Nanotechnology Based Approach for Hepatocellular Carcinoma Targeting

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Abstract

Hepatocellular carcinoma (HCC) is the primary liver cancer that has shown a high incidence and mortality rate worldwide among several types of cancers. A large variety of chemotherapeutic agents employed for the treatment has a limited success rate owing to their limited site-specific drug targeting ability. Thus, there is a demand to develop novel approaches for the treatment of HCC. With advancements in nanotechnology-based drug delivery approaches, the challenges of conventional chemotherapy have been continuously decreasing. Nanomedicines constituted of lipidic and polymeric composites provide a better platform for delivering and open new pathways for HCC treatment. A score of nanocarriers such as surface-engineered liposomes, nanoparticles, nanotubes, micelles, quantum dots, *etc*. has been investigated in the treatment of HCC. These nanocarriers are considered to be highly effective clinically for delivering chemotherapeutic drugs with high site-specificity ability and therapeutic efficiency. The present review highlights the current focus on the application of nanocarrier systems using various ligand-based receptor-specific targeting strategies for the treatment and management of HCC. Moreover, the article has also included information on the current clinically approved drug therapy for hepatocellular carcinoma treatment and updates of regulatory requirements for approval of such nanomedicines.

Keywords: Hepatocellular carcinoma, chemotherapy, nanocarriers, ligands; tumor targeting.

1. Introduction

Liver diseases are one of the leading causes of illness and death worldwide. Each year, 2 million deaths occur due to liver diseases [1] including liver fibrosis, hepatitis (A, B, and C), fatty liver, autoimmune hepatitis, and hepatocellular carcinoma (HCC) [2–4]. Liver tumors are frequent in occurrence and third in the most leading cause of cancer-related death worldwide [5]. Amongst various types of liver cancers, hepatic carcinoma is the most common, which is originated from the hepatocytes [6]. In other cases, secondary liver cancers are not originated from the liver but are formed due to metastasis from other parts of the body. Moreover, intrahepatic cholangiocarcinoma [7] and hepatoblastoma are other less common types of hepatic cancers reported in the literature [8,9].

HCC is a very common form of malignant liver cancer, it is the sixth most common cancer in the world, and accounting for more than 8,40,000 case deaths annually [10–12]. About 90% of HCC developed in patients with major risk factors are primarily infected with chronic hepatitis (type B and C viruses), liver cirrhosis, heavy alcohol consumption, smoking, non-alcoholic fatty liver, obesity, tobacco consumption, and diabetes [13–15]. There are several conventional therapies available for HCC [16], surgical resection [17], ablation [18], transarterial chemoembolization [19], liver transplantation [20], radiation therapy [16], chemotherapy and combinatorial approaches [21].

Surgical interventions facilitating tumor recurrence by local metastasis [22], heat sink effect of ablation [23], complications of transarterial chemoembolization [24], immunosuppressive therapy side effect due to transplantation [25], hepatic toxicity of radiotherapy [26], and chemoresistance in HCC toward chemotherapy [27], are just a few examples of the current conventional strategies used for the treatment of HCC. Besides, these conventional therapies are also associated with many drawbacks like high treatment cost, lack of safety, poor patient compliance, and chances of tumor recurrence.

Conventional chemotherapy treatment, in particular, has several disadvantages such as the inability to provide a sufficient concentration of therapeutic agents for liver disease, low targeting efficiency, poor tumor penetration, and/or the contribution to undesirable effects with systemic toxicity [28]. In order to avoid the serious and intolerable side-effects of the chemotherapy on normal tissues, the idea of exploration of novel tumor-targeting systems have typically taken momentum and greatly encourage the development of nanocarriers with targeting ability to achieve better efficacy with negligible undesirable effects [9]. The administration of a liver-specific drug delivery system helps in reducing the side effects by reducing the distribution of the drugs to the non-target organs and increases the therapeutic efficacy by simultaneously increasing the drug levels in the target cells [29,30].

