoparticles. (**A**) Schematic of zein/CS nanoparticles. (**B**) In-vivo anti-tumor efficacy. (**C**) NIRF imaging of PC-3 tumor xenograft mouse model after intravenous injection of Cy5.5 and Cy5.5-labeled zein/CS NPs. Reprinted from Carbohydrate Polymers, 253, Lee HS, Kang N-W, Kim H, et al. Chondroitin sulfate-hybridized zein nanoparticles for tumor-targeted delivery of docetaxel, 117187, Copyright 2021, with permission from Elsevier.[94]

Niraparib (Nira) to treat breast cancer. In this delivery system as schematically depicted in Figure 6A, the drugs were encapsulated within the Mn-MOFs structure, and the outer surface of the Mn-MOFs nanoparticles was modified with ferritin to target cancer cells (Figure 6B). Upon entry into tumor cells, the Mn-MOFs structure disintegrated, releasing the drugs and effectively killing cancer cells. This nano delivery system successfully reversed the resistance of breast cancer cells to cisplatin, enhanced drug targeting, and reduced systemic toxicity of the drugs.

The integration of imaging and therapy in multifunctional drugs is also a development trend in drug delivery systems, aiming to achieve the integration of diagnosis and treatment. Wu et al[98] developed a hybrid protein shell by combining ferritin with hemoglobin as schematically depicted in Figure 6C, successfully encapsulating the photosensitizer Pplx and the anticancer drug DOX. This system can improve the hypoxic environment of tumors and achieve controlled drug

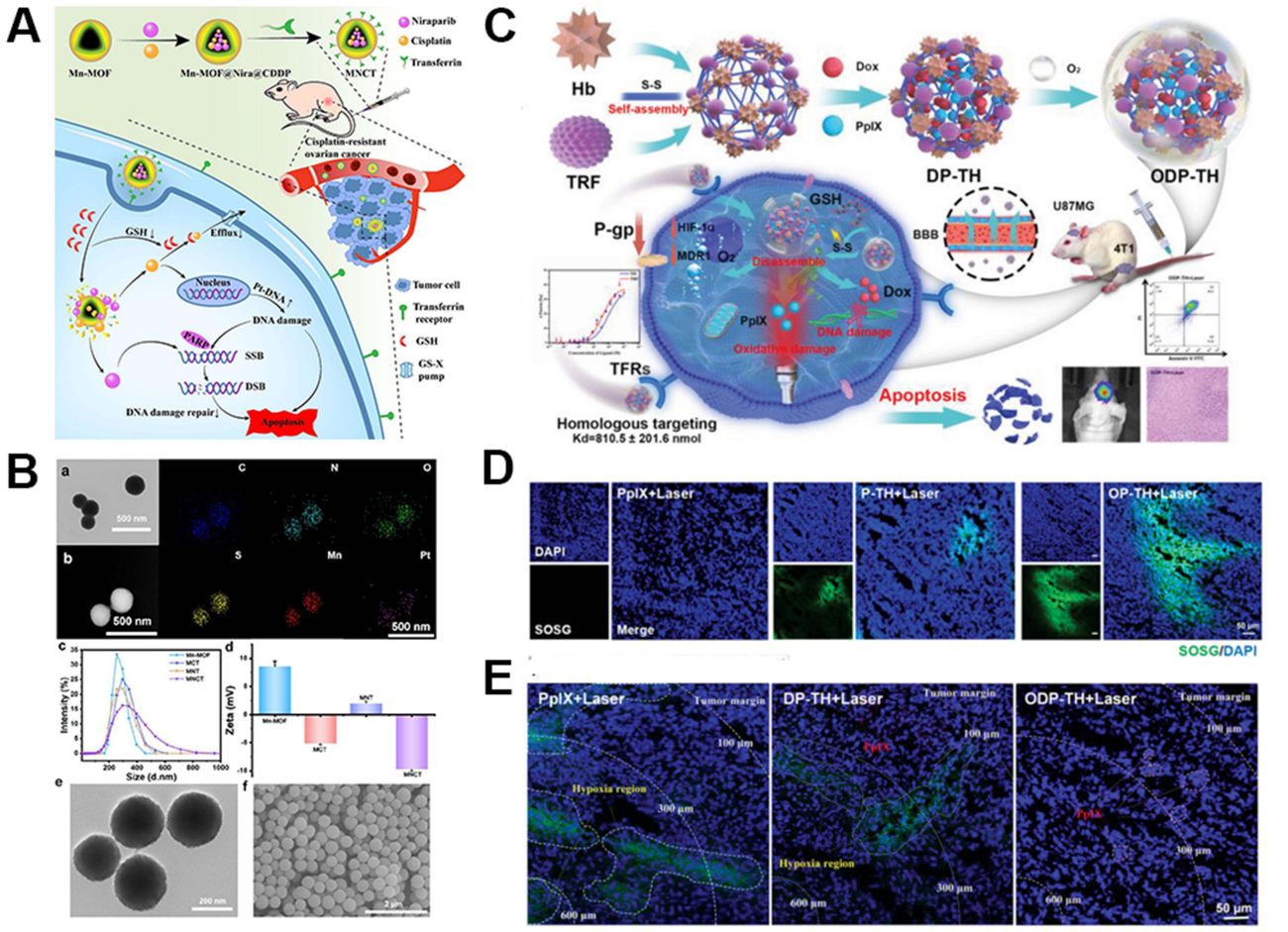


Figure 6 Delivery strategies and applications of ferritin delivery carriers. (**A**) Schematic Illustration of the Multitargeted Nanodrug Delivery System Tf-Mn-MOF@Nira@CDDP (MNCT) to Co-Deliver Cisplatin and Niraparib on Cisplatin-Resistant Ovarian Cancer. (**B**) Characterization of Mn-MOF-based nanoparticles. (a) TEM image of Mn-MOF@Nira@CDDP. Scale bar, 500 nm. (b) HRTEM dark field image and corresponding mapping images of Mn-MOF@Nira@CDDP. Scale bar, 500 nm. (c) Hydration particle size distribution of Mn-MOF, MCT, MNT, and MNCT obtained by DLS. (d) ζ-Potential of Mn-MOF, MCT, MNT, and MNCT obtained by DLS. (e) TEM image of MNCT. Scale bar, 200 nm. (f) SEM image of MNCT. Scale bar, 2 μm. Reprinted with permission from Liu Y, Wang Y, Guan X, et al. Reversal of Cisplatin Resistance in Ovarian Cancer by the Multitargeted Nanodrug Delivery System Tf-Mn-MOF@Nira@CDDP. ACS Appl. Mater. Interfaces. 2023;15(22):26484–26495. Copyright© 2023 American Chemical Society.[97] (**C**) The synthesis and intracellular mechanisms of ODP-TH. (**D**) CLSM images of SOSG (green) probe evaluating the formation of singlet oxygen after treated with PpIX, P-TH, and OP-TH followed by 650 nm laser for 10 min (100 mW /cm^{-2}). (**E**) Ex vivo immunofluorescence images of hypoxia area (green) in tumor stained by Hypoxyprobe. Adapted with permission from S-Y W, Y-X Y, Zhang Q, et al. Multifunctional Protein Hybrid Nanoplatform for Synergetic Photodynamic-Chemotherapy of Malignant Carcinoma by Homologous Targeting Combined with Oxygen Transport. Adv. Sci. 2023;10(5):2203742. (Creative Commons CC BY).[98]

release in the tumor area. In vitro and in vivo experiments demonstrated that the nanosystem enabled Pplx imaging in the tumor region and achieved targeted accumulation, leading to the slow release of the anticancer drug (Figure 6D and E).

Despite significant progress in the preparation and application of nanoparticles based on ferritin nanocarriers, several challenges remain to be addressed. Firstly, there is a need to enhance the encapsulation efficiency and carrying capacity of ferritin-based nanoparticles. Secondly, improvements are required in the stability of ferritin and the efficiency of cellular uptake of the encapsulated molecules. This entails further exploration of the mechanisms and effects of surface modification of ferritin. Lastly, standardization of the ferritin preparation process is necessary to ensure consistent quality and reproducibility across different studies and applications. Addressing these bottlenecks will contribute to the wider and more effective utilization of ferritin-based nanoparticles in various biomedical applications.[96,99]

Proteins exhibit a remarkable diversity, and in this study, we highlight five protein-based anticancer drug delivery carriers (Albumin, Gelatin, Silk fibroin, Zein Ferritin), summarizing their applications in Table 3. In general, proteins possess several advantageous characteristics for cancer drug delivery, including non-toxicity, non-

Table 3 Protein-Based Biopolymeric Drug Delivery Systems for Cancer Therapy

Protein Types	Loaded Drugs	Type of Nanosystems	Application	Aimed Cancer/Cell	Ref
Albumin	Abraxane	NPs	Chemotherapy	TNBC	[100]
Albumin	MnO_2	NPs	Imaging	NCI-H460	[101]
Albumin	CUR	NPs	Diagnosis	Breast cancer	[102]
Albumin	DOX	Nanoclusters	Chemotherapy	Malignant bone tumors	[103]
Albumin	PTX	NPs	Chemotherapy	Breast cancer	[104]
Albumin	DOX	NPs	Chemotherapy	Human pancreatic tumor	[105]
Albumin	PTX,4-HPR	NPs	Chemotherapy	Glioma cells	[106]
Gelatin	Catalase /siRNA	NPs	Immunotherapy	Melanoma model	[107]
Gelatin	ICG/DOX	NPs	Chemo–photothermal therapy	Breast cancer	[108]
Gelatin	Cu, polyaniline (PANI)	NGs	PTT/Photoacoustic imaging	A549	[109]
Gelatin	TA	Nanofiber	Chemotherapy	Osteoarthritis	[110]
Gelatin	Pba, TPZ	NPs	PDT/Chemotherapy	Tumor-bearing mice	[111]
Gelatin	Cisplatin	NPs	Chemotherapy, Imaging	H22	[112]
Silk fibroin	OVA	NPs	Immunotherapy	B16/F10/MB49	[113]
Silk fibroin	MnO_x	Nanomotors	SDT /Chemodynamic therapy	Orthotopic colon tumors	[89]
Silk fibroin	MnO_x, DOX	NPs	PTT/PDT/Chemotherapy	Metastatic breast cancer	[114]
Silk fibroin	Rosuvastatin	NPs	Chemotherapy	TNBC	[115]
Silk fibroin	DOX	NPs	Chemotherapy	MCF-7 cells	[116]
Zein	Docetaxel	NPs	Chemotherapy	PC-3 cells	[94]
Zein	CUR	NGs	Chemotherapy	CT26 cells	[117]
Zein	Honokiol	NGs	Chemotherapy	Breast cancer	[118]
Ferritin	DOX	Nanocage	Chemo-immunotherapy	HCC	[119]
Ferritin	Aloe-emodin	Nanocrystals	PDT	HSC-3 cells	[120]
Ferritin	PAB /L	NPs	Immunotherapy	TNBC	[121]
Ferritin	Camptothecin/ Epirubicin	Nanocage	Chemotherapy	Glioma, metastatic liver cancer, and chemo-resistant breast tumors	[122]
Ferritin	DOX	NPs	Chemotherapy	Pancreatic cancer	[123]

Abbreviations: NPs, nanoparticles; TNBC, triple-negative breast cancer; CUR, curcumin; DOX, doxorubicin; PTX, paclitaxel; 4-HPR, fenretinide; ICG, indocyanine green; NGs, nanogels; PTT, photothermal therapy; TA, tannic acid; Pba, pheophorbide a; TPZ, tirapazamine; PDT, photodynamic therapy; OVA, ovalbumin; SDT, sonodynamic therapy; PAB /L, pseudolaric acid B (PAB) \ lapatinib.

immunogenicity, and extended circulation time. Existing commercial products reinforce our belief that there will be a growing number of protein-based delivery carriers advancing towards clinical applications. However, it is important to acknowledge that protein-based delivery carriers also have their limitations, which we have outlined in the Table 4. As novel protein-based drugs make their way towards clinical usage, several aspects warrant further refinement, such as:

1. Standardization of protein source extraction.
2. Screening for proteins that can effectively target tumors.
3. Investigation of the in vivo release mechanisms of protein-based delivery drugs.
4. In-depth exploration of the structure-function relationships of protein derivative.

Natural Polysaccharides

Natural polysaccharides have a wide range of sources, including chitosan, dextran, pullulan, hyaluronic acid, pectin, gum, lignin, carrageenan, and more, in which a few of them are depicted in Figure 7. Due to their non-toxicity, biodegradability, low immunogenicity, excellent biocompatibility,[124] rich functional groups, low cost, and easy availability, they serve as excellent carriers for drug delivery and find extensive applications as encapsulants and stabilizers in nanocarriers for drug delivery. Additionally, the inherent targeting ability, antioxidant properties, anti-proliferative

Table 4 Characteristics of Protein Anti-Cancer Drug Delivery Carriers

Types of Proteins	Advantages	Disadvantages	Targeted
Albumin	Can target tumor KRAS.	In vivo transport mechanism to be studied; Potential immunogenicity.	Targeting the Gp-60 receptor
Gelatin	Mild conditions for drug encapsulation; Has a cell-binding site (arginine-glycine-aspartic, RGD).	In vivo transport mechanism to be studied; Potential immunogenicity.	–
Silk fibroin	May enhance cancer therapy.	Inhibitory effect on normal cells; Source materials differ significantly in amino acid sequence, morphology, and manufacturing process; Mechanism of drug release unclear;	–
Zein	Plant protein with no risk of animal disease transmission; Insoluble alcohol soluble protein.	Lack of biodegradability information.	–
Ferritin	Targeted, can target tumor TfR1 receptor; Has a cavity dedicated to loading drugs; Good PH stability.	Low drug loading efficiency; Differences in targeting ability for different tumors.	Targeting transferrin receptor 1 (TfR1)

effects, and anti-cancer properties of polysaccharides make them ideal carriers for cancer treatment.[125] In addition, natural polysaccharides possess abundant functional groups on their surface, such as hydroxyl, amino, and carboxyl groups. Through simple chemical modification or modification, a wide range of derivatives can be obtained, and some derivative groups also exhibit bioadhesive properties, which can enhance drug circulation time and cellular uptake rate.[125] Polysaccharides can be utilized not only as drug delivery carriers themselves but also in combination with metal nanoparticles (such as gold nanoparticles, and silver ions), metal oxides (such as iron oxide, copper oxide, and zinc oxide), mesoporous silica, and other delivery systems, forming multifunctional nanocarriers capable of imaging, photothermal therapy, chemotherapy, and other therapeutic modalities.[126]

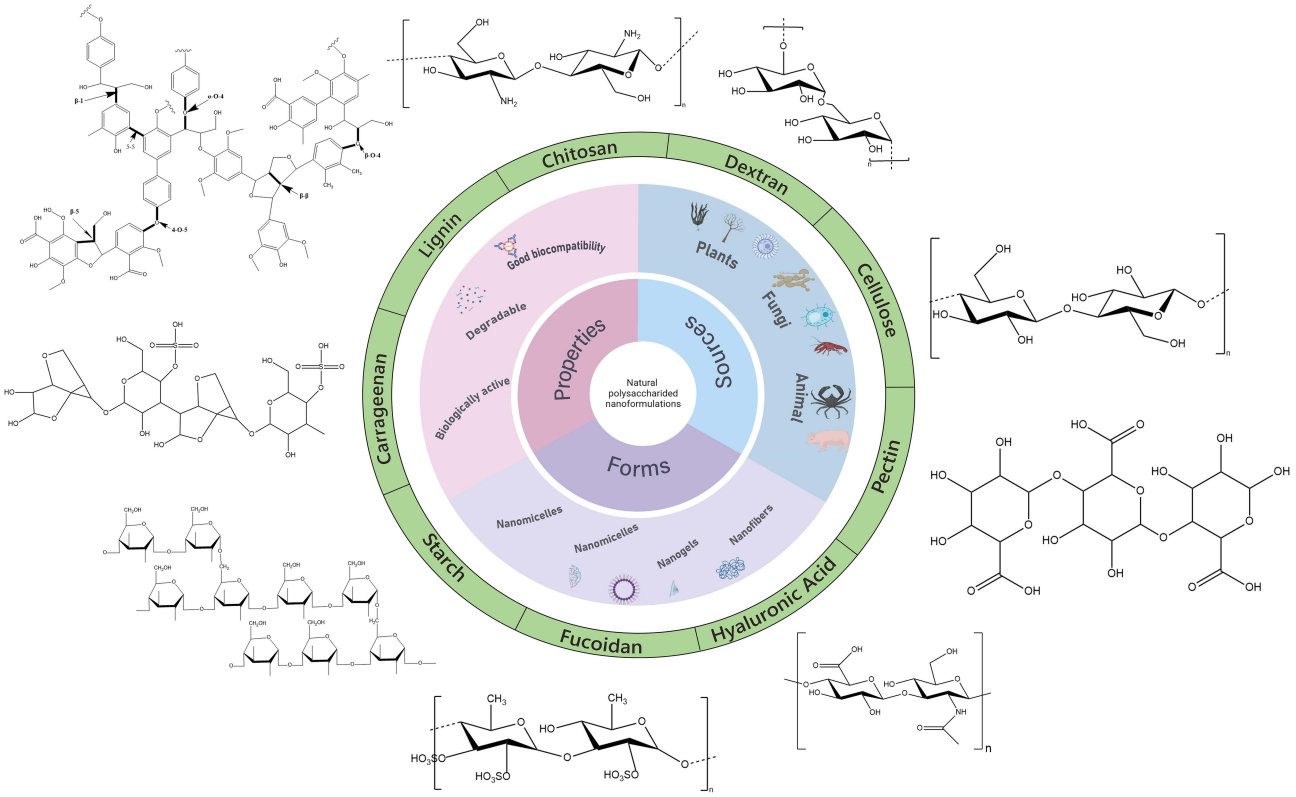


Figure 7 Schematic representation of various members involved in natural polysaccharide-based nano drug delivery carrier for cancer treatment.

