

Review Article

CURRENT PERSPECTIVES ON APPLICATIONS OF NANOPARTICLES FOR CANCER MANAGEMENT

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ABSTRACT

In the realm of cancer diagnostics, imaging and therapeutics, nanocarrier-based drug delivery systems have gained extensive importance owing to their promising attributes and potential to enhance therapeutic effectiveness. The primary area of research revolves around formulating innovative intelligent nanocarriers such as nanoparticles (NPs) which are capable of selectively responding to cancer-specific conditions and efficiently delivering medications to target cells. These nanocarriers, whether operating in a passive or active manner, can transport loaded therapeutic cargos to the tumor site while minimizing drug elimination from the drug delivery systems. This review primarily focuses on presenting recent advancements in the development and utilization of nanoparticles in the treatment of various cancer types, such as pancreatic cancer, prostate cancer, colorectal cancer, cervical cancer, and breast cancer.

Keywords: Cancer, Nanoparticles, Drug targeting, Drug delivery, Applications

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INTRODUCTION

Cancer is characterized by uncontrolled cell growth, resulting in the formation of abnormal cell masses known as tumors. These tumor cells have the ability to multiply and spread throughout the lymphatic, circulatory, and bone marrow systems [1]. Among the various treatment options for cancer, chemotherapy is commonly used, employing chemical agents to kill or inhibit the progression of tumor cells. As tumor cells tend to proliferate rapidly, chemotherapy drugs specifically target these fast-growing cells. However, it should be noted that some normal cells in the body also exhibit rapid growth, making them susceptible to the effects of chemotherapy drugs. Furthermore, cancer medications, including biological, chemotherapy, and hormonal treatments, can reach various organs in the body through the bloodstream [2, 3]. While radiotherapy and surgery are effective treatments for localized and non-metastatic malignancies, they become less effective when tumor cells have spread to other parts of the body [4, 5]. Additionally, conventional medicines often have limited solubility, bioavailability, and therapeutic benefits. Moreover, administering them in high doses can lead to increased toxicity, which needs to be carefully managed. Therefore, the development and advancement of nanotechnology-based drug delivery systems, such as nanoparticles (NPs), have emerged as a significant breakthrough in cancer treatment [6]. An attempt has been made to report such advancements over the last decade in the area of NPs in this present piece of writing by referring to scientific literature and findings from different reputed journals by using keywords such as cancer, nanotechnology, nanotechnology for different types of cancer, etc.

Nanotechnology is a rapidly advancing field that involves the manipulation of NPs, which are solid supramolecular structures with sizes ranging from 10 to 1000 nm. These NPs hold tremendous potential in the field of cancer management, as they can encapsulate, entrap, dissolve, or attach a wide variety of drugs, serving as a reservoir for therapeutic agents. In recent times, NPs have garnered significant interest due to their capabilities as drug carriers, their potential in biomedicine as targeting systems, their applications in bio-imaging, and their ability to facilitate controlled drug release. By utilizing nanocarriers, medications can be protected from degradation, their half-life in the bloodstream can be extended, and

renal clearance can be reduced. Nanocarriers also enhance the effectiveness of cytotoxic drugs, regulate the release kinetics of antitumor medications, and improve the solubility of chemicals [1, 7, 4, 6]. These intelligent nanocarriers, specifically designed for tumor targeting, offer several advantages, including enhanced drug release, improved pharmacodynamic and pharmacokinetic profiles, enhanced intracellular and internalization delivery, controlled and specific targeting, and most importantly, reduced toxicity effects [7-9]. Tumors often exhibit characteristics such as leaky blood vessels and poor lymphatic drainage. In this context, two key types of drug targeting approaches are utilized: active targeting and passive targeting.

Passive targeting

Passive targeting of tumor cells can be accomplished through the exploitation of the enhanced permeability and retention (EPR) effect, which is characteristic of tumor tissues. This effect arises due to the presence of leaky endothelium in tumor vasculature, resulting in a higher accumulation rate of drug-loaded nanocarriers within the tumor compared to healthy tissues. Additionally, the compromised lymphatic system in tumors contributes to the retention of nanoparticles, and both these phenomena collectively define the EPR effect [10]. Passive targeting offers a significant improvement in specificity, around 20-30%, when compared to healthy organs. The effectiveness of EPR-based passive targeting relies on various factors related to nanocarrier properties, such as size, charge, and surface chemistry, as well as the challenges associated with achieving precise cell targeting within malignant tumors [11, 12]. The EPR effect can be further enhanced if smart nanocarriers are able to evade immune surveillance and circulate in the bloodstream for an extended period. This would allow for relatively high concentrations of drug-loaded smart nanocarriers to accumulate at the tumor site within 24-48 h, surpassing the levels observed in normal cells [13].

Active targeting

Active targeting involves the use of surface-modified targeted nanoparticles [14-17]. Tumor cells often exhibit increased expression of specific cell surface antigens and molecules like folic acid. In active targeting, drug-loaded nanocarriers are coupled with ligands that can recognize and bind to these overexpressed targets

on the tumor cell surface. Various ligands have been extensively studied, including antibodies, peptides, aptamers, transferrin, and folate [18]. To overcome the limited water solubility of certain organic solutes, functional organic compounds are typically encapsulated within nanoparticles. Additionally, hydrophilic

coatings on the nanoparticle surface can be combined with amphiphilic surfactants, enabling the effective delivery and distribution of insoluble organic solutes in an aqueous phase [19, 20]. Fig. 1 depicts a schematic representation of diverse applications of NPs in different types of cancer.