Recently, with the rapid progress in nanotechnology development, it has been confirmed that drug delivery systems based on nanocarriers such as liposomes, polymeric micelle, quantum dote, dendrimers, carbon nanotube, nanoshells, and nanoparticles **(Figure 1)**. These systems have demonstrated great potential in the treatment of cancer by increasing the effectiveness of the drugs,

reducing systemic toxicity, improving dissolution of the drugs, increasing stability and release behavior in order to achieve the best therapeutic efficiency [31–33].

The present review highlights various pathways used for targeting drug-loaded nanocarriers to liver carcinoma with some of the receptors specifically overexpressed on the surface of hepatocytes. Besides, the review focuses on the recent developments in the domain of nanocarriers with various functional modifications for drug targeting to HCC.

2. Various approaches used for liver targeting

The effective delivery of therapeutics to the liver can be obtained by passive targeting and active targeting approaches that increase the accumulation of the drugs at the targeted site, consequently, it may limit the adverse effects and improves the therapeutic efficacy of drug therapy [35] (**Figure 2)**. Passive targeting only increases the local concentration of the drugs within the tumor tissues by the enhanced permeability and retention effect (EPR) [36,37]. Active targeting can be achieved by surface modification of the nanocarriers with specific targeting ligands such as proteins, antibodies, peptides, and carbohydrates, which has the affinity to bind a specific-site on the liver cells and facilitates endocytotic uptake into the liver cells [4].

2.1 Passive drug targeting

Accumulation of nanocarriers at specific body sites is possible due to certain key features of the tumor microenvironment. Hence, such targeting is also known as passive drug targeting. The tumor microenvironment differs from normal tissue by features like the presence of highly vascular structure, oxygenation, pH, perfusion, and metabolic activity which facilitate the accumulation of the drugs and nanocarrier in it [39]. These characteristic features facilitate the passive accumulation of nanocarrier therapeutics. The presence of fenestration in the endothelial wall of sinusoids capillaries of the liver and the absence of basal lamina favor the passive accumulation of nanocarriers therapeutics [40]. Nanocarriers with size less than 200 nm can release through the sinusoidal fenestrations and facilitate passive liver targeting. Tumor-specific accumulation or also called the EPR effect which plays a significant role in the passive accumulation of the drugs and nanocarriers due to their extravasation through the leaky vasculature of the tumor **(Figure 3)** [41]. The permeability and extravasation of macromolecules through the leaky tumor vasculature is enhanced by the EPR effect [42], and drainage of tumor tissues through an impaired lymphatic system is favored by retention of the nanostructured therapeutic carriers [43].

2.2 Active drug targeting

Drug delivery to the liver by an active targeting approach is a promising strategy for localizing the drugs to the tumor site. Active drug targeting is achieved by surface engineering of the nanocarriers with receptor-specific ligands such as peptides [45], carbohydrates [46], proteins [47], and antibodies [48], which are specifically bound with the overexpressed receptors on the tumor cells [49]. Various surface receptors expressed on hepatocytes include asialoglycoprotein, glycyrrhizic acid, transferrin, folate, and integrin receptors [40,50]. The targeting ligands facilitate the endocytotic uptake of drugs by receptors into the liver tumor cells, therefore increases selective targeting of the chemotherapeutics to the tumor by avoiding undesirable side-effects [51].

3. Ligand-receptor based active targeting for HCC treatment

Ligand-receptor active targeting plays a critical role in the internalization of the drugs to the hepatocyte cells and subsequent endocytosis of anticancer drugs. It is one of the most common strategies used for targeting HCC which helps improve the targeting ability. Some receptors that are overexpressed on HCC cells include asialoglycoprotein receptor, folate receptor, transferrin receptor, glycyrrhetinic acid receptor and, integrin receptor, thus various ligands that can be attached to such receptors on the surface of hepatoma cells were used to design nanocarrier systems for effective targeting [52]. In this part of the review, a summary of the latest investigations carried out by the researchers for utilizing ligand-receptor mediated active targeting of chemotherapies for targeting of HCC.

