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# Drug Transport via Nanocarrier for Liver Cancer Treatment

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## ABSTRACT

The requirement of having multiple nanocarriers (NCs) and active agents for improved therapy, imaging, and controlled release of medications efficiently in one platform has made the creation of therapeutics and theragnostic nanodrug delivery systems a difficult task for present researchers. Multiple drug resistance (MDR), a high clearance rate, severe side effects, undesirable drug distribution to the specific site of liver cancer, and a low concentration of medication that reaches liver cancer cells are just a few of the drawbacks of traditional liver cancer chemotherapy. As a result, new techniques and NCs must be developed to transport the medication molecules targeted to the malignant hepatocytes in an acceptable number and duration inside the therapeutic window. Because of the great efficacy of drug loading or drug encapsulation efficiency, high cellular uptake, high drug release, and minimal adverse effects, therapeutics and theragnostic systems have benefits over conventional chemotherapy. These NCs have a high drug accumulation rate in tumours while causing minimal toxicity in healthy tissues. This study focuses on current research on NC-based therapies and theragnostic drug delivery systems, omitting nanotechnology's negative consequences in the field of drug delivery systems. Clinical advancements of theragnostic NCs for liver cancer, on the other hand, are not covered in this article. Only the most current breakthroughs in NC-based drug delivery systems for liver cancer

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therapy and diagnosis are discussed in this study. This review will not go over the detrimental effects of individual NCs in the medication delivery system.

**KEYWORDS:** Nanocarrier (NC); Theragnostic; Liver cancer

## 1. Introduction

According to recent statistics, Asia and Africa have the highest frequency of liver cancer patients, whereas Europe has the lowest prevalence [1]. Hepatocellular carcinoma (HCC) is the most frequent type of liver cancer, accounting for 75% to 90% of all cases [2]. Liver transplantation and surgery are common therapeutic choices for HCC patients in the early stages of the disease, but surgery is no longer an option in the majority of cases.

In addition to transplant or surgery, HCC patients will undergo anti-cancer drugs treatment. However, it is limited in its access to liver cancer cells due to drug toxicity/resistance and limited absorption by the tumour cells [3]. Liver chemotherapeutics mostly are anti-angiogenesis tyrosine kinase inhibitors. This chemotherapeutic medication inhibits signalling pathways, causing normal cell processes to be disrupted to some extent. They primarily suppress the development of liver cancer cells, but they also impede the growth of normal cells in the body, such as hair follicles, bone marrow, and gastrointestinal tract cells [4]. Nanotechnology has progressed with theragnostic nanocarrier (NC)-based drug delivery systems (NDDS) to address the constraints of drug toxicity of chemotherapeutic drugs.

NCs are nanoparticles with a diameter of 10–200 nanometers. They are potential drug delivery vehicles [5]. NCs have the ability to reduce cytotoxicity and improve anti-tumour medication therapeutic efficiency [6]. Also, NCs able to react on certain cancer cell surface receptors [7]. The majority of anti-cancer drugs have a low molecular weight and specificity, but cause high toxic effects to human body. They will be eliminated from the blood vessels before they react on the tumour cells. Nanodrug delivery techniques are needed to decrease the side effects of these drugs on healthy cells and obtain increased effectiveness. Though, the created NCs should be biodegradable and able to successfully entrap the drug substances to enter the blood circulation and reach the target site with precise dose [8]. The NDDS can undergo customisation by particularly transporting medications to malignant cells while limiting the risks of unintended distribution to normal cells. As a result, NDDS is the solution to recapitulate the novel therapeutic measure of liver cancer.

## 2. NDDS of liver cancer

NCs become potential methods for drug administration and diagnosis because of their abilities to image sick cells, diagnose the condition or discover cancer cells at an early stage, and simultaneously treat the disease. The system is called as theragnostic NCs, and it can currently diagnose and treat diseases simultaneously. The NDDS should be biodegradable, tiny in size, have a large surface area, and have surface altering characteristics. The NDDS are quickly gaining traction as an intriguing and successful medication delivery device in treating liver cancer. Many researchers have recently created numerous NCs for medicine delivery and imaging to liver tumours. The numerous NCs which can be applied as liver cancer medicine delivery vehicles are shown in **Figure 1**.

