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Revolutionizing Cancer Treatment: The Promising Potential of Nanotherapeutics

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ABSTRACT

Nanotherapeutics has transformed cancer treatment by providing drug molecules at the sites of action with reduced systemic toxicity and maximum therapeutic efficacy. This review gives an overview of recent advancements in nanomedicine such as liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles that provide targeted tumor targeting by passive and active means. The nanocarriers achieve maximum bioavailability, achieve controlled drug release, and improve patient outcome. Besides, nanotechnology has also been incorporated into biomedical imaging, immunotherapy, and artificial intelligence (AI) to enhance diagnostic accuracy, allow personalized therapies, and maximize drug delivery. Iron oxide and gold nanostructures have also shown promise for MRI contrast agents and photothermal therapy using nanoparticles. Despite tremendous advances, clinical translation, mass production, and regulatory approvals pose challenges. Future research needs to address tumor heterogeneity, nanoparticle stability, and patient-specific tolerance to achieve the full potential of nanomedicine. The convergence of AI, immunotherapy, and nanotechnology has much to revolutionize oncology and enhance the survival of cancer patients..

Keywords: *Targeted Nanocarriers, Cancer Nanotherapeutics, Controlled Drug Delivery, AI-Driven Precision Oncology, Multifunctional Nanoparticles, Photothermal and Imaging Agents*

1. INTRODUCTION

One of the deadliest illnesses in the world is still cancer. Both currently available immunotherapies and conventional cancer treatments are non-tumor-targeted drugs with a number of undesirable side effects and an inability to distinguish between healthy and malignant cells. Through tumor tissue-, cell-, or organelle-specific targeting, recent developments in nanotechnology and our growing knowledge of cancer biology and nano-bio interactions have produced a variety of nanocarriers that can optimize the therapeutic effect while lowering off-target toxicity of the loaded anticancer drugs [1]. (Dahua Fan). Cancer is among the world causes of death as shown by the 2022 cancer estimates indicating 1,918,030 new cases of cancer and 609,360 deaths due to cancer every year [2]. The old modes of treatment after seeing a cancer patient are radiotherapy, chemotherapy, and surgery. The strategy choice is influenced by various features, including the stage and location or patient status, impaired by the disease itself and deteriorating with each measure of treatment in the long run [3]. All these treatments will decrease cancer recurrence and mortality but with serious side effects including harmful complications and to the risk of death due to other diseases [4].

The emerging theme of theragnostic, a new principle in which diagnostic and therapeutic capabilities coexist, has drawn concentrated attention on nanoparticles in the past few years. Some nanoparticles were discovered to be intentionally designed to possess dual functionality as multiple-use tools beneficial both for their purpose as medication carriers and for invaluable imaging ability. The cooperative working increases sensitivity and efficacy of anticancer agents, currently becoming a universal mode of investigation for clinical trials[5, 6]. Gold nanoparticles and their analogues have exhibited

tremendous potential for inducing radiosensitivity of cancer cells. Targeted to the tumor directly, the particles increase the absorption of radiation energy, which results in more damage to the cell. Clinical trials are in progress to determine the therapeutic application and viability of the technology for cancer radiotherapy purposes[7-9].

Currently, over 15 cancer nanomedicines have been approved globally, and over 80 novel formulations are being investigated in over 200 clinical investigations. Improvements in nanotechnology and a deeper comprehension of cancer biology and nano-bio interactions have facilitated the creation of customized nanocarriers. At the tissue, cellular, and organelle levels, these carriers offer customized drug delivery, increasing therapeutic efficacy and reducing off-target toxicity [10-12]. Additionally, nanoparticles are essential for biological imaging and have been developed for application in many diagnostic imaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography. They have enormous potential for improving anatomy imaging, early anomaly detection, and online disease monitoring because to their contrast enhancement, signal-to-noise ratio, and particular tissue or cellular targeting characteristics. For instance, while gadolinium-based contrast agents are a common application of MRI, their toxicities and associated adverse reactions have been an issue of concern for regulatory agencies, such as the U.S. Food and Drug Administration (FDA). Because of their superior magnetic properties and favorable biocompatibility, iron oxide nanoparticles (IONPs) have proven to be a safer alternative to contrast agents based on gadolinium. Additionally, the potential uses of molecular MRI are increased by the capacity to functionalize their surface with a range of targeted ligands, such as aptamers, antibodies, peptides, and sugars. Notably, iron oxide nanoparticles (IONPs) have gained considerable attention in recent years for their promising role in cancer imaging [13]

2. FUNDAMENTALS OF NANOTHERAPEUTICS

Nanotechnology has transformed biomedical applications, especially in oncology. Nanotherapeutics is the application of nanoscale materials, usually between 1 and 100 nm, in medicine to provide targeted drug delivery, improve bioavailability, and reduce systemic toxicity. The fundamental principles in nanomedicine are founded on the interaction of nanoparticles (NPs) with biological systems at molecular and cellular levels, ultimately optimizing anticancer therapy efficacy.

Outside oncology, nanotechnology has also facilitated fast and accurate identification of infectious disease-causing pathogens in animals. Assays for detecting viral, bacterial, and fungal pathogens in clinical samples using nanoparticles or nanomaterials with high sensitivity and specificity have been developed. Early diagnosis of the disease and control measures are enabled by these novel detection methods. Numerous nanomaterials have been employed extensively to identify pathogens, including graphene, carbon nanotubes (CNTs), magnetic nanoparticles (MNPs), gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), and quantum dots (QDs). Due to their nanometer-scale size with outstanding optical, electric, and magnetic properties, these nanomaterials have become particularly promising towards multiplexing and speeding up the detection. Besides, various point-of-care diagnosis devices and biosensors using such nanomaterials have also been developed for the detection of veterinary-relevant pathogens [14, 15]. Nanotherapeutics have also been tested in the healing of wounds, especially in antimicrobial treatment involving the application of nanoparticles (NPs). Microorganisms such as bacteria, once present in wounds, have been known to inhibit the process of healing significantly and thus deteriorate the wound further. Antimicrobial nanoparticle dressings, on the other hand—e.g., silver (AgNPs), gold (AuNPs), and zinc oxide (ZnONPs) nanoparticles—can contribute to healing by engaging with the bacterial microenvironment and bringing about a therapeutic response (Jiang & Loo, 2020; Naskar & Kim, 2020).

Furthermore, a number of delivery methods driven by nanotechnology, including hydrogels, hydrocolloids, nanofibers, and nanohybrids, have been developed for wound healing. For instance, nanofiber dressings cover the wound and release moisture and oxygen continuously. To provide longer-lasting protection against infection and speed up and improve wound healing, these dressings can also be functionalized with antimicrobial nanoparticles or combined with antibacterial medications [16].