3.1 Asialoglycoprotein receptors (ASGPR)

Since asialoglycoprotein receptors are present on hepatocytes and other non-hepatic cells, it is strongly expressed by the hepatocytes [4]. Various ligands such as asialofeutin, glycoproteins, carbohydrates, pullulan and, galactoside have been used to achieve the specific liver ASGPR targeting [53]. Yousef *et al*. [54] reported the ability of galactosamine-anchored polyamidoamine dendrimers (PAMAMs) loaded with a potent anticancer agent, curcumin to achieve highly selective cellular uptake through the ASGPR-mediated endocytosis process, which improved the delivery of curcumin into the HCC cells. In another report, Xu *et al*. [55] prepared the solid lipid nanoparticles (SLN) of docetaxel-loaded with galactosylated dioleoylphosphatidylethanolamine, which showed higher cytotoxicity of SLN on the BEL7402 cell line over plain docetaxel (Taxotere®) and enhanced cellular uptake and accumulation of the drug in the hepatoma cells. Similarly, Liang *et al*. [56] developed the paclitaxel-loaded self-assembled nanoparticles conjugated with galactosamine (Gal-P/NPs). *In vitro* cell culture studies of Gal-P/NP on the HepG2 cells revealed comparative inhibition ($p<0.05$) in cell growth as compared to the plain paclitaxel (Phyxols).

3.2 Folate receptors

These receptors are highly overexpressed on the surface of liver carcinoma cells, and its natural ligand is folic acid that has been used to target these receptors. Folate-conjugated drugs bind specifically to folate receptors and promote internalization of the drugs that bind with the folate receptors and uptake by receptor-mediated endocytosis mechanism [57]. The attached drug molecules can be released into the target tumor cells, where they can induce their cytotoxic activity [58]. Li *et al*. [59] developed the folate-PEGylated PLGA nanoparticles co-encapsulated with sorafenib (SRF/FA–PEG–PLGA NP) for targeting to HCC. The nanoparticles showed sustained release and improved cellular uptake of the drug during the *in vitro* study on Bel-7420 cancer cells. Besides, these nanoparticles effectively suppressed the proliferation of tumor cells and improved anti-cancer activity as compared to the free drug. Another study by Niu *et al*. [60] developed the doxorubicin-loaded polymeric micelles functionalized with folate ligand. *In vitro* cellular uptake study showed a controlled release profile of doxorubicin release and enhanced cytotoxicity of micelles on the Bel-7402 cells. Similarly, Zhang *et al*. [61] developed folic acid functionalized polymeric micelles-loaded with superparamagnetic iron oxide nanoparticles and sorafenib for enhanced anticancer activity against HCC. The developed nanoparticles exhibited superior inhibitory activity and *in vitro* apoptosis rate on HepG2 cells than nontargeted micelles.

3.3 Transferrin receptor (TfR)

These receptors are the cell surface receptors overexpressed on many types of cancers including HCC [62]. Therefore, this carrier protein can be utilized as a component of several carrier systems for chemotherapeutic agents [63]. TfR receptor expression on HCC is 100-times higher than the normal cells [64]. Hepatoma cells overexpressed with transferrin receptors have become promising targets for effective chemotherapy against HCC. In a study, Zhang *et al*. [65] prepared transferrin (Tf) modified polymeric nanoparticles for co-administration of cisplatin (DDP) and doxorubicin (DOX) for the treatment of hepatic carcinoma. The nanoparticles cytotoxicity was assessed on HepG2 cell line showed a better antitumor effect. Tf-DDP/DOX-NPs showed exceptional antitumor activity due to the combined action of two drugs and the ability to actively target the tumor cells through Tf ligand. Similarly, Szwed *et al*. [66] demonstrated that doxorubicin-transferrin conjugated nanoparticles showed higher cytotoxicity on HepG2 cells as compared to the free doxorubicin and induced greater oxidative stress.

3.4 Glycyrrhetinic acid receptor (GaR)

These receptors are overexpressed on the surface of hepatocytes and its ligand glycyrrhetinic acid has been widely used to target drugs by different nanocarrier delivery systems, including micelles, nanoparticles, and liposomes [47,67,68] Tian *et al*. [69] reviewed the role of GA and nanocarriers modified with GA as an efficient tool for hepatocyte targeted delivery for the treatment of HCC.