Chitosan

Chitosan is a natural linear cationic polysaccharide derived from the exoskeletons of crustaceans. It is composed of N-acetyl-D-glucosamine and D-glucosamine units. Chitosan possesses several characteristics, including mucoid hesiveness, biodegradability, biocompatibility, and low immunogenicity. It also exhibits anti-tumor properties,[127] making it a promising nanocarrier for cancer drug delivery.

Although chitosan is non-toxic, its inherent positive charge can disrupt cell membranes. Additionally, chitosan has low water solubility and typically dissolves only under acidic conditions. However, by modifying chitosan, its water solubility can be increased, enhancing drug-loading capacity and improving its bioavailability. There are several derivatives obtained from chitosan modification, including thiolated chitosan (TCS) derivatives, amphiphilic derivatives of chitosan (AD) such as carboxymethyl chitosan (CMC), quaternized derivatives of chitosan (QD) like N, N, N-trimethyl chitosan (TMC), and ethylene glycol-chitosan, among others.

Thiolated chitosan (TCS) is prepared by covalently attaching thiol (-SH) groups primarily to the primary amine or hydroxyl groups of chitosan. It exhibits excellent permeability, cohesion, and bioavailability, and it can also target surface ligands.[128] The thiol groups of TCS can form disulfide bonds with cysteine domains of mucin glycoproteins, thereby enhancing its mucoadhesive properties.[129,130] Riwang Li et al developed a thermosensitive hydrogel composed of TCS-encapsulated liposomes loaded with curcumin. Through in vitro and in vivo experiments, they demonstrated that the encapsulation of TCS effectively improved the stability of the material and delayed drug release.

Trimethyl chitosan (TMC) is a quaternized derivative of chitosan that possesses a high positive charge. It exhibits improved water solubility,[131] mucoadhesive properties, permeability, and drug delivery capabilities compared to traditional chitosan.[132] TMC can be further derivatized or grafted to modulate its solubility, cytotoxicity, or cell-targeting abilities. Haiyan Hu et al[133] utilized TMC as the drug carrier and employed human serum albumin (HSA) for surface modification of the delivery system. The results demonstrated that the conjugation of HSA effectively enhanced the penetration ability of the carrier and exhibited pH responsiveness, leading to efficient inhibition of tumor cell growth.

Carboxymethyl chitosan (CMC) is an amphiphilic derivative of chitosan and serves as an excellent delivery vehicle for hydrophobic drugs. It exhibits favorable anticancer[134] and antitumor properties and possesses pH sensitivity, biodegradability, and low immunogenicity, making it a significant player in the field of anticancer/antitumor drug delivery.[135] Researchers have utilized CMC to develop pH-responsive nanomicelles.[136] These micelles are self-assembled from CMC, Vitamin E succinate (VES), and the anticancer drug Doxorubicin. CMC imparts pH responsiveness to the nanomicelles, while VES enhances their targeting capability (Figure 8A). The prepared nanomicelles demonstrate significant swelling properties under low pH conditions, allowing for drug release in an acidic environment as shown in Figure 8B. CMC's abundant carboxyl groups are commonly used for modification and can be utilized to graft targeting ligands. For instance, Yurui Xu et al[137] further modified CMC to develop a dual-responsive nanoparticle system. The nanoparticles encapsulated indocyanine green (ICG) and apoptotic peptides functionalized gold nanoparticles (IK-AuNP), imparting photothermal responsiveness to the material. CMC was modified with RGD to achieve tumor targeting and pH-responsive drug release. These nanoparticles were employed for the treatment of oral cancer and demonstrated excellent tumor targeting in an in situ oral cancer mouse model. Additionally, the combination of NIR and the nanoparticles effectively inhibited tumor growth.

Glycol chitosan (GC) is a chitosan derivative that is conjugated with hydrophilic glycol groups, rendering it water-soluble over a wide pH range from acidic to neutral conditions.[139] GC is typically prepared by reacting chitosan with ethylene oxide and subsequently deacetylating the chitosan. Modification of chitosan with polyethylene glycol (PEG) can improve its solubility, enhance targeting capability, and reduce interactions between nanoparticles and serum proteins,[140] thereby prolonging blood circulation time. Xuejing Zhang et al[141] combined the pH-responsive property of chitosan with the thermoresponsive characteristic of di(ethylene glycol) methyl ether methacrylate (PDEGMA) to develop a dual-responsive nanoparticle system. In vitro and in vivo experiments demonstrated that these nanoparticles exhibited dual responsiveness to low pH and elevated physiological temperature.

Shima Bastaki et al[142] developed a nano particle system for delivering STAT3/PD-L1 dual-targeted siRNAs by combining two types of chitosan, TMC, and TC, known for their excellent permeability and adhesion properties. The nanoparticles were further coated with TAT peptide and hyaluronic acid (HA). The results demonstrated that these

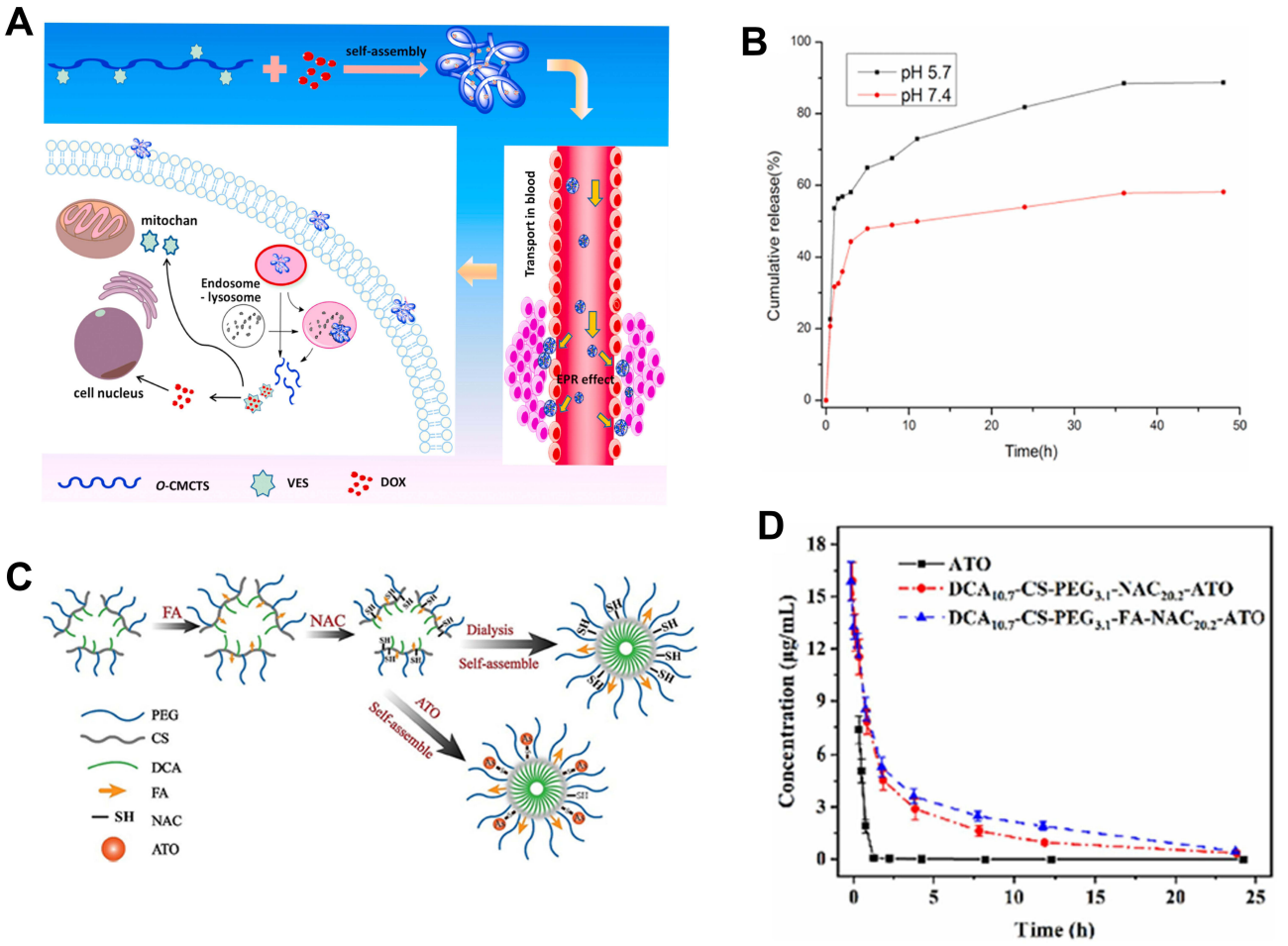


Figure 8 Delivery strategies and applications of chitosan-based delivery carriers. (**A**) Schematic diagram of the O-CMCTS-VES nanoparticles with EPR effect for anticancer therapy. (**B**) In vitro release of DOX/O-CMCTS-VES nanoparticles in PBS buffer solution with different pH values. Adapted with permission from Chen X, Gu J, Sun L, et al. Efficient drug delivery and anticancer effect of micelles based on vitamin E succinate and chitosan derivatives. Bioact. Mater. 2021;6(10):3025–3035. (CC BY 4.0).[136] (**C**) Schematic diagram of the preparation of ATO-loaded CS nanodrugs. (**D**) Pharmacokinetic curves of free ATO, DCA10.7-CS-PEG3.1-NAC20.2-ATO, and DCA10.7-CS-PEG3.1-FA-NAC20.2-ATO. Reprinted from Carbohydrate Polymers, 303, Song X, Wu J, Song W, et al. Thiolated chitosan nanoparticles for stable delivery and smart release of As2O3 for liver cancer through dual actions, 120462, Copyright 2023, with permission from Elsevier.[138]

nanoparticles with dual inhibitory effects exhibited significant inhibition against breast cancer and melanoma cell lines. Animal tumor models also confirmed the strong targeted inhibitory effects of these particles on tumors.

Xiaoli Song et al[138] designed a CS-based multifunctional delivery system with adjustable thiol content. They achieved CS thiolation using -(N-acetyl-L-cysteine) macromolecule (NAC). To improve drug utilization, CS was further modified with polyethylene glycol (PEG), deoxycholic acid (DC), and folate (FA) as shown in Figure 8C. The study revealed that increasing the proportion of NAC enhanced the drug-loading capacity for As_2O_3 (ATO). In vitro, experiments demonstrated that the drug release in a normal PBS environment was less than 25%, while it significantly increased in the presence of high glutathione (GSH) levels (Figure 8D). This indicated the selective release properties of the designed drug. Further, in vivo, experiments also confirmed prolonged blood circulation time of modified ATO and improved tumor-targeting inhibitory effects.

Guanqing Yang et al[143] synthesized a pH-responsive nanogel by succinylating and methacrylating chitosan (methacrylated succinyl-chitosan, MASCS). The nanogel was used for the delivery of DOX, and in vitro and in vivo experiments demonstrated its pH-responsive behavior, allowing drug release under acidic conditions and exhibiting tumor-targeting properties.

Chitosan, as a biopolymer, possesses various advantageous characteristics such as low pH solubility, cationic nature, targeting ability, and antitumor properties (Table 5). These features make it suitable for applications such as chemotherapy drug/gene delivery, photothermal therapy, and imaging. However, the low solubility of chitosan limits its usage. Therefore, modified chitosan derivatives with improved solubility have been developed. Chitosan and its derivatives

Table 5 Chitosan-Based Biopolymeric Drug Delivery Systems for Cancer Therapy

Type of Chitosan	Loaded Drugs	Type of Nanosystems	Zeta Potential (mV)	Loading Content	Encapsulation Efficiency	Diameter (nm)	PDI	Aimed Tumor/Cell	Ref
TMC	siRNA	NPs	~20	/	/	~110	<0.2	B16-F10 and 4T1 cancer cells,	[142]
TMC	siRNA, BV6	NPs	17	/	/	~105	< 0.2	Breast, colorectal, and melanoma cancer cells	[144]
TMC	siRNA	NPs	~20	/	/	~110	<0.2	Breast cancer and melanoma	[142]
TMC	Bufalin, IR780	NPs	TIH,8.6 ±0.2; TBH,4.3 ± 0.7	IR780,8.53%; BF,9.17%	IR780=95.74%, BF= 98.16%	TIH :37.0 ± 3.0, TBH:31.7 ± 3.2	/	Metastatic breast cancer	[133]
CMC	DOX	NPs	−41.5 ± 9.6	/	/	/	/	Carboxymethyl chitosan	[145]
CMC	DOX	NPs	/	13.7	77	199.6 ± 3.7	/	H22	[146]
CMC	MTX, AS1411	NPs	−0.42	13.80%	/	200	/	A549, BALB/c mice	[147]
CMC	ICG /IK-AuNP	NPs	−17	6.47%	95.52%	113	/	Oral cancer	[137]
CMC	DOX	NPs	20~30	DOX:O-CMCTS-VES 1–10=6.1%, DOX:O-CMCTS-VES 2–10=13.0%, DOX:O-CMCTS-VES 3–10=10.6%	DOX:O-CMCTS-VES 1–10=64.3%, DOX:O-CMCTS-VES 2–10=74.5%, DOX:O-CMCTS-VES 3–10=39.7%	208	<0.5	HepG2	[136]
CMC	siMDR1, DOX	NPs	/	/	/	/	/	Breast Cancer	[148]
CS-PEG	siRNA	NPS	14.3	/	/	127	0.29	Breast and colon cancers	[140]
CS-PEG	ICG	Nano-micelles	11.2	89.3%, (3.3 ± 0.2)	–	143	0.15	–	[149]
CS-PEG	DOX	NPs	34.6 ± 2.6	0.11%	80.40%	178.5 ± 4.7	0.21 ± 0.006	Breast cancer	[150]
CS-PEG	PTX	NGs		(13.6 ± 1.3%)	(76.2 ± 8.5%)	~170	/	Breast cancer, MDA-MB-231	[141]
TC	CUR	NPs	37.30 ± 0.56	3.96 ± 0.32%	88.75 ± 1.65	414.0 ± 7.71	/	–	[151]
TC	Cisplatin	NPs	22.3	70.1% ± 1.2%	45% ± 0.28%	265.9	0 0.226	Cervical carcinoma	[152]
MSC	DOX	NGs	30.9	/	/	/	/	SH-SY5Y, HepG2, H22	[143]
TC	Fe3O4/C6	NCPs	–	16.50%	> 80%	161 ± 3	0.081	A549 cells, HeLa cells	[153]

Abbreviations: IK-AuNP, apoptotic peptides functionalized gold nanoparticles.

exhibit pH-responsive properties, enabling targeted drug release in the acidic tumor microenvironment. However, the safety of chitosan in vivo has been less studied. Chitosan can activate dendritic cells and induce macrophage activation. The potential harm to normal cells and the underlying mechanisms of its in vivo effects remains unclear. These factors contribute to the lack of clinical application of chitosan-based anticancer drugs.

Starch

Starch is a source of energy for many plants, such as cereals or grains, roots, tubers, legumes, and fruits. Particularly, grains have a high starch content. Starch, with its basic structural unit being α-D-glucose, can be divided into amylose and amylopectin. Amylose is a linear structure without branching, while amylopectin consists of 24 to 30 glucose residues connected by α-1,4-glycosidic bonds, with branching occurring at α-1,6-glycosidic bonds.[154] Starch, as a natural polysaccharide, possesses excellent biocompatibility, degradability, and stability. It is widely available and easily accessible, making it an approved material by the FDA for pharmaceutical applications, particularly as an excipient in drug formulation.[155] Researchers prepared hydrogels with starch and bovine serum proteins to be used as carriers for Moringa Oil Lam (MOL), which effectively improved the bioavailability of the drug.[156] Despite the numerous advantages of starch as a delivery carrier, it also has limitations such as rapid enzymatic degradation, tendency to aggregate, and swelling properties.[157] Research has shown that by chemically modifying starch and introducing various functional groups, its performance can be enhanced. Some examples of chemical modifications include oxidation, amination, aldehydization, quaternization, acetylation, hydroxyethylation, carboxymethylation, and acetylation.

