Characterization and Application of Nanomaterials 2026, 9(1), 11921.
https://doi.org/10.24294/can11921

Review

Nanotechnology for liver cancer: Innovations, challenges, and future prospects

Aqsa Mehreen[1], Maryam Faiz[2], Mahnoor Azeem[1], Muhammad Naeem[1], Deeba Amraiz[1], Uzma Azeem Awan[1,*]

[1] Department of Biological Sciences, National University of Medical Science, Rawalpindi 46000, Pakistan
[2] Department of Molecular Biology and Genetics, Uskudar University, Istanbul 34662, Turkey
*** Corresponding author:** Uzma Azeem Awan, uzma.awan@numspak.edu.pk

CITATION

Mehreen A, Faiz M, Azeem M, et al. Nanotechnology for liver cancer: innovations, challenges, and future prospects. Characterization and Application of Nanomaterials. 2026; 9(1): 11921. https://doi.org/10.24294/can11921

ARTICLE INFO

Received: 18 November 2025
Accepted: 20 March 2026
Available online: 31 March 2026

Abstract: Liver cancer, particularly hepatocellular carcinoma (HCC), remains a major cause of cancer-related mortality worldwide due to various reasons, including late-stage diagnosis, treatment resistance, and limited therapeutic efficacy. Conventional treatment strategies- surgical resection, chemotherapy, and targeted therapies- pose significant limitations such as poor specificity, systemic toxicity, and disease recurrence, preventing timely treatment. Recent advances in nanotechnology provide promising solutions, particularly in early diagnosis and precision medicine. This review focuses on nanotechnology-based theranostic techniques, including nano biosensing, liquid biopsy innovations, and imaging enhancements. Furthermore, significant improvements in therapeutic strategies, such as nanoparticle-mediated drug delivery and immunomodulation, are discussed, as well as existing challenges and potential prospects. Understanding the potential of these innovations is crucial for establishing more effective, personalized, and minimally invasive strategies for liver cancer management.

Keywords: hepatocellular carcinoma; nanotechnology; cancer diagnosis; liquid biopsy; imaging; precision medicine

1. Introduction

Liver cancer is a significant global health challenge, characterized by the formation of cancerous cells in liver tissues. It is broadly divided into two subtypes: hepatocellular carcinoma (HCC), which accounts for approximately 90% of liver cancer cases, and intrahepatic cholangiocarcinoma (ICC) [1,2]. Major risk factors for malignancy include smoking, prolonged hepatitis B virus (HBV) or hepatitis C virus (HCV), and cirrhosis due to alcohol. Clinically, HCC presents symptoms like right upper quadrant pain and weight loss with non-specific features like anorexia, fever, jaundice, malaise, and stomach discomfort. However, many patients remain asymptomatic in the early stages, prolonging diagnosis and treatment initiation. Men have a higher probability of developing the disease than women, usually occurring with a ratio of 3:1 or 4:1, respectively, in most populations. This epidemiological difference could partly be attributed to higher tobacco use among men [2].

According to Global Cancer Observatory (GLOBOCAN) 2020 statistics, approximately 905,700 liver cancer cases were reported, with 830,200 deaths worldwide. Projecting from the disease's statistical trend, there may be an increase of 55% in new liver cancer cases till 2040, with the apprehension of 1.4 million people being diagnosed with liver cancer. The approximate death toll may reach nearly 1.3 million, consequently, increasing the mortality rate by 56.4% more than in 2020 [3]. The occurrence of HCC in Pakistan is higher in the male population at a rate of 7.6

compared to 2.8 in females per 100,000 people, whereas 60–70% of cases have a direct link to HCV infection [4].

Traditional treatment modalities are unable to prevent liver cancer due to multiple intrinsic limitations, including the inability to cater to cancer heterogeneity, drug resistance, and triggering harmful side effects. The advent of nanotechnology provides a novel, potent theranostic approach to tackle the disease through early detection and non-invasive treatment techniques while diminishing the limitations of conventional therapies through combined theranostic approaches. A specific theranostic agent from an array of nanomaterials can be employed that complements the patient's physiology for effective disease treatment [5]. Liver cancer has become one of the world's major health issues and there is a dire need to improve early detection techniques to prevent disease incidence and mortality and enhance treatment efficacy through the development of novel therapeutic approaches.

Various imaging techniques like angiography, ultrasound (US), and computed tomography (CT) imaging are used to diagnose HCC. Angiography is particularly useful for detecting tumors smaller than 2 cm, but its use is limited. CT scans are used for patients with a high clinical risk of HCC, involving three phases of contrast enhancement [6]. The US is widely used as a primary screening tool since its accuracy exceeds 90% for tumors larger than 30 mm, however, its sensitivity varies, especially in cirrhotic patients [7].

A wide range of conventional treatment modalities is available for managing HCC, including curative approaches such as liver transplantation and surgical hepatic resection; systemic therapies such as immunotherapy and molecularly targeted agents; and locoregional treatments such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). Liver transplantation is considered the best treatment method for HCC as it removes cancerous tissues along with liver tissues that are at risk of developing cancer, restoring liver function [7]. In contrast, hepatic resection only removes the cancerous part of the liver, so the risk of developing cancer in peripheral liver tissues still remains an issue [8]. Tumor ablation therapy, both physical (e.g., cryoablation and RFA) and chemical (e.g., absolute alcohol and trichloroacetic acid), is employed when resection is not possible [9]. It is a less invasive procedure typically used to treat patients with smaller liver tumors [10]. TACE, which blocks blood supply to tumors, is used when other treatments are less feasible. TACE is categorized into two types: conventional transcatheter arterial chemoembolization (cTACE), which involves injecting chemotherapeutic drug mixed with an oil-based agent (lipiodol), followed by an embolic agent to block blood flow to the tumor, while transcatheter arterial chemoembolization (DEB-TACE) involves loading polymeric beads with chemotherapeutic drug that also block the vasculature, feeding the tumor site [11]. Chemotherapy is a type of systemic drug therapy comprising specific drug regimens to inhibit the developing tumor [12]. It remains an option for advanced HCC, using various chemotherapeutic agents such as 5-fluorouracil (5-FU), doxorubicin (DOX), cisplatin (CDDP), epirubicin (EPI), and tamoxifen (TAM), among others. However, it is associated with significant side effects such as weight loss, nausea, and hypertension, and is often discontinued due to the development of drug resistance. Lastly, radiotherapy is a non-invasive procedure that applies ionizing radiation to specific cancer-affected areas in the body, such as liver, to destroy cancer cells. The

ionizing radiation deforms macromolecules, namely proteins, enzymes, and nucleic acids, that are integral parts of a living cell. Breaks in the DNA double helical structure disrupt the genome, inhibiting the cell's proper functioning and consequently leading to cell death [13].

As illustrated in **Figure 1**, a wide range of treatment modalities are present for managing liver cancers such as HCC. After diagnosis, staging is the first step in treatment, by grouping patients according to their expected survival, to ascertain the best course of treatment. Individuals in one stage of the disease should have a similar chance of survival, which is distinct from those in other phases. For early-stage cancer, resection and transplantation are better choices, whereas for intermediate stages, hormonal therapy and chemotherapy are recommended and for later stages, systemic treatments are an option [14].

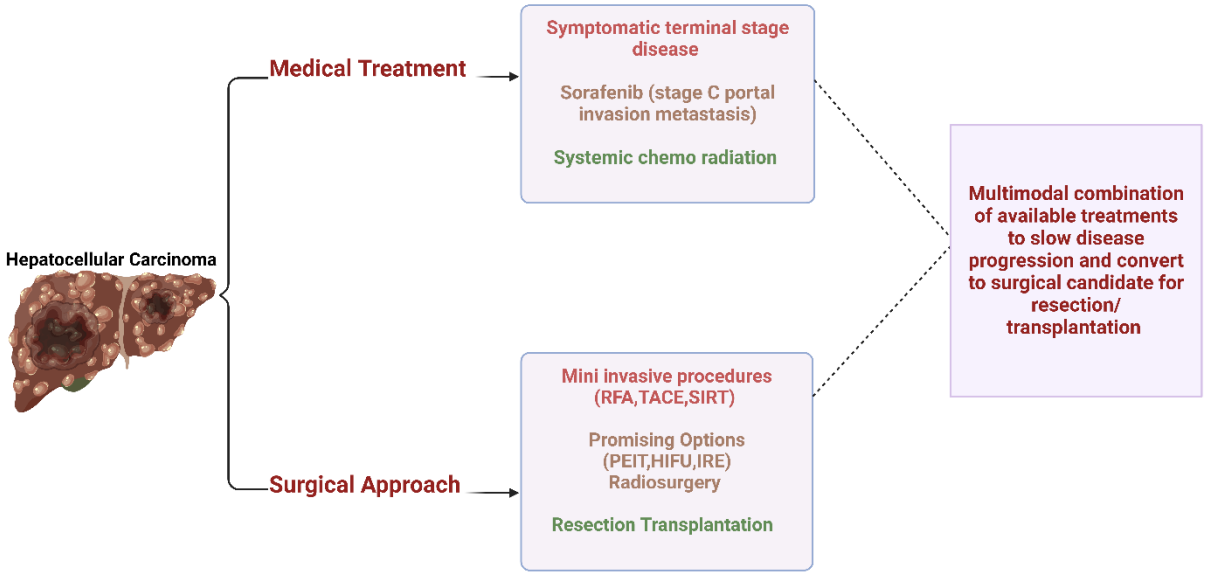

Figure 1. Possible treatment modalities employed according to cancer stage.

Despite the gradual advances in the conventional procedures to diagnose and treat the lethal disease, liver cancer cases are on the rise globally due to treatment inefficiency. Resistance to chemotherapeutics like 5-FU leads to autophagy activation by cancer cells against the drug, a common barrier to effective treatment [14]. Although the high dosage of ionizing radiation kills cancerous cells, tumor cells may still survive and metastasize [7]. Various treatment modalities, along with their mechanisms and limitations, are mentioned below in **Table 1**. With the continual rise in liver cancer cases, it is critical to improve theranostic approaches to reduce the disease incidence rate worldwide.