3. PRINCIPLES OF NANOMEDICINE

Nanomedicine is a multidisciplinary area that brings nanotechnology to medicine to diagnose, treat, and prevent disease at the cellular and molecular levels. In cancer treatment, nanotherapeutics employs engineered nanoscale materials (1-100 nm) to maximize drug delivery, improve therapeutic effects, and minimize systemic toxicity. Such NPs can be engineered to encapsulate chemotherapeutic agents, genetic material, or imaging contrast agents and confer targeted efficacy along with controlled release for better outcomes [17]. Nanomedicine is the application of nanoscale devices and materials for disease diagnosis, monitoring, and treatment. In cancer treatment, nanomedicine seeks to overcome the shortcomings of traditional therapies through the facilitation of targeted drug delivery, controlled release, and enhanced bioavailability. The physical properties of nanomaterials, including their high surface area-to-volume ratio and tunable nature, enable the creation of multifunctional platforms that can deliver therapeutic agents and diagnostic devices at the same time[18-21].

The vasculature is leaky and lymphatic drainage is disrupted within tumors, allowing nanoparticles to remain preferentially localized in tumor tissue via the EPR effect. Passive targeting increases drug concentration locally in the tumor site and reduces the system exposure[22]. Even though the EPR effect is well-referenced, its reliability is tumor type and patient-

dependent (Kobayashi et al., 2014). It is dependent on tumor size, vascular density, and microenvironment as parameters that affect nanoparticle accumulation. Despite this variation, passive targeting through the EPR effect is still one of the fundamental principles in nanomedicine[23]. Using hydrophilic polymers such as polyethylene glycol (PEG) to surface functionalize nanoparticles prevents the reticuloendothelial system from recognizing and eliminating them, extending their circulation periods and maximizing tumor formation. Targeted ligand functionalization of nanoparticles like antibodies or peptides allows active targeting via specific interactions with the cancer cell overexpressed receptors to enhance cellular uptake and therapeutic selectivity[24]. Besides, nanocarriers are also formulated to release their cargo according to tumor-specific signals such as pH, redox, or enzymatic concentrations. Such a mode of controlled release allows maximum therapeutic effect with minimum off-target toxicity. In addition, nanoparticles can be engineered for theranostic use with therapeutic and diagnostic functions. Such integration allows the concurrent delivery of drugs along with real-time measurement of drug action, allowing personalized therapy to be optimized [25].

4. MECHANISMS OF ACTION IN CANCER THERAPY

The capacity of a nanomedicine formulation to target malignant tissue specifically while reducing negative effects on healthy cells is a crucial consideration for choosing it for cancer therapy. Different targeting methodologies have been used to generate a variety of nano-formulations that deliver anticancer medications to tumor locations. The particular carrier system used determines both the advantages of nanocarriers and the effectiveness of drug delivery.

Nanocarriers facilitate the direct transport of therapeutic agents into the bloodstream, ensuring their accumulation at the targeted tumor site. Once delivered, these carriers can trigger reactive oxygen species (ROS) overproduction, leading to DNA damage, apoptosis, and eventual cancer cell death[26, 27]. Two main targeting techniques are used in nano-based drug delivery: active targeting, which entails functionalizing nanoparticles with ligands to improve tumor-specific uptake, and passive targeting, which takes use of the increased permeability and retention (EPR) effect. Under the passive targeting strategy (Fig. 1), specificity at the tumor location is employed in guiding nanoparticles into the tumor area. Major determinants of such an approach include the Enhanced Permeability and Retention (EPR) effect and attributes of the Tumor Microenvironment (TME). Tumor cells induce neovascularization through speedy growth, creating enormous pores within the walls of blood vessels to allow passive accumulation of nanoparticles[28]. Incomplete tumor angiogenesis provides a channel through which particles penetrate the tumor area and collect there. Additionally, compromised lymphatic drainage also adds to increased particle retention, which again facilitates the EPR effect on tumor [29]. The greater interstitial fluid pressure in the tumor microenvironment can, however, impair nanoparticle uptake and cause nonuniform distribution of the particles[30].

Passive targeting relies on the EPR effect, whereby nanoparticles become trapped within tumor tissue as a result of the unique nature of tumor vasculature. Tumors are typically distinguished by leaky and disordered blood vessels with large fenestrations, allowing nanoparticles to gain access and become trapped within the tumor interstitium. The compromised lymphatic drainage within the tumor also facilitates the trapping of the particles and retains therapeutic agents at the tumor site without specific molecular targeting[31].

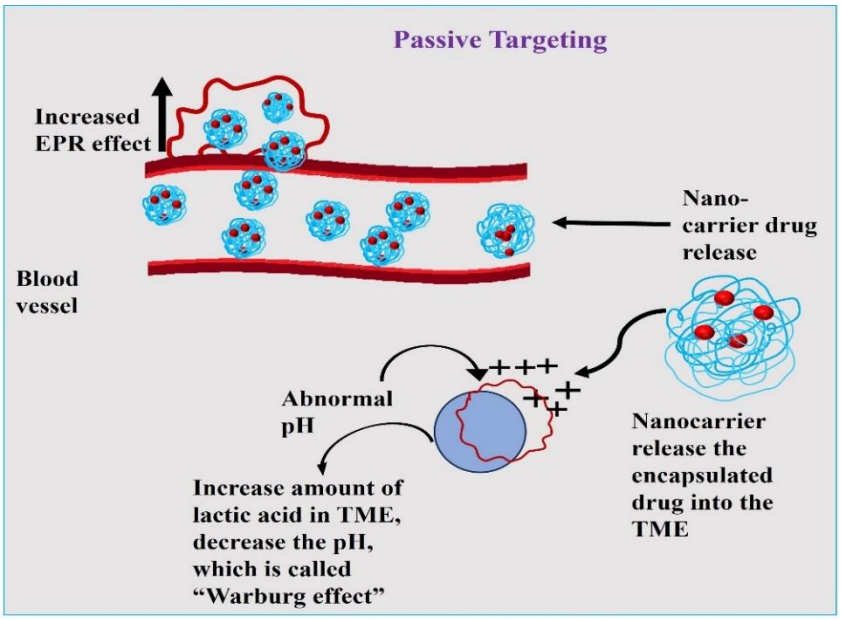

Figure 1 : Passive Targeting

Active targeting is based on the functionalization of nanoparticles with targeted ligands that have the ability to selectively bind and recognize overexpressed receptors on the surface of cancer cells. These ligands can be antibodies, peptides, proteins, nucleic acids, sugars, or small molecules like vitamins. When attached to their target receptors, these ligand-nanoparticle conjugates are internalized by cancer cells via receptor-mediated endocytosis, thus improving delivery and efficacy of therapeutic agents. This strategy is designed to enhance the specificity of therapy in reducing off-target effects by targeting the cancer cells specifically and not influencing normal tissue[32]. Active targeting (Fig. 2) involves the exploitation of the special features of the tumor cells, i.e., the cell surface receptors present abundantly on the cancer cells. Active targeting is attained by modifying different targeting molecules on the carrier so that it becomes attached to the receptors in a specific manner. In this section, we discuss the various targeting strategies utilized by various nanocarriers and their respective merits and demerits.