Hydroxyethylated starch (HES) is one of the commonly used modifications of starch. HES is a type of branched starch, prepared by reacting the amylopectin component of corn or potato starch with ethylene oxide, resulting in a hyperbranched structure. Hydroxyethyl starch has unique pharmacological effects, including Improvement of plasma colloid osmotic pressure and hemodynamics, Anti-inflammatory effects, and Influence on coagulation function.[158] Based on these characteristics, hydroxyethyl starch is clinically used as a plasma substitute and volume expander for the treatment of conditions such as cerebral ischemia, hypovolemic shock, or arterial occlusive diseases. HES has a structure similar to glycogen, is naturally non-immunogenic, and can be hydrolyzed by α-amylase. With multiple hydroxyl functional groups, it can be utilized for targeted cancer therapy by conjugating anticancer drugs and incorporating responsive chemical linkers. Chan Yu et al[159] developed HES-SS-DOX@ICG NPs by conjugating the anticancer drug DOX with HES through disulfide bonds and incorporating the photothermal agent indocyanine green (ICG). These nanoparticles exhibited both light-responsive and chemically-responsive properties. In an H22-tumor-bearing mouse model, it was found that within 14 days, the tumors were eliminated, highlighting their significant clinical potential. By taking advantage of the abundant hydroxyl groups on HES, further modifications can be made to improve its chemical properties. Honglian Wu et al[160] carboxylated HES and conjugated it with polydopamine (PDA) through amide bonds, followed by loading the anticancer drug DOX to prepare DOX@HES-PDA NPs. These nanoparticles demonstrated superior antitumor effects compared to traditional delivery vehicles prepared with PEG, such as DOX@PEG-PDA NPs. In a study involving H22 tumor-bearing mice, continuous administration of DOX@HES-PDA and DOX@PEG-PDA for three days resulted in tumor inhibition rates of 73.1% and 63.3%, respectively. Compared to PEG, HES exhibits superior degradation performance and biocompatibility. Additionally, it contains a higher number of hydroxyl functional groups, making it a promising alternative to PEG.

Furthermore, carboxymethylated starch (CMS) is a negatively charged ether derivative of starch that exhibits water solubility and pH sensitivity.[157] Under low pH conditions, CMS undergoes protonation and adopts a compact state, inhibiting drug release. Conversely, at high pH, the carboxyl groups become ionized, facilitating drug release. Based on these properties, CMS is commonly used in oral drug delivery systems. The pH sensitivity of carboxymethylated starch is also utilized in cancer treatment. Ranjbar et al[161] developed an oral drug delivery system for the treatment of colon cancer. In this system, DOX and 5-fluorouracil (5-FU) were co-loaded onto layered double hydroxide (LDH) nanosheets composed of magnesium and aluminum. The LDH nanosheets were then encapsulated with carboxymethylated starch (CMS). The release efficiency of CMS@LDH(Mg-Al)@DOX, 5-FU, and LDH(Mg-Al)@DOX, 5-FU at different pH values was compared. It was found that in a pH 1.2 environment simulating gastric acid, the drug loaded in LDH(Mg-Al)@DOX, 5-FU was released completely within 120 minutes. In contrast, CMS@LDH(Mg-Al)@DOX, 5-FU exhibited

sustained release for 480 minutes, indicating its ability to overcome degradation in acidic conditions. MTT experiments conducted on Caco-2 cells also demonstrated that CMS@LDH(Mg-Al)@DOX, 5-FU exhibited better biocompatibility. Starch can also be modified based on the charge (positive or negative) of the drug being delivered. Most anticancer drugs are hydrophobic and positively charged, but DOX hydrochloride carries a negative charge. To encapsulate such drugs, modifications can be made to transform starch into an anionic carrier. For instance, Ke Li et al[162] utilized an amphiphilic cationic starch (CSaSt) and hyaluronic acid to prepare nanoparticles capable of co-delivering docetaxel (DOC) and DOX. Transmission electron microscopy (TEM) images revealed the adsorption of DOX on the surface of DOC MC.

The pre-clinical applications of Starch for cancer therapy are described below and summarized in Table 6. Starch is highly hydrophilic, swells on contact with water and is easily degraded by enzymes, so it does not have drug-carrying properties. However, through modification, the drug-carrying capacity of starch can be enhanced. Several types of modified starch have received FDA approval for use as additives or substrates in granules, capsules, tablets, and other pharmaceutical formulations.[163] Nonetheless, utilizing modified starch as a carrier for anticancer drug delivery presents certain challenges that must be addressed. These include the tendency for modified starch to aggregate in water, thereby impacting drug delivery efficiency; potential toxicity associated with the modification process on cellular levels;[164] the need for scalable industrial processes for the preparation and processing of modified starch; and the optimization of modified starch as a suitable carrier for targeted anticancer drug delivery.

Cellulose

Cellulose is a large molecular polysaccharide composed of D-glucose units linked together by β-1,4-glycosidic bonds. It is the most abundant biopolymer in nature, known for its non-toxicity, biodegradability, and environmentally friendly sourcing. Each structural unit of cellulose contains six hydroxyl groups. The unique polymer chain structure of cellulose forms an extensive network of hydrogen bonds both within and between the chains, making it insoluble in common solvents.[184] However, its high degree of functionality makes it easily amenable to surface modification, providing a basis for drug loading.[185] Drugs encapsulated within the porous network structure of cellulose spheres exhibit high stability.

Shihao He et al[186] utilized a green and efficient sonochemical method to prepare carboxymethyl cellulose nanocapsules with shell modification of folic acid. Due to the overexpression of a protein on the surface of many tumor cell membranes that can specifically recognize and bind to folate (known as folate receptor), folate exhibits strong targeting capability. The surface-loaded folate nanocapsules can be targeted to cancer cells through folate receptor-mediated endocytosis, and the encapsulated drugs can be rapidly released in a reducing environment. The nanocapsules in the presence of a reducing agent exhibit excellent drug release capabilities. Therefore, the stability of the nanocapsules in the body can be adjusted by controlling the degree of cross-linking and the thickness of the nanocapsules without compromising the release of drugs after targeting tumor cells.

Cellulose and its derivatives have shown great promise in biosensors, particularly for enhancing the sensitivity to specific types of cancer through signal amplification methods.[187] Nanocellulose-based biosensors exhibit excellent dispersibility and high absorbance capacity, making them suitable for monitoring various biomolecules.[188] Bacterial cellulose nanopaper, known for its outstanding optical transparency, thermal properties, mechanical performance, and biodegradability, has been explored for optical biosensing applications.[189]

Anderson et al[190] reported the synthesis of a novel plasmon-exciton nanohybrid utilizing green nanomedicine approaches. They successfully prepared a stable aqueous dispersion of colloidal supramolecular structures by incorporating gold nanoparticles and ZnS semiconductor quantum emitters (ZnS-QEs) onto carboxymethyl cellulose. The excitonic properties of ZnS-QEs enabled in vitro nanodiagnostics for brain cancer cells, while the plasmonic characteristics of gold nanoparticles facilitated photothermal therapy for cancer cell ablation. The proximity between excitons and plasmonic nanoparticles resulted in unique absorption and emission behaviors in the hybrid nanostructures, imparting them with multifunctionality as both diagnostic and therapeutic tools.

Nanocrystalline cellulose (CNC) is produced from different cellulose sources through chemical and mechanical methods. The commonly used approaches include acid or enzymatic hydrolysis for obtaining nanocellulose (chemical methods) and sonication or high-pressure treatment (mechanical methods).[191] Chaoqun You et al[192] successfully prepared nanocatalysts by conjugating copper ions with gold nanoparticles using CNC as a carrier. This nanocatalyst system can be combined with DOX to

Table 6 Starch-Based Biopolymeric Drug Delivery Systems for Cancer Therapy

Type of Starch	Loaded Drugs	Type of Nanosystems	Diameter (nm)	Drug Release	Aimed Tumor/Cell	Ref
Starch	CG-1521	NPs	200	120h, 64% at pH 6.0, ~40% at pH 7.4	Breast cancer	[165]
Starch	5-aminosalicylic acid	NPs	40	50h, >80% at pH 7.4 in 0mM DTT, 98% at pH 7.4 in 20 mM DTT	HeLa	[166]
Starch	TPD	NPs	22.98±4.23	/	Pancreatic cancer	[167]
Starch	DOX	Nanocapsules	30–100	220h, 13.81 wt% at pH 7.4, 63.14 wt% at pH 5.8	/	[168]
Starch	DOX	NPs	70–200	48h, 75% at pH 7.4	BEL7404	[169]
HES	DOX	NPs	169.1 ± 16.4	24 h, 92% in 2 mM/mL DTT, 38% in 0 mM/mL DTT	H22, HepG2	[170]
HES	DOX	NPs	148.1	14.0% at PH 5.0, 19.2% at PH 7.4	TNBC	[171]
HES	CD44p, Emodin	Polymer micelles	154.5 ± 0.9, pH 7.4 125.8 ± 3.6, pH 6.5	84h, 70.27±0.03% at pH 7.4, 80.96±0.05% at pH 6.5	/	[172]
HES	CUR	Nanomicelles	69	72h, 25% at pH 7.4, 60% at pH 5.0	HeLa, Caco-2	[173]
HES	DOX	NPs	172	/	TNBC	[174]
HES	DOX	Nanomicelles	59 ± 3.9	72h, 70.5% at pH 5.5, 40.9% at pH 5.0, less than 30% at PH 7.4	Bladder cancer	[159]
HES-CHO	DOX, LHRH	Nanomicelles	51	72h, 40.1% at pH 6.8,71.2% at pH 5.5, and less than 30% at PH 7.4	Prostate	[175]
DS	5-Fu	NPs	90	48h, ~70% at pH 5, ~60% at pH 7, and ~50% at PH 9	Breast cancer	[176]
DS	DOX	NPs	100	72h, 34.25 at pH 5.0,9% at pH 7.4	HeLa	[177]
ARS	Methylene blue	NPs	173.4	/	CT-26	[178]
QS	siRNA	NPs	200–400	/	NAR	[179]
BRE	DOX	NPs	86±3.6	96h, ~46% at pH 4.5, ~14% at pH 7.2, and ~20% at PH 9.0	MG-63	[180]
AS	Para-Coumaric acid	NPs	218.97 ±3.07	42h, ~80% at pH 5.4, ~20% at pH 7.4	TNBC	[181]
PULL	PTX	NPs	130 ~ 170	72h, 75% at pH 5.4,74% at pH 7.4	SMMC-772, A549	[182]
TS	CUR	NPs	16 ~ 30	8h, ~70% at pH 5.0, ~60% at pH 7.4	MCF7, HepG2	[183]

Abbreviations: TPD, thienopyrimidine derivative; LHRH, Luteinizing hormone-releasing hormone.

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generate more H2O2, thereby amplifying the efficacy of chemodynamic therapy. In other studies, researchers have synthesized highly functionalized amorphous cellulose chains known as hairy cellulose nanocrystals (HCNCs) through controlled oxidation of cellulose.[193,194] HCNC shares a similar crystal size with CNC but exhibits a larger hydrodynamic size due to its dense protruding polymer structure, along with significant pH and ion-responsive behavior. Sarah A.E. Young et al developed anionic HCNC and combined it with positively charged DOX . The electrostatic adsorption allowed for stable binding of DOX to HCNC, reducing the pronounced nephrotoxic effects of DOX. They quantified the drug desorption by varying conditions such as ionic strength and pH. Compared to other nanoadsorbents, the HCNC they prepared showed a 32-fold increase in DOX adsorption efficiency.[195]

Furthermore, numerous researchers have explored the modification of cellulose, which is insoluble in water and organic solvents, to create hydrogels with micro-nano structures in combination with other components. For instance, Chenyang Xing et al[184] developed a hydrogel by combining black phosphorus (BP) nanosheets with gelled cellulose, enabling its application in photodynamic therapy for superficial tumors. Similarly, Ning et al[196] utilized polydopamine, agarose, and fluorescent nanocellulose to create a hydrogel carrier capable of pH-responsive release of paclitaxel.

We have collected and summarized recent studies on the use of cellulose in nanomedicine for cancer treatment, as presented in Table 7. As mentioned earlier, the pH microenvironment of diseased tissue differs from that of normal tissue. Therefore, most drug releases are measured in a weakly acidic environment. However, due to variations in preparation methods, materials, and applications across different studies, there is significant variability in the release data of drugs in vitro. However, all of them have demonstrated significant cytotoxic effects on cancer cells in vitro. Some researchers have applied nanosystems in photothermal therapy, photodynamic therapy, and radiation therapy to achieve better treatment outcomes.

Cellulose and its derivatives have garnered significant attention in the realm of drug delivery; however, several challenges remain unresolved. While cellulose is naturally produced by plants or bacteria, plant-derived compounds may contain traces of endotoxins, necessitating thorough investigations into long-term toxicity, immunogenicity, and pharmacokinetics in vivo, using appropriate animal models.[204] To date, much of the research has been confined to in vitro assessments of the drug delivery capabilities of nanocellulose hydrogel-based drug carriers. Additionally, the cost of production presents a noteworthy concern. For instance, bacterial fibers are challenging to industrialize due to their high production costs. Addressing these issues is crucial for the advancement and practical application of cellulose-based drug delivery systems.

Dextran

Dextran is a polysaccharide composed of glucose monomers linked by glycosidic bonds. It is typically extracted from grains and fungi. Dextran is highly soluble in water and biodegradable, exhibiting excellent properties in terms of restricting cell adhesion and diffusion. Research has shown that β-Dextran exhibits immunomodulatory activity. It can be selectively recognized by pattern recognition receptors on certain immune cells,[205] including dectin-1, CR3, TLR4, TLR2, scavenger receptors, and lactosylceramide.[206,207] Subsequently, it activates immune cells through a series of signaling pathways, promoting both cellular and humoral immunity.[208] Therefore, Dextran is an excellent immunostimulant. Dextran and its derivatives have been extensively studied for biomedical applications due to their excellent water solubility, biocompatibility, and biodegradability.[209] In addition to serving as carriers for conventional anticancer drug DOX,[210] Dextran as a nanocarrier has gained significant attention in drug delivery and immunoadjuvant applications. Currently, it is widely researched as a nanocarrier for tumor vaccines,[211] chemotherapy drugs,[212] gene therapy,[213,214] photodynamic therapy,[215] and other modalities. We have collected studies from recent years and presented them in Table 8.

Due to the presence of numerous active hydroxyl groups on the molecular chain, Dextran can undergo chemical modifications such as phosphorylation, sulfation,[226] carboxymethylation,[227] and oxidation. Carboxymethyl Dextran (CMD) is a polyanionic polysaccharide with a negative ζ potential. Its functional groups facilitate chemical conjugation and ion complexation with various drugs.[209] Xinping Luo et al[222] developed a nano-probe called DN-ICG, which consists of a CMD conjugated with indocyanine green (ICG) nanoparticles, for dynamic imaging of macrophages. The nano-probe can specifically target tumor-associated macrophages through the interaction between CMD and a specific receptor (SIGN-R1). After hepatic metabolism, the probe can be detected in the tumor stroma, enabling fluorescence imaging of deep-seated hepatopancreatobiliary cancers. Nastaran Moradi et al[228] coated CMD onto superparamagnetic iron oxide nanoparticles and further conjugated anti-CD3 monoclonal antibodies onto the surface of CMD using cyanogen bromide. This approach effectively

Table 7 Cellulose-Based Biopolymeric Drug Delivery Systems for Cancer Therapy

Loaded Drugs	Type of Nanosystems	Encapsulation Efficiency	Loading Content	Diameter (nm)	Drug Release	Ref
CUR	Nanofiber	99.14%	1 mg/ml	/	93h, 50.31% at pH 1.2, 90.72% at pH 5.3, 57.27% at pH 6.8, 74.48% at pH 7.4	[197]
Camptothecin	Nanofiber	65.28%	41.40 ± 3.08%	458.7	48h, 63.4% at pH 6.8, 80.2% at pH 7.4	[198]
DOX	NPs	/	6000 μg	66	/	[195]
DOX, Au NPs	NPs	/	Au:2.5% DOX:7.71%	190.1	48 h, 98.88% at pH 5.5	[192]
PTX	NPs	96.8%	11.50%	226.9 ± 2.75	24h, ~90% at pH 5.5	[199]
Fe3O4 NPs	NPs	/	/	8.02	/	[200]
MTX/CUR	NPs	33% and 75%	3.3% / 7.5%	530	96h, at pH 5.4, MTX and CUR released 56.51% and 53.95%, At pH 7.4, MTX and CUR 52.44% and 47.94%	[201]
FA	Nanocapsules	/	1.2 mg/mL	200–300	48h, 14% in 0mM GSH,25% in 10 μM GSH, 91.2% in 10 mM GSH	[186]
DOX	NPs	94.16 ± 0.05%	2.11 ± 0.10 wt %	25	48h, 52.0% at pH 5.0	[202]
FA, Cdots, DOX	Nanocrystals	1.053 mg/mg (27.3%)	0.15 mg/ml DOX	179.4 ± 16.1	96h, 85.8 ± 1.6% at pH 5.6	[203]
Gold NPs, ZnS-QE	Supramolecular nanoarchitecture	/	/	75 ± 2	/	[190]

Abbreviations: FA, folic acid; Cdots, Carbon dots; ZnS-QE, ZnS semiconductor quantum emitter.