Table 1. Treatment modalities along with their mechanisms and limitations.

Conventional treatment modalities	Mechanism	Limitation (s)	Reference(s)
Liver resection	Surgical removal of cancerous tissues in the liver	Effective only if detected at an early stage. Only removes tissues that are at risk of evolving into cancerous tissues	[7,15]
Liver transplantation	Transplant of a damaged liver with a healthy liver from a donor	Effective only if detected at an early stage. Inaccessibility due to a lack of donors.	[15,16]
Tumor ablation	Destruction of cancerous tissues by application of intense heat (radioablation) or by cooling them to destruction (cryoablation)	Effective only if detected at early stage	[10,17]
Transcatheter Arterial Chemoembolization (TACE)	Two types: cTACE delivers chemotherapeutics with embolic agent by injection whereas DEBTACE involves supplying chemotherapeutics to patients in polymeric beads that also block the vasculature	Repeated use of therapy decreases liver health and subsequently lowers the chances of survival	[11]
Chemotherapy	Utilization of various chemotherapeutic drugs, including cisplatin, sorafenib and, 5-FU that interfere with different mechanisms of cancer cell machinery to inhibit cell proliferation	Detrimental side effects of chemotherapeutics, namely nausea, weight loss, and hypertension. Drug resistance in patients renders treatment ineffective altogether.	[12,18]
Immunotherapy	Modulating the patient's immune cells to display an aggressive immune reaction towards liver tumor	Due to heterogeneity of liver cancer and differences in patient physiology, immunotherapy may vary in effectiveness or not work at all	[13,19]
Radiotherapy	Application of ionizing radiation to interfere with macromolecules related to cancer cells, stimulating cell death	Tumor cells may still survive high dosages of radiation and metastasize	[17,20]

Considering the severe inadequacy of conventional theranostic modalities, exploring other scientific domains such as nanotechnology for cancer theranostics is crucial and requires immediate attention.

This review discusses the significance of nanotechnology in liver cancer diagnosis and treatment procedures. Integration of nanomaterials in conventional liver cancer therapies for effective treatment and certain limitations are also reviewed in detail. Furthermore, the immense potential of nanoparticles (NPs) in cancer treatment through an innovative approach is also highlighted in the article.

2. Nanobased drug delivery system (DDS)

Advancements in nanotechnology bridge numerous gaps in liver cancer treatment procedures by combining conventional and emerging treatment modalities that create a synergistic effect on treatment efficacy. Nanoscience is the scientific study of structures, systems and devices at the nanoscale, ranging from 1–100 nanometers, whereas nanotechnology is the application of the theoretical knowledge to solve practical problems. Nanotechnology is based on two key principles: the size and shape of a NP, which determine its properties and behavior, and the novelty of the nanostructure to benefit from its full potential. Nanomedicine, conversely, is an interdisciplinary field that links nanotechnology, medicine and biology and paves an innovative pathway for diagnosis and management of different diseases, especially cancer. The emergence of nanoscience dates to the 5th century when scientists speculated whether matter is composed of a smaller unit, which we now refer to as an

atom. Over the course of centuries, numerous scientists contributed to the ever-growing field with either theoretical discoveries or by developing novel experimental equipment that further broadened the nanotechnological applications [21]. Under the realm of nanotechnology, numerous structures with unique dimensions and characteristics were created that are collectively known as NPs. This extensive class of NPs could be composed of organic or inorganic materials. NPs possess significant potential and diverse chemical, physical, and biological properties at the nanoscale that make them perfect theranostic agents in cancer mitigation [22].

Nanotechnology has increased the efficacy of cancer treatment through drug delivery systems (DDSs); NPs can be utilized to deliver anticancer drugs by binding or encapsulating it, either covalently or electrostatically. NPs consist of a nanocarrier and an active drug component [12]. Due to their large surface-to-volume ratio, NPs can be heavily loaded with anticancer drugs to increase the likelihood of disease regression [23]. Furthermore, NPs can be engineered to target specific tumor sites in the body, including the liver, conferring precision to the therapeutic approach [24]. As nano systems have characteristics of controlled release, delivery of anticancer drugs in the form of NPs cannot only reduce the required therapeutic dosage but also reduce the administration frequency. Nanocarriers deployed for drug delivery decrease the amount of drug necessary, which reduces the probability of systemic toxicity while ensuring sustained drug release after a single administration, thus enhancing treatment efficacy by targeting liver cancer cells [25]. Fundamentally, NPs deliver therapeutic agents through active and passive targeting. Active targeting is achieved by attaching different targeting moieties like aptamers, antibodies, and ligands to the surface of the nanocarrier, specifically to recognize the target tumor cell, while passive targeting is achieved by enhanced permeability and retention (EPR) effect due to leaky vasculature and long retention time of blood vessels in the tumor microenvironment (TME) [26]. Target mechanisms are further highlighted in **Figure 2**.

A variety of nanocarriers can be used, having their unique advantages, including lower toxicity, increased solubility, stability, and targeted delivery for liver cancer treatment. Key nanocarriers, their properties, and examples of drugs they deliver are summarized in **Table 2**.

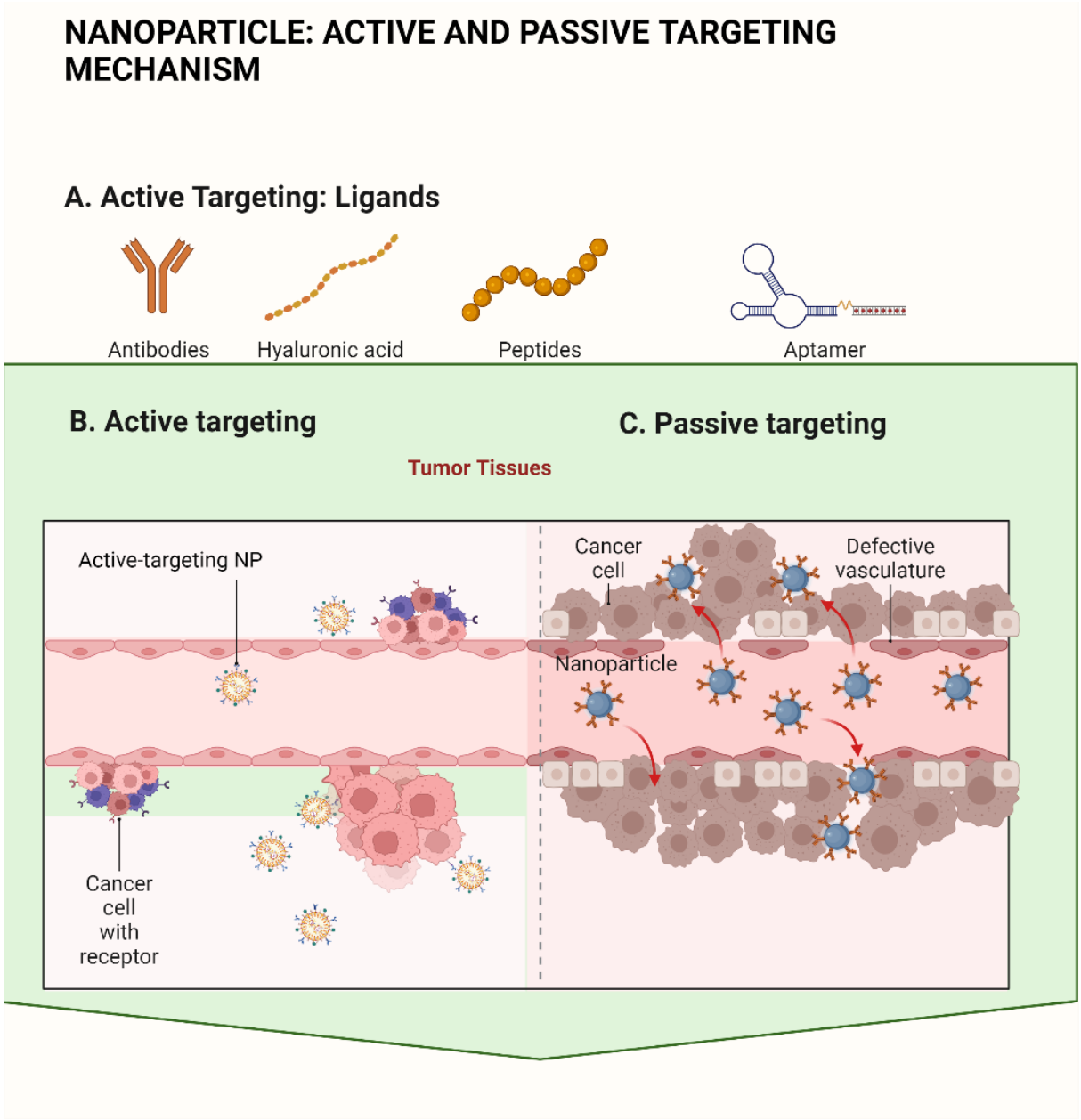

Figure 2. Nanoparticle Targeting Mechanisms.

Table 2. Types of Nanocarriers in Liver Cancer Drug Delivery.