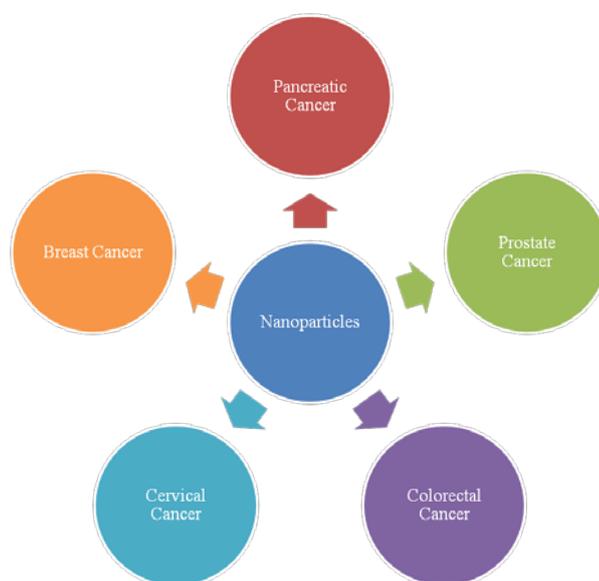


Fig. 1: Schematic presentation of applications of NPs in different types of cancer

Nanoparticles for pancreatic cancer (PC)

Pancreatic cancer (PC) is a highly lethal solid tumor, causing over 250,000 deaths annually worldwide. It is predominantly diagnosed in individuals aged 40 y and older, with a median age of 71 at diagnosis. The incidence of PC varies from 1 to 10 cases per 100,000 people globally, with higher rates observed in developed countries [21]. PC ranks as the eighth leading cause of cancer-related deaths in both men and women globally, and according to the American Cancer Society, it has become the third leading cause of cancer-related deaths in the United States [22, 23]. With a five-year survival rate of less than 5%, PC is a devastating malignancy primarily affecting the exocrine pancreas. The majority (over 90%) of pancreatic malignancies are classified as PC, with approximately 60-70% of cases occurring in the head, neck, or uncinate process of the pancreas. Tumor presentations in the body and tail regions are less common, accounting for 5-10% and 10-15% of PC cases, respectively [24]. At the microscopic level, PC tumors are surrounded by a dense stroma composed of intracellular fibroblasts, inflammatory cells, and extracellular matrix (ECM). The complex interactions between tumor and stromal cells lead to the activation of various signaling pathways, such as TGF- β /SMAD, HGF/Met, matrix metalloproteinases, Hedgehog, and Wnt, through paracrine and autocrine mechanisms. These interactions establish an active microenvironment that promotes tumor invasion and growth [25].

Moreover, pancreatic cancer (PC) is characterized by its propensity for local invasion and distant metastasis. The management of PC is primarily determined by the disease stage at the time of diagnosis. Despite adjuvant therapies following surgery, most patients experience relapse [26-28]. The dismal prognosis of PC can be attributed to late-stage diagnosis, limited biomarkers for early screening, early metastatic spread, and the development of resistance to systemic therapies [28]. While significant progress has been made in the treatment of various tumor types, such as breast, colorectal, prostate, and cervical cancers, through targeted drug delivery strategies that target specific molecular alterations in cancer cells [29-31], the management of PC remains challenging and outcomes remain poor. Therefore, it is crucial to disseminate the latest findings and important conclusions related to PC treatment among the scientific, medical, and research communities [32].

The progression of PC is strongly influenced by the neural microenvironment. In a recent study, researchers focused on controlling the neural microenvironment to regulate the progression of PC by developing neural drug-loaded ferritin nanoparticles (Ft-NPs). These Ft-NPs were designed to target PC tumors through active targeting mechanisms, such as binding to transferrin receptor 1 (TfR1), as well as passive targeting utilizing the enhanced permeability and retention (EPR) effect exhibited by tumors. The researchers loaded carbachol (CAB), an activator of neural activity, and atropine (ATO), an inhibitor of neural activity, into Ft-NPs to create Nano-CAB NPs and Nano-ATO NPs, respectively. Nano-CAB NPs effectively stimulated the neural microenvironment, thereby promoting the progression of pancreatic tumors. On the other hand, Nano-ATO NPs inhibited the neural niche, impairing neurogenesis within tumors and impeding the progression of PC. Consequently, Ft-based nanoparticles present an efficient and safe anticancer system for the targeted delivery of neural drugs [33].

In an alternative approach, researchers investigated the use of magnetic nanoparticles (MNPs) and magnetic resonance imaging (MRI) to target survivin (SUR), an apoptosis inhibitor, in a mouse model of pancreatic tumors. The study involved conjugating survivin antisense oligonucleotide (ASON) with chitosan-coated MNPs to create SUR-MNPs. The accumulation of targeted nanoparticles, as well as non-targeted nanoparticles and nonsense oligonucleotide-MNPs (NSON-MNPs), was assessed in the spleen, kidney, liver, and tumors. The results demonstrated a higher accumulation of targeted nanoparticles in PC BxPC-3 cells compared to non-cancerous cells. Moreover, *in vivo* MRI revealed a significant reduction in T2 signal intensity in the tumors of mice treated with targeted nanoparticles, whereas minor signal changes were observed in tumors of mice treated with non-targeted nanoparticles or NSON-MNPs [34].