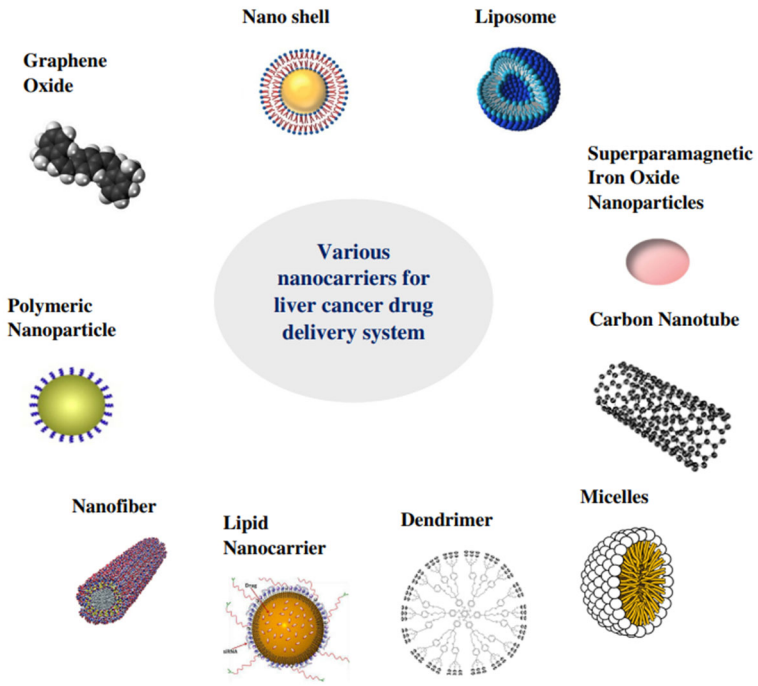


**Figure 1.** Various nanocarriers for liver cancer drug delivery system

## 3. Organic NCs applied in NDDS

For drug delivery systems, a variety of nanostructures made of organic materials are developed. NC liposome uses doxorubicin as an anticancer substance, was the first FDA-approved nanodrug [9,10]. Polymeric NCs are the most potential organic NCs for liver cancer [11]. These NCs are biodegradable, non-toxic to autogenous cells although they are presented in circulation for a long time. The technology also provides a large range of liver cancer treatment medications that could be easily adsorbed, encapsulated, or conjugated on the polymeric NCs' surface [12].

### *3.1 Chitosan (CS)*

CS is a cationic polysaccharide polymer produced by partial deacetylation of chitin. Many researchers have conducted studies on chitosan nanoparticles for liver cancer drug delivery for therapeutic purposes. Ye and colleagues evaluated the effect of chitosan coated doxorubicin loaded NC in liver cancer where it showed excellent inhibitions of cell growth of liver cancer [13]. Loutfy and colleagues synthesized chitosan nanoparticle (CS-NPs) for evaluation of the in vitro human hepatocellular carcinoma (HepG2). They investigated that the cytotoxic effect of CS-NPs towards liver cancer cells is relatively good and they suggested that CS-NPs are suitable for drug delivery proposes for liver cancer [14].

### *3.2 Micelles (PM)*

PM presents as core-shell shape. It able to solubilize medicines and imaging agents, resulting in improved liver cancer diagnosis and treatment. Huang and colleagues created a modification on PM which it is loaded with doxorubicin and made of glycyrrhetinic acid (GA) with promising result in liver targeted therapeutic [15]. Hanafy and colleagues developed a new PM (polyacrylic polygalacturonic acid hybrid) loaded with the TGF inhibitor galunisertib (LY2157299) in treating HCC [16]. Yang and colleagues developed a doxorubicin-loaded NC made of polyethylene glycol-derivatized GA-based PM that was transported to HepG2 cells. In comparison to free doxorubicin, this PM displayed remarkable therapeutic effectiveness in vivo. In a HepG2 xenograft model, it showed good survival and maybe suppressed tumour growth.