Nanocarrier type	Properties	Example drug(s)	References
Liposomes	Biodegradable, biocompatible, enhances drug stability and circulation time.	Doxorubicin (Doxil®)	[27]
Polymeric Nanoparticles	Controlled drug release, biocompatible, widely used for chemotherapy agents.	PLGA-based Paclitaxel, Chitosan-based Curcumin	[28]
Gold Nanoparticles (AuNPs)	Enables photothermal therapy, targeted drug delivery, and imaging applications.	Conjugated Sorafenib	[29]
Silica-Based Nanoparticles (MSNs)	High drug-loading capacity, porous structure for controlled release.	Doxorubicin, Camptothecin	[26]

These nanocarriers have exhibited significantly improved drug availability and targeted delivery in tumors and are proven to be promising for

targeted delivery to liver cancer. Specifically, liposomes have demonstrated increased biocompatibility due to their lipid bilayer, making them a suitable carrier for hydrophilic as well as hydrophobic liver cancer drugs. Leaky vasculature in the liver allows rapid accumulation of liposomes, ensuring effective drug exposure. Among FDA-approved liposome-based drugs, liposomal irinotecan (Onivyde) is also being explored for liver cancer after exhibiting efficacy in pancreatic cancer. Due to their biodegradable exterior, polymeric NPs sustainably release anticancer drugs, allowing low dosage administration and decreasing chances of liver toxicity. Owing to their exceptional capabilities, sorafenib encapsulations are undergoing clinical trials for FDA approval. Inorganic NPs, namely gold NPs (AuNPs) and silica-based NPs, are highly efficient nanocarriers with stable structures and the ability of dual-functionality (drug delivery and treatment evaluation through imaging).

3. Nano diagnostics: Advancements in early detection

Early detection of cancer is revolutionized by highly specific and sensitive isolation of cancer biomarkers by using different tools and techniques such as the nanobiosensors, liquid biopsy and enhancements in imaging techniques. These latest advancements in nanodiagnostics facilitate timely detection, which ultimately leads to improved treatment outcomes.

3.1. Biosensors

Early liver cancer detection is challenging due to its insidious symptoms and tumor heterogeneity however, it can facilitate earlier treatment and increase the average survival rate to 60 months as compared to 8 months of average survival rate if detected at later stages, according to statistical analysis. Biomolecules whose quantity, structure, or reactivity can be measured can indicate normal biological processes or a disease condition, and are referred to as biomarkers [26]. Cancer biomarkers are biological molecules, such as cell-surface proteins, that can be detected using highly sensitive biosensors in the form of NPs. To improve HCC detection at earlier stages, various NP-based biosensors have been developed to integrate into cancer biomarker sensing elements. Specific biorecognition elements that detect HCC-related biomarkers are combined with several nanomaterials to develop biosensors with increased sensitivity and specificity for targeted biomarker isolation and high electrical conductance for rapid signal transduction [27,30]. Multiple HCC-related biomarkers have been recognized which include certain genetic mutations or modifications, nucleic acids such as non-coding ribonucleic acid (RNA) (e.g., microRNA or miRNA) and long non-coding RNAs that are released from tumor cells to circulate in bloodstream, and proteins such as alpha-fetoprotein (AFP), des-γ-carboxyprothrombin (DCP), glypican-3 (GPC3), and osteopontin (OPN). Circulating HCC cells and exosomes also serve as prominent early diagnostic liver cancer biomarkers [31].

Biosensors are diagnostic tools that essentially consist of two components, which enable them to detect certain biomolecules, such as cancer biomarkers: a

biorecognition element and a transducer system. The biorecognition element interacts with a specific biomolecule, also known as the target analyte, in the sample, transmitting signals to the transducer system that produces a quantifiable result. Biorecognition elements vary from antibodies, enzymes, and DNA that form the sensor layer to interact with their specific conjugate analyte for successful biorecognition. Biosensors that include nanomaterials in their structure are classified as nanobiosensors; however, they follow a similar detection mechanism to other biosensors [26]. Nanomaterial-based biosensors have overcome the major issue of HCC biomarker detection: the inability to detect low concentrations of biomarkers. Complementary ligands conjugated with a certain type of NP specifically target HCC biomarkers for rapid chemo-physical signal generation [32].

NP-based biosensors exhibit incredible properties, making them more suitable biosensing devices; nanobiosensors display instant piezoelectric and colorimetric responses due to their nanostructural morphologies. Moreover, nanobiosensors have excellent durability due to NP's superior electrical conductivity as well as mechanical stability. Conventional screening methods, like enzyme-linked immunosorbent assay (ELISA), could be employed for biomarker detection, but are unable to detect cancer biomarkers at lower concentrations. NPs' morphology and material properties make them appropriate to be integrated into diagnostic devices like biosensors. NP-based biosensors like gold aptasensors exhibit high biocompatibility and electron transfer ability for efficient signal transduction.

The efficacy of employed curative therapy, as well as the recovery rate, is comparatively higher if cancer is diagnosed at earlier stages; therefore, it is quintessential to improve and employ diagnostic procedures like biosensing [33]. Coupling nanotechnology with sensing procedures appears to be a promising step to enhance cancer diagnostic techniques.

Nanobiosensors can be expansively categorized based on either their type of bio-recognition element or the transducer utilized in the structure. The types of transducers include optical, electrochemical, piezoelectric, and calorimetric transducers [34].

Optical nanobiosensors are extremely sensitive to specific biomarkers that detect various light signals at distinctive active sites depending upon the nanomaterial used. Surface plasmon resonance (SPR), fluorescence, colorimetric, and surface-enhanced Raman scattering (SERS) are various optical procedures utilized to detect biomarkers.

Electrochemical nanobiosensors follow the principle of electrochemistry as electrons are exchanged between ions when the bioreceptor interacts with the specific biomarker. The chemical reaction generates a signal in the form of an electrical current or a potential difference. The intensity of the signal produced is directly proportional to the concentration of the biomarker [33]. Electrochemical biosensors are subdivided into potentiometric, amperometric, impedimetric, and capacitive biosensors.

Piezoelectric nanobiosensors are mass-sensitive biosensors. Acoustic piezoelectric sensors detect biomarkers when it interacts with cantilevers, stimulating vibration on the sensing layer that leads to subsequent analyte detection [35]. Another common piezoelectric nanobiosensor is a quartz crystal microbalance (QCM) biosensor that consists of an oscillator circuit including a quartz disc with circular electrodes surrounding it from both sides. The interaction of biomarkers with oscillating electrodes changes their frequency. The change in frequency signals

analyte detections that is also directly proportional to analyte concentration. The addition of NPs to the device increases its sensitivity and accuracy [36].

Calorimetric or thermal nanobiosensors detect biomolecules based on the change in heat intensity. The energy released after biological interaction is recorded by a thermistor, determining biomarker detection [37]. **Table 3** summarizes the nanobiosensors and their principle based on transducers.

Table 3. Nanobiosensors and their working principle based on transducers.

Transducer type	Subtype	Principle	Referance(s)
Optical transducers	Surface plasmon resonance (SPR) based	Biomarkers are detected through a change in the excitation range of surface electrons on NPs when shorter wavelength light waves interact with it.	[37]
	Fluorescence	Fluorescent compound radiates to indicate biomarker detection when the biomarker interacts with fluorescent NPs, consequently disrupting their bond.	[38]
	Colorimetric	Color change due to light absorption or reflection indicates biomarker detection when it interacts with NP conjugated dye.	[37]
	Surface-enhanced Raman scattering (SERS) based	Specific light scattering patterns due to the interaction of biomarkers with light	[33]
Electrochemical transducers	Potentiometric	Biomarker detection by voltage generation	[33]
	Amperometric	Changes in electric current indicate specific biomarker interaction	[33]
	impedimetric	Flow of electric charge signals biomarker detection	[33]
	Capacitive	Electrical properties of sensor surface conclude biomarker detection	[36]
Piezoelectric transducers	Acoustic piezoelectric	Biomarker interaction with cantilevers stimulates oscillations and subsequent biomarker detection	[35]
	Quartz crystal balance (QCB) based	Changes in the frequency of oscillations between electrodes due to biomarker interruption detect the analyte	[36]
Calorimetric/Thermal transducer	Thermistor based	Heat intensity changes due to biomarker interaction are recorded by thermistor as an indicator	[36]

Expounding on nanobiosensors, based on the biorecognition element utilized, nucleic acid- based nanobiosensors have DNA, RNA, or aptamer conjugated to the sensor layer that interacts with complementary biomolecule and produces a signal upon hybridization. Immune-based nanobiosensors have either an antibody or antigen immobilized on the sensor layer to target complementary biomarkers with increased specificity. Enzyme nanobiosensors have specific enzymes attached to the sensor layer that interact with their complementary substrate to detect biomarkers. The stability of such a nanobiosensor highly depends on physical environment and the type of enzyme used. Another type of biorecognition element used is a whole cell. Live cells or microbes are utilized as whole-cell bioreceptors to detect intracellular or extracellular biomarkers [39].

Multiple innovative nanobiosensors have been developed for liver cancer detection to improve disease detection methods. Josu é Ismael Garc á-Ram írez et al. produced SERS-based nanostars composed of a gold-silver (Au-Ag) complex that were functionalized with anti-AFP molecule antibodies for the detection of liver cancer biomarker (AFP) in serum samples when a laser was applied. According to the result, the nanobiosensor had a much lower detection limit than ELISA, allowing rapid

detection of AFP at lower concentrations in potential patients with HCC [40]. Another group of researchers designed SERS-based AuNPs (4-MBA@AuNPs@H1 and DTNB@AuNPs@H2) containing short aptamer chains (H1 and H2). Fe_3O_4 magnetic NPs (MNPs) were conjugated with complementary longer aptamers (cDNA1 and cDNA2) that produced a Raman signal upon hybridization with AuNPs. However, conjugated MNPs had higher affinity towards cancer serum biomarkers: AFP and superoxide dismutase (MnSOD). The presence of specific cancer biomarkers propelled MNPs hybridization, resulting in a decrease in Raman signal. The MNPs successfully engaged with biomarkers exhibiting extremely low detection limit (6.23 pg/mL for MnSOD and 5.89 pg/mL for AFP) as the magnetic component allowed clustering of NPs to produce an amplified Raman signal [41].

The ongoing research on nanobiosensors and the results of efficacy provide ample proof of the potential synergistic effect of NPs in liver cancer theranostics.