Another study utilizing Prussian blue staining confirmed that SUR-MNPs exhibited higher accumulation in the tumor mass compared to normal kidney, liver, and pancreatic tissues. These findings indicate that ASON-functionalized MNPs effectively localized to pancreatic tumors, suggesting the potential applicability of SUR-targeted nanoparticles for pancreatic tumor detection [35]. Given the high mortality rate of PC, with nearly 80% of patients succumbing to the disease within the first 6 mo of diagnosis, there is a pressing need

for sensitive diagnostic tools capable of detecting even small tumors at early stages. To address this, magnetic biodegradable nanoparticles were developed using recombinant human serum albumin (rHSA) incorporated into iron oxide (maghemite, γ -Fe₂O₃) nanoparticles. The target receptor chosen in this study was galectin-1, which is upregulated in PC but not in healthy pancreatic tissue or pancreatitis. Galectin-1 was covalently attached to the nanoparticle surface using tissue plasminogen activator-derived peptides (tPA-ligands) due to its high affinity for the target moieties. When administered to mice, these magnetic biodegradable nanoparticles exhibited improved targeting and imaging properties as detected by single-photon emission CT and MRI [36].

The application of ultrashort echo-time (UTE) imaging has proven effective *in vivo* for the detection of tumor-targeted iron oxide nanoparticles (IONPs) using molecular MRI. A study focused on evaluating the UTE imaging technique to enhance the detection of receptor-targeted magnetic nanoparticles in cancer xenograft models, specifically employing positive contrast. The IONPs were conjugated with ligands that target tumor cells expressing the epidermal growth factor receptor. The findings revealed that both UTE and longer echo-time (TE) imaging methods exhibited positive contrast in pancreatic tumors associated with the epidermal growth factor receptor [37]. In terms of transfection agents and their impact on tumor cell biology, the utility of polyethylenimine (PEI)-coated superparamagnetic iron oxide nanoparticles (SPIONs) was investigated. Limited information was available on the effects of PEI-coated SPIONs on pancreatic tumor cells. The study demonstrated that these nanoparticles significantly reduced the expression of MT1-MMP and MMP2 metalloproteinases and inhibited Src kinase activity, leading to powerful inhibitory effects on the migration and invasion of pancreatic tumor cells. Additionally, treatment with PEI-coated SPIONs resulted in reduced density of the pancreatic tumor cell line Pan02. These prepared nanoparticles exhibited promising properties, potentially acting as antimetastatic agents for the management of pancreatic cancer [38].

The influence of different physiological environments on the biological properties of nanoparticles has been extensively investigated. The characteristics of nanoparticles, such as charge, size, and aggregation state, are highly dependent on the biological environment and their physicochemical properties. Upon entry into the biological environment, proteins bind to the surface of nanoparticles, forming a protein coating that confers a biological identity and governs their physiological response. The study enrolled both healthy subjects and patients with histologically confirmed pancreatic cancer. Notably, cancer patients exhibited a significant decrease in the levels of clinically relevant proteins. Both groups of patients were administered two different types of lipid nanoparticles, one positively charged and the other negatively charged (plain and PEGylated). The outcomes revealed substantial alterations in zeta potential between the healthy and pancreatic cancer groups when using plain positively charged lipid nanoparticles [39].

A mathematical model consisting of three stages was developed to explain drug release, degradation, relaxation, and diffusion. The model successfully elucidated the release of PHT-427, a kinase inhibitor and anticancer molecule, encapsulated in poly(lactic-co-glycolic acid) nanoparticles (PLGA NPs). The study employed the single emulsion-solvent evaporation technique for the encapsulation of the AKT/PDK1 inhibitor in nanoparticles. The results demonstrated the successful encapsulation of the inhibitor and its efficient delivery to the intended site [40]. Furthermore, a novel approach involved the development of mesoporous silica nanoparticles (MSNPs) loaded with PTX for intraperitoneal delivery. An *in vivo* study was conducted using xenograft mice implanted with human pancreatic cancer cells (MIA PaCa-2) in the peritoneal cavity. The results demonstrated that PTX-loaded MSNPs exhibited a 3.2-fold increase in residence time within the peritoneal cavity, along with slower absorption into the systemic circulation. Compared to free PTX, PTX-loaded MSNPs showed one-third the systemic exposure and a 6.5-fold increase in accumulation within peritoneal tumors. Moreover, PTX-loaded MSNPs exhibited a 3.5-fold increase in cellular uptake by tumor cells. Thus, the intraperitoneal

administration of MSNPs proved effective in enhancing the accumulation of PTX within peritoneal tumors while reducing systemic exposure [41].