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Table 8 Dextron-Based Biopolymeric Drug Delivery Systems for Cancer Therapy

Type of Dextron	Loaded Drugs	Type of Nanosystem	Zeta Potential (mV)	Diameter (nm)	PDI	Anti-Tumor Activity	Application	Ref
CMD	MnO2	NPs	−23.83 ± 2.11	208.3 ± 14.2	/	The ability to effectively deplete tumor GSH to collapse the tumor antioxidant defense system; Ability to amplify oxidative stress-induced cell necrosis	SDT	[216]
DEX	siRNA	Nanodroplets	−13.1±0.8 to 9.82 ±0.94	111.8 ± 1.9	0.276	Dextran-based condensates allow efficient DNA compression and loading with GSH responsiveness, low cytotoxicity, and higher transfection efficiency	Gene Therapy	[217]
BFP	SeNPs	Nanotubes	−6.65	33	/	BFP-Se nanomaterials barely affected normal cell growth and significantly inhibited the viability of hepatocellular carcinoma cell lines (HCC) in a dose-dependent manner. Capable of disrupting critical antioxidant systems to promote iron death in tumor cells, BFP-Se was able to target into the tumor environment, increasing tumor suppression from 53% to 81% compared to SeNPs alone	Chemotherapy	[218]
Aminated β-glucan	OVA	NPs	25.4 ± 1.7	183.6 ± 0.9	0.113 ± 0.022	Packaging efficiency of more than 80%. Enhanced uptake of antigen by APCs. Promotes macrophage maturation and enhances Th1 and Th2 type immune responses	Immune booster	[219]
Acetalated Dextran	Nutlin-3a	NPs	40±2	221±4	0.12±0.03	GM-CSF and CpG-ODN can promote a strong anti-tumor immune response by recruiting and activating APCs in the presence of antigen. NPs can be targeted for delivery to the tumor system	Chemotherapy with immunotherapy	[212]
PCL-g-Dex	DOX	Micelles	/	142.2	0.16	The DOX loading rate can be changed by adjusting the Dox/co-polymer ratio. The micelles released slowly and completely after seven days at pH 5.5, while the DOX release rate was less than 40% at pH 7.4. The drug-loaded micelles were able to kill cancer cells but had little killing effect on normal cells	Chemotherapy	[210]
DEAE-DEX	mRNA	NPs	~20	120–210	/	A suitable molar ratio of DEAE-Dextran: mRNA (3~10) was found, which provides high cellular uptake efficiency, higher transfection rate, and small particle size.	Gene Therapy	[211]
SpAcDEX	miRNA-21 oligonucleotide (ATMO-21)	NPs	+35.6	175.6	0.53	The ability to target brain cancer cells, thus minimizing damage to normal cells. Inhibits the growth of U87MG cells in a dose-dependent manner. In vivo, tumor model tests demonstrated that the particles have tumor suppressive effects	Gene Therapy	[213]
Thiolated Dextran	miRNA	NPs	20.8 ± 1.2	132 ± 8	0.174 ± 0.01	Significantly improve the permeability and retention time of miRNAs. Effectively enhances the uptake of nanoparticles by cancer cells, leading to higher gene silencing and cancer cell apoptosis.	Gene Therapy	[214]

Methacrylated Dextran	Synthetic long peptides (SLPs)	Nanogels	+24	210	<0.03	Nanogels can be internalized by dendritic cells (DCs) and activate these immature cells	Immunotherapy	[220]
Dex-b-PLGA	/	NPs	between +20 and −15	88 ± 2	/	Capable of negative charge at physiological pH and a positive charge at slightly acidic pH, thus resisting protein adsorption at neutral pH and enhancing cellular uptake of NPs by cells	/	[221]
CMD	ICG	NPs	−13.5 ± 1.7	27.5 ± 5.6	0.5	Ability to target macrophages and enable NIR-II fluorescence imaging in a mouse model of subcutaneous pancreatic tumors	Tumor Imaging	[222]
Dextran Valproate	Valproic acid	NPs	/	179	0.199	/	Gene Therapy	[223]
Dextran Aldehyde	Quercetin	NPs	−47.4	259.7 ± 90.7	/	NPs are non-toxic to HEK-293T cells and are able to induce histone H3 acetylation, which is rapidly taken up by HEK-3 cells.	molecular targeted therapy	[224]
PEG-CMD	Chlorin e6	Nanobubbles	−54.1±6.7	142.3 ± 29.4	/	/	Sonodynamic Therapy	[225]

Abbreviations: DEAE-DEX, polysaccharide diethylaminoethylen (DEAE) – Dextran; SpAcDEX, spermine-modified acetalated dextran; PEG-CMD, PEGylated carboxymethyl dextran. BFP, β-glucan.

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isolates highly pure CD3+ T lymphocytes from whole blood and can be applied in CAR-T cell therapy. Luisa Pedro et al[229] evaluated the safety of superparamagnetic iron nanoparticles for cancer treatment.

These cationic dextran nanoparticles can be used for the delivery of nucleic acids to tumor areas in gene therapy. Cationic dextran nanoparticles can be used to deliver nucleic acids to tumor regions for gene therapy. Chenglong Wang et al[217] designed and synthesized two types of amino-containing cationic copolymers based on dextran, which were self-assembled with anionic genes to form nano-droplets. Nanodroplets can enter cells through endocytosis and subsequently undergo reduction-triggered disruption, releasing siRNA and DNA for expression within the cells. Dextran, as a carrier, offers good transfection efficiency while avoiding the higher cytotoxicity associated with commonly used cationic polymers such as polyethylenimine and polypropylenimine. Additionally, modified dextran derivatives, such as aldehyde-modified dextran prepared by Tao Zheng et al[213] and thiol-modified dextran prepared by Farnaz Sadat Mirzazadeh Tekie et al[214] introduce positively charged groups onto dextran, enabling interaction with negatively charged genes for gene therapy.

Vaccine adjuvants are small molecules, compounds, or macromolecular complexes added to antigens to enhance and modulate their immunogenicity. Dextran, due to its excellent immunomodulatory activity, is highly regarded in the development of immunological adjuvants and cancer vaccines. Jing Wei Jin et al[219] synthesized amine-functionalized β-dextran nanoparticles loaded with CpG oligodeoxynucleotides using ion complexation and investigated their synergistic effects as immune enhancers. These nanoparticles achieved APC targeting through specific recognition by dectin-1 and TLR2, leading to enhanced antigen uptake and expression of relevant proteins, ultimately inducing effective Th1 and Th2 immune responses. Neda Kordalivand et al[220] conjugated antigenic peptides to methylacrylic acid-modified cationic dextran nanoparticles via disulfide bonds (Figure 9A), enabling triggered release of the antigenic peptides under reducing

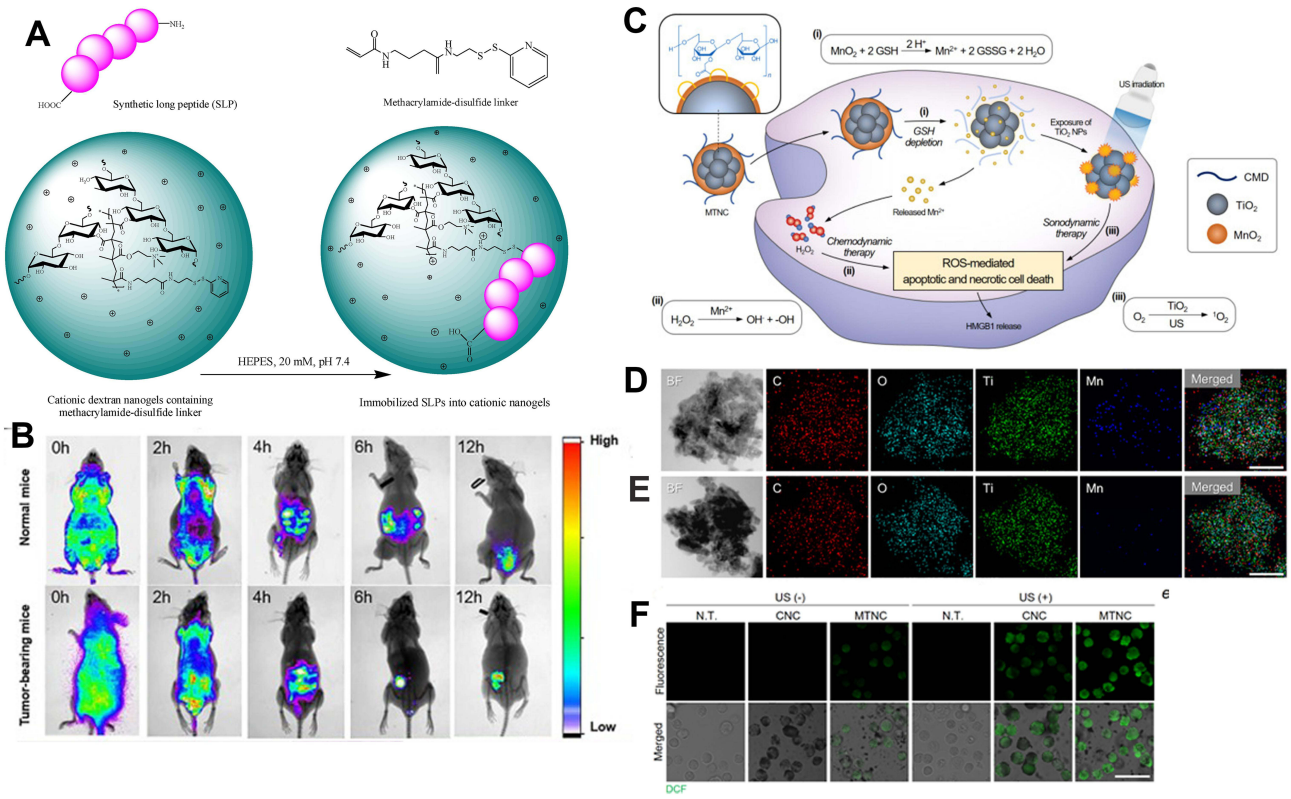

Figure 9 (**A**) Schematic representation of the cationic dextran nanogels containing N-(4-(2-(pyridine-2-yldisulfanyl) ethyl)-amidobutyl) methacrylamide as linker (left), and SLP loaded nanogels (right). Reprinted from Journal of Controlled Release, 315, Kordalivand N, Tondini E, Lau CYJ, et al. Cationic synthetic long peptides-loaded nanogels: an efficient therapeutic vaccine formulation for induction of T-cell responses, 114-125, Copyright 2019, with permission from Elsevier.[220] (**B**) The detected selenium content in serum. Reprinted from Chemical Engineering Journal, 446, Cai L, Zhou S, Yu B, et al. The composites of triple-helix glucan nanotubes/selenium nanoparticles target hepatocellular carcinoma to enhance ferroptosis by depleting glutathione and augmenting redox imbalance, 137110, Copyright 2022, with permission from Elsevier.[218] (**C**) The working mechanism of MTNCs for augmented chemo-SDT of cancer. (**D** and **E**) TEM/EDS mapping image of MTNCs when exposed to 0 mM and 10 mM of GSH for 30 min (scale bars represent 100 nm). (**F**) intracellular ROS detection using DCFDA. Reprinted from Carbohydrate Polymers, 273, Um W, P KEK, Song Y, et al. Carboxymethyl dextran-based nanocomposites for enhanced chemo-sonodynamic therapy of cancer, 118488, Copyright 2021, with permission from Elsevier.[216]

conditions. C. Siewert et al[211] self-assembled messenger RNA (mRNA) with cationic dextran (diethylenimino dextran) to form colloidal nanoparticles, allowing precise control of target selectivity in vivo by controlling the charge ratio. These mRNA vaccines, suitable for intravenous administration, can be used for cancer therapy.

Glutathione (GSH) is an important antioxidant in cells, which inhibits apoptosis by scavenging reactive oxygen species (ROS). In cancer cells, the concentration of GSH is over 100 times higher than in normal tissues.[230] Clearing GSH in tumors and inducing ROS can effectively kill cancer cells. Liqin Cai et al[218] developed beta-dextran nanotubes loaded with selenium nanoparticles (SeNPs) (BFP-Se) for targeted delivery to cancer cells via the enhanced permeability and retention (EPR) effect. BFP-Se directly reacts with GSH and hydrogen peroxide in cancer cells, clearing GSH while generating ROS. This leads to cell apoptosis and ferroptosis, resulting in cancer cell death. The use of dextran nanotubes improves the bioavailability of SeNPs (Figure 9B). Wooram Um et al[216] prepared carboxymethylated dextran-coated nanoparticles with a hydrophilic shell. The nanoparticles have a TiO_2 core and an outer MnO_2 coating as depicted in Figure 9C. The MnO_2 coating acts as a chemical sensitizer to deplete glutathione, while TiO2 acts as a sonosensitizer to generate reactive oxygen species for sonodynamic therapy. The hydrophilic nature of the dextran shell allows prolonged circulation in the bloodstream, thereby enhancing tumor-targeting efficiency (Figure 9D-F).

Dextran is recognized for its anti-protein adsorption, antioxidant, anti-inflammatory, and anti-tumor properties, serving as a potent activator of cellular immunity with strong synergistic effects with anti-cancer antibodies.[231] Certain soluble fungal sources of β-glucans, like shiitake polysaccharides from edible mushrooms and Schisandra glycosides from Schisandra chinensis culture filtrates, have been clinically employed in tumor immunotherapy. Additionally, dextran has been observed to scavenge free radicals produced around tumors. However, dextran itself lacks self-assembly ability and exhibits a strong water retention capacity. Its modification can alter its molecular structure and may even induce cytotoxicity, posing a challenge for dextran-based drug carriers.[232] Moreover, different sources of dextran possess varying structures and bioactivities, necessitating a clear understanding of the conformational relationships between them.[233] Finally, dextran as an immune adjuvant may lead to side effects such as pulmonary edema, platelet dysfunction, cerebral edema, and systemic allergic reactions, which should be carefully considered in the development and use of dextran-based drug delivery systems.[234,235]

Hyaluronic Acid

Hyaluronic acid (HA) is a linear polysaccharide composed of alternating repeating disaccharide units, including β-1,4-D-glucuronic acid and β-1,3-N-acetyl-D-glucosamine. Unlike other polysaccharide-based delivery carriers, HA is a common polysaccharide found in the human body, abundant in connective tissues, skin, and synovial fluid. It is biodegradable and non-immunogenic as it can be degraded by endogenous hyaluronidases and oxidative species (ROS, RNS).[236,237] HA exhibits excellent biocompatibility, degradability, and compatibility with the human immune system. HA is commonly used for surface functionalization of nanocarriers, as it enhances blood circulation time, improves biocompatibility, and actively targets receptors on cancer cells.[238] Receptors such as CD44, CD168 (also known as hyaluronic acid-mediated motility receptor, RHAMM), and lymphatic vessel endothelial hyaluronic acid receptor 1 (LYVE-1) are overexpressed in tumors and can be targeted by HA-functionalized nanocarriers.

CD44 is a key receptor of interest that is overexpressed in solid cancers such as prostate cancer, breast cancer, glioblastoma, colon cancer, and cervical cancer. HA is frequently utilized as the active targeting moiety in drug delivery systems, serving as the outer shell of nanocarriers. By specifically binding to CD44 antibodies present on the surface of cancer cells, HA enables targeted delivery to cancer cells. For instance, Lei Zhu et al[239] exploited this characteristic and developed HA-encapsulated nanoparticles loaded with GKT831, an inhibitor of NADPH oxidases (NOXs). In breast cancer patient-derived xenograft (PDX) tumors in nude mice, these nanoparticles demonstrated a significantly enhanced therapeutic effect when combined with radiotherapy, highlighting their potential in breast cancer treatment.

