



REVIEW ARTICLE

NANOCARRIER SYSTEMS FOR TARGETED CANCER THERAPY: RECENT ADVANCES AND TRANSLATIONAL PERSPECTIVES

Egno Gerald Komba¹ , Said Salim Said^{*2} , Febronia Mkama Alphonc¹ 

¹Jagiellonian University Medical College, Kraków, Poland.

²Zanzibar Food and Drug Agency, Zanzibar, Tanzania.

Article Info:



Article History:

Received: 3 February 2026

Reviewed: 11 March 2026

Accepted: 17 April 2026

Published: 15 May 2026

Cite this article:

Komba EG, Said SS, Alphonc FM. Nanocarrier systems for targeted cancer therapy: Recent advances and translational perspectives. Universal Journal of Pharmaceutical Research 2026; 11(2): 73-87.

<http://doi.org/10.22270/ujpr.v11i2.1543>

*Address for Correspondence:

Said Salim Said, Zanzibar Food and Drug Agency, Zanzibar, Tanzania.

Tel: +255-777594 373

E-mail: saidalriyamy67@gmail.com

Abstract

Cancer is one of the major concerns in the world today, and it accounts for almost 20 million new cases and 10 million deaths annually, leading to significant disability-adjusted life years lost. The total incidence of lung, breast, colorectal, prostate, and stomach cancer accounts for almost half of the total cancer incidence cases worldwide. The burden of cancer is high in low- and middle-income countries, where the mortality and incidence rate is high due to delayed diagnosis and lack of access to efficient treatments. The burden of cancer is expected to rise in the future due to the increasing population and the aging population in the world, and cancer incidence rates are expected to rise in the year 2040 in resource-constrained countries. The burden of cancer is related to cancer types and their association with certain preventable factors and infecting agents; however, the incidence rate of cancer types is escalating, and hence, precise and efficient cancer therapies are the need of the hour. The limitation in traditional cancer therapies, such as chemotherapy, is systemic toxicity, lack of specificity of drugs, and low drug bioavailability, and hence, cancer therapies using nanotechnology show immense promise, especially drug delivery systems such as liposomes, polymeric nanoparticles, dendrimers, micelles, solid lipid nanoparticles, and inorganic nanoparticles. The review aims to critically discuss the construction of nanocarriers, cancer cell targeting, and cancer therapy, and the challenges in cancer nanotherapy.

Keywords: Cancer therapy, polymeric micelles, stimuli-responsive nanoparticles, targeted drug delivery.

INTRODUCTION

Cancer, a significant global health issue, still ranks as one of the leading causes of morbidity and mortality. According to the most recent available statistics, nearly 20 million new cancer cases are diagnosed annually, and mortality from cancer reaches as high as 9.7 to 10 million, or approximately 14 to 15% of total deaths worldwide, contributing substantially to Disability-Adjusted Life Years (DALYs)¹⁻³. A small number of cancer types are responsible for a significant number of cancer cases. Breast cancer in women, lung, colorectal, prostate, and stomach cancer combined account for nearly half of all new cancer cases. In terms of cancer mortality, lung cancer leads, followed by colorectal, liver, breast, and stomach cancer, in that order⁴. Although incidence rates are higher in high-income or “transitioned” countries, the outcomes are worse in low- and middle-income countries, where mortality-to-incidence ratios and DALY rates are higher, indicating a lag in diagnosis and a lack of comprehensive medical

care. Because of the size of the population and the incidence of gastrointestinal cancer, Asia carries the greatest burden of cancer. Meanwhile, countries that are “transitioning” socially and economically, such as those in Africa, Latin America, and South-Central Asia, are witnessing a rapid increase in colorectal and breast cancer^{5,6}. The growth of the world population and the aging of populations are expected to fuel this growth, and predictions are that there will be a 47% increase in cancer cases by the year 2040, or approximately 28 to 29 million, and as high as 35 million by the year 2050, especially in resource-constrained countries^{1,4,7}. A significant percentage of cancer cases are associated with modifiable risk factors. Tobacco, obesity, diet, inactivity, and alcohol, as well as oncogenic infections, such as *Helicobacter pylori*, hepatitis B and C, and human papillomavirus, are estimated to be responsible for 40 to 45% of cancer deaths^{8,9}.

Despite all the preventive measures, the incidence of cancer is on the rise worldwide¹⁰. The therapeutic

options that are currently available for the treatment of cancer include surgery, radiotherapy, cytotoxic chemotherapy, molecularly targeted therapy, immunotherapy, and endocrine therapy. Among these options, chemotherapy is believed to be the mainstay in the treatment of cancer¹¹. However, the efficacy of chemotherapy is limited because of the high toxicity, low bioavailability, and low specificity of the drugs that are used in the treatment of cancer¹². The low water solubility of the drugs used in chemotherapy has also restricted the optimal use of the drugs in the treatment of cancer. In addition, the problem of multidrug resistance is also an impediment in the treatment of cancer¹³. Recently, the application of nanotechnology has opened up new avenues in the treatment of cancer¹⁴. This has led to the development of nanoscale drug delivery systems that have provided precise targeting of the drugs¹⁵. This has led to an enhancement in the pharmacological effects. In addition, nanotechnology has opened up new avenues in the diagnosis and treatment of various diseases. The unique physicochemical properties of these particles allow them to be preferentially taken up in the tumor tissues, which in turn can be used for the targeted therapy of cancer¹⁶. In comparison to free drug formulations, it has also shown better therapeutic index/safety profiles in some cases¹⁷. Drug delivery systems with the help of nanocarriers have shown promise as an innovative tool to overcome the limitations of conventional drug delivery systems by directly addressing the limitations of conventional therapies. These include solubility, circulation time, and bio-distribution, which can be achieved through passive or active targeting¹⁸. Anticancer drugs can stay in systemic circulation for a long time before being retained in the tumor tissues, which can be taken up by cancer cells through receptor-mediated endocytosis¹⁹. This review is based on the current advances in nanocarrier-based drug delivery systems for cancer therapy, which includes targeting, surface engineering, and stimuli-responsive approaches, biological barriers, production, safety, and regulatory considerations, which are of utmost importance in developing intelligent nano medicine for cancer therapy in the future.

METHODS

An extensive literature search was conducted using online databases, including PubMed, Science Direct, Web of Science, SpringerLink, and Google Scholar. Key literature was identified by combining the following keywords: “nanocarriers”, “nanomedicine”, “targeted drug delivery”, “cancer therapy,” “stimuli-responsive nanoparticles”, “polymeric micelles”, “liposomes”, “tumor targeting”, and “drug delivery systems”. Boolean operators, specifically “AND” and “OR”, were also used to refine the search strategy; for example, “nanocarriers AND cancer therapy”, and “polymeric micelles AND tumor targeting”. Literature was selected according to its relevance to the nanocarriers, targeting, stimuli-responsive nanosystems, and challenges in cancer therapy, with

emphasis on the therapeutic performance and mechanism of action.

Targeted delivery strategies

Targeted drug delivery systems play an important role in cancer therapy. The aim is to achieve the highest possible effect from the drug and at the same time reduce its adverse effects on normal tissues. Nanocarriers can be engineered to carry various targeting ligands like antibodies, peptides, and aptamers that have the ability to bind to overexpressed targets on cancer cells²⁰. Active targeting of nanoparticles involves surface functionalization of nanoparticles that carry targeting ligands that have the ability to specifically target specific targets on cancer cells, thus facilitating receptor-mediated endocytosis and delivery of the drug inside the cancer cells²¹. This will result in direct delivery of the drug to cancer cells and exclude normal tissues, thus reducing adverse effects. The pharmacokinetics and pharmacodynamics of drug-delivery particles will be influenced by parameters like particle size, chemistry, and surface charge²². Targeting agents that have the ability to bind specifically to targets that are overexpressed on cancer cells are crucial for targeting cancer cells²³. Passive targeting utilizes the increased permeability and retention effect due to poor lymphatic drainage in cancer tissues, thus enhancing the accumulation of nanoparticles in cancer tissues²⁴. Nanocarriers take advantage of the variations in the physiological microenvironment in the tumor area²⁵. In addition, the passive targeting approach can be supported by the application of active targeting methods that make the most of the unique selectivity of the cancer cells²⁶.

Various factors influence the application of the most appropriate targeting methods in cancer therapy. The factors include the type of cancer, tumor microenvironment conditions, chemo- and/or radiation therapy modalities, and the degree of effect desired²⁷. Combination targeting methods are becoming popular in cancer therapy. Combination targeting methods make the most of the benefits of various targeting methods and take it a step further. Combination targeting methods can be either passive or active targeting methods²⁸. The application of either passive or active targeting methods will be beneficial in increasing the accumulation of the drug at the tumor site and off-target effects. The application of dual-targeted nanocarriers will be beneficial in increasing the specificity and avidity of the nanocarriers to the cancer cells²⁹. The application of dual-targeted nanocarriers will be beneficial in the delivery of drugs to the tumor site³⁰. The application of stimuli-responsive nanocarriers will be beneficial in the control of the release of the drugs at the tumor site.

Nanoparticle formulations

Nanoparticles in drug delivery systems vary in composition, size, and shape. Each nanoparticle will have its own benefits in the treatment of cancer. Several nanocarriers have been developed and studied for the targeted treatment of cancer. These nanocarriers are but a few: liposomes, polymeric nanoparticles, micelles, dendrimers, gold nanoparticles, and carbon nanotubes^{30,31}. Of all the nanocarriers developed and

studied for the targeted treatment of cancer, liposomes are the most studied. Liposomes are small vesicles made up of lipid bilayers. The lipid bilayers are made up of natural and synthetic lipids. Liposomes are the most studied nanocarriers because they are biocompatible and biodegradable and can encapsulate both hydrophilic and hydrophobic drugs^{32,33}.

Liposomes are one of the most developed nanocarriers in the clinical setting. In the clinical setting, several liposomal formulations have been developed and are FDA-approved for the treatment of cancer and infectious diseases. The development and approval of these formulations are evidence of the biocompatibility and biodegradability of liposomes and the ability of liposomes to encapsulate both water-soluble and water-insoluble drugs³⁴. However, conventional liposomes are known to have the drawback of low drug encapsulation efficiency, leakage of the encapsulated drugs during storage, and rapid clearance³⁵. The mechanical and chemical instability of the membrane also make it difficult to produce liposomes in the industrial setting³⁶. In the clinical setting, liposomes have been reported to cause activation of the complement system that results in pseudoallergy and accumulation in the liver and spleen³⁷. The accumulation of liposomes in the liver and spleen and the disruption of the membrane have been reported to be harmful and require careful optimization of the composition of the liposomes³⁸.

Polymeric nanoparticles: can be made from natural or synthetic polymers and in the form of different sizes, shapes, and surface functionalization that is able to have preferential or targeted drug release. Polymeric nanoparticles are usually made from biodegradable polymers and can deliver a drug in a controlled way and at a controlled delivery rate. So, the polymeric nanoparticles' release can be designed to release the drug in a sustained manner, extending the therapeutic window³⁹. They can incorporate targeting ligands and stealth coatings to exploit passive and active tumor targeting^{40,41}. Nonetheless, only a small subset has reached clinical trials, largely because rapid uptake by the reticuloendothelial system (RES) depletes circulating dose before tumor accumulation, constraining efficacy^{41,42}. Stealth strategies (e.g., PEGylation) reduce but do not abolish RES sequestration and can introduce anti-PEG immunity⁴⁰. Additional barriers include complex, multi-step syntheses, batch-to-batch variability, scale-up difficulties, and lingering concerns over polymer degradation products and long-term safety^{42,43}.

Polymeric micelles: are self-assembled aggregates of amphiphilic copolymers that significantly improve the solubility and systemic delivery of hydrophobic drugs. They consist of a hydrophobic core that encapsulates poorly soluble therapeutics and a hydrophilic shell that enhances stability and prolongs circulation in the bloodstream, and several micellar formulations have progressed into clinical trials^{36,40,44}. Stimuli-responsive designs (pH, redox, light) enable controlled release at tumor sites⁴³. However, micelles often exhibit limited kinetic and thermodynamic stability in the bloodstream, leading to premature disassembly and

drug release upon dilution and interaction with serum components^{36,45}. Their nanoscale size favors renal clearance and RES uptake, which together reduce tumor deposition^{36,46}. Restricted tumor penetration, potential polymer related cytotoxicity, and manufacturing challenges in achieving uniform, stable assemblies further constrain robust clinical translation^{43,45,46}.