3.2. Enhanced bio imaging techniques

Molecular diagnostic techniques such as magnetic resonance imaging (MRI), CT, positron emission tomography (PET), and fluorescence imaging (FI) are employed to specifically target liver cancer and metastasis [42]. The advent of nanotechnology in imaging techniques has immensely improved cancer diagnostic approaches. Due to low toxicity and better biocompatibility, nanomaterials can be employed for diagnostics. Their extraordinary ability to reach target sites in the body by passive targeting through the EPR effect or active ligand-mediated targeting makes nanomaterials a convenient choice [43].

MRI is a non-radiological imaging technique that is used to diagnose as well as track disease conditions with the aid of contrast agents (CAs). Usually, CAs are used as water-soluble paramagnetic molecules that produce a high signal-to-noise ratio for a more vivid liver image [43]. Since the hepatic artery supplies blood to HCC tissue, whereas normal liver tissues are supplied with blood from the hepatic portal vein, the contrast imaging in MRI helps diagnose HCC patients. However, conventionally used CAs like iodine compounds may pose a burden on patients' kidneys or trigger allergic reactions [9].

Due to their smaller size, larger loading capacity, and prolonged retention capacity, NPs have emerged as suitable alternatives to conventional CAs for MRI [44]. Research conducted by Chen et al. [45] to develop an iron-platinum (Fe-Pt)-based NP coated with ceramic compound, montmorillonite (MTT), exhibited greater stability, biocompatibility, and magnetic properties as a CA, while determining the contrast properties in an in vivo mouse model with HCC. The NPs actively targeted liver tissue and conveniently accumulated at the tumor site to produce enhanced MRI results. Another research group, Ma et al. [46], developed superparamagnetic iron oxide nanoparticles (SPION) conjugated with antibodies complementary to AFP and glypican-3. The NPs were aimed at detecting HCC since these biomarkers are found in high concentration at the liver tumor site. The results proved that ligand-mediated NPs are excellent CAs in in vitro model.

CT imaging produces high-resolution liver images by using CAs that absorb emitted X-rays to detect the presence of liver tumors. However, the use of iodine-

based CAs poses a high risk of renal toxicity in patients relying on CT imaging [47]. NP-based CAs are being highlighted to be used in imaging techniques due to their ease of synthesis and modification depending upon the requirements. MNPs like AuNPs serve as a safer option for CAs in CT imaging due to higher biocompatibility, stable chemical and physical properties, and tunable surface properties. Previous research developed ligand-conjugated nanocubes as targeted CAs for CT imaging, which produced an enhanced contrast image [48].

PET is another non-invasive but highly sensitive nuclear imaging technique that can be used to detect early-stage lesions. PET procedure requires administration of a radiolabeled drug that is specific to the target site to the patient, followed by a camera to detect two gamma rays released when positrons collide with electrons from the body [49]. A research group developed a multi-modality asialoglycoprotein receptor (ASGPR) targeted agent (ASGPR receptor is highly expressed in liver cancer cells) for PET imaging as well as tumor therapy for in situ experiment. Lactobionic acid (LABO) derivative was utilized for liver tumor targeting that displayed exceptional self-assembling ability in nanoparticulate form at the tumor site, enabling longer retention time as well as enhanced therapeutic effects. Moreover, 18F-lactobionic acid (18F-LABO), used for PET imaging, showed liver tumor site specificity and provided clear tumor images. It also posed a reduced risk of organ toxicity by accumulating in the body as it could not self-assemble in low chemical equivalent environment and was subsequently cleared from the body easily [50].

Optical imaging with fluorescent NPs serves an important role in cancer imaging and treatment surveillance. Fluorescent NPs are an integral part of optical molecular imaging. Commonly used fluorescent NPs include quantum dots (QDs), upconversion and dye-doped NPs [51]. Fluorescent NPs have significantly improved optical imaging by their exceptional optical properties, surface modification capacity, and dual-delivery ability (ability to carry sensing components as well as deliver therapeutic agents). Certain NPs, like carbon dots, have the capability to emit optical signals themselves, while other NPs need to be tagged with fluorophores to be viewed during optical imaging. Besides other various properties, the photostability of NPs enables them to stand out for optical imaging [52].

Zhang et al. [43] constructed an NP designed for HCC drug delivery that was monitored by fluorescence imaging. Nanospheres were formulated with SPIONS for magnetic targeting, cationized amylose for stability, and tetraphenylethylene (TPE) as the fluorescent agent loaded with small interfering RNA (siRNA). As a result, the nanosphere not only silenced the HCC tumor gene but also demonstrated enhanced fluorescent and magnetic imaging properties in vivo and in vitro. **Table 4** summarizes the imaging techniques and the NPs with their advantages that could be utilized in those techniques.

Table 4. Summary of imaging techniques and potential NPs with their advantages.

Imaging techniques	Principle	Potential NPs	Advantages	Referance(s)
MRI	Non-radiological imaging technique that provides HCC tumor image with aid CAs	iron-platinum (FePt)-based NP, superparamagnetic iron oxide nanoparticles (SPIONs)	Larger loading capacity, longer retention, stable biocompatibility, magnetic properties, better contrast results	[44–46]
CT	Utilizes CAs that able to absorb emitted X-rays to produce image	AuNPs, ligand conjugated nanocubes	Higher biocompatibility, stable chemical and physical properties, tunable surface properties, low risk of toxicity, enhanced contrast image	[47,48]
PET	Radiolabeled drug administration is followed by detection of gamma rays emitted when positrons collide with electrons from the body.	Lactobionic acid (LABO) self-assembling NPs	Low risk of toxicity or accumulation in body, better contrast	[49,50]
Fluorescent optical	Fluorescent compound-tagged NPs or fluorescent NPs are utilized to detect optical signals for biomarker detection	QDs, carbon dots, upconversion or dye-doped NPs, SPIONs	exceptional optical properties, surface modification capacity, dual-delivery ability, specific targeting	[51,52]

Although NP-based imaging agents exhibit exceptional properties that improve liver cancer screening, there are certain disadvantages that need to be considered before formulating an appropriate imaging agent. Accumulation of NP-based CAs in liver may cause hepatotoxicity if patients experience long-term exposure, potentially causing liver inflammation and/or hepatocellular oxidative stress. Certain NPs may stimulate unnecessary immune response that may lead to non-cancerous cell damage [53].

3.3. Liquid biopsies

Liquid biopsy is a non-invasive diagnostic procedure employed for HCC early detection. It involves screening of biomarkers like cell-free DNA, tumor cells, and exosomes circulating in the body fluids. It efficiently tracks specific cancer biomarker levels like telomeric repeat-containing RNA [54] and telomerase RNA component (TERC) in plasma to ensure reliable results [55,56]. Circulating tumor cells (CTCs) are tumor cells that have escaped from the original tumor or metastatic tumor, which may enable early HCC detection through blood samples from a patient. Patient can receive tailored anticancer therapies after determining the tumor cell characteristics, genomic heterogeneity, and abundance [57]. An iron oxide (Fe304)-based nanobead was formulated to target HCC-CTCs, with a near infra-red [58] fluorescent agent that had high affinity for tumor enzyme, aminopeptidase N [59], and epithelial cell adhesion molecule (EpCAM) antibody to target EpCAM (usually overexpressed in liver cancers) **Figure 3**. The dual-modality proved efficacious in targeting HCC-CTCs by giving reliable results. The nanobeads specifically targeted tumor sites due to the antibody conjugate and also successfully detected CTCs in vivo, peripheral blood sample monitoring [56]. Fractions of tumor cell-free DNA, because of phagocytized or dying tumor cells, are known as circulating tumor DNA (ctDNA). ctDNA is a valuable biomarker to track patients' therapy due to its similarity to the original tumor's genetic mutations. Subsequently, liquid biopsy to detect ctDNA is crucial for early cancer detection, monitoring, or relapse [60]. Exosomes are the smallest class of

extracellular vesicles released from all types of cells. These exosomes compartmentalize contents from various intracellular organelles, thus are a depiction of the cell's phenotype. Tumor-derived exosomes serve as an excellent cancer biomarker since they are involved in tumor progression. For a more rapid and economically feasible approach, MNPs can be utilized to target extracellular vesicles like exosomes without the need of affinity reagents for a targeted approach. Certain MNPs, such as silica-coated iron oxide NPs (Fe_3O_4@TiO_2), can target extracellular vesicles due to the lipid membrane through affinity separation [61].