RHAMM (CD168) receptor, also known as hyaluronic acid-mediated motility receptor, coexists with CD44 and is expressed in various cancers including breast cancer, ovarian cancer,[240] pancreatic cancer,[241] and prostate cancer (CaP).[242] However, studies have revealed that approximately 23% of cancers overexpress this receptor even in the absence of CD44 expression. As shown in Figure 10A, Chenchen Yang et al[243] utilized this characteristic to develop HA nanogels (HAss nanogels) for targeted delivery of DOX. Using an H22 metastatic tumor model as an animal model, fluorescence results

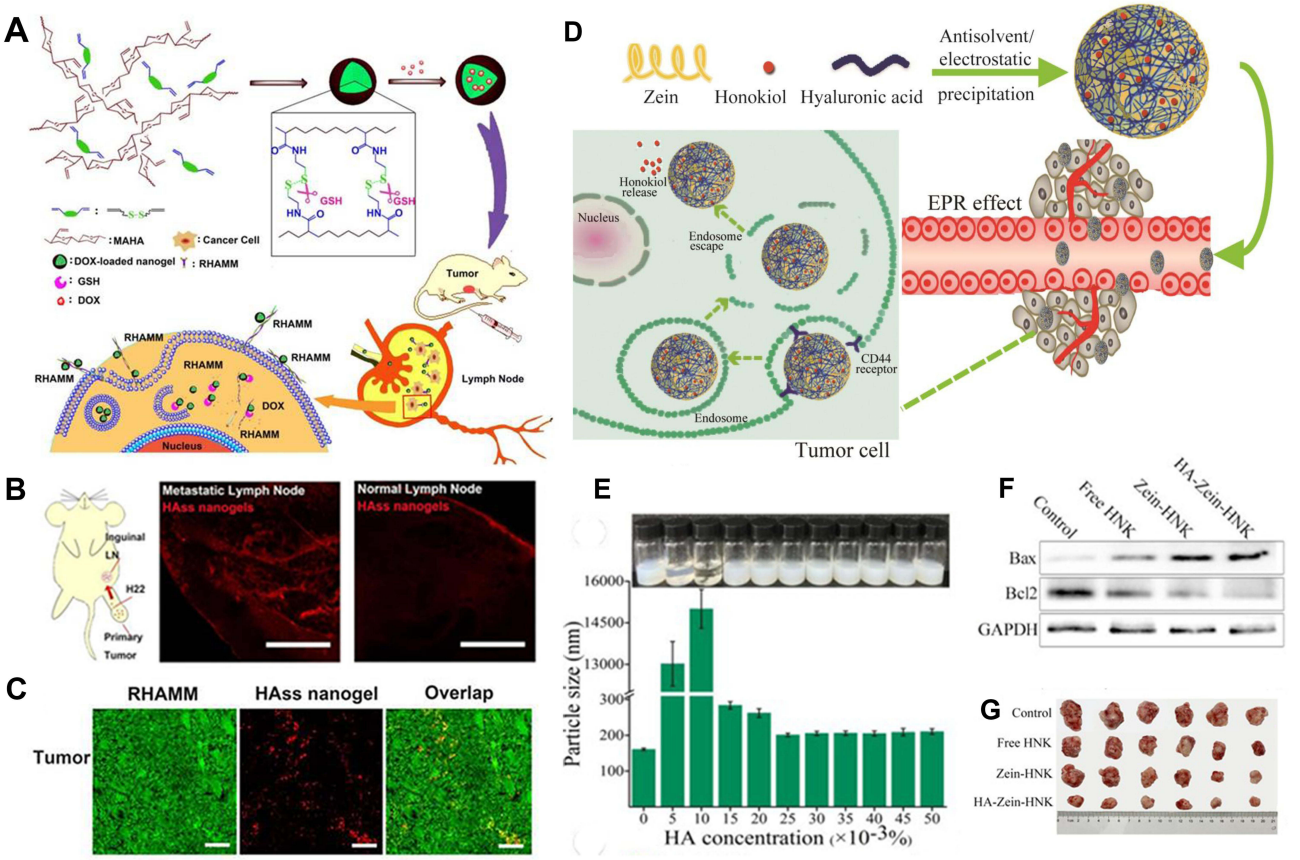

Figure 10 Delivery strategies and applications of HA-based delivery carriers. (**A**) The preparation of HAss nanogels and the targeting of HAss nanogels to RHAMM in cancer cell and lymph node which contains cancer cells with RHAMM overexpression. (**B**) Diagrammatic drawing of establishing lymph node metastases model in mouse and RBITC-HAss nanogels (red) penetrated in metastatic lymph node (left) and normal one (right) at 2 h post-injection ex vivo. The scale bar is 500 μm. (**C**) Immunofluorescence staining sections of RHAMM (green) expression in tumor, RBITC-HAss nanogels (red) penetrated in the tumor at 24 h post-injection. All cell nuclei are not shown in this figure. The scale bar is 100 μm. Adapted with permission from Yang C, Li C, Zhang P, Wu W, Jiang X. Redox Responsive Hyaluronic Acid Nanogels for Treating RHAMM (CD168) Over-expressive Cancer, both Primary and Metastatic Tumors. Theranostics. 2017;7(6):1719–1734. (https://creativecommons.org/licenses/by-nc/4.0/).[243] (**D**) Graphic illustration of the preparation strategy and the antitumor function of HA-Zein-HNK nanoparticles. (**E**) The representative images and particle sizes of HA-Zein-HNK at different HA concentrations. (**F**) Expressions of pro-apoptotic proteins Bax and anti-apoptotic proteins Bcl-2 in 4T1 cells incubation with various HNK formulations. (**G**) The expressions of Vimentin and E-cadherin in 4T1 cells treated by Zein-HNK, HA-Zein-HNK, and free HNK were examined using western blot. Reprinted from Carbohydrate Polymers, 240, Zhang Q, Wang J, Liu D, et al. Targeted delivery of honokiol by zein/hyaluronic acid core-shell nanoparticles to suppress breast cancer growth and metastasis, 116325, Copyright 2020, with permission from Elsevier.[118]

demonstrated the overexpression of RHAMM in H22 tumors (Figure 10B and C), and HAss nanogels were observed in the tumor vicinity, indicating the targeting capability of the nanogels towards H22 tumors. Furthermore, it was shown that the HAss nanogels could inhibit lymph node metastasis. HA, as a drug delivery carrier for cancer treatment, is inherently unstable and susceptible to enzymatic degradation in the body. Researchers often modify HA by introducing branching functional groups to enhance its performance. For instance, Xiaoqin Zhang et al[244] attached Ppa (a specific moiety) and Dendron branches to the side chains of HA, forming a dendritic three-dimensional structure. This modification effectively prolongs the circulation time of the drug in the bloodstream. Additionally, HA can be functionalized with dopamine (DA) to improve its adhesiveness to target tissues or cells.[245]

Indeed, HA can be combined with various photosensitizers, including Photofrin, Chlorin e6, Indocyanine green, or δ-Aminolevulinic acid (ALA),[244] to enhance targeting and maximize the photothermal effect for targeting and killing cancer cells.[246] Due to the abundance of functional groups on its surface, HA can facilitate synergistic effects when combined with other targeted drugs. For example, Xiaodan Wang et al[247] utilized a ramified glyphosate (GA) based on HA to achieve common targeting of liver cancer cells. The degree of GA ramification influences the release rate of the drug, and the toxicity to HepG2 cells depends on the ramification rate. Furthermore, HA's inherent negative charge enables it to act as a carrier for various substances, including PEG, PEI, liposomes, proteins, and other polysaccharides,

through electrostatic interactions, thereby improving targeting and biocompatibility. For instance, the combination of HA with polyethylenimines (PEI), which are high-molecular-weight delivery carriers limited in their use due to cellular toxicity, not only reduces toxicity but also enhances targeting. In a study by Manoj B. Parmar et al[248] a PEI/HA composite carrier was employed for the targeted delivery of small-interfering RNA (siRNA) to inhibit triple-negative breast cancer cells. Moreover, proteins are commonly used as delivery carriers; however, they often exhibit poor stability and tend to aggregate in the body due to electrostatic interactions with plasma proteins. To overcome this challenge, researchers have successfully combined proteins with HA to enhance stability and prevent aggregation, capitalizing on the negative charge of HA.[117] As shown in Figure 10D and E, Qi Zhang et al conducted further research based on this foundation and designed a drug delivery system in which Honokiol (HNK) was loaded onto zein and coated with HA to form a core-shell structure (HA-Zein-HNK). In comparison to the bare Zein-HNK nanoparticles without HA coating, the HA-Zein-HNK nanoparticles exhibited a significant decrease in zeta potential from Zein-HNK+18.66 ± 1.6 mV to −34.54 ± 2.8 mV, indicating the formation of a more stable structure. In vitro drug release studies demonstrated that HA-Zein-HNK exhibited sustained release over the same period of time. Evaluation of the anticancer activity of both types of nanoparticles in BALB/c mice bearing 4T1 tumors revealed that HA-coated nanoparticles displayed superior targeting ability and exhibited better antitumor efficacy compared to free HNK and Zein-HNK[118] (Figure 10F and G).

HA plays a crucial role in the field of cancer drug delivery due to its unique targeting ability and the presence of abundant functional groups (carboxyl, hydroxyl, and aldehyde end groups) that can be easily chemically modified (Table 9). Unlike other multifunctional nanomaterial delivery systems, HA-based delivery systems offer simpler designs without the need for additional ligands, and HA can achieve both active and passive targeting. Furthermore, the enzymatic and oxidative degradation properties of HA in the body enable responsive activation of drug release in a time- and space-dependent manner. However, there are still many issues that limit its further development.[249,250] (1) The targeting ability of HA to CD44 receptors is influenced by its molecular weight. (2) Tumor-targeting properties of HA can be compromised by the presence of enzymes like hyaluronidase in the tumor microenvironment, leading to premature drug release. (3) HA receptors present in hepatic endothelial cells may cause preferential accumulation of hyaluronic acid in the liver, reducing its efficacy at tumor sites. (4) In vivo, HA-based nanoparticles can form a protein corona, affecting their degradation properties and potentially altering their behavior in the body. (5) Modification of HA for drug delivery purposes may alter its binding affinity to receptors, affecting its targeting ability. (6) HA-based drug delivery systems face challenges in industrial-scale production, limiting their widespread application, like the one developed by Alchemia of Australia, has shown promising results in Phase I and Phase II clinical trials, but the phase III clinical trials did not achieve the expected results. Further research and development is needed to address these challenges and improve their clinical efficacy.

Fucoidan

Fucoidan, a naturally occurring marine polysaccharide with a negative charge, is predominantly found in brown algae species such as marine ribs, myrtle algae, and cyanobacteria. Fucoidan exhibits a wide range of biological activities, including anti-tumor, immune regulation, anticoagulation, antioxidant, anti-angiogenic, and anti-metastatic properties.[267] The bioactivity of fucoidan is closely associated with its structural characteristics, including the type, molecular weight, and degree of sulfation of the glucose linkages. Even within the same source, different fucoidan structures can be observed, leading to structural diversity among fucoidan species. As an active anti-cancer molecule, studies have revealed that low-molecular-weight fucoidan with high sulfation exhibits superior anti-cancer effects.[268,269] Fucoidan has the ability to specifically target P-selectin receptors, which are expressed in various solid tumors, including scalp cell cancer, bladder cancer, prostate cancer, lung cancer, and breast cancer.[270,271] In cancer, it promotes adhesion of tumor cells to activated platelets and endothelial cells, leading to cancer metastasis.[270] Leveraging its tumor-targeting properties, researchers have explored the application of fucoidan in tumor drug delivery systems, utilizing it in the form of micelles[272] or nanoparticles[271] to enhance cellular uptake of anti-cancer drugs and achieve targeted delivery, thereby minimizing damage to healthy organs. Further investigations have demonstrated that fucoidan can induce cancer cell autophagy and premature senescence by modulating specific cellular pathways.[273] Wen-Jing Hsu et al[274] conducted studies to elucidate the anti-tumor mechanisms of fucoidan and found that it effectively downregulates the MAPK and

Table 9 HA-Based Biopolymeric Drug Delivery Systems for Cancer Therapy

Type of HA	Loaded Drugs	Type of Nanosystem	Zeta Potential (mV)	Diameter (nm)	PDI	Drug Release (%)	Aimed Cancer/Cell	Ref
HA-APMA	DOX	Nanorods	/	length: 50 ± 4, width: 10 ± 2	/	48h, <10% % at pH 7.4, ~30% at pH 5.5 without hyaluronidase, 8.5% at pH 7.4,46.8% at pH 5.5 with hyaluronidase	Ovarian cancer cells	[251]
HA	CUR	NPs	18.10±1.08	184.1 ± 13.2	0.432	10h, 16.7% at pH 7.4, 30.6% at pH 5.5	Breast cancer	[252]
DAHA	DOX	Nanorods	−16.6	Length: 55.6, Diameter:13.7	/	48h, without NIR, 15% at pH 7.4, 35.3% at pH 6.5, 60% at pH 5.5; with NIR radiation 27% at pH 7.4, 52.95% at pH 6.5, 78% at pH 5.5	Breast cancer, MCF-7	[253]
HA	DOX	Nanocubes	−17.60±0.98	149.22 ± 26.15	/	72h, 78% at pH 5.5,39% at pH 7.4	HCC	[254]
PEG-HA	MTX	NPs		338		72h, 44.12% at pH 7.4, 87.7% at pH 5	MDA-MB-231 and MCF-7	[255]
HA/Catechol-modified chitosan	DOX	NPs	−12.7 ± 0.12	160	0.3 ± 0.01	/	Oral cancer, HN22	[256]
HA/Lf	Lenalidomide	NPs	31.7 ± 1.9	27.4 ± 2.7	0.239	12h, 9.5% ± 1.7% at pH 7.4, 12.2% ± 2.9% at pH6.5, 24.4% ± 2.4% at pH 5.5, 19.3% ± 2.9% at pH 4.8	U87MG	[257]
HA-SH	Ovalbumin	Vaccines	−27.23 mV	175.57	0.2	/	EG.7-OVA tumor-bearing mice	[258]
HA-CpG	DOX	NPs	−21.4	15.9	/	/	Glioblastoma	[259]
HA, GO	DOX	NPs	−22.45 ± 1.22	143.7 ± 3.9	/	at pH 7.4, GSH 10m, 48h ~28%. Without GSH, PH7.4,48h 10%, PH5.5,48h 25% In the presence of HAase, PH7.4 released ~20%, in the presence of HAase and GSH 10mM, PH7.4 released 45%, in the presence of HAase, PH 5.5 released 55%	MDA-MB-231	[260]
HA-NH2	PFOB@IR825-HA-Cy5.5 NPs	NPs	22.9 ± 1.8	80~ 110	/	/	HT-29	[261]
HA/Liposome	Epalrestat (EPS) and DOX	NPs	−10.9 ± 0.51	−10.9 ± 0.51	0.119 ± 0.048	/	TNBC	[262]
TPGS/hyaluronic acid dual-functionalized PLGA	Paclitaxel	NPs	−19.40 ± 0.79	162.30 ±1.80	0.15 ± 0.01	/	TNBC and Melanoma	[263]
HA-Zein	CUR	NGs	~-50	200 ~250	~0.3	4 days released 79%	CT26	[117]

HA-NO3	PTX/ICG	NPS	37.9 ± 0.352	195.6 ± 3.2	0.181 ± 0.012	/	Breast cancer	[264]
HA, Liposome	DOX	NPS	−28.9	165	0.15 ± 0.03	48h released less than 35% at PH7.4	Osteosarcoma	[265]
HA	DOX	NGs	−30.12 ± 3.12	52.4 ± 3.4	/	After 24 h, 20% and 26% were released in the absence of GSH, pH 7.4 and 5.0, respectively, and 69% and 76% were released in the presence of GSH (10 mM), pH 7.4 and 5.0, respectively.	Human prostate cancer, H22 A549 /NIH3T3	[243]
HA, zein	Honokiol	NGs	−34.54 ± 2.8	200	/	After 48h, Zein-HNK released 80.1% and HA-Zein-HNK released 77.5%	Breast cancer, 4T1	[118]
AHA, HECS	DOX and cisplatin	NGs	−28	160	/	After 24 h, DOX was released 51.2% at PH5.5 and 12.45% at PH7.4, CDDP was released 57.68% at PH5.5 and 25.87% at PH7.4.	Breast cancer	[266]
GA, HA	DOX	NGs	−26.4±1.1	235.9±4.1	0.110±0.042	The cumulative release time was 48h, 29% at pH 7.4,35% at pH 6.5,51% at PH5.5	Liver cancer	[247]

Abbreviations: DAHA, Aldehyde/catechol-functionalized hyaluronic acid; HCC, hepatocellular carcinoma; Lf, lactoferrin; GA, glycyrrhetinic acid; AHA, Aldehyde hyaluronic acid; HECS, hydroxyethyl chitosan; GO, Graphene oxide.

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PI3K/AKT pathways, thereby inhibiting AP-1 and NF-κB signaling pathways in triple-negative breast cancer (TNBC). It is noteworthy that different types of fucoidan exhibit distinct anti-cancer mechanisms. Additionally, researchers have explored the anti-angiogenic effects of fucoidan, particularly focusing on the sulfated algae polysaccharide FP08S2.[275] This compound has been shown to inhibit the angiogenic properties of human microvascular endothelial cells (HMEC-1) by blocking the VEGFR08/Erk/VEGF signaling pathway, leading to antimetastatic effects. In vivo, studies using intra-organ tumor xenograft models have further confirmed the anti-tumor activity of fucoidan.