Similarly, dendrimers are mono-disperse, hyperbranched macromolecules with precisely controllable size and dense surface functionality, enabling high drug/ligand loading and sophisticated architectures such as conjugates, Janus structures, and linear dendritic hybrids^{47,48}. They improve solubility, enable multivalent targeting, and can be engineered for BBB penetration^{47,49}. Yet, despite decades of research, clinical translation remains limited, with very few formulations progressing beyond early phase trials^{50,51}. The key barriers include synthetic complexity and cost, regulatory discomfort with heterogeneous surface conjugation, and toxicity associated with cationic surfaces, including hemolysis and complement activation, which necessitate extensive surface shielding (e.g., PEGylation)⁵⁰. Industrially, low drug to carrier mass ratios and challenges in scalable, reproducible multi functionalization reduce commercial attractiveness^{50,51}.

Gold nanoparticles: (AuNPs) are attractive for chemical stability, straightforward synthesis, and facile surface modification, with applications in photothermal therapy, imaging, and theranostics^{36,40}. Their high atomic number affords strong contrast in CT imaging, and dense surface chemistry supports multivalent ligand display. Clinically, however, AuNPs exemplify the broader concerns with inorganic carriers: they are non-biodegradable and prone to long-term accumulation in organs, especially the liver and spleen, raising chronic toxicity concerns⁴⁰. Size and surface chemistry strongly influence RES uptake and clearance, but complete elimination is rarely achieved. Unresolved issues regarding long-term fate, potential immunotoxicity, and regulatory caution toward persistent inorganic materials significantly limit broad therapeutic deployment, particularly for non-life-threatening indications^{36,40}.

Quantum dots: (QDs) offer exceptional fluorescence brightness, photostability, and tunable emission, enabling multiplexed imaging and theranostic designs⁵². Surface modification improves aqueous dispersibility and targeting capability. Nonetheless, most QDs contain heavy metals (e.g., Cd, Pb), and are non-biodegradable, leading to concerns about cytotoxicity, oxidative stress, and long-term tissue retention. Toxicity to lung cells and induction of oxidative damage have been documented, even with coated structures³⁶. These safety issues, coupled with stringent regulatory scrutiny and availability of safer organic or inorganic imaging alternatives, mean that the clinical prospects of QDs as systemic nanocarriers are currently limited, with use largely confined to preclinical imaging and *ex vivo* diagnostics^{36,40}.

Carbon nanotubes: cylindrical structures composed of rolled-up graphene sheets, possess high surface area and mechanical strength, enabling efficient drug loading and targeted delivery to cancer cells⁵³. Carbon nanotubes (CNTs) possess extraordinary surface area, mechanical strength, and ability to traverse cell membranes, enabling high drug loading and potential use in photothermal/photodynamic applications^{36,40}. Their one-dimensional geometry and modifiable surfaces make them attractive multifunctional platforms. However, pristine CNTs display poor aqueous solubility, low biodegradability, and significant toxicity, including inflammation, fibrosis, and asbestos like pathology in some *in vivo* models³⁶. Functionalization can improve dispersibility and reduce acute toxicity, but does not fully address bio-persistence and long-term accumulation, particularly in lungs and reticuloendothelial organs^{36,40}. These safety and bio-persistence concerns, combined with manufacturing heterogeneity (length, diameter, residual catalysts), have sharply constrained clinical translation, relegating CNTs largely to exploratory research rather than near-term pharmaceutical development⁴⁰.

Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers have been recognized as an innovative approach in cancer therapy. Stimuli-responsive nanocarriers respond to stimuli that are present in the tumor microenvironment. The stimuli include pH levels, redox potential, and enzyme activity⁵⁴. They respond either to internal stimuli, which include reduced pH levels in tumor tissues, or external stimuli, which include light or temperature. The utilization of external stimuli enables the development of an accurate and precise drug delivery system⁵⁵. The release of drugs is carefully controlled in order for them to be delivered at appropriate times in appropriate locations in the tumor microenvironment⁵⁶. For example, pH-responsive nanoparticles respond to the acidic nature of tumor tissues. The release of drugs is carried out in response to reduced pH levels in tumor tissues in comparison with normal tissues⁵⁷. Moreover, redox-responsive nanoparticles respond to the high levels of glutathione in cancer cells. Glutathione is known to have the ability to cleave disulfide bonds, which enables the release of drugs. Enzyme-responsive nanoparticles respond to enzymes that have been upregulated in tumor tissues. They ensure that there is a localized release of drugs in tumor tissues⁵⁸. The release of drugs is carried out using conditions that prevail in tumor tissues. This approach is beneficial in that it is not associated with systemic toxicity. Moreover, it is a phenomenon that is more likely in anti-cancer therapy⁵⁹. Thermosensitive liposomes, which are temperature-sensitive nanoparticles, release drugs at appropriate temperatures. This is carried out using an external heat source, which is high-intensity focused ultrasound or near-infrared light⁶⁰. The on-site release of drugs in response to temperature is beneficial in that it is likely to increase the therapeutic index. This is carried out by increasing the concentration of drugs at sites where they are needed. Moreover, thermo-sensitive nanoparticles have an advantage in that they allow for the modulation of release using external

magnetic fields. This is carried out using magnetic nanoparticles⁶¹. Following this line of development, the use of stimuli-responsive nanomaterials in combination with external triggers, such as photothermal or hyperthermia induced methods, is proposed as a new avenue for the development of improved tumor-targeting systems with enhanced therapeutic effects⁶². Among such systems, bio-responsive nanogels are receiving increasing attention for their potential to efficiently encapsulate and release chemotherapeutic and biotherapeutic drugs, thus showing improved antitumor effects *in vitro* and *in vivo*⁶³. Another type of nanosystem, namely, hydrogels, with their high water content and mechanical properties, is also emerging as a promising tool for tumor treatment, particularly due to their stimuli-responsive properties, which enable them to react to various stimuli in the tumor environment⁶⁴. These complex nanosystems, such as those using phase-change materials and copper sulfide nanocrystals, can be used for both endogenous and external stimuli-induced drug release, as well as for synergistic chemo- and photothermal treatments for enhanced tumor inhibition⁶⁵. The versatility of such nanosystems, which can be externally regulated using a magnetic field for their accumulation in the tumor area, is proposed as a new avenue for the development of a versatile drug delivery system using cytostatics for tumor treatment⁶⁶. This method is particularly useful, as the nanoparticles are not affected by the blood flow in the vessel, thus enabling their immobilization in the desired area⁶⁷. Magnetic implants, in particular, can be incorporated in areas of tissues that are affected, providing localized treatment of cancer in bones through the provision of a driving force for drug delivery⁶⁸. These are considered an advanced form of drug delivery systems, moving beyond conventional means of drug delivery. The discovery of smart materials, especially those with an ability to sense internal and external triggers, has greatly impacted drug delivery systems⁶⁹. These materials allow for the spatially and temporally controlled release of drugs, which are encapsulated in these systems. This is considered an improvement in drug delivery systems, enhancing their efficacy and reducing systemic toxicity. These systems should allow for controlled mechanisms of drug uptake and release to function as efficient drug delivery systems. Ideally, these systems should also have theranostic properties. Further advancements in this field include the discovery of magnetic nanogels, which can be used to turn drug delivery systems on and off rapidly using oscillating magnetic fields⁷⁰. This is considered an improvement in drug delivery systems, providing precise control of drugs. In addition, these systems can be used to overcome multidrug resistance in cancer cells⁷¹. This is considered an advantage of these advanced systems of drug delivery. Various nanocarriers, such as dendrimers, organic micelles, metal oxide nano-particles, quantum dots, and inorganic mesoporous silica, have been used to overcome these challenges. Nanomedicines are considered an attractive option for cancer therapy⁷². These are considered an improvement

in drug delivery systems, enabling dynamic adjustments in therapeutic interventions in real-time⁷³.

Externally triggered smart materials show promise for precise therapy, but there are fundamental challenges. Delivering external stimuli to deep tissues is complex. Light-responsive and photothermal systems are limited by scattering and absorption, often restricting activation to superficial or endoscopically accessible areas unless invasive light guides are employed^{74,75}. Magnetic fields, RF and ultrasound can reach deep sites, yet they require sophisticated applicators, real-time imaging and patient-specific modeling to achieve adequate field strength at the target while avoiding off-target heating or mechanical damage^{76,77}. In hyperthermia-responsive systems, the therapeutic window is narrow: temperature-sensitive carriers must switch sharply within a few degrees around clinically achievable mild hyperthermia (39 to 43 °C), and their release kinetics must match feasible clinical heating protocols⁷⁸. This demands careful integration of material design with realistic thermal dosimetry and stringent temperature constraints for normal tissues. In parallel, toxicological and stability issues of smart materials remain major translational bottlenecks. Different findings consistently underline that nano-platforms based on polymers, lipids, metals/metal oxides, and MOFs can show size-, composition, and surface-dependent organ accumulation, immunogenicity, and long-term uncertainty, and that the absence of standardized toxicity assessment and clear preclinical-clinical correlations is a key reason why complex stimulus-sensitive DDS have not yet reached routine clinical use^{79,80}. Many smart hydrogels, nanogels, and thermo-responsive polymers also struggle with long-term physicochemical and functional stability: crosslinking density, degradation, and protein corona formation can alter swelling, mechanical integrity, responsiveness, and release profiles over time, especially in complex biofluids⁷⁴⁻⁸¹. Dual- or multi-stimulus systems add further design and manufacturing complexity and may amplify failure modes if one component loses activity⁸².

Polysaccharide-based nanocarriers

Polysaccharide-based nanocarriers such as hyaluronic acid, chitosan, and alginate have been found to be of considerable interest in targeted cancer therapy because of their biocompatibility and biodegradability⁸³. In addition, these materials have the ability to target the disease site. For instance, hyaluronic acid is a natural polysaccharide that binds with the CD44 receptor. CD44 is overexpressed in various cancer cells⁸⁴. Therefore, this property of hyaluronic acid makes it useful in targeted cancer therapy and gene therapy⁸⁵. Chitosan is another polysaccharide-based nanocarrier that is derived from chitin. Chitosan has mucoadhesive properties that make it useful in the permeation of drugs. Therefore, it can be used in the development of drugs that are intended for oral and transdermal delivery⁸⁶. Alginate is an anionic polysaccharide that is obtained from brown algae. Alginate has the ability to form hydrogels under mild conditions. Therefore, it can be used in the encapsulation of drugs and cells⁸⁷. The nanocarriers can be engineered in such a way that the

release of the drugs is tailored. In this way, the dissociation of the drug and the nano-shell is prevented. This helps in the prevention of the dissociation of the drug from the nano-shell before it reaches the tumor site. In this way, the drugs are prevented from accumulating in the healthy tissues. This approach is quite useful in the enhancement of the therapeutic index because the concentration of the drugs is maximized at the tumor site⁸⁸. In addition, the development of the nanocarriers with the appropriate size is quite useful in the enhancement of the therapeutic efficacy. The inherent characteristics of these polysaccharide-based nanocarriers, such as their low immunogenicity and their easily modifiable physicochemical properties, also render them suitable for diverse surface functionalization strategies to further enhance their specificity and drug loading capacity^{67,89}. Biodegradable polyelectrolyte microcapsules, for example, are supramolecular structures that can be degraded by enzymes in viable cells under physiological conditions and thus present a highly potent strategy for targeted drug delivery of antineoplastic agents⁹⁰. The potential of these polysaccharide-based nanocarriers also extends to their integration into intelligent drug delivery systems that can respond to tumor-specific cues and thus facilitate drug release in an 'on-demand' fashion⁹¹. Chitosan nanoparticles, for example, owing to their excellent biocompatibility and biodegradability, are now being explored as suitable platforms for the oral delivery of challenging therapeutic macromolecules and exhibit sustained and controlled release profiles⁹². These polymeric systems can be further optimized to include responsive elements that trigger drug release in response to tumor microenvironmental cues, such as pH, temperature, and concentration of enzymes⁹³.