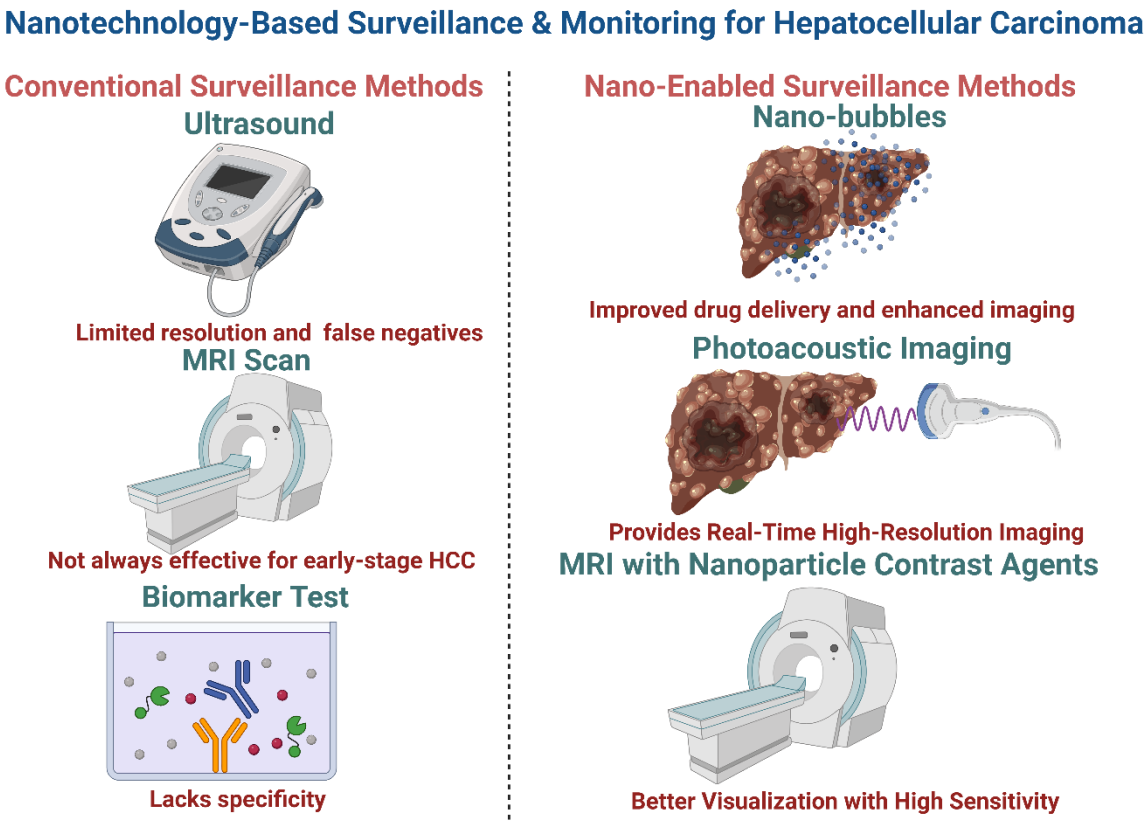

Figure 3. Nanotechnology-based surveillance methods enhance imaging resolution, tumor visualization, and drug delivery for improved HCC detection and monitoring.

4. Nanotechnology in surveillance and personalized medicine

Effective surveillance and personalized medicine hold an utmost critical place for improving HCC outcomes. Conventionally employed techniques depend only on the use of biomarkers and lack sensitivity and specificity, which are crucial for earlier detection of cancer. With the advancement in nanomedicine, enhanced imaging and real-time precision monitoring are enabled by using nano-based multifunctional probes and CAs. These advancements bridge the gap between early detection and effective treatment, significantly improving patient prognosis.

4.1. Surveillance techniques

Tracking AFP concentrations in HCC patients through imaging techniques like US is a reliable method for liver cancer surveillance. However, disease surveillance

requires intensive diagnostic focus. To address this issue, nanomaterials such as nanobubbles (NBs) and pro-bexarotene nanobubbles (PBNBs) assist in disease tracking by efficiently accumulating at the HCC tumor site for better visualization in imaging procedures. Moreover, thermal effects of the US on NBs increase tissue penetration, increasing the probability of effective drug delivery and effective ablation therapy [56]. Real-time HCC imaging may better equip professionals to take further necessary steps for disease control that can be made possible through highly sensitive and specific photoacoustic imaging (PAI) [62]. Combined imaging techniques like PAI/MRI for real-time HCC tracking can expedite treatment procedures while using NP-based MRI CAs and PAI materials further improve screening capacity, as it is able to detect HCC sized even less than 1cm [63].

4.2. Personalized medicine

Personalized medicine, also known as precision medicine, aims to provide patients with therapeutic agents tailored to their personal phenotypes and genetic makeup to avoid treatment ineffectiveness. Recently, nanomedicine has been coupled with personalized medicine to cater to patients' individualistic therapeutic needs. Personalized medicine uses omics and epigenetics studies to assist patients' individual health conditions. Nano and personalized medicine correspond in various diagnostic and therapeutic techniques. Personalized medicine begins with pharmacogenetic testing to treat patients according to their genetics. Nanomaterials are used to precisely target patients' specific genes to obtain genetic sequences for developing tailored medicines [64]. Super enhancers (SE) are elements from genomic DNA that comprise a cluster of regulatory enhancers that influence cell and tissue-specific gene regulation, consequently, determining cell fate and identity. Since it causes overexpression of various coding genes, including long non-coding RNA and is associated with cancer such as HCC, it allows cancer diagnosis and anti-tumor therapy. However, upregulated oncogenic long non-coding RNA via SE is not well studied for HCC but may prove to be a major breakthrough. Research led by Yuan et al. characterized SE-driven HSAL3, a long non-coding RNA promoting HCC tumor proliferation. For HCC antitumor therapy, researchers synthesized lipid-based siHSAL3-loaded NP (small interfering RNA that specifically targets and silences HSAL3). The targeted therapy approach proved efficacious by halting HCC tumor growth in vivo and in vitro [65].

Although utilizing specific siRNA and plasmid DNA (pDNA) to modulate HCC tumor regression may be effective, certain barriers prevent them from being used in their full potential, namely, short molecular half-life in blood circulation, lack of tumor cell uptake, and nuclear entry. To improve siRNA/pDNA specific HCC drug therapy, Huang et al. produced NPs that not only targeted HCC-related tumors for antitumor activity but also stimulated immune response for rigorous anticancer effect. Lipid bilayered NPs were produced with dendrimer-calcium phosphate (CaP) core and nucleic acid (siRNA targeting PD-1 and pDNA encoding IL-2) encapsulation and thymine-capped polyamidoamine (PAMAM) dendrimers to facilitate nuclear entry and stimulate immune response. These NPs targeted the HCC tumor specifically through the HCC-targeting peptide (SP94). The experimental model displayed safe but effective HCC-related antitumor activity. The nucleic acids downregulated

immune checkpoints like PD-1, whereas upregulated cytokine production stimulated the immune response [66].

5. Key advances in nanotherapeutics

Nanotechnology has been a popular topic in cancer research due to the immense potential in improving existing curative therapies as well as unveiling new strategies to prevent liver cancer. Recent developments in the utilization of NPs in DDS have improved adequate drug bioavailability and decreased its adverse side effects on normal cells: two major challenges in chemotherapy. Carefully structured, NPs have higher biocompatibility, enhancing the drug solubility of chemotherapeutics like sorafenib that are sparingly soluble otherwise, thus enhancing drug bioavailability [67]. Nanoparticulate drug delivery technologies prevent drug degradation while also reducing unwanted toxicities linked to anticancer drug molecules [68]. NPs have the potential to treat cancer efficiently because they have the capability to pass all the biological and physical barriers that conventional procedures cannot usually cross. Current discoveries in nanotechnology and the development of smart nanomaterials have significantly improved liver cancer theranostics. Smart nanomaterials have enabled efficient detection and regression of liver cancer in combined therapies. Nanomaterials, used in cancer treatments, are synthesized with biodegradable or non-biodegradable substances. Commercially available non-biodegradable nanomaterials include polyvinyl alcohol (PVA) and polyethylene glycol (PEG) [69]. Poly lactic-co-glycolic acid (PLGA), a biodegradable NP used in cancer therapy, hydrolyses into two endogenous metabolite monomers with nominal systemic toxicity [70].

5.1. Internal stimuli responsive smart drug delivery systems (DDS)

Smart DDS includes stimuli-responsive nanomaterials that respond to a broad range of internal (pH changes, redox conditions, enzymatic activity and certain biomolecular concentrations) and external stimuli (application of magnetic or electric field, US waves etc.) that facilitate sustainable anticancer drug release with minimal adverse effects on normal cells. pH- responsive nanomaterials take advantage of the body's varied pH conditions amongst different regions; TME has a lower pH where these NPs can change size and alter their charge to control time and location of drug release and inhibit tumor proliferation. Temperature-responsive nanomaterials have the ability to switch from hydrophilic to hydrophobic or vice versa; this transition enables NPs to release the drug at a targeted site. Such NPs also release anti-cancer drugs in regions with higher temperatures, such as tumor sites. Another incredible stimuli-responsive nanomaterial invented is the enzyme-responsive NPs that release drugs in the presence of certain enzymes, namely protease, lipase, and azoreductases present in TME, which break down the NP bonds to release drugs. Redox-responsive nanomaterials react to certain chemical conditions in TME like glutathione concentrations. Glutathione interacts with nanostructures, breaking specific bonds like disulfide, inducing drug release. NPs can be attached to a particular ligand to target specific tumor sites to boost drug delivery [69]. For example, Wu et al. [69] designed poly (3-hydroxybutyrate-co-3-hydroxyvalerate) PHBV nanocarrier for the chemotherapeutic drug, paclitaxel. The NP was coated with polydopamine (PDA-

PHBV-PTX-NPs) that had Arginine-Glycine-Aspartic acid (RGD) peptide conjugated to its surface to ensure a specific target to HCC cells. RGD ligand targets integrin receptors to enter tumor cells, yet PHBV NPs cannot combine with the RGD peptide due to lack of functional groups. However, the stimulus-responsive ability of the PDA NPs enabled them to oxidize dopamine structure and form a polymer film around the particle that can combine with the ligand easily. Results proved that fluorescently labelled RGD NPs had a higher uptake by tumor cells with lower systemic toxicity than other NP classes. Fluorescence imaging showed higher accumulation of drug concentration in tumor tissues. **Table 5** summarizes the nanomaterials that respond to internal stimuli for efficient drug release.

Table 5. Summary of internal stimuli-responsive nanomaterials.