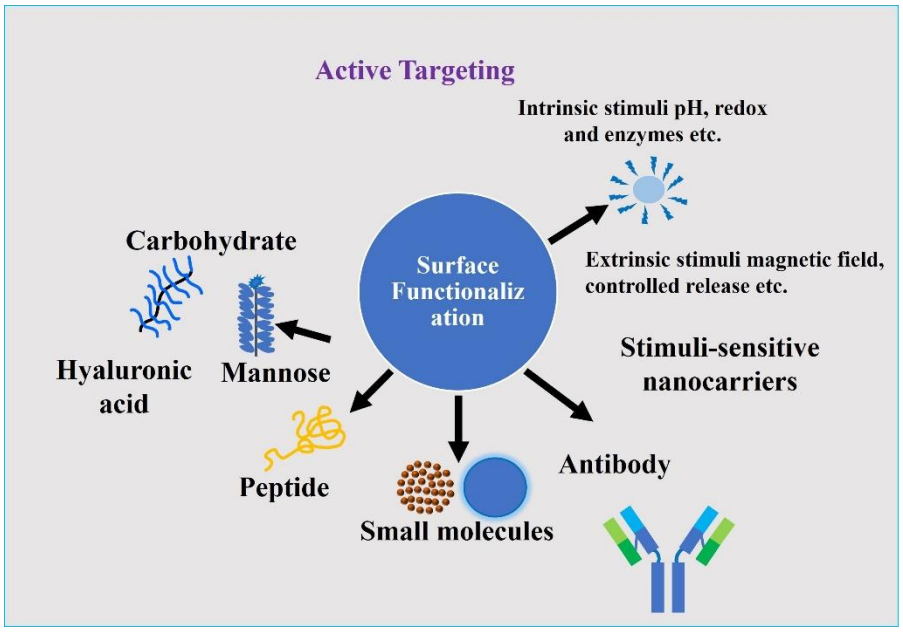

Figure 2 : Active Targeting

5. CLASSIFICATION OF NANOCARRIERS

There has been a series of nanocarriers designed to facilitate an improvement in anticancer agent delivery, as outlined below **(Fig 3)**.

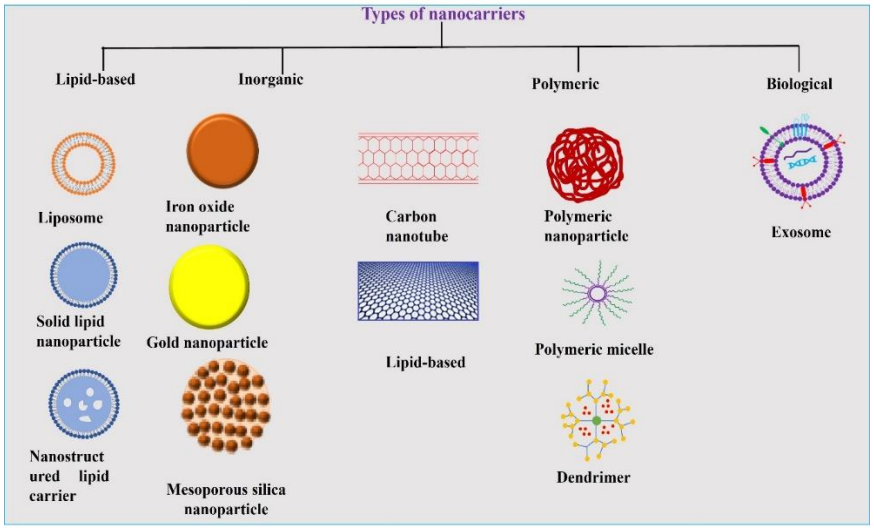

Figure 3 : Types of Nanocarriers

5.1 Liposomes

Liposomes are spherical lipid vesicles with an aqueous interior and one or more concentric bilayers. Because of its structural adaptability, it may effectively transport a variety of medicinal medicines by enclosing both lipophilic and hydrophilic molecules inside the nanocarriers. Liposomes are generally considered to be safe medication delivery nanocarriers since they are composed of biocompatible and biodegradable lipids like cholesterol and phospholipids [33, 34]. Furthermore, liposomes can be functionalized with a variety of biomolecules to improve target specificity, increase cellular uptake, prolong their circulation half-life, and facilitate stimuli-responsive drug release [35, 36]. Their effective clinical translation can be attributed to these beneficial qualities. While many liposomal formulations are awaiting regulatory approval or are conducting clinical trials, a few of them have already been incorporated into clinical practice [37-39].

In a clinical study comparing Doxil® (PEGylated doxorubicin liposomes), biphasic clearance was observed, with around one-third of the dosage being removed from the plasma during the early distribution phase (1–3 hours). The leftover Doxil® now has a 42–46 hour terminal half-life. Free doxorubicin has a relatively short initial dispersion half-life of roughly five minutes and a terminal half-life of 25 to 30 hours. Doxorubicin's clearance and volume of distribution were greatly reduced by liposomal entrapment, which resulted in an AUC that was about 300 times higher than that of the free medication[40]. Consisting of one or more phospholipid bilayers, liposomes have high biocompatibility and the ability to entrap hydrophilic as well as hydrophobic drugs. Additionally, their surfaces can be functionalized with targeting ligands to increase specificity towards cancer cells, further maximizing their therapeutic index[41]. Lipid nanoformulations have evolved a lot in clinical oncology, some going through the phases of clinical trials and some reaching the marketplace effectively. Such nanodrug formulations have evidenced to be beneficial compared to the conventional therapies by way of greater circulation time, improved plasma half-life, more tumor uptake, and better therapeutic activity at low off-target toxicity[42].

Currently, several lipid-based nanoformulations are in clinical trials, and the anticipated completion of these trials varies from 2023 to 2032 [43]. Some of the lipid-based nanomedicines have also gained regulatory approval for the treatment of different cancers in the United States and Europe[44]. Among them are formulations that contain one or more drugs, such as vincristine (Marqibo®), doxorubicin (Doxil®, Myocet®, Caelyx®, Zolsketil®), daunorubicin (Daunoxome®, Vyxeos®), cytarabine (Vyxeos®), irinotecan (Onivyde®), mifamurtide (Mepact®), 5-aminolevulinic acid (Ameluz®), and vincristine (Marqibo®). Many cancers, including sarcomas, lymphomas, leukemias, pancreatic carcinoma, colorectal cancer, ovarian cancer, breast cancer, multiple myeloma, and skin cancer, are treated with these authorized medications.[43] . Figure 4 is a systematic overview of their respective usages in cancer therapy.