Furthermore, Fucoidan demonstrates its versatility beyond being a carrier for anti-cancer nanopharmaceuticals by its potential in combination with imaging agents for localized tumor tracking. By leveraging Fucoidan's targeting ability towards P-selectin, researchers have developed a nanogel for injection that serves both as a photothermal therapy agent and an imaging tool as schematically depicted in Figure 11A. In this approach, chlorin e6 (Ce6) and Fucoidan are incorporated into a hydrogel called CFN-gel. When compared to free Ce6, CFN-gel exhibited increased cellular and tumor tissue uptake of Ce6, leading to

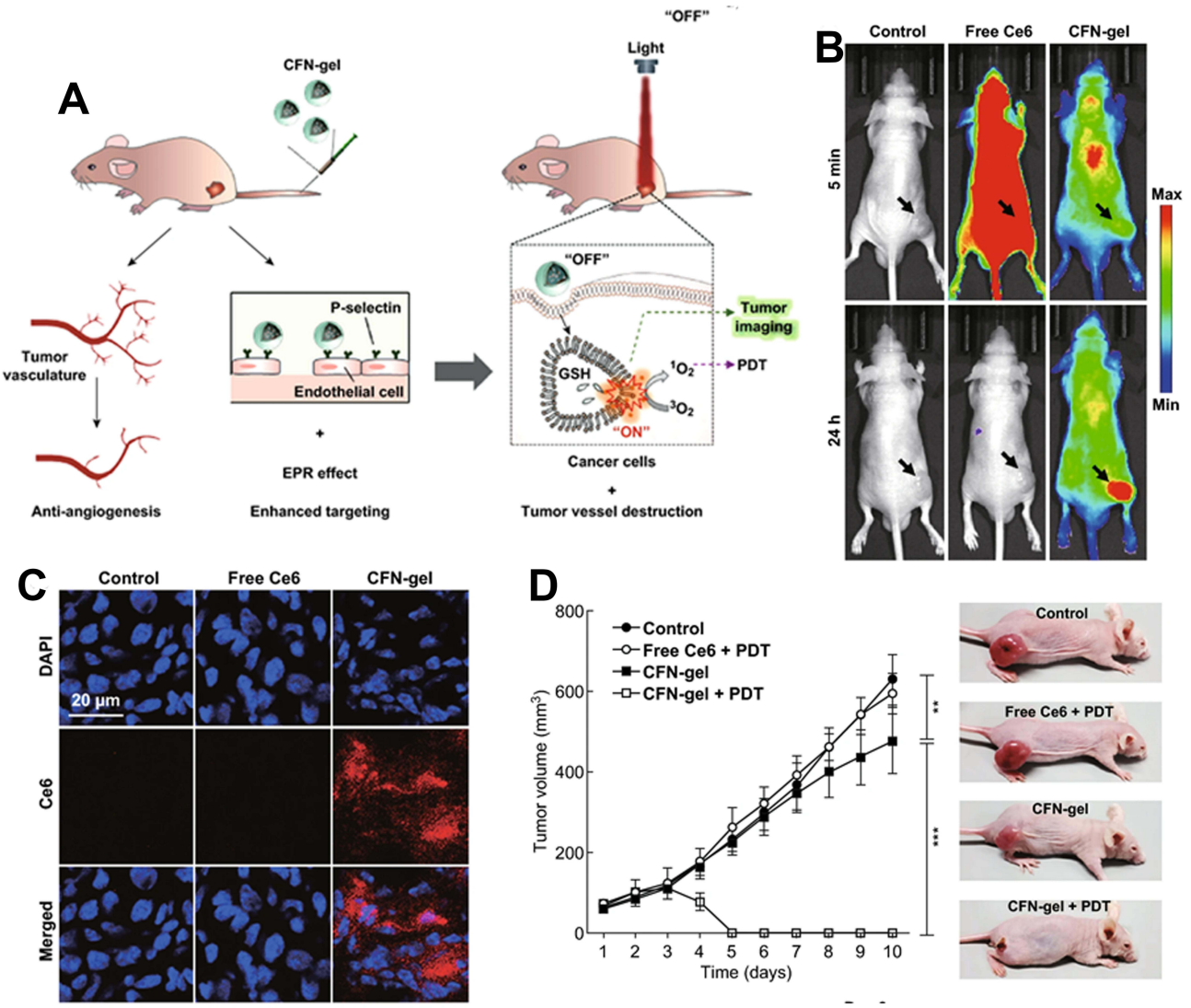

Figure 11 Delivery strategies and applications of fucoidan-based delivery carriers. (**A**) Schematic illustration of CFN-gel and its mode of action. (**B**) NIR fluorescence images of PBS-, free Ce6- or CFN-gel-treated mice. After 5 min and 24 h of intravenous injection of PBS (100 μL), free Ce6 (5 mg Ce6 kg^{-1}), or a CFN-gel (5 mg Ce6 equiv. kg^{-1}), NIR fluorescence images of the HT1080 tumor-bearing mice were obtained. (**C**) confocal fluorescence microscopic images of tumor sections prepared 24 h post-injection. Nuclei in the tumor sections were stained using DAPI. (**D**) Left: tumor growth curves of mice. Control group (n = 7), free Ce6 + PDT (n = 5), CFN-gel (n = 7) and CFN-gel + PDT (n = 5). PBS, free Ce6, or Ce6–fucoidan was injected intravenously on day 1. Light illumination (670 nm, 50 mW cm^{-2}, 20 J cm^{-2}) of the tumors was conducted on day 2 for PDT. Right: representative photographs of the mice obtained on day 10. Adapted with permission from Cho MH, Li Y, Lo P-C, Lee H, Choi Y. Fucoidan-Based Theranostic Nanogel for Enhancing Imaging and Photodynamic Therapy of Cancer. Nano-Micro Lett. 2020;12(1):47. https://creativecommons.org/licenses/by-nc/4.0/).[276]

enhanced fluorescent imaging capabilities (Figure 11B and C). The inherent tumor-targeting ability of Fucoidan allows the gel to concentrate specifically at the tumor site, thereby exerting its anti-tumor effects (Figure 11D). This combination of Fucoidan and imaging agents holds promise for precise and effective tumor imaging and therapy.[276]

Fucoidan has antioxidant, anticoagulant, antithrombotic, anti-inflammatory, antiviral, antilipidemic, antimetastatic, antidiabetic and anticancer effects. Although fucoidan extracts have been widely used in various health care products, including food supplements and cosmetics, there is no clinical drug based on fucoidan, mainly because of (1) Fucoidan's complex structure and challenging purification process contribute to its relatively high cost compared to other polysaccharides.[277] Research efforts should focus on developing more efficient and cost-effective methods for isolating and purifying fucoidan. (2) Fucoidan exists in various structural forms, leading to differences in its biological activities, including its anti-tumor effects. Further studies are needed to elucidate the structure-function relationships of different fucoidan variants and their specific effects on cancer cells.[278] (3) While fucoidan has demonstrated promising anti-cancer effects in preclinical studies, its safety profile in vivo requires further investigation. Comprehensive toxicity studies are necessary to evaluate potential adverse effects and ensure its safety for clinical use.

Pectin

Pectin is a plant-derived polysaccharide that serves as a major constituent of the plant cell wall, primarily found in citrus fruits, apples, potatoes, and other sources. It is composed mainly of methylated D-galacturonic acid units, forming a cell ring structure. Pectin can be categorized into various types based on its different structural components, including homogalacturonan (HG), Type I Rhamnogalacturonans (RG-I), Type II Rhamnogalacturonans (RG-II), Xylagalacturonan (XGA), and ApioGalacturonan (AGA). Pectin rich in RG-I exhibits notable bioactivity.[279] In recent years, pectin has gained significant attention due to its non-toxic nature, biodegradability, excellent biocompatibility, and cost-effectiveness.[280] Consequently, it has found extensive applications in various fields, such as food, pharmaceuticals, and cosmetics. Similar to other polysaccharides, pectin possesses a range of beneficial properties, including anti-inflammatory, antioxidant, anti-cancer, and immune regulatory effects. Additionally, it has demonstrated the ability to lower blood sugar and cholesterol levels. These advantageous characteristics have further expanded its utilization in the biomedical field.

Pectin can be further classified into high methoxy pectin (HMP) and low methoxy pectin (LMP) based on the degree of esterification of the semi-lactobacillic acid residues. High methoxy pectin has a degree of esterification greater than 50%, while low methoxy pectin has a lower degree of esterification. LMP has been found to reduce intestinal inflammation, while HMP can alleviate overall and local inflammations.[281] The degree of esterification also affects the hydrophobic, viscosity, and molecular weight of the pectin. Researchers have investigated the impact of different degrees of esterification on drug encapsulation and observed that as the degree of esterification increases, the particle size of nanoparticles also increases, the zeta potential decreases, and the efficiency of drug encapsulation improves with better thermal stability.[282] However, the excellent water resistance of HMP can lead to poor drainage properties. To overcome this, researchers have discovered that combining HMP with surfactants can enhance drug encapsulation efficiency by introducing hydrophobic groups to the delivery carrier.[283]

The anticancer efficacy of pectin is primarily achieved through its ability to inhibit tumor cell growth, induce apoptosis (cell death) in tumor cells, and suppress tumor cell migration.[284] Pectin can be formulated into various drug preparations, such as films,[285] gels,[286] microspheres,[287] nanoparticles,[288] and pearls,[289] to facilitate targeted drug delivery and sustained release. These different formulations provide versatile options for the administration of anticancer agents and hold promise for the treatment of cancer.

Pectin is a natural ligand for hepatic cells, and sorafenib (SF) is a standard therapeutic drug for hepatocellular carcinoma (HCC). However, SF has poor water solubility. Jaleh Varshosaz et al[290] developed pectin-deoxycholic acid (P-DOCA) copolymeric micelles loaded with SF using pectin. This formulation enabled targeted delivery of SF through intravenous injection. While nanoparticles can enter tumor cells through the EPR effect, their cellular uptake rate is often low. Prolonging the circulation time in the bloodstream is a strategy to increase drug accumulation in tumor tissues. Researchers coated pectin-doxorubicin conjugates (PDC-NPs) with red blood cells in a biomimetic fashion, which effectively improved the stability and cellular uptake of PDC-NPs.[283] Moreover, the semi- lactic acid residues of pectin

can target the asialoglycoprotein receptors (ASGPRs) on liver cancer cells, thereby enhancing targeted therapy for hepatocellular carcinoma.[281]

Dietary pectin's anti-cancer applications are primarily focused on the treatment of colorectal cancer due to its ability to inhibit the growth of harmful bacteria.[284] However, pectin exhibits significant swelling characteristics, which can lead to premature and complete drug release, limiting its use.[281] The abundant functional groups in pectin, such as hydroxyl, carboxyl, and amide groups, provide possibilities for its modification. In order to enhance the application of pectin in cancer treatment, researchers have explored various modification techniques, including chemical modification,[291] ultrasound,[292] heat treatment, irradiation,[293,294] and enzyme treatment.[295] One of the modified pectin derivatives, pH-modified citrus pectin (MCP), has shown excellent anti-cancer efficacy in the treatment of various cancers such as breast cancer, gastric cancer, colorectal cancer, and pancreatic cancer.[296]

The potential of pectin as an anti-cancer drug delivery system cannot be overlooked; however, there are still some challenges that need to be addressed. The structure of pectin is complex, and pectin extracted from different sources and using different extraction processes can exhibit structural variations.[297] These structural differences also lead to variations in functionality. Achieving consistent structural and functional properties of pectin requires further improvement and optimization of the preparation processes. Furthermore, while numerous studies have demonstrated the superiority of pectin and its derivatives in the treatment of colorectal cancer, their effectiveness, mechanisms, and pharmacokinetics in other types of cancer still require further investigation. More research is needed to explore the potential of pectin in these areas.

Carrageenan

Carrageenan, a type of marine anionic polysaccharide predominantly found in red algae, are sulfated polysaccharides composed of alternating 3-β-D-galactopyranose (G-units) and 4-linked α-D-galactopyranose (D-units) or 4-linked 3,6-anhydro-α-D-galactopyranose (DA-units) repeat disaccharide units. Depending on the variations in the position and quantity of DA units and sulfate groups, carrageenan can be classified into several distinct structural types. The three most common types are kappa (κ-), iota (ι-), and lambda (λ-) carrageenan. The solubility of carrageenan is associated with the presence of sulfate groups and cation content, allowing it to form highly viscous solutions in water. As a result, carrageenan is widely used as a thickening and gelling agent in the food and pharmaceutical industries. Due to its remarkable gelling properties, excellent biocompatibility, and degradation characteristics, carrageenan plays a significant role in the field of drug delivery, particularly as an oral drug matrix or in localized drug delivery systems.[298] Furthermore, carrageenan exhibits antioxidant, anti-proliferative, and anti-tumor activities, making it useful as an anti-cancer adjuvant, immunostimulant, and antimutagen.[299] It can also be formulated into beads[300] or microspheres through electrostatic or chemical interactions with drugs for cancer drug delivery purposes.[301]

The application development of carrageenan in cancer treatment is still in the preclinical research stage, primarily due to the lack of clear understanding regarding its mechanism of action in regulating the tumor microenvironment. Further in-depth investigations are necessary to elucidate its potential role in cancer therapy.[302] And studies have suggested that carrageenan may induce inflammation in the gastrointestinal tract, leading to intestinal lesions and impairments in gut barrier function. Additionally, carrageenan's sulphate groups may interact with proteins in the blood, potentially affecting blood clotting mechanisms and platelet function.[303]

Lignin

Lignin is a three-dimensional, amorphous, non-linear biopolymer composed of phenolic units, primarily found in the secondary cell walls of plants. It is one of the most abundant natural polymers on Earth, second only to cellulose in terms of phosphorous content. Lignin can be extracted through various processes, resulting in four main types: Kraft lignin (KL), soda lignin, lignosulfonate, and organic solvent lignin.[304]

Lignin exhibits a wide range of pharmacological properties, including antioxidant, antibacterial, anti-inflammatory, intestinal, immunosuppressive, and anti-tumor activities, which contribute to its increasing importance in the field of medicine.[304] Its anti-cancer effects are attributed to its ability to eliminate free radicals from the tumor microenvironment and induce high levels of reactive oxygen species (ROS), resulting in the death of cancer cells. This property also enables

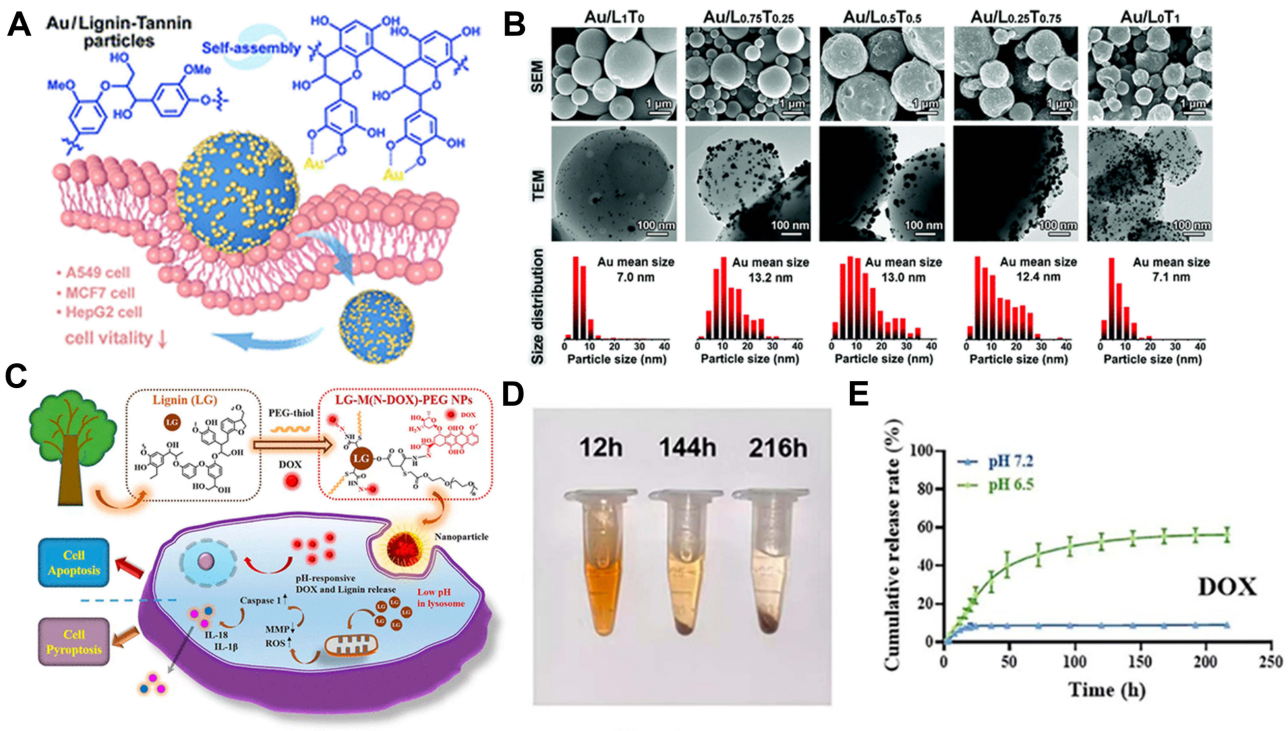

Figure 12 Delivery strategies and applications of lignin-based delivery carriers (**A**) Schematic of the Synthesis Route of Au/lignin–tannin particles. (**B**) SEM and TEM images of Au/LT particles, and size distribution of Au particles. Used with permissions of Royal Society of Chemistry, from Synthesis of Au/lignin–tannin particles and their anticancer application, Jiang Z, Duan J, Guo X, Ma Y, Wang C, Shi B, 23, 18, 2021; permission conveyed through Copyright Clearance Center, Inc..[307] (**C**) Schematic of the Synthesis Route of LG-M(N-DOX)-PEG Copolymer and illustration of the dual pH-responsive LG-M(N-DOX)-PEG NPs. (**D**)Digital photo of LG-M(N)-PEG solution after the release of lignin for different times at pH = 6.5. (**E**) In vitro release profiles of DOX from LG-M(N-DOX)-PEG NPs at different pH values (6.5 and 7.2). Adapted with permission from Yang Z, Zhou Z, Li Y, et al. Assessing the Potential of New Lignin-Based pH-Responsive Nanoparticles as Drug Carriers for Cancer Treatment. ACS Sustainable Chem. Eng. 2022;10(32):10590–10603. Copyright© 2022 American Chemical Society.[308]

lignin to be utilized as a carrier for anti-cancer drugs.[305] For instance, Zhou et al[306] developed a nanostructure by linking lignin with β-rings as shown in Figure 12A and B, which effectively encapsulated the anti-cancer drug HCPT and demonstrated significant inhibition of Hela cell growth. Furthermore, researchers have leveraged the benzene ring structure present in lignin, which exhibits self-assembly properties through π-π interactions.[307] This composite structure demonstrated significantly improved loading capacity for Au nanoparticles and enhanced restorative properties. The anti-cancer effects of the Au/lignin-tannin (TL) composite nanoparticles were evaluated through toxicity trials on HepG2 cells, MCF7 cells (a breast cancer cell line), and A549 cells (a human lung cancer cell line). The results confirmed the anti-cancer activity of the Au/TL composite nanoparticles, highlighting their potential in cancer treatment.