In the context of managing pancreatic cancer, the effects of cyclopamine, a potent inhibitor of the hedgehog signaling pathway with anti-fibrotic activity, on the penetration and efficacy of nanotherapeutics were investigated. For this purpose, cyclopamine nanoparticles were prepared, and the results demonstrated that they improved tumor perfusion and disrupted tumor extracellular fibronectins. These nanoparticles also alleviated tumor vessel compression and exhibited enhanced intra-tumoral distribution and accumulation. Consequently, cyclopamine nanoparticles hold significant potential for enhancing therapeutic efficacy in pancreatic cancer patients [42]. Several studies and reviews have highlighted the increased mortality rate in pancreatic cancer due to various factors, such as the growth of the stromal barrier, multidrug resistance, a hypoxic environment resulting from hypoperfusion, and the presence of cancer stem cells (CSCs). To address these challenges, a nanocarrier system was developed by combining quercetin (QUER) and 5-Fluorouracil (5-FU). Both drugs were individually and jointly loaded into chitosan nanoparticles. The results demonstrated notable entrapment efficiency of the dual-drug-loaded carrier system with chitosan: QUER: 5-FU ratio of 3:1:2. Both drugs exhibited extensive association with the chitosan matrix. Additionally, in both 2D and 3D cultures, the dual-drug-loaded carrier system exhibited significant toxicity against pancreatic cancer cells [43].

Gemcitabine (GEM)-loaded human serum albumin nanoparticles (GEM-HSA-NPs) were synthesized and evaluated for their *in vivo* effectiveness against the pancreatic cancer cell line BxPC-3. The study revealed that GEM-HSA-NPs exhibited increased encapsulation and drug-loading rates, demonstrating superior efficacy compared to free GEM [44]. Moreover, doxorubicin-loaded gold nanoparticles (DOX-GNPs) were synthesized using a green chemistry approach and evaluated for their anticancer potential against human pancreatic cancer cell lines. The synthesized DOX-GNPs were characterized and subjected to an *in vitro* anticancer assay, which demonstrated no significant difference in percentage cell viability compared to free DOX in the pancreatic cancer cell lines [45].

Nanoparticles for prostate cancer (PC)

Prostate cancer (PC) is a prevalent and recurrently diagnosed cancer among men worldwide, ranking as the second most common cancer and a leading cause of mortality with 258,000 deaths reported in 2008 [30]. In the United States alone, approximately 230,000 and 280,000 cases of PC were estimated in 2014 and 2015, respectively, while Europe reported around 417,000 cases [47, 48]. Over the past 20 y, the survival rate for various stages of PC has significantly increased from 69% to approximately 99% due to earlier detection, public awareness, and advancements in treatment. However, the death rate for PC is more than twice as high for African-American men compared to Caucasian men [49, 50]. Key risk factors include family history, age, and racial origin, although the development of PC involves interactions between environmental and endogenous factors [51]. Treatment options for PC vary depending on the type of cancer. Localized prostate cancer can be successfully treated with radiotherapy or surgery, but metastatic PC remains incurable. Chemotherapy becomes the treatment of choice after the development of castration resistance, extending the lifespan of patients by a few months [52].

Nanotechnology plays a critical role in the management of prostate cancer. In one study, thermosensitive poly(N-isopropylacrylamide-acrylamide-allylamine)-coated magnetic nanoparticles (PMNPs) were synthesized for active targeting and imaging of PC. These nanoparticles were further conjugated with prostate cancer-specific R11 peptides (R11-PMNPs). The nanoparticles exhibited superparamagnetic properties, and *in vitro* analysis demonstrated their compatibility with normal prostate epithelial cells and human dermal fibroblasts at concentrations up to 500 μ g/ml after 24 h of incubation. Moreover, prostate cancer cells PC3 and LNCaP showed higher uptake of R11-PMNPs compared to PMNPs. *In vivo* biodistribution studies confirmed increased accumulation of R11-

PMNPs in tumors compared to other vital organs, unlike PMNPs without R11 conjugation [53].

Another approach aimed to protect curcumin from oxidative degradation by encapsulating it in a nanoparticulate system with radical scavenging capabilities. pH-sensitive redox nanoparticles loaded with curcumin (RNPN) were prepared using self-assembling amphiphilic block copolymers conjugated with nitroxide radicals, which act as reactive oxygen species (ROS) scavengers. The developed curcumin-loaded RNPN system demonstrated suppressed tumor growth *in vivo*, attributed to enhanced bioavailability and significant ROS scavenging at the tumor sites [54]. Poly(lactic-co-glycolic acid)-curcumin nanoparticles (PLGA-CUR NPs) were evaluated for their therapeutic potential in prostate cancer. These nanoparticles effectively internalized into PC cells and released active curcumin in the cytosolic region, leading to improved therapeutic action. In cell proliferation studies, the prepared NPs demonstrated a significant role in inhibiting proliferation and colony formation capability of PC cells compared to free curcumin [55].

Docetaxel (DTX) is a highly effective agent for extending survival and improving the quality of life in patients with metastatic castration-resistant prostate cancer (mCRPC). However, its long-term use is limited by cumulative toxicity and the development of drug resistance. To overcome these limitations, DTX was evaluated by superficial conjugation to carboxymethylcellulose nanoparticles. Remarkably, a single dose of these synthesized nanoparticles resulted in a complete regression of PC3 tumor xenografts in mice [56].