Internal stimuli	TME conditions	Mechanism	Reference(s)
pH	Acidic/Low pH	Nanocarriers can alter their size or charge in order to release loaded drug	[69]
Temperature	High temperature	Nanocarriers can switch charges to become hydrophilic or hydrophobic according to the drug for efficient release	[69]
Enzyme	Presence of polymerases	Enzymes present in the environment break down bonds in the nanocarrier releasing the drug as a result	[69]
Redox	Presence of certain reducing or oxidizing agents	Presence of reducing agent such as glutathione interacts with nanocarrier and breaks disulfide bonds specifically for drug release	[69]

5.2. External stimuli-responsive nanomaterials

Nanomaterials used in DDS that respond to external stimuli include magnetic-responsive nanomaterials. This type of DDS uses MNPs that are directed to the tumor site by an external magnetic field to accumulate and increase drug concentration at the tumor site. Photo-responsive NPs release anticancer drugs at the targeted site when light is applied, propelling a structural change in the NP by bond breakage with the drug. Electrical- responsive nanostructures are conductive polymers that release drugs upon application of an electric current. Ultrasonic-responsive NPs have the incredible ability to penetrate deep into the tissues and stimulate nanomaterial drug release in multiple ways; ultrasonic waves rapidly heat polymeric bonds in NPs, enabling the release of the drug or causing poration in the particle for burst release. Ultrasonic-responsive NPs can also direct themselves to TME due to the radiations emitted by the ultrasonic waves [69]. **Table 6** summarizes the nanomaterials that respond to external stimuli for targeted drug release.

Table 6. Summary of external stimuli-responsive nanomaterials.

External stimuli	Mechanism	Reference(s)
Magnetic Field	Metallic nanocarriers are employed to concentrate drug at the tumor site after magnetic field application	[69]
Photothermal energy	Structural change caused by photothermal application enables drug release from nanocarriers	[69]
Electric Field	Conductive polymers are employed to release drug at targeted sites upon the application of an electric field	[71]
Ultrasonic waves	Ultrasonic waves stimulate bond breakage between nanocarriers and drugs or poration in nanocarriers for drug release	[72]

Ongoing research in nanomedicine and integration of nanotechnology in multimodal liver cancer treatments brings hope to reinforce existing therapy approaches. Combination therapies employ more than one theranostic approaches to minimize side effects, maximize therapeutic outcomes, and reduce the possibility of tumor relapse. Nanomaterials are utilized in various stages of liver cancer therapy, including diagnosis, tumor imaging, drug delivery, and palliative care. Combining nanomaterials with sensing technology has greatly improved tumor detection at earlier stages than traditional imaging techniques, allowing doctors to treat the disease while it is still progressing. Through dual-drug delivery, various materials like Au are used for NPs to deliver different chemotherapeutic drugs, in varied concentrations, in a single particle through compartmentalization for adequate anticancer effects. This technique proved to lower drug side effects over single simultaneous drug administration [71]. Radiotherapy can be used in concert with nanotechnology for targeted delivery of radiosensitizers, by loading NPs with radioisotopes, to tumor sites, sparing normal cells from the adverse effects. NPs can also be utilized as carriers for therapeutic or silencing genes in gene therapy for palliative or curative approaches. Combined gene therapy reduces immunogenicity and toxicity [73].

6. Challenges and barriers

Despite the notable advances in nanomedicine and liver cancer theranostics due to the advent of nanotechnology, there are certain intrinsic limitations amongst nanotechnological applications preventing their clinical translation and widespread adoption. Designing appropriate nanocarriers for various DDS remains a complex and resource-intensive process [74]. For a heterogeneous disease like liver cancer, tumor-targeted biosensors also need to be heterogeneous and highly specific according to patient stratification [71]. Furthermore, toxicity studies propose that NPs can potentially stimulate unnecessary immune reactions, such as allergic reactions, upon extended exposure or interaction with certain leukocyte surface receptors. Thus, inadequate data on interactions of NPs with biological systems obscure treatment safety and hinder the rapid integration of NP-based cancer theranostic approaches in healthcare systems. Rapid NP clearance from the body is another major reason that prevents them from being used in cancer theranostics; NPs are directed towards Kupffer cells in the liver that phagocytize them to prevent accumulation, which, in response, decreases treatment efficacy [75].

The possibility of synthesizing patient-specific NP-based anticancer agents increases the likelihood of treatment efficacy; however, it complicates large-scale production and subsequent clinical translation. Researchers produce specific NP agents through precisely tailored laboratory protocols; however, following various protocols to produce unique NPs complicates and prevents large-scale production, as the likelihood of errors increases [76].

A major regulatory hindrance in the widespread use of NPs in cancer treatments is that the FDA (Food and Drug Administration) has not laid out proper control measures to screen and approve them as commercially usable. The FDA set guidelines for nanomaterials used in food, cosmetics, animal feed etc., but not specifically in drugs. Since scientists claim that NPs react differently from their bulk counterparts on

the human body, the use of wide classes of nanomaterials in combination therapies further complicates the standardization process [69]. Most importantly, NP-based agents incorporate multiple domains, including drugs, biological systems, and devices, that further obscure and complicate standardization procedures and prevent authorities from setting definite regulatory guidelines. From an ethical and economic standpoint, synthesis of unique NPs and running clinical trials poses a huge financial burden that demotivates investors and slows down incorporation of such novel agents in health care system [77]. Considering the safety-related issues, certain nanocarriers release drugs slowly, reducing the therapeutic effect at the tumor site, causing toxicity and harmful side effects in consequence [78]. Stimuli-responsive NPs are unable to perform in their complete capacity as endogenous stimuli like pH and temperature changes cannot be controlled, challenging rate of drug release at the targeted site. External stimuli- responsive MNPs may cause metal toxicity by accumulating in vital organs, whereas US-responsive NPs, though they reach deeper and more complex tumor sites, may form irreversible pores in the cell membrane or cause tissue damage by heating [79].

7. Future directions

With the advancement in the field of nanotechnology and its advent in cancer treatments, it has unlocked new possibilities of incorporating nanomaterials into existing therapies for efficacious tumor inhibition with minimal side effects on non-cancerous cells. For instance, research on nanotechnology- based immunotherapy unraveled promising methods for cancer treatment. Covering cancer cell membrane fractions (CCMF) from tumor lysate on NPs leads to an aggressive immune response against tumors in animal models for lung cancer that can also be adapted for other cancers. Through another approach to activate anti-cancer immune response, immunogenic cell death of the melanoma cell line was induced using NPs that activated CD8+ T cells in a murine model, due to mass release of tumor antigens and danger signals, for an intense immune response against the tumor [80]. Moreover, a research exploited the stimuli-responsive property of NPs to design dual-responsive nano-carriers that responded to UV rays (external stimuli) and high glutathione levels (internal stimuli), common to TME, to target liver cancer. Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), an MRI CA, was loaded in NP for guided tumor treatment. The experimental design displayed significant therapeutic effects and proved to be a reliable curative approach [21].

Nanotechnology- based CRISPR/Cas9 (Clustered Regularly Interspaced Palindromic Repeats- associated protein 9) therapy is a synergistic anticancer therapy combining two potentially revolutionizing techniques. CRISPR technology utilizes Cas9 endonuclease to break into double-stranded DNA at specific sites. This technique is employed for therapeutic purposes in diseases like cancer by modulating gene expression. The effectiveness of the CRISPR technology is mainly dependent on the delivery of enzymes to the target site, which could be improved by using nanocarriers like polymers and metal-organic structures, etc., for higher biocompatibility, lower immunogenicity in comparison with conventional delivery modes [21].

Utilizing nanotechnological applications in combination with conventional cancer treatments confer a synergistic effect on tumor inhibition. Ongoing research in nanomedicine provide concrete evidence on how nanomaterials can improve cancer treatments at various stages, including cancer diagnosis. Diagnosing an asymptomatic disease, liver cancer, at early stages would be a huge breakthrough for professionals to start treatments to prevent cancer proliferation. Delivering chemotherapeutics with NPs at tumor regions precisely can potentially increase anticancer drug response, stimulating tumor regression with minimal detrimental effect on non-cancerous cells. Combination therapies such as nanotechnology-based CRISPR therapy hold immense potential to decrease cancer progression.

To expedite clinical translation of NP-based liver cancer theranostic agents, regulatory institutes should practice flexibility while setting a regulatory framework for approval of unique nanomaterials. Nanomaterial feasibility and safety should be assessed simultaneously through multiple domains, including FDA and the International Medical Device Regulators Forum (IMDRF), to increase the possibility of approval and rapid incorporation of novel approaches in the healthcare system. Moreover, databases should be established for regulatory agencies to gather their data related to nanomaterial evaluation to minimize redundancy and ensure reliability.

Furthermore, researchers should consistently report quality research and successful NP-based theranostic models to motivate investors and healthcare systems for necessary action [77].

8. Conclusion

To summarize, nanotechnology offers a wide range of promising cancer treatment strategies, considering the extensive classes of NPs that can be employed in combination therapies and nanotechnological applications for an efficient anticancer effect. Introduction of nanotechnology in conventional therapies enhances the therapeutic effect on liver cancer patients. Although certain technical limitations and a lack of approval for commercial use constrain them from being exploited in their maximum capacity, nanomaterial applications could be perfected through further experimentation. Streamlining regulatory procedures through the collaboration of multiple regulatory bodies would accelerate approval and integration of NP-based liver cancer theranostic agents. Moreover, establishing a database for gathered data would allow for the reliability and safety of proposed nanomaterials. Rigorous research efforts through quality experiments on novel nanomaterials would promote rapid clinical translation. Nano DDS are highly favorable as they have characteristics for the highest membrane permeability, better bioavailability, extended bioactivity and low toxicity to healthy tissues [21]. Nanomaterial application is in the initial stages, but with further in-depth research, it holds the potential to inhibit liver cancer incidence and mortality.