To ensure the successful translation of these polysaccharide-based nanocarriers into the clinic, it is essential to consider the inherent heterogeneity of natural polysaccharide materials and their inherent complexity in drug delivery systems. Chitosan, alginate, fucoidan, hyaluronic acid, and pectin are examples of natural polysaccharides that exhibit source-dependent variability in molecular weight, degree of substitution, and charge density⁹⁴. Such variability in their inherent properties can manifest as significant differences in nanoparticle size, drug loading capacity, and drug release characteristics, which can be problematic in large-scale production and drug approval⁹⁵. In physiological media, many polysaccharide-based systems face colloidal instability under neutral pH and ionic strength; for example, chitosan nanocarriers may lose surface charge and aggregate or prematurely disassemble, necessitating stabilization strategies such as chemical modification, ionic or covalent crosslinking, or hybridization with synthetic polymers or inorganic components to preserve structural integrity and controlled release *in vivo*^{96,97}. At the same time, polysaccharides are not pharmacologically inert excipients: marine and terrestrial polysaccharides can interact with immune cells and receptors, conferring valuable immunostimulatory or immunomodulatory properties that are

exploited in cancer immunotherapy, but also raising the possibility of unintended complement activation, cytokine release, or off-target immune responses, which depend sensitively on structure, dose, and formulation context^{98,99}.

Polymeric micelles as drug delivery systems

Polymeric micelles have surfaced as multifunctional nanoparticles and hold immense potential in various scientific domains¹⁰⁰. Micelles are widely employed to enhance the efficacy and mitigate the harmful side effects of drugs, owing to their ability to extend circulation time and promote uptake via the enhanced permeability and retention effect¹⁰¹. Polymeric micelles, self-assembling nanostructures formed by amphiphilic polymers, present a unique platform for drug delivery due to their core-shell architecture, biocompatibility, and ability to solubilize hydrophobic drugs¹⁰². The hydrophobic core serves as a reservoir for drug encapsulation, while the hydrophilic shell stabilizes the micelle in aqueous environments and prevents opsonization by the immune system. Stimuli-responsive micelles can be designed to release their drug cargo in response to specific triggers, such as pH, temperature, redox potential, or enzymatic activity, enabling precise control over drug release at the tumor site. This targeted release mechanism can significantly improve therapeutic indices by concentrating drug delivery at pathological sites while minimizing systemic exposure and associated toxicities¹⁰³. Despite these advantages, the *in vivo* stability of many micelle systems remains a challenge, often leading to premature drug release and non-specific tissue accumulation¹⁰⁴.

Moreover, conventional self-assembled micelles are only thermodynamically stable above the CMC; after intravenous injection, strong dilution and interaction with serum proteins can drive dissociation, premature drug release, and loss of targeting advantages¹⁰⁵. Achieving reproducible large-scale manufacturing with consistent drug loading, long-term colloidal stability, and well-characterized *in vivo* behavior remains difficult, especially for complex cross-linked or multi-stimuli responsive systems¹⁰⁶. However, innovations in block copolymer design and cross-linking strategies are actively addressing these limitations, enhancing micellar integrity and prolonging systemic circulation (107). The physical entrapment of water-insoluble small molecules into the micelle core represents a highly feasible pathway for clinical translation¹⁰². For instance, polymeric micelles formed from amphiphilic block copolymers can significantly improve the solubility and bioavailability of hydrophobic anticancer drugs, facilitating their effective delivery to tumor tissues¹⁰⁸. These nano scale carriers also exhibit prolonged circulation times and reduced systemic toxicity, contributing to improved therapeutic outcomes^{109,110}. Specifically, doxorubicin-loaded mixed micelles have shown promise in enhancing anticancer sensitivity, demonstrating how tailored micellar formulations can augment therapeutic efficacy¹¹¹. Furthermore, the precise control over drug release kinetics and the ability to selectively accumulate at

diseased sites underscore the advanced capabilities of polymeric micelles in modern nanomedicine.

Surface modification and targeting ligands

Surface modification of nanocarriers with targeting ligands, such as antibodies, peptides, aptamers, or small molecules, enables selective recognition and binding to cancer cells, enhancing drug delivery and therapeutic efficacy¹¹². Antibody-conjugated nanoparticles can target specific tumor-associated antigens, triggering receptor-mediated endocytosis and the subsequent release of intracellular drugs. Peptide-modified nanocarriers can bind to overexpressed receptors on cancer cells, facilitating targeted drug delivery and imaging. Aptamer-functionalized nanoparticles can recognize and bind to specific molecular targets on cancer cells, enabling targeted drug delivery and gene therapy. This active targeting approach, combined with the inherent benefits of nanocarriers, offers a pathway to significantly improve therapeutic outcomes and reduce systemic side effects in cancer treatment¹¹³. However, despite surface functionalization, nanocarriers still struggle with autonomous navigation to the target, necessitating further advancements in self-propelling and navigational functionalities for precise intracellular delivery and deep tissue penetration¹¹⁴. Further research is focusing on integrating microfluidic systems and external magnetic fields to guide these nanocarriers with enhanced precision, enabling real-time localization and release at the cellular level within complex biological environments¹¹⁵. This integrated approach promises to overcome current limitations in targeted therapy by ensuring optimal drug concentration at the diseased site, thereby maximizing therapeutic impact and minimizing off-target effects^{116,117}.

Clinical trials and translational studies

The clinical translation of drug delivery systems using nanocarriers has also witnessed considerable progress. Several formulations have been approved for cancer therapy¹¹⁸. Doxil, which is a liposomal doxorubicin formulation, was the first nanotechnology-based formulation that was approved for cancer therapy. It has been reported that Doxil shows improved efficacy with reduced cardiotoxicity in comparison with the conventional doxorubicin formulation. Abraxane, which is an albumin-bound nanoparticle formulation of paclitaxel, shows improved efficacy with reduced toxicity in metastatic breast cancer, non-small cell lung cancer, and pancreatic cancer¹¹⁹. Among the liposomal formulations, Doxil/Caelyx, which is PEGylated liposomal doxorubicin (80-90 nm), was approved by the FDA in 1995 and by the EMA in 1996 for HIV-associated Kaposi's sarcoma, ovarian cancer, metastatic breast cancer, and multiple myeloma. DaunoXome, which is non-PEGylated liposomal daunorubicin (45 nm), was approved by the FDA in 1996 for HIV-associated Kaposi's sarcoma. Lipo-Dox, which is another formulation of doxorubicin in liposomes (180 nm), was approved in Taiwan in 1998 for Kaposi's sarcoma, breast cancer, and ovarian cancer¹²⁰. DepoCyt, which is a liposomal cytarabine with larger particles (10-20 μ m), was approved by the FDA in 1999 for neoplastic meningitis. Subsequently,

Myocet, which is non-PEGylated liposomal doxorubicin (190 nm), was approved by the EMA in 2000 for breast cancer therapy. Abraxane, which is an albumin-bound nanoparticle formulation of paclitaxel (130nm), was approved by the FDA in 2005 and by the EMA in 2008 for non-small cell lung cancer, metastatic pancreatic cancer, and metastatic breast cancer¹²¹. For instance, in 2006, the FDA approved Oncaspar, a PEGylated L-asparaginase conjugate (50-200nm), for leukemia treatment¹²². Genexol-PM, a PEG-PLA polymeric micelle encapsulating paclitaxel (20-50 nm), was approved in 2007 in South Korea for the treatment of breast, lung, and ovarian cancers^{123,124}. Other emerging nanomedicine platforms include MEPACT (mifamurtide) – a non-PEGylated formulation of a liposome – which was approved by the EMA in 2009 for osteosarcoma. NanoTherm, iron oxide nanoparticles of 15-20 nm, was approved by the EMA in 2010 for use in the treatment of glioblastoma multiforme through magnetic thermal ablation¹²⁵. The FDA subsequently approved Marqibo, a non-PEGylated formulation of a vincristine liposome (100 nm), in 2012 for Philadelphia chromosome-negative acute lymphoblastic leukemia¹²⁶. More recently, MM-398, a PEGylated formulation of a liposome encapsulating irinotecan (80-140 nm), was approved by the FDA in 2015 for the treatment of metastatic pancreatic cancer in the second-line setting¹²⁵. In 2017, NU-0129, a formulation of gold nanoparticles encapsulating gold cores and siRNAs, was used in clinical trials for glioblastoma multiforme¹²⁷. In the same year, MM-398, a formulation of a liposome encapsulating irinotecan (80-140 nm), was used in Phase I-III clinical trials for small cell lung cancer, metastatic pancreatic adenocarcinoma, and pediatric solid tumors¹²⁸⁻¹³⁰. Polymeric nanocarriers are also well represented in the drug delivery field. For instance, Genexol-PM, a polymeric micelle formulation of paclitaxel, with a particle size of <50 nm, was used in Phase I/II clinical trials for gynecologic cancers, hepatocellular carcinoma, advanced breast cancer, and non-small cell lung cancer¹²⁹⁻¹³³. Similarly, CRLX101, a formulation of a polymer conjugate of camptothecin, with a particle size of 30 The silica-gold nanoparticles (150 nm) system, AuroLase was tested in Phase I clinical trials for prostate, head and neck, and lung cancer^{136,137}. Gold-based systems like these are commonly studied for photothermal therapeutic applications. There are many liposomal formulations that are at the forefront in clinical trials. A liposome injection for vincristine sulfate (100 nm) is in Phase I/II clinical trials for Kaposiform hemangioendothelioma, Kasabach-Merritt syndrome, tufted angioma, rhabdomyosarcoma, recurrent adult acute myeloid leukemia, lymphoblastic leukemia, various lymphomas (non-Hodgkin's, follicular, mantle-cell, small-cell, and B-cell marginal zone), and Waldenstrom's Macroglobulinemia^{126,138}. An anti-EGFR immuno-liposome for delivering doxorubicin (130-200 nm) is in phase II clinical trials for breast cancer¹³⁹.

Another liposomal formulation, mitoxantrone HCl liposome injection (plm60-s) (60nm), is in Phase II clinical trials for breast cancer, diffuse large B-cell

lymphoma, non-Hodgkin's lymphoma, and peripheral T/NK lymphomas¹⁴⁰. Earlier-stage liposomal candidates include CPX-351 (2014), a liposomal formulation assessed in Phase I trials for acute myeloid leukemia¹⁴¹, and Lipocurc, a liposomal curcumin formulation evaluated in Phase I/II studies for advanced cancers refractory to standard therapy¹⁴². Gene-based nanomedicine is represented by SGT-53, a liposomal vector delivering plasmid DNA encoding wild-type human p53, investigated in Phase I/II trials for glioblastoma, other neoplasms, and metastatic pancreatic cancer¹⁴³⁻¹⁴⁵. LiPlaCis, a liposomal cisplatin formulation, advanced to Phase I/II trials for advanced or refractory solid tumors, including metastatic breast cancer¹⁴⁶. In 2012, PROMITIL, a liposomal mitomycin-C (~90 nm), entered Phase I trials for solid tumors¹⁴⁷. Additionally, in 2011, Abraxane, a protein-drug conjugate consisting of albumin-bound paclitaxel (130nm), was evaluated in Phase II trials for breast cancer¹⁴⁸.

Despite the clinical success of several nanocarrier-based drugs, challenges remain in terms of scalability, reproducibility, and regulatory approval^{149,150}. Most research remains limited to *in vivo* and *in vitro* studies¹⁵¹. Translational hurdles persist, primarily due to the complex biological barriers, tumor heterogeneity, and systemic clearance mechanisms that still challenge optimal drug accumulation at target sites¹⁵². A major translational barrier is the variability and context-dependence of the EPR effect in humans. While preclinical xenograft models and rodent tumors often display strong and relatively homogeneous EPR, human tumors show highly heterogeneous, sometimes transient EPR that varies between tumor types, primary versus metastatic lesions, and even between lesions in the same patient^{153,154}. Clinical and comparative imaging data indicate that only a subset of human tumors (e.g., some carcinomas) exhibits robust EPR-mediated accumulation, and the magnitude of uptake is far lower and more variable than in mice¹⁵⁵. This mismatch between animal models and human pathophysiology is widely regarded as a key reason for clinical failures.

Nano medicines relative to expectations based on preclinical studies. Inadequate modeling of tumor heterogeneity, metastasis, and human-like vasculature further limits predictive value and contributes to disappointing trial outcomes^{155,156}. Beyond limited efficacy, toxicity and long-term biosafety remain central concerns. Nanoparticles can induce oxidative stress, damage membranes, organelles, and DNA, and engage cell-surface receptors to trigger unintended immune and inflammatory responses¹⁵². Toxicological profiles are highly dependent on size, shape, composition, surface charge, and coating, which are often modified during scale-up or functionalization, complicating risk assessment^{153,157}. For inorganic and metal-containing systems, nanoscale manipulation can fundamentally alter toxicology compared with bulk materials, raising concerns about chronic accumulation and delayed organ toxicity, particularly under repeated dosing regimens typical of oncology¹⁵⁷. These uncertainties contribute to conservative clinical trial

designs and slow regulatory acceptance, and help explain why most approved cancer Nano drugs are relatively simple liposomes or albumin nanoparticles with well-characterized materials¹⁵⁸.