### *3.3 Liposome*

Liposomes are biodegradable compounds that are reasonably stable. The medicines are encased in the liposome's inner core [17]. Wang and colleagues investigated liposomes coated with CD147 antibodies, which can be found abundantly in liver cancer cell lines. This NC showed higher cytotoxicity on Huh-7, HepG2 cells and HCC3736 model, according to the results [18]. Persico and colleagues evaluated the cytotoxicity of hepatoblastoma (HB) in the HepG2 cells using both liposomes coated with chitosan and without chitosan but loaded with butyric acid (BA). This study found that the former showed more cytotoxic effect [19].

### *3.4 Dendrimer*

Antitumor medication delivery techniques based on dendrimers have a significant advantage. Dendrimer is a unique NC because of its physico-chemical features, like mono-dispersity and high drug delivery property [20]. It also possesses effective renal filtration characteristics [21]. Wojnarowicz and colleagues created multifunctional dendrimer-based NCs coated with polydopamine (PDA) and magnetite nanoparticles (Fe3O4). These manufactured NCs had been found to be harmless, and they can successfully load drug photothermal and anti-cancer substances at low nanoparticle concentrations [22]. Liver cancer medications are hydrophobic, and dendrimers' inner core and branches can encapsulate hydrophobic pharmaceuticals. Fu and colleagues produced a multifunctional dendrimer-based NC for liver cancer therapy that was conjugated with polyethylene glycol, modified with lactobionic acid, and encapsulated with doxorubicin. The NC efficiently limits the proliferation of liver cancer cells, according to the researchers [23]. The modification of a nanoconjugate of glycyrrhizin-dendrimer with carbon nanotube was carried out by Jain and colleagues [24]. The dendrimer and carbon nanotubes loaded and entrapped doxorubicin, a liver cancer medication. The NC appears as an excellent transport for encapsulating ionizable medicines of liver cancer, according to cytotoxicity, loading, and release experiments.

### *3.5 Lipid NCs*

Lipid-based NCs could be potential NDDS vehicle. Bond and colleagues created a nanostructured lipid carrier for the sorafenib medicine to evaluate the cytotoxicity to free drug [25]. Zhao and colleagues created a

lipid NC that transports the doxorubicin and curcumin drugs in a mouse model. Based on their findings, lipid NC managed to prevent tumour development due to its high encapsulation effectiveness and sustained release profile [26].

### *3.6 Organic nanofiber*

The anti-cancer drug-bearing nanofiber able to prevent liver cancer cell metastasis and tumour development at the same time. To test the efficacy of both drug and gene delivery to liver cancer, Ebara and colleagues created an organic nanofiber carrying chemotherapeutic drug paclitaxel and therapeutic gene miRNA-145. It has been demonstrated that reducing the development of a liver tumour and preventing metastasis is possible [27]. Ji and colleagues created doxorubicin-conjugated nanofibers with a sustained release medication ability for suppressing tumour development in a mouse model using the SMMC7721 cell line [28]. A doxorubicin-loaded nanofiber was studied as a anti-cancer approach acting on liver cancer by Liu and colleagues. The generated nanofiber was shown to have strong anti-tumour activity [29].

## 4. Inorganic NCs

Physical features of inorganic NCs include optical absorption, fluorescence and magnetic moment, which are important reactive groups for various molecules to target the cells actively.

### *4.1 Graphene oxide-based NCs*

The drug loading capacity of graphene oxide NCs is outstanding. Individual graphene sheets have a strong electron transfer property, making them a promising carrier for medication delivery [30]. Graphene-based NCs can develop specialised interactions with distinct medicinal molecules due to their large surface area [31]. Yang and colleagues reported a graphene oxide-based targeted drug delivery system containing carboxymethyl chitosan, fluoroscein isothiocyanate, lactobionic acid, and doxorubicin. After 24 hours of incubation, the NC caused cell death and showed enhanced biocompatibility with liver cancer cell lines [32]. Yuan and colleagues discovered a combination of folic acid, monoclonal antibodies, and gold nanoparticles-based graphene nanocomposites increased HepG2 cell death while also allowing for drug targeting and controlled release [33].