References

1. Zhou J, Sun H, Wang Z, et al. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). Liver Cancer. 2020; 9(6): 682–720. doi: 10.1159/000509424
2. Wang J, Qiu K, Zhou S, et al. Risk factors for hepatocellular carcinoma: an umbrella review of systematic review and meta-analysis. Annals of Medicine. 2025; 57(1): 2455539. doi: 10.1080/07853890.2025.2455539
3. Guo Q, Zhu X, Beeraka NM, et al. Projected epidemiological trends and burden of liver cancer by 2040 based on GBD, CI5plus, and WHO data. Scientific Reports. 2024; 14(1): 28131. doi: 10.1038/s41598-024-77658-2
4. Hafeez Bhatti AB, Dar FS, Waheed A, et al. Hepatocellular Carcinoma in Pakistan: National Trends and Global Perspective. Gastroenterology Research and Practice. 2016; 2016: 1–10. doi: 10.1155/2016/5942306
5. Zhu Y, Ge D, Wang J, et al. Emerging nanomedicine for liver diseases treatment. Journal of Nanobiotechnology. 2025; 23(1): 786. doi: 10.1186/s12951-025-03832-x
6. Chen Z, Xie H, Hu M, et al. Recent progress in treatment of hepatocellular carcinoma. American Journal of Cancer Research. 2020; 10(9): 2993–3036.
7. Nakajima M, Tokumitsu Y, Shindo Y, et al. The Recent Development of the Surgical Treatment for Hepatocellular Carcinoma. Applied Sciences. 2021; 11(5): 2023. doi: 10.3390/app11052023
8. Koza A, Bhogal RH, Fotiadis N, et al. The Role of Ablative Techniques in the Management of Hepatocellular Carcinoma: Indications and Outcomes. Biomedicines. 2023; 11(4): 1062. doi: 10.3390/biomedicines11041062
9. Seth I, Siu A, Hewitt L, et al. Clinical Practice Guidelines For the Management of Hepatocellular Carcinoma: A Systematic Review. Journal of Gastrointestinal Cancer. 2023; 55(1): 318-331. doi: 10.1007/s12029-023-00961-0
10. Chang Y, Jeong SW, Young Jang J, et al. Recent Updates of Transarterial Chemoembololization in Hepatocellular Carcinoma. International Journal of Molecular Sciences. 2020; 21(21): 8165. doi: 10.3390/ijms21218165
11. Hamaya S, Oura K, Morishita A, et al. Cisplatin in Liver Cancer Therapy. International Journal of Molecular Sciences. 2023; 24(13): 10858. doi: 10.3390/ijms241310858
12. Hou Z, Liu J, Jin Z, et al. Use of chemotherapy to treat hepatocellular carcinoma. BioScience Trends. 2022; 16(1): 31–45. doi: 10.5582/bst.2022.01044
13. Rui R, Zhou L, He S. Cancer immunotherapies: advances and bottlenecks. Frontiers in Immunology. 2023; 14: 1212476. doi: 10.3389/fimmu.2023.1212476
14. Maki H, Hasegawa K. Advances in the surgical treatment of liver cancer. BioScience Trends. 2022; 16(3): 178–188. doi: 10.5582/bst.2022.01245
15. Huang A, Yang XR, Chung WY, et al. Targeted therapy for hepatocellular carcinoma. Signal Transduction and Targeted Therapy. 2020; 5(1): 146. doi: 10.1038/s41392-020-00264-x
16. Izzo F, Granata V, Grassi R, et al. Radiofrequency Ablation and Microwave Ablation in Liver Tumors: An Update. The Oncologist. 2019; 24(10): e990–e1005. doi: 10.1634/theoncologist.2018-0337
17. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nature Reviews Disease Primers. 2021; 7(1): 6. doi: 10.1038/s41572-020-00240-3
18. Cheng K, Cai N, Zhu J, et al. Tumor-associated macrophages in liver cancer: From mechanisms to therapy. Cancer Communications. 2022; 42(11): 1112–1140. doi: 10.1002/cac2.12345
19. Chen W, Chiang CL, Dawson LA. Efficacy and safety of radiotherapy for primary liver cancer. Chinese Clinical Oncology. 2021; 10(1): 9. doi: 10.21037/cco-20-89
20. Bayda S, Adeel M, Tuccinardi T, et al. The History of Nanoscience and Nanotechnology: From Chemical–Physical Applications to Nanomedicine. Molecules. 2019; 25(1): 112. doi: 10.3390/molecules25010112
21. Priya M R K, Iyer PR. Antiproliferative effects on tumor cells of the synthesized gold nanoparticles against Hep2 liver cancer cell line. Egyptian Liver Journal. 2020; 10(1): 15. doi: 10.1186/s43066-020-0017-4
22. Mintz KJ, Leblanc RM. The use of nanotechnology to combat liver cancer: Progress and perspectives. Biochimica et Biophysica Acta (BBA)–Reviews on Cancer. 2021; 1876(2): 188621. doi: 10.1016/j.bbcan.2021.188621
23. Gabizon AA, Gabizon-Peretz S, Modaresahmadi S, et al. Thirty years from FDA approval of pegylated liposomal doxorubicin (Doxil/Caelyx): an updated analysis and future perspective. BMJ Oncology. 2025; 4(1): e000573. doi: 10.1136/bmjonc-2024-000573

24. Wang J, Zhang Y, Liu L, et al. Combined chemo/photothermal therapy based on mesoporous silica-Au core-shell nanoparticles for hepatocellular carcinoma treatment. Drug Development and Industrial Pharmacy. 2019; 45(9): 1487–1495. doi: 10.1080/03639045.2019.1629688
25. Zhang Y, Li M, Gao X, et al. Nanotechnology in cancer diagnosis: progress, challenges and opportunities. Journal of Hematology & Oncology. 2019; 12(1): 137. doi: 10.1186/s13045-019-0833-3
26. Dai Y, Han B, Dong L, et al. Recent advances in nanomaterial-enhanced biosensing methods for hepatocellular carcinoma diagnosis. TrAC Trends in Analytical Chemistry. 2020; 130: 115965. doi: 10.1016/j.trac.2020.115965
27. Kurczewska J. Chitosan-Based Nanoparticles with Optimized Parameters for Targeted Delivery of a Specific Anticancer Drug—A Comprehensive Review. Pharmaceutics. 2023; 15(2): 503. doi: 10.3390/pharmaceutics15020503
28. Yue M, Yang R, Jiang Y, et al. Precise construction of Regorafenib-loaded gold nanoparticles: investigation of antiproliferative activity and apoptosis induction in liver cancer cells. Journal of Experimental Nanoscience. 2023; 18(1): 2254006. doi: 10.1080/17458080.2023.2254006
29. Corma A, Botella P, Rivero-Buceta E. Silica-Based Stimuli-Responsive Systems for Antitumor Drug Delivery and Controlled Release. Pharmaceutics. 2022; 14(1): 110. doi: 10.3390/pharmaceutics14010110
30. Chinnappan R, Makhzoum T, Arai M, et al. Recent Advances in Biosensor Technology for Early-Stage Detection of Hepatocellular Carcinoma-Specific Biomarkers: An Overview. Diagnostics. 2024; 14(14): 1519. doi: 10.3390/diagnostics14141519
31. Ghosh G. Early detection of cancer: Focus on antibody coated metal and magnetic nanoparticle-based biosensors. Sensors International. 2020; 1: 100050. doi: 10.1016/j.sintl.2020.100050
32. Atapour A, Khajehzadeh H, Shafie M, et al. Gold nanoparticle-based aptasensors: A promising perspective for early-stage detection of cancer biomarkers. Materials Today Communications. 2022; 30: 103181. doi: 10.1016/j.mtcomm.2022.103181
33. Mondal R, Dam P, Chakraborty J, et al. Potential of nanobiosensor in sustainable agriculture: the state-of-art. Heliyon. 2022; 8(12): e12207. doi: 10.1016/j.heliyon.2022.e12207
34. Pathak S, Bazazordeh S, Çamlıca B, et al. Multianalyte nano-biosensor diagnostics: advances through microfluidic and AI integration. Frontiers in Bioengineering and Biotechnology. 2025; 13: 1715719. doi: 10.3389/fbioe.2025.1715719
35. Debnath N, Das S. Nanobiosensor: Current trends and applications. In: NanoBioMedicine. Singapore: Springer Singapore; 2020: p. 389–409. doi: 10.1007/978-981-32-9898-9
36. Shandilya R, Bhargava A, Bunkar N, et al. Nanobiosensors: Point-of-care approaches for cancer diagnostics. Biosensors and Bioelectronics. 2019; 130: 147–165. doi: 10.1016/j.bios.2019.01.034
37. Munawar A, Ong Y, Schirhagl R, et al. Nanosensors for diagnosis with optical, electric and mechanical transducers. RSC Advances. 2019; 9(12): 6793–6803. doi: 10.1039/c8ra10144b
38. Ahmad M, Hasan M, Tarannum N, et al. Recent advances in optical and photoelectrochemical nanobiosensor technology for cancer biomarker detection. Biosensors and Bioelectronics: X. 2023; 14: 100375. doi: 10.1016/j.biosx.2023.100375
39. Xu X, Zhou X, Xiao B, et al. Glutathione-Responsive Magnetic Nanoparticles for Highly Sensitive Diagnosis of Liver Metastases. Nano Letters. 2021; 21(5): 2199–2206. doi: 10.1021/acs.nanolett.0c04967
40. García-Ramírez JI, Luna-Cervantes M, Izaguirre-Hernández IY, et al. SERS-Based Immunoassay for α-Fetoprotein Biomarker Detection Using an Au-Ag Nanostars Platform. Biosensors. 2025; 15(9): 632. doi: 10.3390/bios15090632
41. Sheng J, Wang R, Yang H, et al. Surface-enhanced Raman scatting microfluidic chip based on the identification competition strategy were used for rapid and simultaneous detection of liver cancer related proteins. Photodiagnosis and Photodynamic Therapy. 2024; 49: 104336. doi: 10.1016/j.pdpdt.2024.104336
42. Jia W, Han Y, Mao X, et al. Nanotechnology strategies for hepatocellular carcinoma diagnosis and treatment. RSC Advances. 2022; 12(48): 31068–31082. doi: 10.1039/d2ra05127c
43. Malla RR, Kumari S, Kgk D, et al. Nanotheranostics: Their role in hepatocellular carcinoma. Critical Reviews in Oncology/Hematology. 2020; 151: 102968. doi: 10.1016/j.critrevonc.2020.102968
44. Chan MH, Lu CN, Chung YL, et al. Magnetically guided theranostics: montmorillonite-based iron/platinum nanoparticles for enhancing in situ MRI contrast and hepatocellular carcinoma treatment. Journal of Nanobiotechnology. 2021; 19(1): 308. doi: 10.1186/s12951-021-01052-7
45. Ma XH, Wang S, Liu SY, et al. Development and in vitro study of a bi-specific magnetic resonance imaging molecular probe for hepatocellular carcinoma. World Journal of Gastroenterology. 2019; 25(24): 3030–3043. doi: 10.3748/wjg.v25.i24.3030