Snake venom from *Walterinnesia aegyptia* (WEV) was demonstrated to have anti-tumor activity against prostate cancer and multiple myeloma cell lines. In this study, the isolated venom was treated with silica nanoparticles (WEV+NP) and its therapeutic efficacy was evaluated *in vivo* using mouse models. Treatment with WEV+NP significantly reduced prostate tumor volumes, increased reactive oxygen species (ROS) levels, and dynamically decreased chemokine levels. These findings highlight the potential of the developed nanoparticulate system for the sustained delivery of snake venom to prostate cancer cells [57].

Gold nanoparticles (AuNPs) serve as a versatile nanomaterial platform in biomedical research. In the context of prostate cancer, AuNPs were synthesized and functionalized to target the prostate-specific membrane antigen (PSMA) expressed in prostate cancer cells. Streptavidin-coated AuNPs conjugated with a PSMA inhibitor exhibited high and selective binding to PSMA-expressing LNCaP cells compared to non-targeted AuNPs. This designed system demonstrated its potential for targeted delivery in prostate cancer therapy [58]. Casein nanoparticles (CASNPs) were synthesized for encapsulating flutamide (FLT) to develop FLT-loaded CASNPs. The aim was to control drug release, enhance anti-cancer activity, and reduce hepatotoxicity. CASNPs exhibited sustained drug release for up to 4 d and demonstrated higher anti-tumor activity in PC-bearing rats when administered intravenously for 28 d. These NPs resulted in a significant decrease in prostate-specific antigen (PSA) serum levels and reduced relative weights of prostate tumors. Furthermore, they exhibited enhanced anti-proliferative, anti-angiogenic, and apoptotic effects compared to the drug solution [59]. Overall, nanoparticles have shown significant potential in the management of prostate cancer, providing improved drug delivery, enhanced therapeutic efficacy, and reduced side effects.

Nanoparticles for colorectal cancer

Cancer is a devastating disease that continues to claim numerous lives each year [60]. With a global increase in cancer cases, it has become one of the most significant challenges to human health, accounting for 1.8 million reported new cases and 9.6 million deaths in 2018 [61]. Colon cancer, ranking as the third most common cancer worldwide, stands as a leading cause of mortality, particularly in the United States [62, 63]. The development of colon cancer is attributed to the accumulation of genetic and epigenetic modifications, which contribute to its progression. However, early symptoms of colon cancer are often subtle and may include blood in the stool, anemia, and weight loss, manifesting predominantly in middle and advanced stages [64]. Lifestyle factors such as improper diet, smoking, and lack of physical activity also play a significant role

in promoting tumor growth. Furthermore, various factors, including cytokines, growth factors, and certain chemicals, contribute to the progression of colon cancer [65]. The lack of early detection methods and effective drug delivery strategies has made colorectal cancer a deadly disease globally. In this context, nanotechnology has emerged as a promising approach, particularly in drug delivery, targeting pathological sites with higher success rates. Nanoparticles (NPs) have gained considerable attention for their applications in the therapy and imaging of colon cancer [66-68].

In a particular study, researchers encapsulated 5-FU within biodegradable polycaprolactone nanoparticles (NPs) and discovered its effectiveness in inhibiting the proliferation of colorectal carcinoma cells compared to other NPs and the drug solution [69]. Another study demonstrated the efficacy of wheat germ agglutinin-mediated chitosan-based NPs loaded with 5-FU and epigallocatechin-3-gallate against colon cancer. These NPs exhibited prolonged circulation time and enhanced drug localization at the tumor site [70]. Magnetic NPs have also shown promise as nanocarriers in biomedical applications due to their biocompatibility and unique physicochemical properties that facilitate targeted interactions with cells. For instance, dextran-coated superparamagnetic iron oxide solid lipid NPs loaded with DOX and decorated with folate residues selectively accumulated DOX at colon tumor sites after oral administration, utilizing external stimuli driven by the tumor microenvironment [71]. Another formulation involved magnetic solid lipid NPs containing iron oxide cores embedded within a glyceryl tri myristate solid matrix, which exhibited a decrease in cell viability in human HT29 colon adenocarcinoma cells upon exposure to alternating electromagnetic fields [72].

Inhibition of colon cancer cells by 20% was achieved through the use of biocompatible polymer/carbohydrate-coated magnetic NPs, which disrupted cellular interactions and the cell cycle [73]. Gold NPs containing radio-labeled resveratrol showed enhanced targeting efficacy on colon adenocarcinoma cells in rats compared to radio-labeled resveratrol alone [74]. Hyaluronic acid (HA) and SN38-loaded gold NPs demonstrated site-specific targeting effects through the photothermal properties of gold NPs, effectively inhibiting cancer cell proliferation [75]. NPs composed of chitosan and PEGylated chitosan, prepared using the ionic gelation technique and encapsulated with anti-catenin siRNA, successfully decreased catenin protein levels in colon cancer cell cultures [76]. Additionally, gold nanoparticles stabilized by polyphenol and encapsulating green-synthesized *Abutilon indicum* leaf extract exhibited potent cytotoxic properties against cancer cells [77]. Combinatorial NPs encapsulating the well-known anticancer phytochemical curcumin (Cur) and 5-FU were developed using N, O-carboxymethyl chitosan, resulting in increased efficacy for colon cancer treatment and higher drug levels in the bloodstream [78].