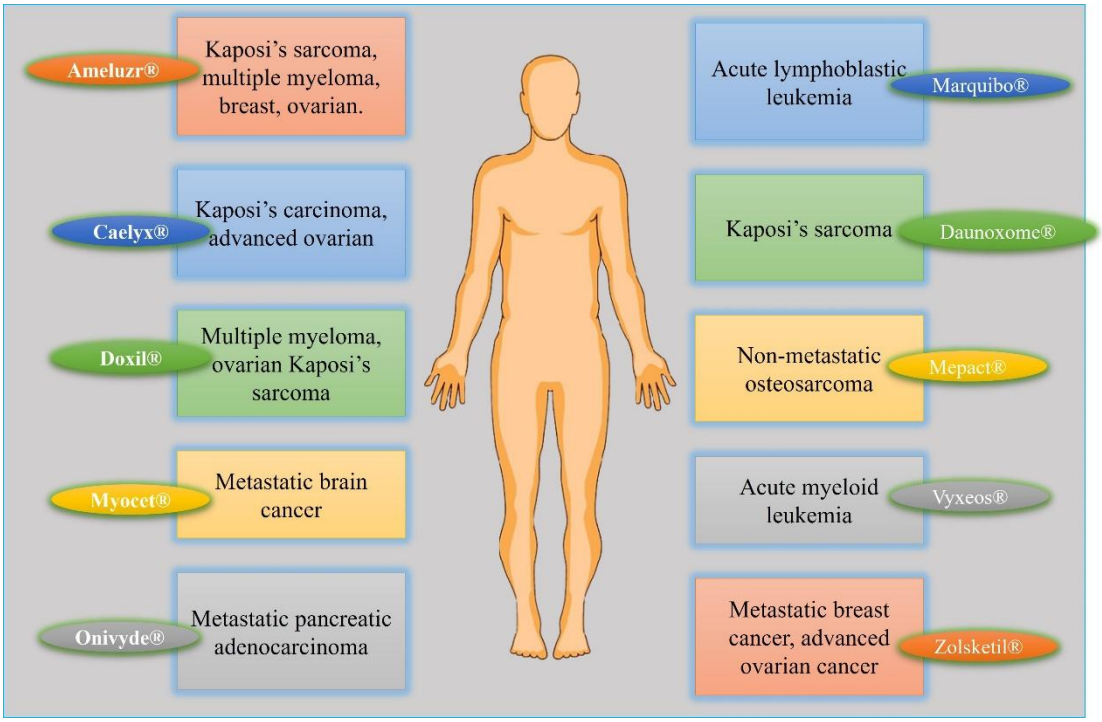

Figure 4 : Lipid based nano formulations

5.2 Polymeric Nanoparticles

Nanoparticles are extremely small particles designed at the nanoscale level, providing novel characteristics for biomedical

purposes. Extracellular vesicles (EVs), metallic nanoparticles, polymeric nanoparticles (PNPs), and nanoparticles linked to monoclonal antibodies (mAbs) are the most advanced nanoparticle systems used in cancer treatment[45]. Polymeric nanoparticles based on biodegradable polymers have the ability to release drugs in a controlled manner and protect therapeutic molecules from premature degradation. These nanoparticles can be made responsive to unique stimuli within the tumor microenvironment, like changes in pH or enzyme levels, which will facilitate improved targeted delivery of drugs and therapeutic response[45]. Polymeric nanoparticles (PNPs) are colloidal macromolecules between 10 to 1000 nm in size. PNPs, when utilized as drug delivery systems, entrap drugs for extended delivery at the target site of cancer[46]. In accordance with their structure, drugs may be trapped inside the nanoparticle core to produce nanocapsules or attached to the particle surface to produce nanospheres.

Over time, nanoparticle preparation has advanced in sophistication. The most often used nonbiodegradable polymers in the early years were polymethyl methacrylate (PMMA), polyacrylamide, polystyrene, and polyacrylates.[47, 48]. With advances in nanotechnology, however, biodegradable polymer-based PNPs have subsequently appeared to advance drug biocompatibility and stability. For volatile drugs, stability is afforded by PNPs, whereas for chemical drugs, PNPs can exhibit a variety of administration routes—e.g., oral and intravenous administration—along with enhanced drug-loading capacity over free drugs. In addition, PNPs possess protective properties owing to the prevention of premature degradation of drugs and thus a reduction in toxicity in regular tissues. For example, cisplatin-loaded PNPs with dexamethasone or α-tocopheryl succinate are used in chemotherapy to avoid cisplatin-induced ototoxicity[49]. Biopolymers like chitosan, heparin, and albumin have been utilized in certain FDA-approved drug delivery systems. For instance, low-molecular-weight chitosan nanoparticles with a cholesterol core and hydrophilic mPEG shell to increase the drug's solubility demonstrated effective paclitaxel administration and good encapsulation efficiency [50]. Besides, silk fibroin nanoparticles from a natural protein polymer have been of particular interest in drug delivery because they can be utilized for delivering anticancer agents. Other than these benefits, the difficulty of dealing with polymers' heterogeneity, the high production cost, and intricate manipulation processes have kept natural polymers from wide application[51]. Synthetic polymers with enhanced drug delivery efficiency are therefore being produced in larger quantities as substitutes[52].

5.3 Dendrimers

Dendrimers are unique macromolecules with a well-defined hyperbranched architecture. The most impressive characteristic is the branching since they form highly branched systems with huge surface modification possibilities. Dendrimers have diameters ranging from 1–10 nm, but specifically engineered larger varieties reach 14–15 nm[53, 54].

Structurally, dendrimers have three elements: an inner core for encapsulation of the theranostic agent through noncovalent bonding, branched interior layers conferring the dendritic shape, and a peripheral functionalized layer consisting of varying chemical groups. Several dendrimers have been studied as a means to treat cancer, which includes polyamidoamine (PAMAM), polypropylenimine (PPI), poly(ethylene glycol) (PEG), 2,2-bis(hydroxymethyl) propionic acid (BisMPA), 5-aminolevulinic acid (5-ALA), and triethanolamine (TEA)[55]. Due to their well-defined architecture and abundance of surface functional groups, these highly branching, tree-like macromolecules make it simple to conjugate several drug molecules with targeting ligands. Their highly defined architecture enables size and surface property control with high accuracy, facilitating their use in more targeted drug delivery and therapy applications[23]. Due to their unique structural properties, dendrimers possess some advantages over other nanomaterials, such as controlled molecular weight, modifiable branched structure, narrow polydispersity, and improved solubilization and bioavailability of lipophilic drugs. Their cationic positively charged surface is capable of stable nucleic acid complexation, making them highly efficient nanocarriers for gene delivery[45].