Immunogenicity and off-target immune effects are critical concerns in nano-immunotherapy and RNA or biologic delivery. Exogenous nano carriers may activate complement and innate immune pathways, causing hypersensitivity, cytokine release, or immune suppression, while repeated dosing can induce anti-cancer antibodies that alter pharmacokinetics and efficacy. Ensuring selective antitumor immune-stimulation without systemic immunotoxicity, therefore, remains a major challenge¹⁵⁹. In the blood-stream, nanocarriers rapidly form a protein corona that alters their biological identity, masking targeting ligands, promoting opsonization, and increasing uptake by the mononuclear phagocyte system, particularly in the liver and spleen¹⁵³. This reduces tumor delivery and can modify toxicity profiles. Controlling corona formation is challenging due to patient-specific plasma composition and dynamic *in vivo* conditions, while rapid macrophage clearance, hepatic and splenic filtration, renal excretion, and potential long-term tissue accumulation further limit circulation time and intratumoral exposure^{152,159,160}. Clinical translation of advanced nanocarriers is limited by challenges in robust, scalable, and reproducible manufacturing. Complex multi-component systems require precise control of size, surface chemistry, and drug loading, increasing batch variability and complicating GMP scale-up^{152,157,161}. Difficulty in preserving critical quality attributes during industrial production raises costs, favoring simpler liposomal and polymeric formulations with more tractable process control^{152,153,158}. Therefore, there is emphasis placed on the need for further research to develop new strategies that can overcome these challenges, including the development of new targeting ligands, drug release systems, and pharmacokinetic profiles for the improvement of the clinical utility of these nanocarriers¹⁵². In addition, the application of artificial intelligence in conjunction with machine learning may greatly improve the development of new nanocarrier designs and their interactions in complex biological systems, thereby promoting the clinical translation of these nanocarriers¹⁶². Furthermore, the immunological effects of nanocarriers are important in the long-term safety and efficacy of these nanocarriers. Therefore, immunogenicity studies are important in the development process of these nanocarriers. In addition, quality control of nano medicines is important in the production of these nanocarriers to make them safe and effective in the clinical utility process¹⁶³.

Overcoming biological barriers for targeted delivery

The nanocarriers have the ability to cross physiological barriers such as the blood-brain barrier, tumor microenvironment, and drug resistance, thereby enhancing the efficiency of drug localization¹⁶⁴. The localization of anticancer drugs in tumor tissues with minimal localization in other parts of the body could be responsible for enhancing the efficacy of anticancer

drugs while minimizing toxicity¹⁶⁵. The dynamics of tumor microenvironment have been significant in enhancing the efficient design of nanoparticles, thereby ensuring effective drug delivery¹⁶⁶. The application of nanotechnology in cancer therapy is a dynamic field with tremendous potential for cancer therapy¹⁶⁷. Engineered nanoparticles have been effective in protecting anticancer drugs from early degradation, extending the half-life of anticancer drugs, and accumulating anticancer drugs in tumor tissues using the EPR effect¹⁶⁸⁻¹⁷⁰. The rationale behind targeted drug delivery is targeting anticancer drugs specifically in cancer cells, thereby minimizing the impact of anticancer drugs on normal cells¹⁷¹.

Targeted drug delivery is an approach that uses nanoscale drug delivery vectors, which may be derived from organic compounds, that target anticancer drugs specifically in cancer cells¹⁷². The drug delivery vectors may also be engineered in a manner that they release anticancer drugs in response to tumor-specific stimuli, thereby enhancing effective release of anticancer drugs¹⁷³. The advancement in biotechnology has been significant in synthesizing effective drug delivery vectors, including liposomes, dendrimers, metal nanoparticles, and magnetic nanoparticles. Beyond therapy, such platforms offer opportunities for simultaneous diagnosis and disease monitoring¹⁷⁴. Passive targeting strategies exploit the abnormal architecture of tumor vasculature and deficient lymphatic drainage, characterized by vascular fenestrations typically ranging from 100 to 780 nm¹⁷⁵. Nanoparticles engineered within this dimensional window can preferentially accumulate in tumor tissues, thereby enhancing local drug concentration and therapeutic response¹⁷⁶.

Targeted therapeutic strategies are aimed at achieving the optimal concentration of drugs that are delivered directly to the target tissues where the disease manifests, while ensuring that the optimal concentration of drugs is maintained for a long time¹⁷⁷. The introduction of nano-based drug delivery systems has resulted in a significant increase in attributes such as drug bioavailability, *in vivo* stability, intestinal absorption pattern, solubility, and the targeted and long-lasting distribution of drugs, as well as the therapeutic efficacy of a number of anticancer drugs¹⁷⁸. The efficacy of a number of drugs, including anticancer drugs, is improved by nano-based drug delivery systems, which enhances drug bioavailability/biodistribution¹⁷⁹.

By enabling more accurate localization of drugs at pathological sites, nanotechnology has significantly advanced precision medicine approaches¹⁸⁰. Due to their small dimensions, nano drugs are capable of traversing narrow capillary networks and lymphatic endothelium, which may contribute to prolonged systemic circulation and improved interaction with target tissues. Once accumulated at the tumor site, nanocarriers can facilitate efficient cellular internalization and induce cytotoxic effects within malignant cells¹⁸¹. A central objective of nanotechnology in oncology is to concentrate therapeutic action at the intended site while minimizing adverse systemic

reactions commonly associated with conventional chemotherapy¹⁸². Recent progress in cell-mediated nanoparticle delivery systems has further strengthened tumor-targeting strategies¹⁸³. Such biomimetic platforms provide advantages such as enhanced biocompatibility, extended circulation time, intrinsic homing capacity, and the ability to overcome physiological barriers. Additionally, localized hyperthermia applied to solid tumors can stimulate vascular permeability and cellular responses, thereby improving nanomedicine penetration and retention¹⁸⁴. Nanocarriers also enable the transport of diverse therapeutic payloads, including small-molecule drugs, genes, and proteins, directly into cancer cells, improving treatment outcomes while reducing collateral toxicity¹⁷³. This is particularly relevant given the well-recognized limitations of traditional chemotherapeutics, such as poor aqueous solubility, limited tumor selectivity, and susceptibility to multidrug resistance. Nano formulations of natural anticancer compounds have similarly demonstrated improved stability, biodistribution, targeting efficiency, and therapeutic potency¹⁸⁵. Overall, nanoparticle-based systems offer versatile solutions to many of the constraints associated with conventional cancer treatment modalities¹⁸⁶.

Application of Nanocarriers in Cancer Therapy

In targeting multiple biological levels

Nanocarriers can be engineered to act hierarchically at the level of tumor tissue, cancer cells, and specific organelles, thereby improving therapeutic precision. Fan *et al.*, showed that size, surface ligands, and charge can be tuned to first promote tumor accumulation, then receptor-mediated uptake by cancer cells, and finally subcellular targeting (e.g., mitochondria or nuclei) to maximize drug action while limiting off-target toxicity¹⁶¹. Cell-membrane-coated systems further extend this concept: by cloaking nanoparticles with cancer cell or immune cell membranes, Li *et al.*, achieved prolonged circulation, homotypic binding to tumor tissue, and improved intracellular delivery across several biological barriers¹⁸⁷. These strategies illustrate how nanocarriers can be designed to sequentially navigate blood, stroma, cell membrane, endosomal compartments, and organelles, rather than acting at a single biological level^{161,187}.

In overcoming multidrug resistance

A second key application is the reversal of multidrug resistance (MDR) through nano-enabled delivery. Yao *et al.*, summarized how nanoparticles can circumvent efflux transporters (e.g., P-gp) by favoring endocytic uptake and high intracellular payload concentrations, which restored sensitivity to doxorubicin and paclitaxel in resistant cell lines and xenografts¹⁶⁴. In addition to bypassing pumps, nanocarriers can co-deliver chemotherapeutics with P-gp inhibitors or siRNA targeting resistance-related genes, leading to more sustained MDR reversal¹⁶⁴. TME-responsive nano drug delivery systems also address microenvironment-driven resistance: Shao *et al.*, reported platforms that respond to acidic pH or hypoxia in the tumor, releasing drugs and adjuvants precisely where physicochemical conditions promote resistance, thereby improving cytotoxic efficacy in MDR models¹⁸⁸.

In enhancing radiotherapy with smart platforms

Nanocarriers are increasingly used as radiosensitizing platforms that modify both tumor cells and their microenvironment. Feng *et al.*, constructed a ZIF-8-based nanoplatform co-loading indocyanine green and rapamycin, designed to disassemble in the tumor microenvironment and provide photothermal therapy together with radiotherapy sensitization¹⁸⁹. Rapamycin inhibited mTOR signaling, enhanced DNA damage, and promoted immunogenic cell death, while the photothermal effect further compromised tumor viability, resulting in marked radiosensitization and tumor growth inhibition in HepG2 xenografts¹⁸⁹. TME-responsive carriers that alleviate hypoxia or modulate redox status have similarly been shown to improve radiotherapy outcomes by increasing reactive oxygen species generation and reducing DNA repair capacity in tumor cells^{188,189}.

Supporting and potentiating cancer immunotherapy

Nanocarriers also act as powerful tools to potentiate cancer immunotherapy by delivering immune modulators to specific immune or stromal cell populations. Lu *et al.*, reported nanoparticles designed to repolarize tumor-associated macrophages from an M2- to an M1-like phenotype, promote dendritic cell maturation, and enhance T-cell infiltration, which together remodeled an immunosuppressive TME into an immune-permissive niche. Such systems were able to synergize with immune checkpoint blockade by increasing intratumoral effector T cells and reducing regulatory populations¹⁹⁰. Peng *et al.*, showed that TME-responsive nanomedicines, triggered by acidity or high ROS, can confine the release of immunostimulatory agents to tumors, amplifying local immune activation while minimizing systemic immune related adverse events¹⁹¹. These examples highlight how nanocarriers can orchestrate multi-cellular immune networks within the TME to improve the depth and durability of immunotherapy responses.

Exploiting and remodeling the tumor microenvironment

Finally, nanocarriers are increasingly designed to exploit and actively remodel the tumor microenvironment itself. Aldhubiab *et al.*, described multiple platforms that regulate hypoxia, pH, and redox balance, degrade dense extracellular matrix, and interfere with immunosuppressive mediators, thereby improving drug penetration and sensitizing tumors to therapy¹⁵⁹. For instance, oxygen-generating or hypoxia-responsive nanoparticles can relieve hypoxia-induced resistance and enhance both chemo- and radiotherapy, while matrix-degrading carriers improve the intratumoral distribution of payloads^{159,188}. In lung cancer, Sarma *et al.*, showed that bio functionalized nanocarriers equipped with ROS-modulating inorganic components and TME-targeting ligands could modulate cancer-associated fibroblasts, suppress TAM and MDSC activity, and normalize vasculature, leading to improved penetration and antitumor effects in non-small-cell lung cancer models¹⁹². Collectively, these studies demonstrate that nanocarriers can be rationally

designed not only to survive the hostile TME but to reprogram it into a more treatment-sensitive state¹⁹⁰.

CONCLUSIONS

Nanocarrier based drug delivery systems have greatly contributed to the development of targeted cancer therapies by overcoming the major drawbacks of conventional chemotherapy. The conventional chemotherapy methods have been plagued by issues such as systemic toxicity, lack of tumor selectivity, low bioavailability of drugs, and the development of multidrug resistance. The nanocarriers have been able to address these issues by improving the solubility and stability of drugs, increasing the circulation time of drugs in the body, and providing the ability to control the release of drugs. The nanocarriers have also been able to improve the ability of drugs to reach the tumor sites. The nanocarriers that have been developed and tested in cancer therapy include liposomes, polymeric nanoparticles, dendrimers, micelles, and inorganic nanoparticles. The development of these nanocarriers has been highly beneficial in addressing the issues that have been experienced with conventional chemotherapy. However, despite the benefits that the nanocarriers have provided in the development of targeted cancer therapies, there are several issues that need to be addressed. For instance, the long-term safety and accumulation of these nanocarriers in the body are issues that need to be addressed. In the future, the development of nanocarriers should be focused on the development of multifunctional nanocarriers that can be tailored to respond to different stimuli. The nanocarriers should be designed in such a way that they can be tailored to the patient. The nanocarriers should be optimized in terms of their size and surface characteristics.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all researchers who supported during this work.