In a recent study, researchers developed mesoporous silica nanoparticles (NPs) encapsulating the anticancer drug DOX and functionalizing them with an aptamer targeting the epithelial cell adhesion molecule. This modification allowed for the targeted delivery of DOX to colon cancer cells, resulting in an improved therapeutic index and reduced side effects [79]. The field of simultaneous cancer diagnosis and treatment, known as theranostics, is rapidly evolving. One notable advancement is the utilization of multi-functional branched glycopolymer-PTX-DOTA-gadolinium ion nanoparticles, which exhibit great potential for cancer theranostics. These nanoparticles demonstrate significant inhibition of tumor progression, enhanced MRI contrast intensity, and excellent biocompatibility [80].

Nanoparticles for cervical cancer

Cervical cancer stands as the second leading cause of death among women worldwide [29]. Developing countries, alongside Africa and America, face a significant burden of breast and cervical cancer due to the absence of well-established screening and early detection programs. Initially, human papillomavirus (HPV) infection was believed to be the primary predisposing factor for cervical cancer. However, it was later confirmed, after 2000, that HPV is indeed the key etiological factor. The HPV virus functions by inhibiting programmed cell death (apoptosis) and producing proteins that

suppress the activity of crucial genes involved in cell growth regulation, such as P53 and retinoblastoma genes. Factors such as early sexual activity, multiple sexual partners, and HIV infection contribute to the increased risk of cervical cancer [81-83].

Additionally, smoking poses a risk as it negatively impacts the immune system, thus promoting the development of cancer. Various types of cervical carcinoma exist, including squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, villoglandular adenocarcinoma, small cell carcinoma, glassy cell carcinoma, neuroendocrine carcinoma, and melanoma. Typically, cervical cancer progresses gradually, starting with the growth of abnormal cells on the cervical surface. A significant number of cervical cancers arise from squamous cells, leading to a precancerous condition known as dysplasia [84]. Women with persistent HPV infections are particularly vulnerable to developing precancerous lesions and/or cervical cancer [85-87]. Therefore, it is crucial to widely disseminate the most recent advancements and significant findings in cervical cancer treatment to scientific and research communities. Nanoparticles (NPs) have the potential to revolutionize cancer treatment by serving as a reservoir for drugs, allowing for their encapsulation, entrapment, dissolution, or attachment to a nanoparticle matrix [88, 89].

Cisplatin, when trapped within folic acid-conjugated gelatin nanoparticles, exhibited enhanced drug delivery capabilities for cancer treatment, resulting in a higher cellular uptake of 81% compared to plain gelatin nanoparticles, which had an uptake of 51% [90]. Nanoparticles loaded with the bioflavonoid naringenin, prepared using the nanoprecipitation technique, demonstrated increased cytotoxic efficacy in human cervical cancer cells. This was accompanied by elevated levels of intracellular reactive oxygen species (ROS), lipid peroxidation, and a decrease in glutathione (GSH) levels, surpassing the effectiveness of free naringenin treatment [91]. Oligonucleotide intercalator phenanthridinium-functionalized mesoporous silica nanoparticles exhibited potent inhibition of cell growth by binding to cytoplasmic oligonucleotides, particularly in HeLa cells, due to the presence of phenanthridium groups on the nanoparticle's surface. These nanoparticles showed good biocompatibility, cellular trafficking properties, and potential for various biomedical applications [92].

Silver nanoparticles synthesized using green leaf extract from *Podophyllum hexandrum* selectively induced DNA damage and caspase-mediated cell death in human cervical cancer cells [93]. Crystalline gold nanoparticles synthesized using *Podophyllum hexandrum* L demonstrated effective anticancer activity by inducing oxidative stress, cell cycle arrest, DNA damage, and activation of the caspase cascade, ultimately leading to mitochondrial dysfunction and apoptosis in cancer cells [94]. Nanostructured lipid particles loaded with bleomycin sulphate enhanced the oral bioavailability of the drug by preventing first-pass metabolism and increasing intestinal lymphatic uptake. This resulted in improved toxicity and apoptosis against cervical cancer cells [95]. Curcumin-loaded poly(lactic-co-glycolic acid) nanoparticles, designed to improve solubility and stability, were conjugated with anti-P-glycoprotein antibody. These nanoparticles showed promise as either multidrug resistance modulators or anticancer drugs, providing benefits for cancer patients [96].

Extensive research has been conducted on the use of doxorubicin (DOX) for treating cervical cancer. One study focused on the preparation of long-circulating self-assembled nanoparticles encapsulating DOX. These nanoparticles were made using an amphiphilic block copolymer composed of polynorbornene-cholesterol and poly(ethylene glycol). The findings revealed that these nanoparticles exhibited significantly greater inhibition of tumor growth compared to free DOX. It was concluded that these nanoparticles could serve as valuable carriers for improving the delivery of hydrophobic anticancer drugs to tumors [97]. Another study explored the use of pH-responsive charge-reversal polymer-coated mesoporous silica nanoparticles loaded with DOX hydrochloride. These nanoparticles effectively delivered and released DOX hydrochloride to the nucleus of HeLa cells, as observed through confocal laser scanning microscopy [98]. Additionally, DOX-loaded nanoparticles were prepared using cyclodextrin-containing

pH-sensitive poly(2-(dimethylamino)ethyl methacrylate) star polymer. These nanoparticles exhibited higher cytotoxicity and cellular uptake and were able to effectively suppress tumor growth without significant side effects [99].