Moreover, the surface properties of lignin can be further modified to enhance its performance. Researchers have developed a method to prepare lignin nanoparticles coated with thermogen and modified with mUNO,[309] which acts as a double stimulant targeting the TLR7/8 toll-like receptor and as an M2 pattern-like cell marker, respectively. This modified lignin nanoparticle system has the ability to induce polarization of tumor-associated macrophages from the M2 to M1 phenotype. Consequently, it exerts a destructive effect on tumor cells, showcasing its potential for tumor-targeted therapy.

In addition, researchers have performed chemical modification on lignin by introducing hydrazine and β-thiopropionate ester bonds into its structure, imparting pH-responsive properties.[308] These modified lignin nanoparticles were then loaded with the anti-cancer drug DOX to investigate their efficacy in cancer treatment, which is schematically depicted in Figure 12C. In vitro experiments demonstrated that the prepared nanoparticles exhibited drug release at pH 6.5 while showing minimal release at pH 7.2 (Figure 12D and E). Furthermore, cell studies revealed that LG-M (N-DOX)-PEG NPs exhibited non-toxicity towards normal cells and inhibited the growth of tumor cells. Compared to free DOX, the

nanoparticles exhibited higher cellular uptake rates. In vivo, tumor models also demonstrated that the nanoparticles had superior tumor inhibitory effects compared to free DOX and saline injections alone.

Lignin-based nanoparticles and hydrogels have been explored as promising drug delivery systems due to their biocompatibility, biodegradability, and tunable properties. As research in this area progresses, more efforts are expected to be dedicated to overcoming the challenges associated with lignin-based materials and unlocking their full potential in cancer therapy. Future developments may focus on optimizing lignin extraction methods, elucidating its degradation pathways in vivo, and exploring novel strategies for functionalizing lignin-based drug delivery systems.[310]

Others

Sodium alginate, a natural polysaccharide derived from seaweed,[311] has also been investigated for its potential in the delivery of anti-cancer nanomedicines. Huang et al[312] designed a biotinylated nano-micelle system loaded with DOX using the self-crosslinking properties of sodium alginate for the treatment of hepatocellular carcinoma. This nano-micelle system utilized the immune properties of sodium alginate in combination with DOX to synergistically inhibit tumor cells, while the biotin moiety targeted tumor cells. In vitro and in vivo experiments demonstrated that the biotinylated nano-micelles exhibited enhanced targeting efficiency, and the combination of sodium alginate and DOX exhibited improved cytotoxicity against tumor cells. However, research on sodium alginate as a drug delivery carrier for anti-cancer therapy is still relatively limited. This could be attributed to the large molecular weight, complex structure, low bioavailability, and unclear impact on the body's mechanisms associated with natural sodium alginate. Some studies have suggested that low molecular weight sodium alginate exhibits better biocompatibility compared to high molecular weight sodium alginate. Furthermore, it possesses anti-inflammatory, antioxidant, antimicrobial, and anticancer properties, making it a promising candidate as a novel delivery carrier.[313]

Plant gums can serve as immunoadjuvants.[314] There is a wide variety of natural plant gums that find extensive applications as diluents, adhesives, emulsifiers, thickeners, and more. Common examples of plant gums include gum Arabic (GA), gellan gum (GG), xanthan gum, guar gum, tragacanth gum (TG), gum ghatti (GGH), and cashew tree gum (Anacardium occidentale L.), among Others. Among these, gum Arabic is the most widely used.[315] Gum Arabic is a polysaccharide of mixed nature derived from the Acacia tree.[316] It exhibits excellent biocompatibility, high water solubility, and abundant functional groups, allowing for drug loading through conjugation. Additionally, the targeting effect of the galactose unit facilitates drug delivery to liver cancer cells.[317] Oxidation is a common modification technique for polysaccharides. N. S. El-Sayed et al[318] have oxidized gum Arabic, introduced aldehyde groups, and then conjugated 9-aminophenanthrene (9-AA) via Schiff's base formation to achieve pH-responsive drug release. Composite carriers have shown improved functional characteristics compared to pure delivery vehicles. By combining maize prolamin with gum Arabic. J. Jin et al[319] have developed maize prolamin-GA-EGCG composite nanoparticles. The presence of gum Arabic significantly enhances the loading efficiency compared to maize prolamin-EGCG nanoparticles. Z. Feng et al[320] have directly incorporated 2-acrylamido-2-methyl-propanesulfonic acid (AMPS) onto xanthan gum, enabling the presence of disulfide bonds in the nanoparticles to achieve stimulus-responsive release of glutathione, thereby achieving targeted drug delivery and controlled release.

In summary, natural polysaccharides exhibit excellent biocompatibility, remarkable biodegradability, low biotoxicity, and an abundance of bioactive functional groups, all of which make them stand out as promising candidates for cancer drug delivery carriers. The rich functional groups of natural polysaccharides have created a great variety of polysaccharide derivatives, and the principles of common modifications of natural polysaccharides are shown in the Figure 13. We have summarized the characteristics of the listed polysaccharides and potential improvement strategies in Table 10. While each type of polysaccharide may have its limitations, effective enhancements can be achieved through chemical modification or modification methods.

Liposomes

Liposomes represent a distinct class of biopolymers, exhibiting a bilayered or multilayered spherical vesicular structure primarily composed of amphiphilic phospholipids and cholesterol. Liposomes are clinically recognised as delivery carrier for anticancer drugs, and most of the anticancer nano-formulations currently approved by the FDA are liposome-based.

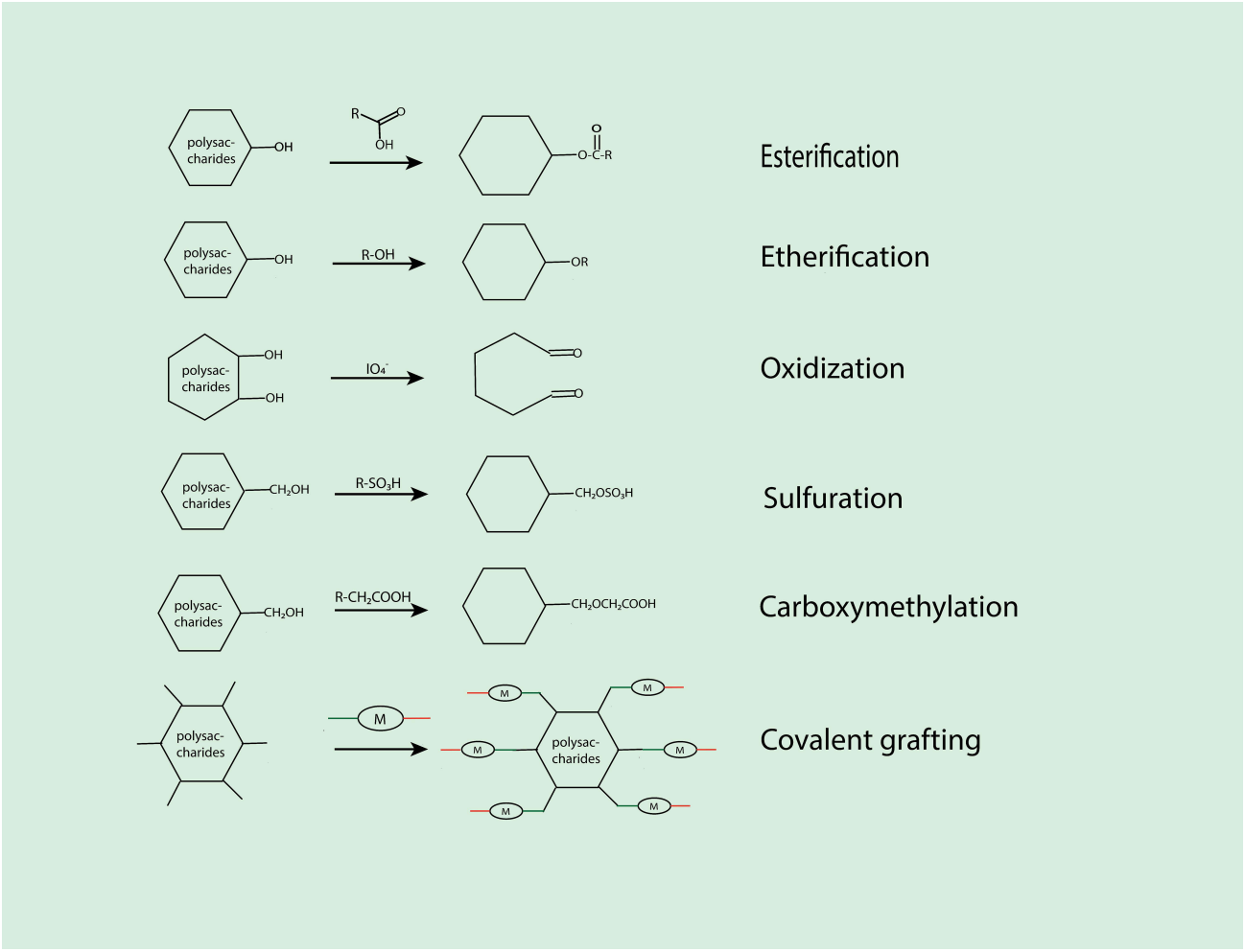

Figure 13 Schematic of the principles of polysaccharide modification methods.

Primary liposomes are mainly composed of phospholipids and cholesterol, and such unmodified liposomes have significant drawbacks, including inefficient loading of hydrophilic drugs, easy leakage of drugs from liposomes, and rapid clearance of liposomes by the RES in the blood circulation.[321] In order to prolong the circulation time, hydrophilic polymers coated with polyethylene glycol are effective in avoiding RES clearance, such as Caelyx, Myocet, and Doxil. However, these long-circulating liposomes also exhibit some disadvantages, such as low cellular uptake, the fact that these liposomes are mainly used for passive targeting to the tumor site, poor selectivity in cancer cells, and the limited space for loading the drug inside the liposome. Nowadays, the research on liposome formulations mainly focuses on the direction of improving targeting, drug-carrying performance and overcoming drug resistance, and the main strategy is to carry out surface modification,[322] as shown in the Figure 14.

Surface modification mainly includes, (1) incorporating functional fragments into liposomes; (2) Applying functional coatings on the surface, typically involving polymers such as PEG or targeting ligands like hyaluronic acid; (3) modifying surface charge; (4) conjugating targeted peptides or proteins onto the surface. Additionally, liposome modification may involve dual-carrier systems or combination therapy approaches, further expanding the versatility and efficacy of liposomal formulations. Vidhi M. Shah et al utilized sphingomyelin cholesterol (SPM/Chol) liposome preparation CPD100Li loaded with periwinkle alkaloids alongside an ion carrier (A23187) for treating ovarian cancer.[323] Their findings indicated that the presence of A23187 effectively enhanced the stability of the liposomes and prolonged in vivo circulation time. In another study, a hypoxia-sensitive liposome drug delivery system was developed by incorporating a nitroimidazole derivative (a nitroaromatic) into the phospholipid bilayer of liposomes.[324] This system exhibited

Table 10 Characterizations of Polysaccharide-Based Nanodelivery Carriers and Modification Methods

Types of Natural Polysaccharides	Target Receptor	Advantages	Disadvantages	Modification Methods
Chitosan	–	• Natural linear cationic polysaccharide • Good biocompatibility • Adhesive properties, can be used for oral drugs. • Increased solubility in acidic environments, can be used for PH-responsive drug release	• Poor water solubility, • some cytotoxicity	• Thiolated to improve adhesion properties • Carboxymethylation for amphiphilicity • Methylation to improve water solubility • Glycolisation to prolong blood circulation
Starch	–	• Degradable • Stable • Widely available	• Easy to aggregate and swell • poor resistance to enzymatic degradation	• Hydroxyethylation, unique pharmacological effects • Carboxymethylation, PH sensitivity
Cellulose	–	• The most abundant in nature; • Drug carriers based on cellulose and its derivatives can be loaded with small molecules through physical interactions such as hydrophobic and hydrogen bonding as well as chemical modes such as covalent linkages.	• Water-insoluble	• Hydroxypropyl cellulose (HPC) by propylene oxide modification or carboxymethyl cellulose (CMC) by carboxymethylation
Dextran	Targeted anti-cancer antibody CR3	• Electrically neutral polysaccharide • Excellent biosafety • Molecular structure with a large number of free hydroxyl groups, easy to be chemically modified	• Side effects such as thrombocytopenia and hepatotoxicity	• Esterification • Etherification • Oxidation
Hyaluronic acid	CD44, RHAMM	• Good biodegradability and targeting properties	• Accumulates in the liver and is easily degraded in vivo	• Coating for other delivery vehicles
Fucoidan	P-selectin	• Anti-tumor • Immunomodulatory • P-selectin targeting	• Uniform source • Large structural differences	• Graft copolymers
Lignin	–	• Molecules with amphiphilic character • Antioxidant and UV-resistant properties, as well as good antimicrobial activity	• Heterogeneity of natural lignin • The extraction process introduces toxic chemical reagents • Biocompatibility mechanisms are not yet fully understood • Large particle size, non-homogeneity, poor dispersion and irregular morphology	• Hydroxyl group functionalization • Graft copolymers
Carrageenan	–	• Negatively charged • High viscosity in water for oral drug delivery • Anticoagulant, Anticancer, Antihyperlipidemic and Immunomodulatory activities	• Easily degraded • Lacks drug delivery mechanism • Does not have any cell binding sites	• Graft copolymers • Persulfated, Desulfated, Acetylated and Phosphorylated
Pectin	–	• Non-toxic • Easily degradable • Anti-inflammatory, Antioxidant, Anticancer • Can target hepatocytes	• Possesses significant solubility	• Alkaline modification • Sulphated, Acetylated and Phosphorylated