5.4 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are more stable in aqueous solutions because of the surfactant coating that is applied to their lipid matrix. Fatty acids like stearic, palmitic, and capric acids; triglycerides like tristearin, tripalmitin, trimyristin, and trilaurin; partial glycerides like glyceryl behenate, glyceryl stearate, and glyceryl palmitostearate; steroids like cholesterol; and waxes are among the lipids used in the preparation of SLN [37]. Commonly used surfactants include sorbitan esters, polysorbates, sodium glycocholate, poloxymers, and lecithin, as well as their mixtures. Though wide ranges of lipids and surfactants are employed in the preparation of SLNs, they have to be selected cautiously as they directly influence particle size, surface charge, stability, drug loading, and release patterns[56]. SLNs, which are a solid lipid core surfactant-stabilized, combine the advantages of liposomes and polymeric nanoparticles. These systems possess controlled drug release, high drug loading, and improved stability[57]. Metal-Based Nanoparticles: Gold or iron oxide nanoparticles have unique magnetic and optical characteristics and are being used in theranostics, i.e., diagnosis as well as therapy. They find extensive use in methods like photothermal therapy and as magnetic resonance imaging (MRI) contrast agents[41].

5.5 Gold Nanoparticles

Gold nanoparticles (AuNPs) have been of particular interest in cancer diagnosis and treatment because of their distinctive physicochemical, optical, and electronic properties[58]. They possess good drug carrier properties with good

biocompatibility, stable dispersion, high stability, extensive surface area for drug loading, and facile surface functionalization[7].

The unique optical property of AuNPs is efficient scattering and light absorption. Upon exposure to an electromagnetic field, conduction electrons on the AuNP surface exhibit collective behaviour by resonant coupling with the impinging electromagnetic field, or surface plasmon resonance (SPR)[59]. Significantly, SPR behavior of AuNPs is greater compared to non-plasmonic nanoparticles of similar dimensions[60]. The effect exhibits strong sensitivity towards particle size, shape, chemical makeup, and concentration[60]. Beyond that, AuNPs are even multifunctional drug delivery agents owing to surface chemistry, and that can be tuned to support the attachment of drug molecules so that tumor targeting may be intensified. For instance, eugenol-functionalized AuNPs were reported as having anticancer action[61].

5.6 Carbon/carbon-based materials

Numerous carbon-based compounds, including fullerenes, carbon nanotubes, and carbon dots, have been investigated for potential use in biomedicine [62-64]. Low-dimensional sp2 hybridized carbon materials with comparable physical and chemical characteristics, graphene and carbon nanotubes hold great promise for use in nanomedicine [65]. Among the cited materials, carbon nanotubes and graphene at the nanoscale possess good near-infrared (NIR) absorbing characteristics, hence they are good candidates for drug delivery and photothermal therapy (PTT)[66]. Intracellular gene delivery, protein, and chemotherapy drugs are delivered by means of the nanocarriers. Carbon nanotubes are single-walled (SWCNTs) or multi-walled (MWCNTs) in nature and with high surface area, thus enhancing biodistribution and pharmacokinetics[67].

Similar to other carbon materials, carbon nanotubes have to be functionalized in order to enhance their dispersion in an aqueous environment and also for delivery targeting. A recent report was successful in developing quantum dot (QD)-based MWCNT nanocomposites for photothermal applications[68]. Intratumoral delivery of such nanocomposites was investigated on A549 cell line-induced tumors in nude mice and proved to be an efficient tumor inhibition [69].

6. APPROVED NANO-FORMULATIONS FOR CANCER THERAPY

Since the early 1990s, nano-formulations have been recognized as a promising therapeutic option for cancer treatment with some receiving regulatory approvals worldwide. Zinostatin stimalamer was the first commercially marketed nano-formulation, which was launched in Japan for hepatocellular carcinoma, and Doxil was approved for pegylated liposomal formulation for ovarian cancer in the United States [70]. Over time, various classes of nano-formulations, including liposomes, polymeric micelles, metal nanoparticles, and lipid-based carriers, have been approved for medical applications. Among liposomal formulations, DaunoXome® has been used for HIV-associated Kaposi's sarcoma, while Myocet® has been indicated for metastatic cancer therapy. Marqibo® has received approval for lymphoma and leukemia treatment, whereas Lipusu has shown efficacy in managing gastric, ovarian, and lung cancers [71]. Even more recently, Vyxeos, a liposomal dual-drug formulation of daunorubicin and cytarabine, has been approved for the treatment of acute myeloid leukemia (AML). Furthermore, irinotecan-loaded PEGylated liposomes (Onivyde®) and cytarabine-loaded liposomes (DepoCyt®) have been approved for the treatment of lymphomatous meningitis and pancreatic adenocarcinoma, respectively[41]. Other nano-formulations have also received regulatory approval, extending their relevance in contemporary oncology beyond liposomal delivery systems. Polymer-protein conjugates and polymeric nanoparticles also emerged strongly in clinical oncology. SMANCS, for instance, has become available in Japan for renal carcinoma treatment, and Eligard®, a polymeric nanoparticle formulation of prostate cancer, have been brought into the clinic successfully[72].

In addition, various other nano-drug formulations have also become available, such as Nanoxel®, which is an Indian-approved drug for metastatic breast, ovarian, and lung cancer, and Apealea®, a polymeric micellar paclitaxel that has been approved by the European Medicines Agency (EMA) for use in peritoneal and ovarian cancer. Iron oxide nanoparticles like NanoTherm® have also been targeted for therapy in glioblastoma and prostate cancer.The continuous advancement in nanotechnology has significantly enhanced drug delivery, circulation time, and tumour targeting. Yet, even with these benefits, some nano-formulations remain challenges as far as toxicity and regulatory matters are concerned, which shows that there is a need for research and optimisation.