AUTHOR'S CONTRIBUTIONS

Komba EG: writing the original draft, methodology, investigation. **Said SS:** literature survey, data processing. **Alphonse FM:** literature survey, critical review. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

None to declare.

REFERENCES

1. Bray F, Laversanne M, Sung H, *et al.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024 May;74(3):229-63. <https://doi.org/10.3322/caac.21834>
2. Wu Z, Xia F, Lin R. Global burden of cancer and associated risk factors in 204 countries and territories, 1980-2021: A systematic analysis for the GBD 2021. *J Hematol Oncol J Hematol Oncol* 2024 Nov 29; 17(1):119. <https://doi.org/10.1186/s13045-024-01640-8>
3. Hanahan D. Rethinking the war on cancer. *Lancet* 2014; 383(9916):558-563. [https://doi.org/10.1016/S0140-6736\(13\)62226-6](https://doi.org/10.1016/S0140-6736(13)62226-6)
4. Sung H, Ferlay J, Siegel RL, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021 May;71(3):209-49. <https://doi.org/10.3322/caac.21660>
5. Lin L, Li Z, Yan L, *et al.* Global, regional, and national cancer incidence and death for 29 cancer groups in 2019 and trends analysis of the global cancer burden 1990-2019. *J Hematol Oncol J Hematol Oncol* 2021 Nov 22;14(1):197. <https://doi.org/10.1186/s13045-021-01213-z>
6. Morgan E, Arnold M, Gini A, *et al.* Global burden of colorectal cancer in 2020 and 2040: Incidence and mortality estimates from GLOBOCAN. *Gut* 2023 Feb;72(2):338-44. <https://doi.org/10.1136/gutjnl-2022-327736>
7. Soerjomataram I, Bray F. Planning for tomorrow: Global cancer incidence and the role of prevention 2020-2070. *Nat Rev Clin Oncol* 2021 Oct;18(10):663-72. <https://doi.org/10.1038/s41571-021-00514-z>
8. Arnold M, Abnet CC, Neale RE, *et al.* Global burden of 5 major types of gastrointestinal cancer. *Gastroenterol* 2020 Jul;159(1):335-349.e15. <https://doi.org/10.1053/j.gastro.2020.02.068>
9. Tran KB, Lang JJ, Compton K, *et al.* The global burden of cancer attributable to risk factors, 2010-19: A systematic analysis for the global burden of disease study 2019. *The Lancet* 2022 Aug;400(10352):563-91. [https://doi.org/10.1016/S0140-6736\(22\)01438-6](https://doi.org/10.1016/S0140-6736(22)01438-6)
10. You W, Henneberg M. Cancer incidence increasing globally: The role of relaxed natural selection. *Evol Appl* 2018 Feb;11(2):140-52. <https://doi.org/10.1111/eva.12523>
11. Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. *Nat Rev Immunol* 2008 Jan;8(1):59-73. <https://doi.org/10.1038/nri2216>
12. Navya PN, Kaphle A, Srinivas SP, *et al.* Current trends and challenges in cancer management and therapy using designer nanomaterials. *Nano Converg* 2019 Dec;6:1. <https://doi.org/10.1186/s40580-019-0193-2>
13. Del Genio V, Bellavita R, Falanga A, *et al.* Peptides to overcome the limitations of current anticancer and antimicrobial nanotherapies. *Pharmaceutics* 2022 Jun 10;14(6):1235. <https://doi.org/10.3390/pharmaceutics14061235>
14. Wadekar PP, Patil JA. A review on gold nanoparticles synthesis and characterization. *Universal J Pharm Res* 2017; 2(4): 58-62. <http://doi.org/10.22270/ujpr.v2i4.RW5>
15. Hussain Z, Khan JA, Murtaza S. Nanotechnology: An emerging therapeutic option for breast cancer. *Crit Rev Eukaryot Gene Expr* 2018;28(2):163-75. <https://doi.org/10.1615/CritRevEukaryotGeneExpr.2018022771>
16. Sinha R, Kim GJ, Nie S, Shin DM. Nanotechnology in cancer therapeutics: Bioconjugated nanoparticles for drug delivery. *Mol Cancer Ther* 2006 Aug 1;5(8):1909-17. <https://doi.org/10.1158/1535-7163.MCT-06-0141>
17. Ajith S, Almomani F, Elhissi A, Hussein GA. Nanoparticle-based materials in anticancer drug delivery: Current and future prospects. *Heliyon* 2023 Nov 1;9:11. <https://doi.org/10.1016/j.heliyon.2023.e21227>
18. Aslam MS. Long chain polymeric carbohydrate dependent nanocomposites in tissue engineering. *Universal J Pharm Res* 2020; 5(4):65-70. <https://doi.org/10.22270/ujpr.v5i4.441>

19. Choi KY, Chung H, Min KH, *et al.* Self-assembled hyaluronic acid nanoparticles for active tumor targeting. *Biomater* 2010 Jan;31(1):106-14.
<https://doi.org/10.1016/j.biomaterials.2009.09.030>
20. Cheng X, Xie Q, Sun Y. Advances in nanomaterial-based targeted drug delivery systems. *Front Bioeng Biotech* 2023 Apr 13;11:1177151.
<https://doi.org/10.3389/fbioe.2023.1177151>
21. Nadeem A, Saqib Z, Arif A, *et al.* Hybrid hydrogels incorporating nanoparticles, their types, development, and applications: A comprehensive review of nanogels. *Universal J Pharm Res* 2024; 9(5): 142-149.
<http://doi.org/10.22270/ujpr.v9i5.1202>
22. Debbage P. Targeted Drugs and Nanomedicine: Present and Future. *Curr Pharm Des* 2009 Jan 1;15(2):153-72.
<https://doi.org/10.2174/138161209787002870>
23. Dadwal A, Baldi A, Kumar Narang R. Nanoparticles as carriers for drug delivery in cancer. *Artif Cells Nanomed Biotechnol* 2018 Nov 5;46(sup2):295-305.
<https://doi.org/10.1080/21691401.2018.1457039>
24. Greish K. Enhanced permeability and retention effect for selective targeting of anticancer nanomedicine: Are we there yet? *Drug Discov Today Technol* 2012 Jun;9(2):e161-6.
<https://doi.org/10.1016/j.ddtec.2011.11.01>
25. Kutova OM, Guryev EL, Sokolova EA, *et al.* Targeted delivery to tumors: Multidirectional strategies to improve treatment efficiency. *Cancers* 2019 Jan 10;11(1):68.
<https://doi.org/10.3390/cancers11010068>
26. Dhanasekaran S, Chopra S. Getting a handle on smart drug delivery systems - A comprehensive view of therapeutic targeting strategies. *Smart Drug Delivery System*. InTech; 2016. <https://doi.org/10.5772/61388>
27. Kydd J, Jadia R, Velpurisiva P, *et al.* Targeting strategies for the combination treatment of cancer using drug delivery systems. *Pharmaceut* 2017 Oct 14;9(4):46.
<https://doi.org/10.3390/pharmaceutics904004>
28. Ghiarasin R, Simionescu N, Coroaba A, *et al.* SI-ATRP decoration of magnetic nanoparticles with PHEMA and post-polymerization modification with folic acid for tumor cells' specific targeting. *Int J Mol Sci* 2021 Dec 23;23(1):155.
<https://doi.org/10.3390/ijms2301015>
29. Salahpour Anarjan F. Active targeting drug delivery nanocarriers: Ligands. *Nano-struct nano-objects* 2019 Jul;19:100370. <https://doi.org/10.1016/j.nanos.2019.100370>
30. Onoue S, Yamada S, Chan K. Nanodrugs: Pharmacokinetics and safety. *Int J Nanomed* 2014 Feb;10:25.
<https://doi.org/10.2147/IJN.S38378>
31. Zhu Y, Liao L. Applications of nanoparticles for anticancer drug delivery: A Review. *J Nanosci Nanotech* 2015 Jul 1;15(7):4753-73. <https://doi.org/10.1166/jnm.2015.10298>
32. Nilsson C, Barrios-Lopez B, Kallinen A, *et al.* SPECT/CT imaging of radiolabeled cubosomes and hexosomes for potential theranostic applications. *Biomaterials* 2013 Nov;34(33):8491-503.
<https://doi.org/10.1016/j.biomaterials.2013.07.055>
33. Basile L, Pignatello R, Passirani C. Active targeting strategies for anticancer drug nanocarriers. *Curr Drug Deliv* 2012 Apr 1;9(3):255-68.
<https://doi.org/10.2174/156720112800389089>
34. Nsairat H, Khater D, Sayed U, *et al.* Liposomes: Structure, composition, types, and clinical applications. *Heliyon* 2022 May;8(5):e09394.
<https://doi.org/10.1016/j.heliyon.2022.e09394>
35. Mehta M, Bui TA, Yang X, *et al.* Lipid-based nanoparticles for drug/gene delivery: An overview of the production techniques and difficulties encountered in their industrial development. *ACS Mater Au* 2023 Nov 8;3(6):600-19.
<https://doi.org/10.1021/acsmaterialsau.3c00032>
36. Roszkowski S, Durczynska Z. Advantages and limitations of nanostructures for biomedical applications. *Adv Clin Exp Med* 2024 Jun 11;34(3):447-56.
<https://doi.org/10.17219/acem/186846>
37. Jiang Y, Li W, Wang Z, Lu J. Lipid-based nanotechnology: liposome. *Pharmaceutics* 2023 Dec 26;16(1):34.
<https://doi.org/10.3390/pharmaceutics16010034>
38. Lombardo D, Kiselev MA. Methods of liposomes preparation: formation and control factors of versatile nanocarriers for biomedical and nanomedicine application. *Pharmaceutics* 2022 Feb 28;14(3):543.
<https://doi.org/10.3390/pharmaceutics1403054>
39. Zhong Y, Meng F, Deng C, Zhong Z. Ligand-directed active tumor-targeting polymeric nanoparticles for cancer chemotherapy. *Biomacromol* 2014 Jun 9;15(6):1955-69.
<https://doi.org/10.1021/bm5003009>
40. Alshawwa SZ, Kassem AA, Farid RM, *et al.* Nanocarrier drug delivery systems: characterization, limitations, future perspectives and implementation of artificial intelligence. *Pharmaceutics* 2022 Apr 18;14(4):883.
<https://doi.org/10.3390/pharmaceutics14040883>
41. Milligan JJ, Saha S. A Nanoparticle's journey to the tumor: strategies to overcome first-pass metabolism and their limitations. *Cancers* 2022 Mar 29;14(7):1741.
<https://doi.org/10.3390/cancers14071741>
42. Beach MA, Nayanathara U, Gao Y, *et al.* Polymeric nanoparticles for drug delivery. *Chem Rev* 2024 May 8;124(9):5505-616. <https://doi.org/10.1021/acs.chemrev.3c007>
43. Rajabi M, Feyzbakhsh H. Polymeric nanocarriers in drug delivery, bioimaging, and biosensing: Advances and perspectives on nanomicelles, nanogels, and dendrimers. *RSC Adv* 2025;15(48):40400-38.
<https://doi.org/10.1039/D5RA05399D>
44. Sultana N, Bora P, Sarma B. Nanocarriers in drug delivery system: Eminence and confront. *Smart Nanocontainers*. Elsevier; 2020;159-78.
<https://doi.org/10.1016/B978-0-12-816770-0.00010-1>
45. Zheng X, Xie J, Zhang X, *et al.* An overview of polymeric nanomicelles in clinical trials and on the market. *Chin Chem Lett* 2021 Jan;32(1):243-57.
<https://doi.org/10.1016/j.ccl.2020.11.029>
46. Ding H, Su L, Xie Z, *et al.* Morphological insights in oxidative sensitive nanocarrier pharmacokinetics, targeting, and photodynamic therapy. *J Mater Chem B* 2025;13(12):3852-63.
<https://doi.org/10.1039/D4TB02194K>
47. Hsu H, Bugno J, Lee S, Hong S. Dendrimer-based nanocarriers: A versatile platform for drug delivery. *WIREs Nanomed Nanobiotech* 2017 Jan;9(1):e1409.
<https://doi.org/10.1002/wnan.1409>
48. Dey AD, Bigham A, Esmaili Y, *et al.* Dendrimers as nanoscale vectors: Unlocking the bars of cancer therapy. *Semin Cancer Biol* 2022 Nov;86:396-419.
<https://doi.org/10.1016/j.semcancer.2022.06.003>
49. Bharadwaj P, Roullin VG, Chain JL. Crossing the blood-brain barrier: Advances in dendrimer-based nanocarriers for central nervous system delivery. *Nanoscale* 2025;17(40):23202-27.
<https://doi.org/10.1039/D5NR02548F>
50. Svenson S. The dendrimer paradox - high medical expectations but poor clinical translation. *Chem Soc Rev* 2015;44(12):4131-44. <https://doi.org/10.1039/C5CS00288E>
51. Mignani S, Shi X, Guidolin K, *et al.* Clinical diagonal translation of nanoparticles: Case studies in dendrimer nanomedicine. *J Controlled Release* 2021 Sep;337:356-70.
<https://doi.org/10.1016/j.jconrel.2021.07.036>
52. Zhang W, Yu W, Ding X, *et al.* Self-assembled thermal gold nanorod-loaded thermosensitive liposome-encapsulated ganoderic acid for antibacterial and cancer photo-chemotherapy. *Artif Cells Nanomed Biotech* 2019 Dec 4;47(1):406-19.
<https://doi.org/10.1080/21691401.2018.1559177>
53. Werengowska-Ciećwierz K, Wiśniewski M, Terzyk AP, Furmaniak S. The chemistry of bioconjugation in nanoparticles-based drug delivery system. *Adv Condens Matter Phys* 2015;2015:1-27.
<https://doi.org/10.1155/2015/198175>
54. Ciftci F, Özarslan AC, Kantarci İC, *et al.* Advances in drug targeting, drug delivery, and nanotechnology applications: Therapeutic significance in cancer treatment. *Pharmaceutics* 2025 Jan 16; 17(1):121.
<https://doi.org/10.3390/pharmaceutics17010121>
55. Kumar M, Jha A, Dr M, Mishra B. Targeted drug nanocrystals for pulmonary delivery: A potential strategy for lung cancer therapy. *Expert Opin Drug Deliv* 2020 Oct 2; 17(10):1459-72.
<https://doi.org/10.1080/17425247.2020.1798401>
56. Mi P. Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. *Theranostics* 2020;10(10):4557-88. <https://doi.org/10.7150/thno.38069>