### *4.2 Polylactic-co-glycolic acid (PLGA)*

PLGA nanoparticles are copolymers made up of two monomers which are lactic and glycolic acids. PLGA is a synthetic polymer that can be obtained. The US Food and Medication Administration and the European Medicines Agency have both authorised PLGA for drug administration due to its biocompatibility [34]. Recent research has discovered PLGA nanoparticles possess a high drug loading capacity, high specificity, and able to deliver the drugs effectively to patients with liver cancer. Gao and colleagues developed PLGA nanoparticles coated with lipid and went through modification with a CXCR4 antagonist to deliver sorafenib to HCC patients. The anti-angiogenic effect of the sorafenib-loaded PLGA NC was shown to be enhanced, as was the tumour

growth and survival of the orthotopic HCC animal model [35]. Li and colleagues developed PLGA nanoparticles loaded with oleanolic acid (OA) coupled with tocopheryl polyethylene glycol 1000 succinate (TPGS) to boost the effectiveness of chemotherapeutic effect. Dangi and colleagues found that PLGA nanoparticles conjugated with lactobionic acid and loaded with 5-Fluorouracil (5-FU) had better chemotherapeutic activity than free 5-FU on the HepG2 cells [36].

### *4.3 Carbon nanotubes (CNTs)*

CNTs are materials with a needle-like form which able to transport medicines to biological components [37]. According to He and colleagues, CNTs are effective NDDS vehicle, due to their high electrical, great mechanical potency, and thermal conductivity [38]. In an in vivo liver cancer model, Qi and colleagues employed CNTs to transport doxorubicin medication and observed remarkable antitumor efficacy in Hep2 cell lines [39]. Ji and colleagues investigated the regulated release of doxorubicin-loaded chitosan folic acid conjugate single walled CNTs in HCC cell lines. In nude mice, the CNT-based NC can destroy the HCC cells and suppress liver cancer development more effectively than free doxorubicin [40].

### *4.4 Superparamagnetic iron-oxide nanoparticles (SPIONs)*

SPIONs showed promise in the treatment and diagnostics of liver cancer. To investigate the effect of SPIONs and sorafenib on liver cancer, Azzariti and colleagues conducted modification on polyethylene-glycol micelles to load with SPIONs and sorafenib. SPIONs able to target particular spots in liver cancer due to the magnetic field's influence. They managed to discover that this NC exhibited high regulated drug loading effectiveness and improved inhibitory impact in HepG2 cells.

### *4.5 Nanoshells*

Nanoshells are self-assembled polymer that forms a core shape and have been utilised for liver imaging in the past [41]. According to Liu and colleagues, gold nanoshells demonstrated good targeting capacity to liver cancer cells such as BEL7404 and BEL7402, while having no effect on normal healthy liver cells such as HL-7702.53.

### *4.6 Inorganic Nanofiber*

Zhang and colleagues studied the effects of cisplatin-loaded multilayered polylactide electrospun nanofibers in mice with liver cancer. In the H22 cell lines, they test the inhibitory effect of this nanofiber. The nanofibers increased tumour cytotoxicity and medication release, as well as preventing tumour recurrence after HCC surgery.

## 5. NCs involved in NDDS for liver cancer

To cure and diagnose cancer, theragnostic delivery entails combining diagnostic and therapeutic chemicals on a vehicle. At the cellular and molecular level, theragnostic NCs have discovered to diagnose and treat disorders. Currently, the theragnostic delivery-based strategy for treating liver cancer is being investigated. Chemotherapeutic medicines, peptides and gene are among the therapeutic agents in theragnostic NC. Gadolinium (Gd), superparamagnetic iron oxides and quantum dots (QDs) are popular diagnostic agents employed in theragnostic NCs for optical and nuclear imaging, magnetic resonance imaging (MRI) and computed tomography [42]. Zhang and colleagues employed lipid-micelles as a NC and gadolinium as a contrast substance in HepG2 tumour-bearing mice for MRI/photoacoustic imaging (PAI) [43].