Table 1 : Approved nano-formulations for cancer therapy

S.No	Product	Drug	Nanotechnology platform	Cancer type	Approval	Toxicity
1	Mepact	Muramyl tripeptide phosphatidyl ethanolamine	Liposome	Non-metastatic osteosarcoma	2009 (EMA)	Fatigue, chills, fever, headache, and myalgias
2	Lipusu	Pacitaxel	Liposome	Non-small-cell	2013	Nausea, vomiting,

				lung tumors and breast cancer	(EMA)	dyspnea, peripheral neuritis
3	NanoTerm	Fe_2O_3	Superparamagnetic iron oxide nanoparticles with an amino silane coating	Glioblastoma, prostate, and pancreatic cancers	2013 (EMA)	Moderately negative impact
4	Ameluz	5-Aminolevulinic acid	5-aminolevulinic acid, E211, SoyPC, and PG-containing gel	Nodular and/or superficial basal cell carcinoma	2011 (EMA)	Transient pain and erythema
5	Genexol-PM	Paclitaxel	Polymeric micelle	Lung cancer that is not tiny cell	2006 (South Korea)	Myalgia, neutropenia, and neuropathy
6	Nanoxel	Docetaxel	Polymeric micelle	NSCLC, AIDS-related Kaposi's sarcoma, and breast and ovarian malignancies	2006 (India)	vomiting, diarrhea, alopecia, paresthesia, nausea, anemia, and myalgia
7	Marquibo	Vincristine	Liposome	Leukemia	2012 (FDA)	The toxicity of drugs and their negative side effects
8	Onivyde	Irinotecan	Liposome	Pancreatic cancer	2015 (FDA)	Neutropenia, vomiting, nausea, diarrhea, and febrile neutropenia
9	Vyxeos	Daunorubicin and cytarabine	Liposome	Acute meyleoid leukemia (AML)	2017 (EMA)	Sepsis, bacteremia, febrile neutropenia, hypoxia, hypertension, and pneumonia
10	Oncaspar	l-asparaginase	PEGylated conjugate	Acute lymphoblastic leukemia	2006 (FDA)	Venous thromboembolism, pancreatic, and hyperglycemia
11	DPH107	Pclitaxel	Lipid nanoparticle	advanced stomach cancer	2016 (Korea)	Leukopenia and neutropenia
12	NBTXR3	External radiation stimulates hfnium oxide nanoparticles to increase tumor cell death through electron generation.	Hafnium oxide nanoparticle	Squamous cell cancer that has spread locally	2019 (CE Mark)	Pain at the injection site, low blood pressure, and skin damage from radiation
13	Apealea	Paclitaxel	Polymeric micelles	Cancer of the fallopian tube, peritoneum, and ovaries	2018 (EMA)	Neutropenia, nausea, vomiting, diarrhea, and peripheral neuropathy
14	Kadcyla	DM1	Through the sturdy thioether linker	HER2+ breast	2013 (FDA,	Fatigue, nausea, headache,

			MCC, transtuzumab is covalently bonded to DM1.	cancer	EMA)	constipation, thrombocytopenia, increased liver enzymes as well as epistaxis
15	Pazenir	Paclitaxel	Paclitaxel comes as an infusion powder and is manufactured as albumin-bound nanoparticles	Non-small cell lung cancer, pancreatic adenocarcinoma that has spread, and metastatic breast cancer	2019 (EMA)	Impact non-cancerous tissues, including nerve and blood cells

NANOTECHNOLOGY IN IMMUNOTHERAPY

Immunotherapy exploits the immune system of the body to fight cancer [73]. Clinical trials and studies today are aimed at three major stages of the adaptive immune response. Cancer vaccines have a very important role in the sense that they induce differentiation and maturation of antigen-presenting cells, which are dendritic cells (DCs),[74] to improve the presentation of tumor antigens to lymphocytes, thereby triggering an antitumor immune response [75]. A second strategy is to directly stimulate activation and differentiation of lymphocytes, most notably T cells. They are taken from a patient's blood and activated either by gene modification—like chimeric antigen receptor T cell (CAR-T) therapy—or by direct stimulation with tumor antigens. After activation, cytotoxic T cells (Tc) are reinfused into the patient to kill cancer cells [76]. But the tumor microenvironment is very immunosuppressive since cancer cells have immune checkpoint receptors that protect them from cytotoxic T cell attack [76]. Immunocheckpoint inhibitors (ICIs) are used to combat this by blocking these checkpoints and boosting the immune system's ability to recognize and destroy cancerous cells [76]. Immunotherapy has been the center of attention in the last five years with a number of modalities having received much clinical approval[77]. It has proved to be highly effective in treating aggressive tumors like melanoma,[78] urothelial carcinoma, and prostate cancer and has even resulted in remission in previously terminal cases [79].

Although promising, immunotherapy has grave challenges. A major one of them is heterogeneity among patients—although certain patients benefit drastically with minor side effects, other patients generate vigorous autoimmune responses. Another drawback is that, whereas immunotherapy of solid tumors exists, there are limitations on antibodies and immune cells to permeate deeply in strongly dense and ill-vascular tumors[80], i.e., desmoplastic tumors [81]. It is evident that the combination of immunotherapy with other forms of cancer treatment will be more beneficial and decrease side effects, for a more comprehensive healing of cancer [82].

CONVERGENCE OF NANOTECHNOLOGY AND AI IN LIVER CANCER

The fast-paced developments in nanotechnology and artificial intelligence (AI) are revolutionizing the majority of the scientific fields, especially liver cancer treatment. The convergence of these technologies carries tremendous potential to transform diagnosis, drug delivery, and therapy through enhanced precision, efficiency, and personalization [83].

AI facilitates the operation of nanotechnology by leveraging its processing power to create optimized nanocarriers, track drug release, and enhance therapeutic efficacy. The synergy allows for more effective and targeted treatment regimens, ultimately leading to improved patient outcomes.

This part discusses major case studies and illustrations that exhibit simultaneous application of nanotechnology and AI, such as AI-augmented nanocarrier design optimization, use of AI in monitoring drug release and therapeutic performance, and the effects of this synergy on precision medicine [84]. **Figure 5** displays the convergence of machine learning (ML), medical imaging, and AI algorithms in medicine and how they help to improve diagnostic accuracy, make personalized therapies possible, and make robot-assisted surgery possible, leading to improved patient care.