57. Deirram N, Zhang C, Kermaniyan SS, et al. pH-responsive polymer nanoparticles for drug delivery. *Macromol Rapid Commun* 2019 May;40(10):1800917. <https://doi.org/10.1002/marc.201800917>
58. Thomas RG, Surendran SP, Jeong YY. Tumor microenvironment-stimuli responsive nanoparticles for anticancer therapy. *Front Mol Biosci* 2020 Dec 18;7:610533. <https://doi.org/10.3389/fmolb.2020.610533>
59. Fleige E, Quadir MA, Haag R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: Concepts and applications. *Adv Drug Deliv Rev* 2012 Jun;64(9):866-84. <https://doi.org/10.1016/j.addr.2012.01.020>
60. Dunkel P, Ilaš J. Targeted cancer therapy using compounds activated by light. *Cancers* 2021 Jun 29;13(13):3237. <https://doi.org/10.3390/cancers13133237>
61. Shan C, Ru J, Zhang M, et al. A novel drug-drug nanohybrid for the self-delivery of porphyrin and cis -platinum. *RSC Adv* 2019;9(63):37003-8. <https://doi.org/10.1039/C9RA07085K>
62. Roma-Rodrigues C, Raposo LR, Valente R, et al. Combined cancer therapeutics-Tackling the complexity of the tumor microenvironment. *WIREs Nanomed Nanobiotech* 2021 Sep;13(5):e1704. <https://doi.org/10.1002/wnan.1704>
63. Huang D, Qian H, Qiao H, et al. Bioresponsive functional nanogels as an emerging platform for cancer therapy. *Expert Opin Drug Deliv* 2018 Jul 3;15(7):703-16. <https://doi.org/10.1080/17425247.2018.1497607>
64. Solanki R, Bhatia D. Stimulus-responsive hydrogels for targeted cancer therapy. *Gels* 2024 Jul 1;10(7):440. <https://doi.org/10.3390/gels10070440>
65. Chen J, Wang Y, Ma B, et al. Biodegradable hollow mesoporous organosilica-based nanosystems with dual stimuli-responsive drug delivery for efficient tumor inhibition by synergistic chemo- and photothermal therapy. *Appl Mater Today* 2020 Jun;19:100655. <https://doi.org/10.1016/j.apmt.2020.100655>
66. Toropova Y, Korolev D, Istomina M, et al. Controlling the movement of magnetic iron oxide nanoparticles intended for targeted delivery of cytostatics. *Int J Nanomed* 2021; 16:5651-64. <https://doi.org/10.2147/IJN.S318200>
67. Lan H, Jamil M, Ke G, Dong N. The role of nanoparticles and nanomaterials in cancer diagnosis and treatment: A comprehensive review. *Am J Cancer Res* 2023;13(12):5751-84.
68. Price PM Mahmoud WE, Al-Ghamdi AA, Bronstein LM. Magnetic drug delivery: Where the field is going. *Front Chem* 2018 Dec 11;6:619. <https://doi.org/10.3389/fchem.2018.00619>
69. Cai W, Wang J, Chu C, et al. Metal-Organic Framework-based stimuli-responsive systems for drug delivery. *Adv Sci* 2019 Jan;6(1):1801526. <https://doi.org/10.1002/advs.201801526>
70. Hoare T, Santamaria J, Goya GF, et al. A magnetically-triggered composite membrane for on-demand drug delivery 2011. <https://doi.org/10.48550/ARXIV.1103.4711>
71. Chen Y, Chen H, Shi J. Inorganic nanoparticle-based drug codelivery nanosystems to overcome the multidrug resistance of cancer cells. *Mol Pharm* 2014 Aug 4;11(8):2495-510. <https://doi.org/10.1021/mp400596v>
72. Munawar J, Khan MS, Zehra Syeda SE, et al. Metal-organic framework-based smart nanoplatforams for biosensing, drug delivery, and cancer theranostics. *Inorg Chem Commun* 2023 Jan;147:110145. <https://doi.org/10.1016/j.inoche.2022.110145>
73. Ali Hazis NU, Aneja N, Rajabalaya R, David SR. Systematic patent review of nanoparticles in drug delivery and cancer therapy in the last decade. *Recent Adv Drug Deliv Formul* 2021 Sep 24;15(1):59-74. <https://doi.org/10.2174/1872211314666210521105534>
74. Mucicoy S, Álvarez Echazú MI, Antezana PE, et al. Stimuli-responsive materials for tissue engineering and drug delivery. *Int J Mol Sci* 2020 Jul 2;21(13):4724. <https://doi.org/10.3390/ijms21134724>
75. Teixeira Do Nascimento A, Stoddart PR, Goris T, et al. Stimuli-responsive materials for biomedical applications. *Adv Mater* 2025 Sep; 37(36):e07559. <https://doi.org/10.1002/adma.202507559>
76. Seynhaeve ALB, Amin M, Haemmerich D, et al. Hyperthermia and smart drug delivery systems for solid tumor therapy. *Adv Drug Deliv Rev* 2020;163-164:125-44. <https://doi.org/10.1016/j.addr.2020.02.004>
77. Amin M, Huang W, Seynhaeve ALB, Ten Hagen TLM. Hyperthermia and temperature-sensitive nanomaterials for spatiotemporal drug delivery to solid tumors. *Pharmaceutics* 2020 Oct 22;12(11):1007. <https://doi.org/10.3390/pharmaceutics12111007>
78. Sponchioni M, Capasso Palmiero U, Moscatelli D. Thermo-responsive polymers: Applications of smart materials in drug delivery and tissue engineering. *Mater Sci Eng C* 2019 Sep;102:589-605. <https://doi.org/10.1016/j.msec.2019.04.069>
79. Zheng R, Yu C, Yao D, et al. Engineering stimuli-responsive materials for precision medicine. *Small* 2025 Jan;21(1):2406439. <https://doi.org/10.1002/sml.202406439>
80. Liu D, Yang F, Xiong F, Gu N. The smart drug delivery system and its clinical potential. *Theranostics* 2016;6(9):1306-23. <https://doi.org/10.7150/thno.14858>
81. Gonçalves A, Cabrita R, Matos J, et al. Dual-stimuli-responsive poly(vinyl alcohol) nanofibers for localized cancer treatment: Magnetic hyperthermia and drug release studies. *J Drug Deliv Sci Technol* 2024 Apr;94:105492. <https://doi.org/10.1016/j.jddst.2024.105492>
82. Raza A, Rasheed T, Nabeel F, et al. Endogenous and exogenous stimuli-responsive drug delivery systems for programmed site-specific release. *Molecules* 2019 Mar 21;24(6):1117. <https://doi.org/10.3390/molecules24061117>
83. Ranjbari J, Mokhtarzadeh A, Alibakhshi A, et al. Anti-cancer drug delivery using carbohydrate-based polymers. *Curr Pharm Des* 2018 Feb 12;23(39):6019-32. <https://doi.org/10.2174/1381612823666170505124927>
84. Wickens JM, Alsaab HO, Kesharwani P, et al. Recent advances in hyaluronic acid-decorated nanocarriers for targeted cancer therapy. *Drug Discov Today* 2017;22(4):665-80. <https://doi.org/10.1016/j.drudis.2016.12.009>
85. Srinivasan M, Rajabi M, Mousa S. Multifunctional nanomaterials and their applications in drug delivery and cancer therapy. *Nanomaterials* 2015 Oct 14;5(4):1690-703. <https://doi.org/10.3390/nano5041690>
86. Afzal O, Altamimi ASA, Nadeem MS, et al. Nanoparticles in drug delivery: From History to Therapeutic Applications. *Nanomaterials* 2022 Dec 19;12(24):4494. <https://doi.org/10.3390/nano12244494>
87. Veselov VV, Nosyrev AE, Jicsinszky L, et al. Targeted delivery methods for anticancer drugs. *Cancers* 2022 Jan 26;14(3):622. <https://doi.org/10.3390/cancers14030622>
88. Sonam B Bisen. Review on nanoparticles used in drug delivery for cancer. *GSC Biol Pharm Sci* 2021;16(1):062-9. <https://doi.org/10.30574/gscbps.2021.16.1.0194>
89. Chai M, Wang S, Chen Y, et al. Targeted and intelligent nano-drug delivery systems for colorectal cancer treatment. *Front Bioeng Biotechnol* 2025 Apr 25;13:1582659. <https://doi.org/10.3389/fbioe.2025.1582659>
90. Vergaro V, Scarlino F, Bellomo C, et al. Drug-loaded polyelectrolyte microcapsules for sustained targeting of cancer cells. *Adv Drug Deliv Rev* 2011 Aug;63(9):847-64. <https://doi.org/10.1016/j.addr.2011.05.007>
91. Hossein MN. Polymeric nanostructures as colloidal drug delivery systems: Thermosensitive hydrogels containing self-assembled micelles. *J Nanomed Nanotech* 2015;06:4. <https://doi.org/10.4172/2157-7439.1000301>
92. Imam SS, Alshehri S, Ghoneim MM, et al. Recent advancement in chitosan-based nanoparticles for improved oral bioavailability and bioactivity of phytochemicals: Challenges and perspectives. *Polymers* 2021 Nov 22;13(22):4036. <https://doi.org/10.3390/polym13224036>
93. Alkanawati MS, Machtakova M, Landfester K, Thérien-Aubin H. Bio-orthogonal nanogels for multiresponsive release. *Biomacromol* 2021 Jul 12;22(7):2976-84. <https://doi.org/10.1021/acs.biomac.1c00378>
94. Jiang Y, Yan C, Li M, et al. Delivery of natural products via polysaccharide-based nanocarriers for cancer therapy: A review on recent advances and future challenges. *Int J Biol Macromol* 2024 Oct;278:135072. <https://doi.org/10.1016/j.ijbiomac.2024.135072>
95. Wang H, Hunter R, Zhang Q, et al. The application of marine polysaccharides to antitumor nanocarriers. *Carbohydr Polym* 2024 Oct;342:122407.