Researchers also synthesized magnetic iron oxide nanoparticles using aqueous extract from brown seaweed. These nanoparticles demonstrated cytotoxic effects on cervical cancer cells by inducing apoptosis [100]. Targeted nanoparticles based on transferrin-conjugated amphiphilic copolymers loaded with paclitaxel (PTX) showed increased activity, thanks to the presence of transferrin, and facilitated tumor-specific therapy [101].

Biocompatible amphiphilic pentablock copolymeric nanoparticles loaded with docetaxel (DTX) were prepared using poly(lactide-co-glycolide) and pluronic F68 through emulsion solvent evaporation and simple dialysis. These nanoparticles exhibited significant cytotoxicity against cervical cancer cells [102]. Nanoparticles incorporating methotrexate and 5-FU together showed enhanced anticancer efficacy compared to free individual drugs or their nanoparticle formulations alone [103].

Nanoparticles for breast cancer (BC)

Breast cancer (BC) is a highly prevalent and fatal disease affecting women worldwide, according to the International Agency for Research on Cancer (IARC) [104]. Despite advancements in diagnosis and treatment, BC remains one of the deadliest cancers. The main source of BC originates from the epithelial cells lining the terminal duct of the lobule unit in the breast. These cancer cells can be categorized as non-invasive or *in situ* when they are confined within the basement membrane of the ducts and lobules. Invasive BC occurs when cancer cells spread beyond the basement membrane into the surrounding normal tissues [105].

Ductal carcinoma, lobular carcinoma, and inflammatory mammary cancer are some of the different types of BC. The TNM (tumor, node, metastasis) staging system is used to classify the various stages of breast carcinoma. TNM stages I, II, and IIIA are considered operable, and patients in these early stages who receive appropriate treatment have a 5-year survival rate exceeding 75% [106]. However, there is a need for more effective treatment options for BC patients. Novel delivery systems offer promising approaches for early detection and treatment. Current cancer research focuses on improving BC treatment through the use of various novel drug delivery systems, including nanoparticles. Commonly used polymers for nanoparticle preparation include poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and modified PLGA. In one study, star-shaped copolymer-based nanoparticles loaded with docetaxel (DTX) were prepared using a modified nanoprecipitation method. These nanoparticles exhibited significantly higher cytotoxicity compared to commercially available Taxotere® formulation, possibly due to increased encapsulation efficiency and drug loading. *In vivo* studies also demonstrated the superior antitumor efficacy of these nanoparticles [107].

A novel polymeric nanocarrier was developed using cholic acid-core star-shaped PLGA-based nanoparticles to achieve controlled and sustained delivery of simvastatin. These nanoparticles exhibited significantly higher cytotoxicity and effectively inhibited tumor growth by internalizing into MDA-MB-231 human breast cancer cells. They also demonstrated a notable reduction in the expression of the cell cycle protein cyclin D1 compared to pristine simvastatin and linear PLGA nanoparticles loaded with simvastatin [108].

Additionally, nanoparticles have been utilized to enhance the solubility of poorly water-soluble drugs like curcumin. Encapsulation of curcumin in PLGA nanoparticles improved its bioavailability by protecting it from the environment and enabling its release in the cytoplasm, leading to G2 receptor-blocking action on MCF-7 cancer cell lines [109]. Smart nanoparticles stabilized with dendrimers and loaded with the hydrophobic drug paclitaxel (PTX) demonstrated pH-dependent drug release for targeted delivery. These nanoparticles exhibited stability at physiological pH and efficiently suppressed cancer cell growth while inducing apoptosis. They also displayed excellent biocompatibility compared to PTX alone [110].

Dual drug-loaded silica nanoparticles, incorporating PTX and suramin, were synthesized using triple targeting ligands specific to neoangiogenesis and cancer. These nanoparticles exhibited enhanced uptake and superior therapeutic efficacy against breast cancer cells. They effectively immobilized the activated endothelial cells, preventing their migration [111]. Antioxidant nanoparticles loaded with Vitamin C and E were prepared using extracts from *Hibiscus rosa-sinensis* petals and chitosan, a biocompatible, biodegradable, and cationic polymer with targeting ability. These nanoformulations showed excellent hemocompatibility, high encapsulation efficiency (around 76%), and significantly increased anticancer activity against breast cancer cell lines (MCF-7) [112].