### *5.1 Gadolinium (Gd) as a diagnostic substance for liver cancer*

Gd has been approved by the FDA as a diagnostic substance for MRI in detection of liver tumours in patients with liver cancer. Liu and colleagues developed gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA) to aid in the early detection of HCC at tumour site [44]. Gd-based peptide dendritic MRI probes for liver imaging were synthesised, characterised, and imaged, and showed significant result when identifying cancers in vitro and in vivo [45].

### *5.2 Superparamagnetic iron oxide (SPIO) nanoparticles (SPIONs) as a diagnostic substance for liver cancer*

Because of their magnetic properties, SPIONs are relevant to the NDDS. SPIONs are employed as diagnostic substances for MRI to identify liver cancer because the magnetic field allows them to be targeted to specific tumour locations. In a liver cancer cell line, SPIONs are employed as both therapeutic and MRI contrast substances. SPIONs were discovered to be destroyed in the body into soluble iron and non-toxic ions and then eliminated from the circulation through phagocytosis. These substances will be broken down in the lysosomes of cells [46].

Ferumoxytol (dextran-coated) and Ferucarbotran (carboxydextran-coated) are two examples of SPIO in the market. Being MRI contrast agents, they have been designed and clinically evaluated. Ferumoxytol is made up of iron oxide nanoparticles that are encased in a carbohydrate shell. It is a possible imaging method for assessing some liver tumours [47]. Azzariti and colleagues used polyethylene glycol-modified phospholipid micelles to make SPIONs and a sorafenib-loaded nanoformulation [48]. They looked into medication delivery for HCC and discovered that using magnetic targeting, SPION managed to improve imaging. However, due to passive build-up in the liver, spleen, and lymph nodes, iron oxide nanoparticles have little clinical value in imaging these organs. As a result, the FDA has revoked iron oxide nanoparticles' approval, and their use as MRI contrast substances in the United States has been terminated.

### *5.3 Quantum dots (QDs) as a diagnostic substance for liver cancer*

QDs are widely applied in the theragnostic of liver cancer due to their photoluminescence characteristics. Olerile and colleagues demonstrated that nanostructured lipid carrier (NLC)-loaded QDs may detect HepG2 cells from liver malignancies [49]. According to Das & Mohapatra, they found QDs are very useful in liver cancer detection and imaging [50]. Shao and colleagues used QD-based liposomes as a vehicle for suicide gene therapy in liver cancer [51]. Al-Jamal and colleagues found that using QD fluorescence, near-infrared fluorescence imaging showed promising result in mouse liver cancer cells [52].

## 6. Targeting ways for NDDS in liver cancer

Active and passive targeting interactions are used in NC medication delivery to tumour cells. In active targeting, ligands that are complementary to the tumour target locations are bonded to the surface of each NC. The NC surface is covered with stabilising chemicals in passive targeting, which aid in crossing the tumour vascular barrier through intercellular gaps. "Enhanced permeability and retention" is the name for this (EPR). The EPR effect is commonly used to accumulate medicines loaded in NCs by passive targeting [53]. Scientists are currently working on developing and designing an NCs system that may transport therapeutic agents towards liver cancer cells through a passive targeting pathway according to the EPR effect or an active targeting pathway regulated by tumour-specific targeting ligands. Both targeting ways have the potential to accumulate chemotherapeutic medicines in target liver cells while reducing drug accumulation in healthy regions [54]. After being injected, NCs quickly move from the systemic circulation to the arteries and bypass the vascular barrier to reach the tumour site. NCs must interact with the tumor's microenvironment once they have penetrated the vascular barrier.

### *6.1 Passive targeting to liver*

The transport of NCs to the tumour location via leaky vasculature that creates a conduit for the nanosized carrier to reach tumour cells via passive diffusion is referred as passive targeting. Based on Bae and Park, tumour tissue possesses abnormally leaky vasculature, allowing NCs to infiltrate. The EPR effect is the name for this phenomenon [55]. The passive targeting strategy is commonly based on the NC's physical features, such as size, drug surface, and carriers that boost NC accumulation in the liver cells [56]. According to Prabhu and colleagues, passive targeting of cancer cells is also influenced by factors like temperature, aberrant vasculature, pH value, and surface charge of tumour cells [57]. Ferreira and colleagues also showed that various physicochemical parameters of NCs, including size, molecular weight, hydrophobicity and hydrophilicity, are important for passive targeting [58].