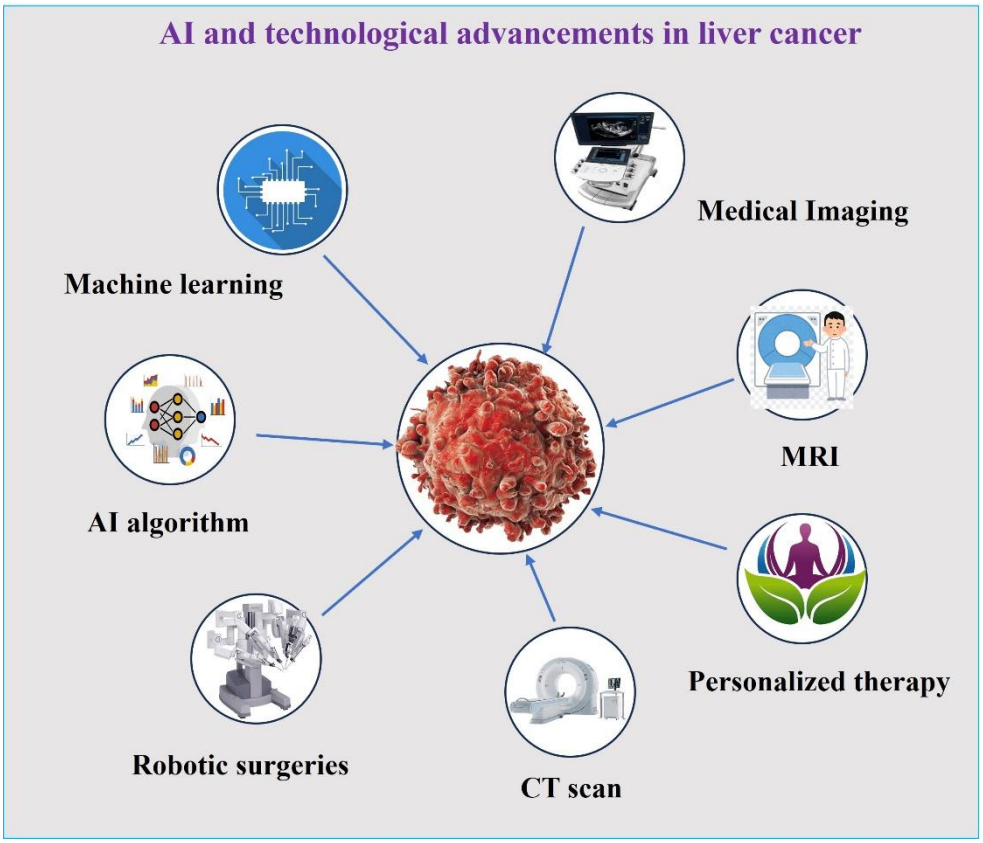

Figure 5 : AI and Technological advancements in liver cancer

BENEFITS AND CHALLENGES OF USING NANOMATERIALS IN CANCER TREATMENT

Compared to conventional chemotherapy, nanomaterials used in cancer treatment offer a number of advantages, but there are drawbacks to their use as well. Prolonged proliferative signaling, growth suppressor avoidance, resistance to cell death, replicative immortality, angiogenesis stimulation, invasion and metastasis activation, chronic inflammation, genomic instability, and mutations are all significant aspects of tumor development [81, 85]. Because of its non-selective mechanism of action and indiscriminate cytotoxicity to both cancer and healthy cells, conventional chemotherapy and radiation therapy are frequently plagued with inefficiency and pervasive side effects. Thus, the key to successful cancer eradication is striking the right dosage vs. an extremely sophisticated targeted drug delivery system (DDS) [86].

To access tumor deposits, systemically delivered chemotherapeutic drugs, oral or intravenous, have to cross different physiological barriers of the body, including the tumor microenvironment (TME), vasculature, the mononuclear phagocyte system (MPS), the blood-brain barrier, and renal filtration. Although the presence of such barriers is necessary to safeguard the normal tissues from infection in normal physiology, it also becomes operational to thwart anticancer agent delivery. Moreover, cancer cells have unique growth patterns compared to regular cells, and the tumor tissue contains densely packed extracellular matrix, excessive angiogenesis due to over levels of angiogenic factors, and elevated interstitial fluid pressure—all adding to drug delivery complexity. Bypassing them continues to be one of the central thrusts of activity in cancer treatment engineering with nanotechnology [45].

FDA-APPROVED ANTIBODY NANODRUGS IN CANCER THERAPY

Antibody-drug conjugates (ADCs) are an exciting class of anticancer targeted drugs, with the potential to marry the selectivity of monoclonal antibodies and the intense cytotoxicity of chemotherapy drugs. ADCs represent bioengineered biopharmaceuticals designed to selectively target and deliver cytotoxic drugs to malignant cells with the goal of maximizing therapeutic effect while reducing off-target cytotoxicity to normal tissues.

Numerous ADCs were approved by regulatory authorities over the years for treating various malignancies, including solid tumors and blood cancers. The ADCs in question are heterogeneous with respect to critical features such as antibody target, cytotoxin payload, and linker technologies that underlie their distinct therapeutic characteristics and medical use.

An overview of ADCs approved by FDA and EMA, along with their respective target cancers and mode of action, is found in (**Table 2)** [87]**.**

Table 2 : FDA-approved antibody nanodrugs in cancer therapy

Drug	Product	Molecular target	Cell targeting	Company	Approval year	Indication
Tisotumab vedotin-tftv	Tivdak	Tissue factor	Cancer and stroma cells of TMF	Seagen Inc	2021	Metastatic or recurrent cervical cancer
Lancastuximab tesirine-lpyl	Zynlonta	CD19	Follicle dendritic cells and B cells	ADC Therapeutics	2021	Large B-cell lymphoma
Sacituzumab govitecan	Trodelvy	Trop-2	Cancer cells	Immunomedics	2020	People who have had at least two previous therapies for metastatic triple-negative breast cancer (mTNBC) (for patients with relapsed or refractory metastatic illness)
Belantamab mafodotin-blmf	Blenrep	BCMA	B-cells	GlaxoSmithKline	2020	Refractory or relapsed multiple myeloma
Trastuzumab deuxtecan	Enhertu	HER2	Cancer cells	AstraZeneca/ Daiichi Sankyo	2019	Patients with HER2-positive breast cancer that is incurable or has spread after receiving two or more previous anti-HER2-based regimens
Enfortumab vedotin	Padcev	Nectin-4	Cancer cells	Astellas/Seattle Genetics	2019	Patients with meastatic or locally progressed urothelial carcinoma who have been treated with paclitaxel and a PD-1 or PD-L1 inhibitor
Polatuzumab vedotin-piiq	Polivy	CD79	B-cells	Genentech, Roche	2019	Refractory or relapsed diffuse large B-cell lymphoma (R/R) (DLBCL)
Moxetumomab pasudotox	Lumoxiti	CD22	Leukemia cells	AstraZeneca	2018	Relapsed or refractory hairy cell leukemia (HCL)

Inotuzumab ozogamicin	Besponsa	CD22	B-cells	Pfizer/Wyeth	2017	Acute lymphoblastic leukemia with CD22-positive B-cell precursor that has relapsed or is resistant
Gemtuzumab ozogamicin	Mylotarg	CD33	Myeloblast, Myeloid stem cells, monoblasts, monocytes/macrophages, granulocytes precursor, and mast cells	Pfizer/Wyeth	2017;2000	Acute myelogenous leukemia (AML) relapse
Brentuximab vedotin	Adcetris	CD30	Lymphoid cells	Genetics of Seattle, Millennium/Takeda	2011	Both relapsed HL and sALCL