Trastuzumab, a human monoclonal antibody, was utilized to specifically target cancer cells that overexpress human EGFR-2. Lipid-based nanoparticles (NPs) loaded with rapamycin (an imaging agent) were developed for targeted therapy of breast cancer (BC). The results demonstrated enhanced therapeutic efficacy of the drug when formulated in NPs compared to the pure drug [113]. Gold nanoparticles can be directed to the mitochondria of BC cells, inducing apoptosis and promoting cell death. These nanoparticles hold potential for use in photothermal therapy for BC [114]. Enzyme-sensitive amphiphilic peptide dendritic copolymer-based nanoparticles loaded with DOX exhibited efficient apoptosis of cancer cells *in vitro*. They demonstrated prolonged retention and accumulation within tumor cells while reducing DOX-induced toxicities, making them a promising drug delivery system for enhanced BC therapy [115]. An enzyme-responsive peptide dendrimer DOX conjugate-based nanoparticles exhibited significantly high antitumor activity, inducing cell death in the 4T1 breast tumor model [116]. pH-responsive nanoparticles composed of dendronized heparin DOX conjugate showed strong antiangiogenic effects, potent antitumor activity, and induced apoptosis in BC cells, making them suitable for cancer therapy [117].

Triple-negative breast cancer (TNBC) is a highly invasive cancer with an increasing number of cases each year, necessitating the development of effective therapeutic strategies. Nanoparticles were designed to enhance accumulation and penetration deep into tumor tissues. To improve cancer targeting, angiopep-2 was anchored on the surface of nanoparticles to facilitate binding with low-density lipoprotein receptor-related protein (LRP) overexpressed in TNBC. Additionally, particle size-reducible nanoparticles were developed using gelatin nanoparticles loaded with dendrigraft poly-lysine (DGL) and DOX to achieve high penetration and prolonged tumor retention [118].

A novel multistage system with targeting capabilities and size-changeable properties was developed to inhibit tumor growth and metastasis. The system consisted of small gold nanoparticles (AuNPs) attached to matrix metalloproteinase-2 (MMP-2) degradable gelatin nanoparticles (GNPs). DOX, an anticancer agent, was linked to AuNPs via a pH-sensitive hydrazone bond and decorated with a tandem peptide of arginyl glycyl aspartic acid (RGD) and octarginine to enhance tumor targeting efficiency. The developed nanoparticles (G-AuNPs-DOXRRGD) exhibited pH-dependent DOX release and demonstrated shrinking behavior after 24 h of incubation with MMP-2. Excellent penetration efficiency was confirmed through collagen diffusion and tumor spheroid penetration studies. *In vivo* evaluation in mice bearing 4T1 xenografts revealed active targeting of the 4T1 tumor, interstitial matrix penetration, and deep tumor accumulation [119].

Mesoporous silica nanoparticles (MSNPs) have emerged as a promising nanotechnology for the targeted delivery of anticancer drugs. These nanoparticles possess desirable properties for biomedical applications, such as excellent chemical stability, a large surface area, and customizable pore sizes and volumes, enabling the efficient incorporation of significant drug quantities [120]. Magnetic nanoparticles (MNPs) have revolutionized the diagnosis and clinical treatment of cancer by enabling the identification of cancerous lesions. At the cellular level, MNPs exhibit specific magnetic characteristics and biological interactions. Methotrexate (MTX) conjugates coated with glycine-functionalized MNPs (F-Gly-MTX MNPs) were synthesized via an amidation reaction using the co-

precipitation method. The biocompatibility of these MNPs was assessed through haemolysis assays and cytotoxicity studies on HFF-2 and HEK-293 cell lines. Drug delivery in these MNPs relies on the release of MTX triggered by peptide bond cleavage within the lysosomal compartment [121]. Arginine-functionalized iron oxide MNPs were conjugated with MTX and evaluated for cell cytotoxicity on normal cell lines (HFF-2) and through haemolysis assays, confirming their biocompatibility. Release studies conducted under low pH conditions, with and without proteinase K, demonstrated that MTX was released through peptide bond cleavage by proteinase K at acidic pH [122].

An inverse microemulsion system was developed for the synthesis of monodisperse magnetic mesoporous silica nanoparticles with a core-shell structure. This preparation method involves a water-in-oil (w/o) microemulsion system where the silica precursor is dispersed in cyclohexane as the continuous phase, and magnetic seeds (Fe₃O₄ nanoparticles) with urea are contained within water droplets as the aqueous phase. The surfactant and co-surfactant used in this system are cetyltrimethylammonium bromide (CTAB) and 1-butanol, respectively. The results demonstrated that the magnetic mesoporous silica nanocomposites prepared through this method hold great potential for applications in cancer drug delivery [123].

Along with the active pharmaceutical agents many natural products such as phytochemicals, including camptothecin, vincristine, vinblastine, quercetin, epigallocatechin gallate, etc. can also be used to design drug delivery systems to treat different types of cancer [124]. Nanotechnology holds significant and promising potential to design, develop and innovate novel and advanced drug delivery systems for managing cancer by offering numerous opportunities [125].

CONCLUSION

Nanocarriers have emerged as a groundbreaking scientific development, playing a vital role in various biological applications, particularly in the field of anticancer drug delivery. In comparison to traditional cancer chemotherapy, nanocarriers have demonstrated significant advancements in terms of drug efficacy, prolonged circulation time, repeated administration, and controlled and targeted drug release in response to specific stimuli. Consequently, nanocarriers, such as nanoparticles (NPs), can be precisely engineered to release drugs at the desired site within the body. The utilization of NPs in diagnostic and therapeutic approaches holds immense potential for enhancing cancer therapy. With further progress and innovation, these nanosystems are poised to be widely adopted for effective cancer treatment.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Authors declare no conflicts of interest.

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