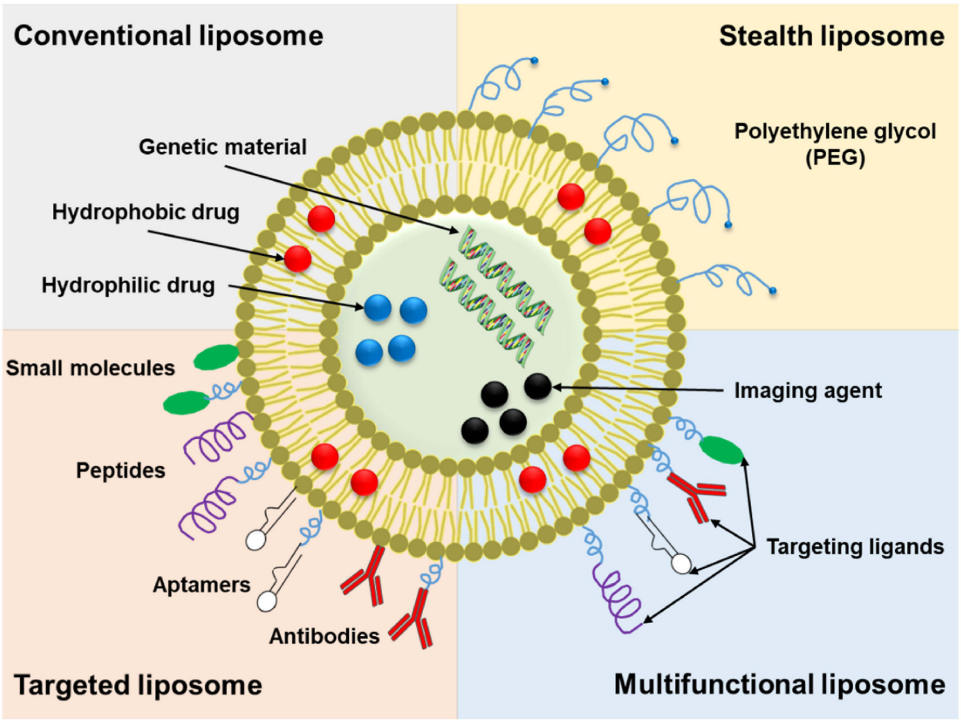

Figure 14 Liposomes and the way liposomes are modified. Adapted with permission from Nel J, Elkhoury K, Velot É, et al. Functionalized liposomes for targeted breast cancer drug delivery. Bioact. Mater. 2023;24:401–437. https://creativecommons.org/licenses/by-nc/4.0/).[322]

oxygen-dependent drug release, effectively triggering drug release in hypoxic conditions. The system demonstrated efficacy in treating CDX (cell line-derived xenograft) and clinically relevant PDX (patient-derived xenograft) models. PEG is a commonly used modifier for liposome surface modification, which can effectively prolong the cycling time of liposomes but lacks targeting. Yang Wang et al conjugated a pH-responsive cell-penetrating peptide (TH peptide) in tandem with a tumor-targeting RGD motif to form a TH-RGD on the surface of PEGylated liposomes.[325] They co-loaded the autophagy-inhibiting drug hydroxychloroquine (HCQ) and anticancer drugs within these liposomes. Their smart delivery system, capable of charge reversal under acidic conditions, demonstrated selective and effective internalization. Polysaccharides exhibit excellent biocompatibility and can effectively improve liposomal carrier stability when used as a coating. The choice of coating can be tailored to specific requirements. For instance, hyaluronic acid possesses tumor-targeting properties and can serve as a targeting coating. Chitosan exhibits pH-responsive characteristics, making it suitable for use as a stimulus-responsive coating.[326,327] Carrageenan is capable of resisting gastric acid digestion, aiding liposomes in traversing the gastrointestinal system.[328] Additionally, pectin demonstrates anti-tumor activity and enhances liposome stability.[329] Cholesterol is a crucial component of most lipid nanocarriers and plays a pivotal role in determining the surface properties of liposomes. Research has demonstrated that smaller particle size can mitigate RES clearance and improve tumor penetration. The analogue cumaric acid (AA) is a cholesterol analogue, and researchers compared DOX-encapsulated AA liposomes (DOX-AALip) with conventional liposomes (DOX-Lip), and found that DOX-AALip exhibited smaller particle size and higher rigidity, which significantly prolonged liposome circulation time, and accumulated more in primary tumors and lung metastases.[330]

The latest research on liposomes is organized in Table 11. Liposome-based anticancer drugs, while already in clinical use, are not without limitations. These include biological instability, immune responses, lack of tissue specificity and targeting, as well as the complexity and high cost of the preparation process.[331] Therefore, there is a pressing need for continued exploration of new and alternative options in cancer treatment.

Table 11 Liposome Nanodelivery Systems for Cancer Therapy

Type of Nanosystems	Loaded Drugs	Diameter (nm)	Zeta Potential (mV)	PDI	Functional Modifications	Aimed Cells	Aimed Tumor	Animal Models	Ref
Hypoxia-sensitive liposome	Vinblastine-N-oxide (CPD100)	142±4.16	155.4 ± 4.2	0.11 ±0.005	A23187	ES2 cells	Ovarian cancer	Female Swiss Webster mice	[323]
Hypoxia-sensitive liposome	DOX	181 ± 3	−34.4 ± 1.3	0.34 ± 0.07	Nitroimidazole derivative,	RM-1, FaDu cells	Hypoxic tumor	Cell line and patient-derived xenograft	[324]
Liposome	DOX	92.2±0.4	−16.3	0.21±0.01	Albumin-binding domain (ABD)	4T1	Breast cancer	Mice bearing 4 T1 tumors	[332]
PH-sensitive liposome	HCQ, DOX	121.89±1.59	pH 7.4, −4.36 ± 0.16, pH 6.5, 12.12 ± 0.08	–	TH peptide, RGD	B16F10, MCF-7	–	B16F10 xenograft-bearing mice	[325]
GSH- sensitive liposome	DOX	65.2 ± 5.7	−14.6 ± 3.3	–	GSH	BxPC3, Huh7	HCC\ poorly permeable pancreatic tumors	Mice bearing subcutaneous BxPC3 tumors	[333]
MMP sensitive liposome (Cleavable)	DOX	140	−17.6 ± 0.6	0.059 ± 0.025	PEG	PC3 cells	–	PC3 cells derived xenograft	[334]
Liposome	DOX	–	–	–	Nanobowl	4T1	Breast tumor	Orthotopic 4T1 breast tumor mouse model	[335]
Dual-layered Au-liposome	–	72.84±22.49	−17.7	–	64Cu\PEG	4T1	–	Orthotopic 4T1 breast tumor mouse model	[336]
Targeting liposome	PTX	112.5±4.1	−34.4±0.8	0.25 ±0.009	Ginsenosides	BGC-823	Gastric cancer	BGC-823 cells derived xenograft	[337]
Thermosensitive magnetic liposomes	Irinotecan, Fe3O4	193.7 ± 2.3	2.3 ± 0.1	0.22 0.01	CET	U87 cell	Brain tumor	U87 cells derived xenograft	[338]
PET imaging liposomes		129.0 ± 2.2	−16.53 ± 1.3	–	Glucose- and DOTA-Cu2+	A431	–	A431 derived xenograft	[339]
Targeting liposome	DTX	96.7±4.5		–	Ginsenoside Rg3	4T1	TNBC	Orthotopic TNBC model	[340]
Liposome	Clodronate	101.8±24.4	− 21 ± 5.04	0.2		4T1 cells	4T1 breast cancer-bearing mice	–	[341]
Liposomes with targeted	Photochlor (HPPH)\ evofosfamide	128.7 ± 75.0	29.97 ± 3.5	–	Chitosan oligosaccharide	MDA-MB-231	TNBC	MDA-MB-231 tumor model	[342]

Dual-Targeting liposome	Cabozantinib\ IDO	115.53±2.35	0.14±0.01	115.53 ±2.35	–	4T1	TNBC	TNBC xenograft-bearing mice	[343]
Liposome	DOX	200	–	–	Holo-Lf	4T1	–	4T1 xenograft-bearing mice	[344]
Liposome	ASOs	150 ± 36	−6.67 ± 0.18	0.0838	Tumor-penetrating peptide, iRGD	22Rv1, LNCaP, and VCaP	Bone metastasis model, 4T1 orthotopic tumor model	–	[345]
Liposome	DMC	40	–	–	Pyrophaeophorbid	CT26	Mice bearing CT26 tumor	Colorectal cancer	[346]
PH-sensitive liposome	UA	135.4 ± 0.636	7.8	0.3	Chitosan	U14cell			[326]
Targeting liposome	HAPO-1048, IR-1048	135.2	–32.97±2.36	–	HA	UM-UC-3	Bladder cancer	Orthotopic BC model	[347]
Targeting liposome	Honokiol	162.6 ± 3.8	−38.24	0.26 ± 0.02	HA	4T1 cells	Breast cancer	4T1 tumor-bearing mouse model	[348]

Abbreviations: HCQ, hydroxychloroquine; GSH, glutathione; CET, Cetuximab; DTX, docetaxel; TNBC, triple-negative breast cancer; IDO, Indoleamine 2,3-dioxygenase; Holo-Lf, holo-lactoferrin; ASOs, antisense oligonucleotides; HCC, hepatocellular carcinoma; ASOs, antisense oligonucleotides; DMC, demethylcantharidin; UA, ursolic acid.

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Summary and Prospect

The medical application of nanotechnology has revitalized medical research, particularly in the field of tumor therapy, by overcoming the limitations of traditional treatment modalities. This has spurred researchers' enthusiasm for exploring the potential of nanomedicine in cancer treatment. The efficacy of anti-cancer nanomedicines primarily relies on the delivery carrier, and researchers have successfully designed numerous synthetic nanocarriers that exhibit excellent drug-loading capacity and targeting capabilities. Biopolymers, as delivery carriers for tumor-targeted nanodrugs, offer inherent advantages such as biocompatibility, biodegradability, and low toxicity, making them highly promising in this context. However, there are still unresolved challenges associated with the sourcing and purification of biopolymers. Different sources of biopolymers exhibit structural variations that can influence their functional properties. Synthetic biopolymers, designed to mimic natural counterparts, often fall short in terms of functionality. Therefore, the development of an effective purification process is crucial to advance the field of biopolymer-based anti-cancer nanomedicines. We have summarized the characteristics and improvement methods for natural biopolymers (proteins, polysaccharides, liposomes), as detailed in the Table 12.

Proteins have several advantages as anticancer drug delivery vehicles. Firstly, their natural origin ensures excellent biocompatibility and degradability, thereby reducing the risk of adverse effects during drug delivery. Secondly, certain proteins have innate targeting ability and specificity, enabling them to facilitate targeted drug delivery to tumors tissues or cells, thereby improving efficacy. Finally, the presence of functional groups on proteins enables facile modification, opening avenues for the development of multifunctional therapeutic strategies tailored to specific cancer types or patient needs. There have been successful examples of clinical applications of proteins as delivery vehicles, but so far only one protein has been commercialised for cancer drug delivery. The primary challenge hindering widespread adoption is the inherent instability of proteins, which are susceptible to degradation by enzymes and clearance by the immune system in the body. To address this issue, researchers have explored various strategies to enhance the stability and delivery performance of proteins, including modifications and optimization of the manufacturing processes. However, structural modifications may impact protein functionality and, in some cases, lead to denaturation, reducing binding sites and potentially eliciting immunogenic responses. Additionally, proteins derived from animal sources pose risks of disease transmission.

Natural polysaccharides offer significant potential in oncology therapy due to their diverse properties and interactions with biological systems. These biopolymers, with their antioxidant, anti-inflammatory, and anti-tumor properties, can serve as effective delivery carriers or coatings for anti-cancer drugs. Polysaccharides bind to pattern recognition receptors (PRRs) on

Table 12 Characteristics and Improvement Strategies of Biopolymer-Based Nano-Anti-Cancer Delivery Drugs

Types of Biopolymers	Advantages	Disadvantages	Improvement Strategies
Proteins	• The main components are amino acids, biocompatible • Non-toxic and non-immunogenic • High uptake rate • With functionalize sites • Suitable for delivery of protein-based and gene-based drugs • Long in vivo circulation time • Can be preferentially up taken in tumor tissues	• Poor stability • Limited drug compatibility • Poor targeting	• Association with polymer molecules to improve stability • Modification by small molecule peptides or compounds to enhance targeting • Optimization manufacture process
Natural polysaccharides	• Abundance and sustainability • Versatility • Targeting specificity • Good biocompatibility and biodegradability • Immunomodulatory effects	• Complexity of modification • Heterogeneity • Potential immunogenicity • Regulatory challenges related to safety, efficacy, and quality control	• Protein or targeting molecule modification to improve targeting • Chemical modification or combination with inorganic metal materials
Liposomes	• Good drug-loading performance • Biocompatible and Biodegradable • Flexibility in formulation	• Instability • Short shelf-life • Immunogenicity • Difficulty in targeting specific tissues	• Encapsulation of biomolecules • Surface modification • Incorporation of other agents

cell membranes, such as scavenger receptors (SRs), Toll-like receptors (TLRs), complement receptor 3 (CR3), C-type lectin receptors (CLRs), and mannose receptors (MRs), triggering intracellular signaling cascades that mediate cellular physiological mechanisms, including activation of the immune response.[349] Different cancers and tumor microenvironments present unique challenges, and natural polysaccharides can be tailored accordingly. For instance, drug delivery systems for the colon require resistance to absorption and degradation in the upper gastrointestinal tract, making polysaccharides like starch, fiber, and pectin suitable candidates due to their high acid resistance. In contrast, drug delivery systems for the gastrointestinal tract need pH release properties.[350] Chitosan, for example, interacts with gastric mucosa via hydrogen bonding, non-covalent bonding, electrostatic interaction, and hydrophobic interaction, enhancing its adhesion to the mucin in gastric mucosa.[351] This property enables targeted therapies, ensuring precise delivery of drugs to affected areas. Moreover, certain polysaccharides possess inherent tumor-targeting properties, enhancing delivery efficiency, therapeutic accuracy, and reducing systemic damage.[352] Hyaluronic acid and fucoidan, for instance, can target proteins expressed in tumor tissue or activate macrophages in the tumor microenvironment, improving the efficacy of drug delivery systems. Polysaccharides exhibit anticancer properties primarily through scavenging free radicals and modulating the immune microenvironment. Examples include dextran and lignans, which possess antioxidant and immunomodulatory effects. Additionally, most natural polysaccharides carry a negative charge, enabling them to serve as effective delivery carriers by avoiding rapid clearance in vivo. Moreover, their abundance of functional groups allows for further enhancement of their types and functions through modification or branching polymers. Polysaccharides can also be utilized to coat liposomes, enhancing their targeting and stability while conferring specific functions. Examples of polysaccharides used for liposome coating include chitosan, hyaluronic acid, and glucose. This coating enhances the efficacy of liposomal drug delivery systems, providing targeted and stable delivery of therapeutic agents. However, the clinical application of polysaccharide-based anticancer drugs faces several challenges. Firstly, the reliance on the tumor microenvironment's heterogeneity for polysaccharide-based nanotherapies is hindered by its limited significance, leading to non-specific drug accumulation in normal tissues. Secondly, although polysaccharide-based drugs possess inherent targeting abilities and anticancer properties, the specific mechanisms of action are yet to be elucidated. Thirdly, the potential toxicity of polysaccharide-based drugs to other tissues or organs is uncertain and requires further investigation. Additionally, the degradation and circulation mechanisms of these drugs within the body are not well-defined, lacking reliable data on the absorption or excretion of degraded small molecules. Lastly, limited research on the pharmacokinetics of polysaccharide-based drugs, often confined to preclinical animal models, hinders conclusive evidence of their equivalent therapeutic effects in humans, thereby restricting their clinical application.

Unlike proteins and polysaccharides, liposomes possess a straightforward structure, and their preparation process is amenable to industrialization. The numerous clinical applications of liposomes in nanomedicine highlight their significance in anticancer therapeutics. PEGylated liposomes effectively enhance the circulation duration of liposomes. However, they also disrupt the binding of drugs to cancer cells. Moreover, liposomes lack tumor-targeting capabilities and exhibit instability, resulting in premature drug leakage.

Despite these unresolved issues, the advantages of biopolymers remain significant. Presently, a common strategy involves addressing the limitations of delivery carriers through modification or combining them with other carriers. For example, in the combination of liposome with protein/polysaccharide, liposomes serve to encapsulate the drug, proteins extend the circulation time of liposomes, and polysaccharides enhance the stability of liposomes or improve their targeting capabilities. Similarly, in the combination of protein with polysaccharide, polysaccharides enhance the drug loading and release profile, while proteins aid in targeting enhancement or circulation time improvement. In the future, as research progresses, an increasing number of biopolymer-based nanomedicines are anticipated to be employed in cancer treatment.

Conclusion

This article provides an overview of the current research status and limitations of biopolymer-based nanocarriers for tumor drug delivery. Current nanomedicine delivery strategies primarily rely on the passive targeting strategy of the EPR effect in tumors. However, the delivery efficiency is low, which hinders the clinical application of anticancer nanomedicines. Biopolymers stand out as promising candidates for anticancer nanodrug delivery carriers due to their excellent biocompatibility. Moreover, some biopolymers possess inherent ligands on the surface of human cells, enabling active targeting capabilities. These properties offer potential solutions to overcome the limitations of current delivery strategies based on

the EPR effect. The heterogeneity of the tumor microenvironment and the limited differences from normal tissues make solely relying on the EPR effect insufficient for achieving effective targeting.

As with any emerging field of science, the clinical translation of biopolymer-based nanomedicines in cancer therapy faces several challenges and barriers. Looking ahead, the future development of biopolymer-based anticancer drugs can be approached in several ways:

1. Safety and Standardization: Given their biological origin, ensuring the safety and standardization of the preparation process for biopolymer-based agents is paramount. While liposome-based drugs are relatively simpler to prepare and have seen FDA approval, proteins and natural polysaccharides sourced from diverse origins pose challenges in standardization. Establishing standardized processes not only ensures safety but also facilitates industrial-scale production.
2. Comprehensive Studies on Efficacy and Toxicology: There is a need for comprehensive studies to assess the efficacy, tissue uptake, pharmacokinetics, and potential toxicological risks of biopolymer-based nanomedicines in vivo. Preclinical studies often rely on mouse models, but variations in the immune system between species can limit the extrapolation of results to clinical settings. Robust data from diverse models are necessary to support clinical applications.
3. Multimodal Therapy: Multimodal therapy, combining different therapeutic modalities, is a growing trend in nanomedicine. Biopolymer-based nanomedicines should be developed with a multifunctional and multimodal therapeutic approach in mind. Co-delivery of synergistic drug combinations can overcome multidrug resistance mechanisms and enhance therapeutic efficacy compared to monotherapy.[353]

We believe that with continued advancements and successful clinical applications, biopolymer-based nanomedicines hold promise as effective tools in cancer therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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