KEY HIGHLIGHTS AND RESEARCH PERSPECTIVES

Nanotherapeutics came into being as a new paradigm in the treatment of cancer, providing accurate targeting of cancer cells, better surgery with tumor removal, and amplified effects of radiation therapy. All these gains surpass the loopholes that exist in conventional therapies like surgery, chemotherapy, and radiation. Nanoparticles have the ability to specifically target tumor regions by incorporating therapeutic drugs, and the surface can be designed to deliver specific release in the biological system. Pharmacokinetic optimization and reduced systemic toxicity make nanotechnology increase drug delivery to tumor tissue, thus introducing better therapeutics with novel nanoformulations. Smart nanoparticles that can sense biological stimuli are an advanced drug delivery system for effective and targeted cancer therapy. Nanomedicine also improves bioavailability and minimizes side effects through active and passive targeting mechanisms that specifically target cancer cells. Lastly, nucleic acid delivery with nanocarriers stabilizes molecules and prolongs therapeutic action, making it a successful method of targeting previously "undruggable" cancer proteins [41, 88].

Morani et al., (2025) synthesized paclitaxel (PAC)-loaded nanoparticles from hyaluronic acid (HA), graphene quantum dots (GQDs), and adipic acid dihydrazide (ADH) to improve the solubility of PAC and minimize toxicity for targeted breast cancer treatment. The developed nanotherapeutic system was thoroughly characterized using UV–Visible spectroscopy, fluorescence analysis, and SEM–HR-TEM imaging. Characterization data showed that PAC-loaded nanoparticles were of 25–50 nm average particle size and possessed a high drug-loading capacity of 93.56%. Drug release profiles showed a pH-sensitive and sustained release, releasing about 70% of PAC at pH 5 (tumor microenvironment) and only 20% at pH 7.4 (physiological environment). Cytotoxicity assays against MCF7 breast cancer cells validated HA-ADH-GQDs biocompatibility, and cell uptake experiments showed improved internalization upon HA-targeting. Stability experiments also showed uniform drug loading with minimal physicochemical change. The results indicate PAC@HA-ADH-GQDs nanocomposites are of significant potential as a targeted, pH-sensitive drug delivery system with fluorescence imaging capability for the treatment of breast cancer [89].

Sawera et al., (2025) investigated the anticancer potential of Aloe vera nanoparticles (AVNPs) against oral tumor growth in an in vivo rat model. Aloe vera, which possesses anti-inflammatory and pro-apoptotic activity, was transformed into nanoparticles through a green synthesis process that is environmentally friendly. The green synthesized AVNPs were characterized for their structural and morphological features by Scanning Electron Microscopy (SEM) and Dynamic Light Scattering (DLS). 4-nitroquinoline 1-oxide (4NQO)-induced oral carcinogenesis in Sprague-Dawley rats treated with therapeutic effect of AVNPs by assessing tumor volume, histopathological changes, and apoptotic marker expression was assessed. Results showed marked reduction in the size of tumors along with increased expression of apoptotic markers with a rise in Caspase-3 and Caspase-9 to 12.3 and 14.8, respectively. These results confirm that AVNPs are highly effective in initiating apoptosis and inhibiting tumor progression, and as such, represent a potential natural agent for the chemotherapeutic treatment of oral cancer therapy. [90].

Xiang et al., (2025) investigated the tumor-suppressive function of circular RNA circBNC2 in metastatic castration-resistant

prostate cancer (mCRPC) and its regulatory function in ferroptosis. Bioinformatics was used to quantify the expression of circBNC2 in PCa tissues, and follow-up in vitro and in vivo experiments were performed to determine its influences on cell proliferation, migration, and ferroptosis. Functional experiments demonstrated that circBNC2 suppresses tumor growth through its function as a molecular sponge for miR-4298 and thus increased expression of the ferroptosis regulator ACSL6. In addition, a novel nano delivery system formed by nano bowls (NBs) co-delivering docetaxel (DTX) and circBNC2 (Dc-NBs) was constructed, which showed potent suppression of tumor growth in both subcutaneous and metastatic PCa models. These results highlight the therapeutic significance of circBNC2-mediated ferroptosis and place Dc-NBs on a very potent nanotechnology-based therapeutic regimen for precision therapy of mCRPC. [91].

Xiaoli et al., (2024) developed a high-valence selenium (Se) nanotherapeutic platform (MUC16-SeMnf@Res) for cancer treatment of ovarian cancer (OC) by targeting transmembrane mucin 16 (MUC16) and disrupting redox homeostasis. The nanoplatform was prepared through a redox reaction of triclinic selenium (t-Se) and manganese dioxide nanoflowers (Mnf) to produce Se4+ and Mn2+, enabling the production of reactive oxygen species (ROS) and glutathione (GSH) depletion. Structural and chemical characterization by SEM, TEM, XPS, and UV–Vis spectroscopy validated the integrity and composition of the nanosystem. In vitro and in vivo experiments proved that the nanocomposite significantly inhibited OC cell growth and migration by induction of mitochondrial damage, caspase-activated apoptosis, and MUC16 downregulation. These results introduce MUC16-SeMnf@Res as a potential nanotherapeutic approach for precision-targeted OC therapy by taking advantage of redox modulation for improved anticancer activity and preserving biocompatibility [92].

7. CONCLUSION

Nanotherapeutics is a novel strategy for cancer treatment using nanotechnology that improves drug delivery, reduces systemic toxicity, and increases therapeutic efficacy. Nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, and metal nanoparticles have been engineered to provide targeted tumor delivery through passive and active targeting mechanisms. These developments overcome the shortcomings of traditional therapies by optimizing bioavailability, minimizing side effects, and facilitating controlled drug release. Furthermore, nanomedicine also plays significant roles in imaging and diagnostics, and iron oxide nanoparticles have been found to be beneficial as MRI contrast agents.

The use of artificial intelligence (AI) in nanomedicine also enhances drug formulation, precision medicine, and real-time monitoring of the efficacy of treatment. Besides, new uses for immunotherapy, photothermal therapy, and gene delivery are indicative of the growing significance of nanotherapeutics in cancer therapy. In spite of significant advances, clinical translation, mass production, and approval remain challenging. Tumor heterogeneity, nanoparticle stability, and personalization of medicine strategies need to be tackled by future research. With ongoing progress in nanotechnology, it has tremendous potential to revolutionize cancer therapy, enhance patient survival, and minimize side effects of treatment

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