- <https://doi.org/10.1016/j.carbpol.2024.122407>
96. Wu D, Li Y, Dai Y, et al. Stabilization of chitosan-based nanomedicines in cancer therapy: A review. *Int J Biol Macromol* 2025 May;309:143016. <https://doi.org/10.1016/j.ijbiomac.2025.143016>
 97. Bhat AA, Gupta G, Alharbi KS, et al. Polysaccharide-based nanomedicines targeting lung cancer. *Pharmaceutics* 2022 Dec 13;14(12):2788. <https://doi.org/10.3390/pharmaceutics14122788>
 98. Li Q, Liu X, Yan C, et al. Polysaccharide-based stimulus-responsive nanomedicines for combination cancer immunotherapy. *Small* 2023 Jun;19(23):2206211. <https://doi.org/10.1002/smll.202206211>
 99. Zeng Y, Xiang Y, Sheng R, et al. Polysaccharide-based nanomedicines for cancer immunotherapy: A review. *Bioact Mater* 2021 Oct;6(10):3358-82. <https://doi.org/10.1016/j.bioactmat.2021.03.008>
 100. Hari SK, Gauba A, Shrivastava N, et al. Polymeric micelles and cancer therapy: An ingenious multimodal tumor-targeted drug delivery system. *Drug Deliv Transl Res* 2023 Jan;13(1):135-63. <https://doi.org/10.1007/s13346-022-01197-4>
 101. Yu G, Yang Z, Fu X, et al. Polyrotaxane-based supramolecular theranostics. *Nat Commun* 2018 Feb 22;9(1):766. <https://doi.org/10.1038/s41467-018-03119-w>
 102. Hwang D, Ramsey JD, Kabanov AV. Polymeric micelles for the delivery of poorly soluble drugs: From nanoformulation to clinical approval. *Adv Drug Deliv Rev* 2020;156:80-118. <https://doi.org/10.1016/j.addr.2020.09.009>
 103. Sun H, Meng F, Cheng R, et al. Reduction-responsive polymeric micelles and vesicles for triggered intracellular drug release. *Antioxid Redox Signal* 2014 Aug 10;21(5):755-67. <https://doi.org/10.1089/ars.2013.5733>
 104. Fan W, Zhang L, Li Y, Wu H. Recent progress of crosslinking strategies for polymeric micelles with enhanced drug delivery in cancer therapy. *Curr Med Chem* 2019 Jul 8;26(13):2356-76. <https://doi.org/10.2174/0929867324666171121102255>
 105. Zheng Y, Oz Y, Gu Y, et al. Rational design of polymeric micelles for targeted therapeutic delivery. *Nano Today* 2024 Apr;55:102147. <https://doi.org/10.1016/j.nantod.2024.102147>
 106. Cho S, Rasoulianboroujeni M, Kang RH, Kwon GS. From conventional to next-generation strategies: Recent advances in polymeric micelle preparation for drug delivery. *Pharmaceutics* 2025 Oct 21;17(10):1360. <https://doi.org/10.3390/pharmaceutics17101360>
 107. Kotta S, Aldawsari HM, Badr-Eldin SM, et al. Progress in polymeric micelles for drug delivery applications. *Pharmaceutics* 2022 Aug 5;14(8):1636. <https://doi.org/10.3390/pharmaceutics14081636>
 108. Radeva L, Yordanov Y, Spassova I, et al. Double-loaded doxorubicin/resveratrol polymeric micelles providing low toxicity on cardiac cells and enhanced cytotoxicity on lymphoma cells. *Pharmaceutics* 2023 Apr 19;15(4):1287. <https://doi.org/10.3390/pharmaceutics15041287>
 109. Talegaonkar S, Ahmad A, Tariq M, et al. Emerging trends in oral bioavailability enhancement. *Int J Drug Regul Aff* 2018 Feb 11;1(2):20-38. <https://doi.org/10.22270/ijdra.v1i2.108>
 110. Romberg B, Hennink WE, Storm G. Sheddable coatings for long-circulating nanoparticles. *Pharm Res* 2008 Jan;25(1):55-71. <https://doi.org/10.1007/s11095-007-9348-7>
 111. Chen YC, Chang CJ, Hsiue GH, Chiang YT. Doxorubicin-loaded mixed micelles using degradable graft and diblock copolymers to enhance anticancer sensitivity. *Cancers* 2021 Jul 29;13(15):3816. <https://doi.org/10.3390/cancers13153816>
 112. Chan JM, Valencia PM, Zhang L, et al. Polymeric nanoparticles for drug delivery. *Cancer Nanotechnology*. Humana Press. *Methods in Molecular Biology* 2010; 163:75. https://doi.org/10.1007/978-1-60761-609-2_11
 113. Ioele G, Chieffallo M, Occhiuzzi MA, et al. Anticancer drugs: Recent strategies to improve stability profile, pharmacokinetic and pharmacodynamic properties. *Molecul* 2022;27(17):5436. <https://doi.org/10.3390/molecules27175436>
 114. Andhari SS, Wavhale RD, Dhobale KD, et al. Self-propelling targeted magneto-nanobots for deep tumor penetration and pH-responsive intracellular drug delivery. *Sci Rep* 2020 Mar 13;10(1):4703. <https://doi.org/10.1038/s41598-020-61586-y>
 115. Pantshwa JM, Kondiah PPD, Choonara YE, et al. Nanodrug delivery systems for the treatment of ovarian cancer. *Cancer* 2020 Jan 15;12(1):213. <https://doi.org/10.3390/cancers12010213>
 116. Zheng Y, Gao Y. Molecular targeted nanotheranostics for future individualized cancer treatment. *Expert Opin Drug Deliv* 2020 Aug 2;17(8):1059-62. <https://doi.org/10.1080/17425247.2020.1772748>
 117. Wang X, Li C, Wang Y, et al. Smart drug delivery systems for precise cancer therapy. *Acta Pharm Sin B* 2022;12(11):4098-121. <https://doi.org/10.1016/j.apsb.2022.08.013>
 118. Alasvand N, Urbanska AM, Rahmati M, et al. Therapeutic nanoparticles for targeted delivery of anticancer drugs. *Multifunc Systems Comb Deliv Biosensing Diagnost Elsevier*; 2017:245-59. <https://doi.org/10.1016/B978-0-323-52725-5.00013-7>
 119. Sakamoto JH, Van De Ven AL, Godin B, et al. Enabling individualized therapy through nanotechnology. *Pharmacol Res* 2010 Aug;62(2):57-89. <https://doi.org/10.1016/j.phrs.2009.12.011>
 120. Cainelli F, Vallone. Safety and efficacy of pegylated liposomal doxorubicin in HIV-associated Kaposi's sarcoma. *Biol Targets Ther* 2009 Aug;385. <https://doi.org/10.2147/BTT.S3915>
 121. Chang TC, Shiah HS, Yang CH, et al. Phase I study of nanoliposomal irinotecan (PEP02) in advanced solid tumor patients. *Cancer Chemother Pharmacol* 2015 Mar;75(3):579-86. <https://doi.org/10.1007/s00280-014-2671-x>
 122. Bawa R, Audette GF, Rubinstein I. *Handbook of clinical nanomedicine: Nanoparticles, imaging, therapy, and clinical applications*. Jenny Stanford Publishing; 2016. <https://doi.org/10.1201/b19915>
 123. Tomao S. Albumin-bound formulation of paclitaxel (Abraxane ABI-007; ABI-007) in the treatment of breast cancer. *Int J Nanomed* 2009;99. <https://doi.org/10.2147/IJN.S3061>
 124. Kim TY, Kim DW, Chung JY, et al. Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. *Clin Cancer Res Off J Am Assoc Cancer Res* 2004 Jun 1;10(11):3708-16. <https://doi.org/10.1158/1078-0432.CCR-03-0655>
 125. Tran S, DeGiovanni P, Piel B, Rai P. Cancer nanomedicine: A review of recent success in drug delivery. *Clin Transl Med* 2017 Dec;6(1):e44. <https://doi.org/10.1186/s40169-017-0175-0>
 126. Silverman JA, Deitcher SR. Marqibo® (vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. *Cancer Chemother Pharmacol* 2013 Mar;71(3):555-64. <https://doi.org/10.1007/s00280-012-2042-4>
 127. A Phase 0 first-in-human study using NU-0129: A Spherical Nucleic Acid (SNA) gold nanoparticle targeting BCL2L12 in recurrent glioblastoma multiforme or gliosarcoma patients 2017; NCT03020017. <https://clinicaltrials.gov/study/NCT03020017>
 128. A Randomized, Open-label phase 2 study of Nanoliposomal Irinotecan (Nal-IRD)-containing regimens versus nab-paclitaxel plus gemcitabine in patients with previously untreated. *Metastatic Pancreatic Adenocarcinoma* 2015. <https://clinicaltrials.gov/study/NCT02551991>
 129. Phase 1 Dose-escalating Study of MM-398 (Irinotecan sucrosolate liposome injection) plus intravenous cyclophosphamide in recurrent or refractory pediatric solid tumors 2013; NCT02013336. <https://clinicaltrials.gov/study/NCT02013336>
 130. Resilient: A randomized, open label phase 3 study of irinotecan liposome injection (ONIVYDE®) versus topotecan in patients with small cell lung cancer who have progressed on or after platinum-based first-line therapy 2017; NCT03088813. <https://clinicaltrials.gov/study/NCT03088813>
 131. A phase ii trial of doxorubicin and genexol-PM in patients with advanced breast cancer 2013; NCT01784120. <https://clinicaltrials.gov/study/NCT01784120>
 132. Phase II study of weekly Genexol®-PM plus gemcitabine in subjects with recurrent and metastatic adenocarcinoma of the pancreas 2016; NCT02739633. <https://clinicaltrials.gov/study/NCT02739633>