The liver endothelium wall features sinusoids capillaries with 100–200 nm fenestrations that allow NCs to passively accumulate in malignant tissues. NCs smaller than 200 nm are easier to remove through greater sinusoidal fenestrations, allowing passive targeting into the liver [59]. According to Bae & Park, the benefit of

passive targeting is that pharmaceuticals in NCs stay in the bloodstream for longer duration. When NCs enter the bloodstream, they generate a "protein corona" by interacting non-specifically with serum proteins. It may trigger NC aggregation and affect the functionality of the carriers after interacting with biological fluids, depending on the physicochemical features of the NCs. Because of the EPR effect, protein corona causes minimal drug accumulation in cancer cells. The size and surface features of protein corona were discovered to have an impact on the outcome of passive targeting [60]. These NCs are taken up by the liver Kupffer cells (KCs) when they arrive on the sinusoidal wall and cause accumulation in the liver [61]. The medicine can be delivered into the liver cancer cells in a sufficient amount. As a result, polymers, stabilisers, or proteins may need to be added to the surface of NCs to improve their affinity for cells and minimise protein corona [62].

### *6.2 Active targeting to liver*

When NCs bind to ligands or targeting moieties, active targeting occurs. On the surface of NCs, specific receptors or antigens molecules are attached, which target the active site of the tumour, followed by the accumulation of drug NCs. KCs, endothelial cells, hepatocytes, and HCC possess different receptors that bind to different surface ligands on NCs. These ligands were identified by their receptors on liver cancer cells, allowing the NDDS to connect to the cell surface and release the medicine into tumour cells. HCC cells, for example, have an asialoglycoprotein (ASGP) receptor to which NC ligands such as galactoside, lactose and pullulan are complementary to it [63]. After the binding of NCs, bioactive moieties like anti-cancer drugs or therapeutic genes are discharged into the liver cancer location.

The NCs were able to bind to multiple types of receptors in various liver cells include hepatocyte, HCC, hepatic stellate cells (HSC), KCs, and endothelial cells. The active targeting moieties on the NC must make physical contact with the receptor on liver cancer cells. Besides, the vehicles should pass through the stomach and intestine, and be recognised by the liver cell receptor.

Glypican-3A is a promising biomarker for HCC that was recently discovered. Scientists created many gene silencing strategies for liver tumour targeting, like antisense approaches and short activating RNAs (saRNAs). The enhancer binding protein alpha (CEBPA) is upregulated by saRNA. HCC development is slowed down by overexpression of C/EBP alpha gene. The stimulation of the C/EBP pathway is a therapeutic target for saRNA in the prevention of liver tumour growth. In human HCC, the CEBPA gene found a saRNA sequence that upregulates CEBPA mRNA. This saRNA suppresses the proliferation of liver cancer cell lines in vitro by activating the CEBPA mRNA [64]. Kim and colleagues investigated the anticancer effect of N-acetylgalactosamine (GalNAc) conjugated to antisense oligonucleotides (ASO) in an HCC tumour model. The tiny GTP-binding protein ADP-ribosylation 4C (ARL4C) is substantially expressed in initial HCC tumours [65]. Harada and colleagues developed a modified ASO that lowered ARL4C expression in HCC. They believe ARL4C ASO could be used as a new targeted nucleic acid for the treatment of primary liver cancer [66].

## 7. Conclusion

NCs for liver cancer have showed promise in terms of alleviating issues in liver cancer chemotherapy. Great drug loading capacity, high stability, excellent tolerability, drug degradation, reduced multidrug resistance, controlled release, and sustained administration of therapeutic medications are all possible with NCs. Therapeutics and theragnostic drug delivery NC technologies, as a result, provide significant benefits over traditional therapy. The invention of various nanotechnology platforms, like theragnostic NCs, has great potential as the future generation of medicine, allowing for early disease identification, simultaneous monitoring and treatment, and targeted therapeutic measure with low toxicity.

## Conflict of interest

The authors report no conflicts of interest in this work.

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