46. Sawhney G, Bhardwaj AR, Sanu K, et al. Nanotechnology at the forefront of liver cancer diagnosis. In: Nanophototherapy. Amsterdam, The Netherlands: Elsevier; 2025. pp. 575–593. doi: 10.1016/b978-0-443-13937-6.00004-4
47. Meng X, Wu Y, Bu W. Functional CT Contrast Nanoagents for the Tumor Microenvironment. Advanced Healthcare Materials. 2020; 10(5): 2000912. doi: 10.1002/adhm.202000912
48. Goel S, England CG, Chen F, et al. Positron emission tomography and nanotechnology: A dynamic duo for cancer theranostics. Advanced Drug Delivery Reviews. 2017; 113: 157–176. doi: 10.1016/j.addr.2016.08.001
49. Lu X, Fu Y, Zhu Y, et al. Construction of in-situ self-assembled agent for NIR/PET dual-modal imaging and photodynamic therapy for hepatocellular cancer. Journal of Nanobiotechnology. 2024; 22(1): 614. doi: 10.1186/s12951-024-02879-6
50. Jin KT, Yao JY, Ying XJ, et al. Nanomedicine and Early Cancer Diagnosis: Molecular Imaging using Fluorescence Nanoparticles. Current Topics in Medicinal Chemistry. 2020; 20(30): 2737–2761. doi: 10.2174/1568026620666200922112640
51. Pratiwi FW, Kuo CW, Chen BC, et al. Recent Advances in the use of Fluorescent Nanoparticles for Bioimaging. Nanomedicine. 2019; 14(13): 1759–1769. doi: 10.2217/nnm-2019-0105
52. Zhang H, Deng L, Liu H, et al. Enhanced fluorescence/magnetic resonance dual imaging and gene therapy of liver cancer using cationized amylose nanoprobe. Materials Today Bio. 2022; 13: 100220. doi: 10.1016/j.mtbio.2022.100220
53. Yu X, Zhang Q, Wang L, et al. Engineered nanoparticles for imaging and targeted drug delivery in hepatocellular carcinoma. Experimental Hematology & Oncology. 2025; 14(1): 62. doi: 10.1186/s40164-025-00658-z
54. Gabbia D, De Martin S. Toward a New Era in the Management of Hepatocellular Carcinoma: Novel Perspectives on Therapeutic Options and Biomarkers. International Journal of Molecular Sciences. 2023; 24(10): 9018. doi: 10.3390/ijms24109018
55. Addissouky TA, Sayed IETE, Ali MMA, et al. Latest advances in hepatocellular carcinoma management and prevention through advanced technologies. Egyptian Liver Journal. 2024; 14(1): 2. doi: 10.1186/s43066-023-00306-3
56. Ahn JC, Teng P, Chen P, et al. Detection of Circulating Tumor Cells and Their Implications as a Biomarker for Diagnosis, Prognostication, and Therapeutic Monitoring in Hepatocellular Carcinoma. Hepatology. 2021; 73(1): 422–436. doi: 10.1002/hep.31165
57. Xia W, Li H, Li Y, et al. In Vivo Coinstantaneous Identification of Hepatocellular Carcinoma Circulating Tumor Cells by Dual-Targeting Magnetic-Fluorescent Nanobeads. Nano Letters. 2020; 21(1): 634–641. doi: 10.1021/acs.nanolett.0c04180
58. Niroumand U, Motazedian MH, Ahmadi F, et al. Preparation and characterization of artemether-loaded niosomes in Leishmania major-induced cutaneous leishmaniasis. Scientific Reports. 2024; 14(1): 10073. doi: 10.1038/s41598-024-60883-0
59. Medda S, Mukhopadhyay S, Basu MK. Evaluation of the in-vivo activity and toxicity of amarogentin, an antileishmanial agent, in both liposomal and niosomal forms. Journal of Antimicrobial Chemotherapy. 1999; 44(6): 791–794. doi: 10.1093/jac/44.6.791
60. Li L, Zhang L, Montgomery KC, et al. Advanced technologies for molecular diagnosis of cancer: State of pre-clinical tumor-derived exosome liquid biopsies. Materials Today Bio. 2023; 18: 100538. doi: 10.1016/j.mtbio.2022.100538
61. Wu H, Wang M, Liang L, et al. Nanotechnology for Hepatocellular Carcinoma: From Surveillance, Diagnosis to Management. Small. 2021; 17(6): 2005236. doi: 10.1002/smll.202005236
62. Liu T, Liu L, Li L, et al. Exploiting targeted nanomedicine for surveillance, diagnosis, and treatment of hepatocellular carcinoma. Materials Today Bio. 2023; 22: 100766. doi: 10.1016/j.mtbio.2023.100766
63. Alghamdi MA, Fallica AN, Virzì N, et al. The Promise of Nanotechnology in Personalized Medicine. Journal of Personalized Medicine. 2022; 12(5): 673. doi: 10.3390/jpm12050673
64. Yuan XQ, Zhou N, Wang JP, et al. Anchoring super-enhancer-driven oncogenic lncRNAs for anti-tumor therapy in hepatocellular carcinoma. Molecular Therapy. 2023; 31(6): 1756–1774. doi: 10.1016/j.ymthe.2022.11.013
65. Huang KW, Hsu FF, Qiu JT, et al. Highly efficient and tumor-selective nanoparticles for dual-targeted immunogene therapy against cancer. Science Advances. 2020; 6(3): e.aax5032. doi: 10.1126/sciadv.aax5032
66. Baig B, Halim SA, Farrukh A, et al. Current status of nanomaterial-based treatment for hepatocellular carcinoma. Biomedicine & Pharmacotherapy. 2019; 116: 108852. doi: 10.1016/j.biopha.2019.108852
67. Wu S, Fan K, Yang Q, et al. Smart nanoparticles and microbeads for interventional embolization therapy of liver cancer: state of the art. Journal of Nanobiotechnology. 2023; 21(1): 42. doi: 10.1186/s12951-023-01804-7

68. Abdul Rahim R, Jayusman PA, Muhammad N, et al. Recent Advances in Nanoencapsulation Systems Using PLGA of Bioactive Phenolics for Protection against Chronic Diseases. International Journal of Environmental Research and Public Health. 2019; 16(24): 4962. doi: 10.3390/ijerph16244962
69. Radu ER, Semenescu A, Voicu SI. Recent advances in stimuli-responsive doxorubicin delivery systems for liver cancer therapy. Polymers. 2022; 14(23): 5249. doi: 10.3390/polym14235249
70. Wu M, Zhong C, Zhang Q, et al. pH-responsive delivery vehicle based on RGD-modified polydopamine-paclitaxel-loaded poly (3-hydroxybutyrate-co-3-hydroxyvalerate) nanoparticles for targeted therapy in hepatocellular carcinoma. Journal of Nanobiotechnology. 2021; 19(1): 39. doi: 10.1186/s12951-021-00783-x
71. Han Q, Du L, Zhu L, et al. Review of the Application of Dual Drug Delivery Nanotheranostic Agents in the Diagnosis and Treatment of Liver Cancer. Molecules. 2023; 28(20): 7004. doi: 10.3390/molecules28207004
72. Kher C, Kumar S. The Application of Nanotechnology and Nanomaterials in Cancer Diagnosis and Treatment: A Review. Cureus. 2022; 14(9): e29059. doi: 10.7759/cureus.29059
73. Lammers T. Nanomedicine Tumor Targeting. Advanced Materials. 2024; 36(26): e.2312169. doi: 10.1002/adma.202312169
74. Farjadian F, Ghasemi A, Gohari O, et al. Nanopharmaceuticals and Nanomedicines Currently on the Market: Challenges and Opportunities. Nanomedicine. 2018; 14(1): 93–126. doi: 10.2217/nnm-2018-0120
75. Yu X, Zhang Q, Wang L, et al. Engineered nanoparticles for imaging and targeted drug delivery in hepatocellular carcinoma. Experimental Hematology & Oncology. 2025; 14(1): 62. doi: 10.1186/s40164-025-00658-z
76. Huang F, Chen L, Zhang X, et al. Engineered nanomedicine targets liver cancer stem cells to treat liver cancer disease. Journal of Materials Chemistry B. 2025; 13(41): 13184–13205. doi: 10.1039/d5tb01278c
77. Xu J, Liu Y. Nanomaterials for liver cancer targeting: research progress and future prospects. Frontiers in Immunology. 2025; 16: 1496498. doi: 10.3389/fimmu.2025.1496498
78. Joshi VB, Geary SM, Gross BP, et al. Tumor lysate-loaded biodegradable microparticles as cancer vaccines. Expert Review of Vaccines. 2014; 13(1): 9–15. doi: 10.1586/14760584.2014.851606
79. Yao W, Liu C, Wang N, et al. An MRI-guided targeting dual-responsive drug delivery system for liver cancer therapy. Journal of Colloid and Interface Science. 2021; 603: 783–798. doi: 10.1016/j.jcis.2021.06.151
80. Xu X, Liu C, Wang Y, et al. Nanotechnology-based delivery of CRISPR/Cas9 for cancer treatment. Advanced Drug Delivery Reviews. 2021; 176: 113891. doi: 10.1016/j.addr.2021.113891