133. A Phase II study of weekly Genexol-PM in patients with advanced hepatocellular carcinoma after failure of sorafenib 2016; NCT03008512. <https://clinicaltrials.gov/study/NCT03008512>
134. A Phase I/II trial of EP0057, a nanoparticle camptothecin with olaparib in patients with relapsed/refractory small cell lung, bladder and prostate cancers 2016; NCT02769962. <https://clinicaltrials.gov/study/NCT02769962>
135. Pilot trial of CRLX101 in the treatment of patients with advanced gastric, gastroesophageal, or esophageal squamous or adenocarcinoma 2012; NCT01612546. <https://clinicaltrials.gov/study/NCT01612546>
136. A study of MRI/US fusion imaging and biopsy in combination with nanoparticle directed focal therapy for ablation of prostate tissue 2016; NCT02680535. <https://clinicaltrials.gov/study/NCT02680535>
137. Anselmo AC, Mitragotri S. A review of clinical translation of inorganic nanoparticles. *AAPS J* 2015 Sep;17(5):1041-54. <https://doi.org/10.1208/s12248-015-9780-2>
138. A Randomized phase 2 study of vincristine versus sirolimus to treat high risk kaposiform Hemangioendothelioma (KHE). 2014; NCT02110069. <https://clinicaltrials.gov/study/NCT02110069>
139. Anti-EGFR-immunoliposomes loaded with doxorubicin in patients with advanced triple negative EGFR positive breast cancer - A multicenter single arm phase II Trial 2016; NCT02833766. <https://clinicaltrials.gov/study/NCT02833766>
140. A phase 1/2 study of mitoxantrone hydrochloride liposome infusion in patients with non-Hodgkin's lymphoma 2016; NCT02856685. <https://clinicaltrials.gov/study/NCT02856685>
141. Cortes JE, Goldberg SL, Feldman EJ, et al. Phase II, multicenter, randomized trial of CPX-351 (cytarabine:daunorubicin) liposome injection versus intensive salvage therapy in adults with first relapse AML. *Cancer* 2015 Jan 15;121(2):234-42. <https://doi.org/10.1002/ncr.28974>
142. A phase Ib dose escalation study on the safety, tolerability and activity of liposomal curcumin in patients with locally advanced or metastatic cancer [Internet]. 2014 [cited 2014 Mar 1]. Located at: NCT02138955. <https://clinicaltrials.gov/study/NCT02138955>
143. Senzer N, Nemunaitis J, Nemunaitis D, et al. Phase I study of a systemically delivered p53 nanoparticle in advanced solid tumors. *Mol Ther* 2013 May; 21(5):1096-103. <https://doi.org/10.1038/mt.2013.32>
144. Phase II study of combined temozolomide and targeted P53 gene therapy (SGT-53) for treatment of patients with recurrent glioblastoma 2014; NCT02340156. <https://clinicaltrials.gov/study/NCT02340156>
145. Phase II study of combined targeted p53 gene therapy (SGT-53) plus gemcitabine/nab-paclitaxel for treatment of metastatic pancreatic cancer 2014; NCT02340117. <https://clinicaltrials.gov/study/NCT02340117>
146. Phase I/II study to evaluate the safety and tolerability of LiPlaCis (Liposomal Cisplatin Formulation) in patients with advanced or refractory tumours 2013; NCT01861496. <https://clinicaltrials.gov/study/NCT01861496>
147. A Phase I, dose-escalating, safety study of an intravenously administered pegylated liposomal mitomycin-C Lipid-based Prodrug (PL-MLP, PROMITIL) in cancer patients with solid tumors 2012; NCT01705002. Available from: <https://clinicaltrials.gov/study/NCT01705002>
148. Efficacy and tolerability of nanoparticle albumin bound paclitaxel (abraxane) in patients 65 and older with locally advanced or metastatic breast cancer 2011; NCT01463072. <https://clinicaltrials.gov/study/NCT01463072>
149. Gao Z, Mansor MH, Winder N, et al. Microfluidic-assisted ZIF-silk-polydopamine nanoparticles as promising drug carriers for breast cancer therapy. *Pharmaceutics* 2023;15(7):1811. <https://doi.org/10.3390/pharmaceutics15071811>
150. Ejigah V, Owoseni O, Bataille-Backer P, et al. Approaches to improve macromolecule and nanoparticle accumulation in the tumor microenvironment by the enhanced permeability and retention effect. *Polymers* 2022 Jun 27;14(13):2601. <https://doi.org/10.3390/polym14132601>
151. Gavas S, Quazi S, Karpinski TM. Nanoparticles for cancer therapy: Current progress and challenges. *Nanoscale Res Lett* 2021;16(1):173. <https://doi.org/10.1186/s11671-021-03628-6>
152. Chehelgerdi M, Chehelgerdi M, Allela OQB, et al. Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. *Mol Cancer* 2023 Oct 9;22(1):169. <https://doi.org/10.1186/s12943-023-01865-0>
153. Cheng Z, Li M, Dey R, Chen Y. Nanomaterials for cancer therapy: Current progress and perspectives. *J Hematol Oncol J Hematol Oncol* 2021 Dec; 14(1):85. <https://doi.org/10.1186/s13045-021-01096-0>
154. Sun R, Xiang J, Zhou Q, et al. The tumor EPR effect for cancer drug delivery: Current status, limitations, and alternatives. *Adv Drug Deliv Rev* 2022 Dec;191:114614. <https://doi.org/10.1016/j.addr.2022.114614>
155. Abdullah KM, Sharma G, Singh AP, Siddiqui JA. Nanomedicine in cancer therapeutics: current perspectives from bench to bedside. *Mol Cancer* 2025 Jun 9;24(1):169. <https://doi.org/10.1186/s12943-025-02368-w>
156. Zi Y, Yang K, He J, et al. Strategies to enhance drug delivery to solid tumors by harnessing the EPR effects and alternative targeting mechanisms. *Adv Drug Deliv Rev* 2022 Sep;188:114449. <https://doi.org/10.1016/j.addr.2022.114449>
157. Rana I, Oh J, Baig J, et al. Nanocarriers for cancer nanomedicine. *Drug Deliv Transl Res* 2023 Jul;13(7):1936-54. <https://doi.org/10.1007/s13346-022-01241-3>
158. Shi Y, Van Der Meel R, Chen X, Lammers T. The EPR effect and beyond: Strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. *Theranostics* 2020;10(17):7921-4. <https://doi.org/10.7150/thno.49577>
159. Aldhubiab B, Almuqbil RM, Nair AB. Harnessing the power of nanocarriers to exploit the tumor microenvironment for enhanced cancer therapy. *Pharmaceutics* 2025 May 19;18(5):746. <https://doi.org/10.3390/ph18050746>
160. Vagena IA, Malapani C, Gatou MA, et al. Enhancement of EPR effect for passive tumor targeting: Current status and future perspectives. *Appl Sci* 2025 Mar 14;15(6):3189. <https://doi.org/10.3390/app15063189>
161. Fan D, Cao Y, Cao M, et al. Nanomedicine in cancer therapy. *Signal Transduct Target Ther* 2023 Aug 7;8(1):293. <https://doi.org/10.1038/s41392-023-01536-y>
162. Trofin AM, Scripcariu DV, Filipciuc SI, et al. From nature to nanomedicine: Enhancing the antitumor efficacy of rhein, curcumin, and resveratrol. *Medicina (Mex)* 2025 May 26;61(6):981. <https://doi.org/10.3390/medicina61060981>
163. Akinc A, Maier MA, Manoharan M, et al. The onpatro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. *Nat Nanotechnol* 2019 Dec;14(12):1084-7. <https://doi.org/10.1038/s41565-019-0591-y>
164. Yao Y, Zhou Y, Liu L, et al. Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. *Front Mol Biosci* 2020 Aug 20;7:193. <https://doi.org/10.3389/fmolb.2020.00193>
165. Zhao Q, Cheng N, Sun X, Yan L, Li W. The application of nanomedicine in clinical settings. *Front Bioeng Biotech* 2023; 11:1219054. <https://doi.org/10.3389/fbioe.2023.1219054>
166. Mahdavi Firouzabadi B, Gigliobianco MR, Joseph JM, Censi R, Di Martino P. Design of nanoparticles in cancer therapy based on tumor microenvironment properties. *Pharmaceutics* 2022;14(12):2708. <https://doi.org/10.3390/pharmaceutics14122708>
167. Qiao W, Wang B, Wang Y, et al. Cancer therapy based on nanomaterials and nanocarrier systems. *J Nanomater* 2010; 2010(1):796303. <https://doi.org/10.1155/2010/796303>
168. Zein R, Sharrouf W, Selting K. Physical properties of nanoparticles that result in improved cancer targeting. *J Oncol* 2020; 1-16. <https://doi.org/10.1155/2020/5194780>
169. Gonçalves M, Mignani S, Rodrigues J, Tomás H. A glance over doxorubicin based-nanotherapeutics: From proof-of-concept studies to solutions in the market. *J Controlled Release* 2020;317:347-74. <https://doi.org/10.1016/j.jconrel.2019.11.016>
170. Montané X, Bajek A, Roszkowski K, et al. Encapsulation for cancer therapy. *Molecules* 2020 Mar 31;25(7):1605. <https://doi.org/10.3390/molecules25071605>
171. Gidwani B, Vyas A. A comprehensive review on cyclodextrin-based carriers for delivery of chemotherapeutic cytotoxic anticancer drugs. *BioMed Res Int* 2015;2015:1-15. <https://doi.org/10.1155/2015/198268>
172. Victoir B, Croix C, Gouilleux F, Prié G. Targeted Therapeutic Strategies for the Treatment of Cancer. *Cancers* 2024 Jan 22; 16(2):461. <https://doi.org/10.3390/cancers16020461>

173. Majumder J, Taratula O, Minko T. Nanocarrier-based systems for targeted and site specific therapeutic delivery. *Adv Drug Deliv Rev* 2019;144:57-77. <https://doi.org/10.1016/j.addr.2019.07.010>
174. Yadav R, Chawra HS, Dubey G, et al. Herbal based nanoparticles as a possible and potential treatment of cancer: a review. *Explor Target Anti-Tumor Ther* 2025 Jan 3;6: 1002285. <https://doi.org/10.37349/etat.2025.1002285>
175. Sakhtianchi R, Atyabi F, Yousef P, et al. Targeted delivery of doxorubicin-utilizing chitosan nanoparticles surface-functionalized with anti-Her2 trastuzumab. *Int J Nanomed* 2011;1977. <https://doi.org/10.2147/IJN.S21523>
176. Luo F, Zhong T, Chen Y, et al. Dual-ligand synergistic targeting anti-tumor nanoplatfoms with cascade-responsive drug release. *Pharmaceutics* 2023 Jul 24;15(7):2014. <https://doi.org/10.3390/pharmaceutics15072014>
177. Yetisgin AA, Cetinel S, Zuvin M, Kosar A, Kutlu O. Therapeutic nanoparticles and their targeted delivery applications. *Molecules* 2020 May 8;25(9):2193. <https://doi.org/10.3390/molecules25092193>
178. Alshammari MK, Almomen EY, Alshahrani KF, et al. Nano-enabled strategies for the treatment of lung cancer: potential bottlenecks and future perspectives. *Biomedicines* 2023 ;11(2):473. <https://doi.org/10.3390/biomedicines11020473>
179. Ulldemolins A, Seras-Franzoso J, Andrade F, et al. Perspectives of nano-carrier drug delivery systems to overcome cancer drug resistance in the clinics. *Cancer Drug Resist* 2021. <https://doi.org/10.20517/cdr.2020.59>
180. Xu F, Liu Y, Que Z, et al. Recent advancements in lung cancer metastasis prevention based on nanostrategies. *Adv Sci* 2025 Jun;12(23):2409293. <https://doi.org/10.1002/advs.202409293>
181. Karthic A, Roy A, Lakkakula J, et al. Cyclodextrin nanoparticles for diagnosis and potential cancer therapy: A systematic review. *Front Cell Dev Biol* 2022; 10:984311. <https://doi.org/10.3389/fcell.2022.984311>
182. Martínez G, Merinero M, Pérez-Aranda M, et al. Environmental impact of nanoparticles' application as an emerging technology: A Review. *Materials* 2020 Dec 31;14(1):166. <https://doi.org/10.3390/ma14010166>
183. Chen X, Sun J, Ye T, Li F. Neutrophil-camouflaged stealth liposomes for photothermal-induced tumor immunotherapy through intratumoral bacterial activation. *Pharmaceutics* 2025; 17(5):614. <https://doi.org/10.3390/pharmaceutics17050614>
184. Frazier N, Ghandehari H. Hyperthermia approaches for enhanced delivery of nanomedicines to solid tumors. *Biotechnol Bioeng* 2015 Oct;112(10):1967-83. <https://doi.org/10.1002/bit.25653>
185. Chavda VP, Patel AB, Mistry KJ, et al. Nano-drug delivery systems entrapping natural bioactive compounds for cancer: Recent progress and future challenges. *Front Oncol* 2022;12: 867655. <https://doi.org/10.3389/fonc.2022.867655>
186. Kucuksayan E, Bozkurt F, Yilmaz MT, et al. A new combination strategy to enhance apoptosis in cancer cells by using nanoparticles as biocompatible drug delivery carriers. *Sci Rep* 2021 Jun 22;11(1):13027. <https://doi.org/10.1038/s41598-021-92447-x>
187. Li Y, Sun H, Cao D, et al. Overcoming biological barriers in cancer therapy: Cell membrane-based nanocarrier strategies for precision delivery. *Int J Nanomed* 2025 Mar;Volume 20:3113-45. <https://doi.org/10.2147/IJN.S497510>
188. Shao X, Zhao X, Wang B, et al. Tumor microenvironment targeted nano-drug delivery systems for multidrug resistant tumor therapy. *Theranostics* 2025 Jan 2;15(5):1689-714. <https://doi.org/10.7150/thno.103636>
189. Feng Y, Li Z, Song L, et al. A ZIF-8-based dual-modal smart responsive nanoplatfom for overcoming radiotherapy resistance in advanced tumors. *Nanoscale* 2025;17(19):12134-48. <https://doi.org/10.1039/D5NR01093D>
190. Lu Q, Kou D, Lou S, et al. Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. *J Hematol Oncol J Hematol Oncol* 2024 Apr 2;17(1):16. <https://doi.org/10.1186/s13045-024-01535-8>
191. Peng S, Xiao F, Chen M. Tumor-microenvironment-responsive nanomedicine for enhanced cancer immunotherapy. *Adv Sci* 2022;9(1): 2103836. <https://doi.org/10.1002/advs.202103836>
192. Sarma K, Akther MH, Ahmad I, et al. Adjuvant novel nanocarrier-based targeted therapy for lung cancer. *Molecules* 2024;29(5):1076. <https://doi.org/10.3390/molecules29051076>