Anirudhan and Binusreejayan [70] developed a dextran-based nanoscale drug carrier (GHDx) for curcumin delivery. Liver-directed curcumin is loaded in GHDx. *In vitro* cytotoxicity study on HepG2 and L929 cells demonstrated that GHDx-loaded with curcumin exhibited high toxicity with sustained drug release profile to liver cells. Chen *et al*. [71] formulated a glycyrrhetinic acid-modified curcumin supramolecular gel which exhibited good water solubility and sustained release delivery of curcumin in buffer solution under *in vitro* studies. *In vivo* studies showed enhanced cellular uptake and better inhibition ability on HepG2 cells. Zhang *et al*. [72] prepared doxorubicin-loaded glycyrrhetinic acid-modified alginate nanoparticles, which revealed significantly higher concentration in the liver tumor induced in mice than nonglycyrrhetinic acid-modified doxorubicin nanoparticles and plain doxorubicin. Similarly, in another study, Tain *et al*. [73] prepared doxorubicin-loaded glycyrrhetinic acid-modified sulfated chitosan micelles which demonstrated excellent *in vivo* inhibitory effect against HepG2 cells. The antitumor effect was extremely high with doxorubicin-loaded with the micelles than surface unmodified micelles.

3.5 Integrin receptor (IgR)

These receptors are found on most types of human cancer, including HCC. Various types of integrins, in particular, α1β1, α5β1, and α9β1 are expressed on the surface of normal hepatocyte to maintain a normal cell-matrix connection [74,75]. In hepatocyte tumor cells, integrins α3β1 and α6β4 are overexpressed [76]. The RGD peptide (Arg-Gly-Asp) acts as a targeting ligand on the surface of nanocarrier systems to deliver an antitumor drug to hepatocytes [77]. Chen *et al*. [78] developed integrin receptor-targeted RGD-modified liposomal paclitaxel formulation by conjugating a specific Arg-Gly-Asp (RGD) ligand with 1,2-distearoyl-phosphatidylethanol-aminepolyethyleneglycol-2000. The study demonstrated the high efficacy of RGD-LP-PTX being easily uptaken by HepG2 cells than plain liposomes without RGD. *In vitro* evaluation of the formulation indicated inhibition of tumor growth in HepG2-bearing mice by RGD-LP-PTX formulation than LP-PTX or free PTX.

4. Different nanotechnology-based carriers for HCC targeting

Recently, innovation in the field of nanotechnology has been exploited different novel nanotechnologies approaches for the diagnosis and management of the HCC [79]. Novel nanocarriers are highly helpful to overcome the unwanted side-effects of chemotherapeutic agents by improving the pharmacokinetic profile of the drug by specific accumulation in the tumor site for enhancing the treatment effectiveness [80,81], In this part of the review, we provide a brief overview of the most recent examples of novel targeted delivery systems using various types of nanocarriers for delivering chemotherapeutic agents for HCC treatment [82]. Some of the extensively investigated nanocarriers for cancer treatment include nanoparticles, polymeric micelles, liposomes carbon nanotubes, dendrimers, quantum dots, nanofibers, and lipid nanoparticulate

carriers. Such nanosystems have shown great potential in liver cancer chemotherapy by enhancing the performance of the existing drugs, reducing their systemic side-effects, and increasing therapeutic efficacy [83–85]. Select instances of the nanocarriers used for drug targeting to the HCC in literature have been reported in this section of the manuscript (**Table 2**).

4.1 Nanoparticle-based nanocarriers

Nanoparticles are small colloidal particles with a size range of 1 to 100 nm [86]. A wide range of NPs have been developed to target of drugs, especially polymeric nanoparticles, ceramic nanoparticles, metal nanoparticles, lipid nanoparticles, carbon-based nanoparticles [87,88]. Antitumor agents are either captured in or and adsorbed on the surface of NPs in order to efficiently transport the anticancer agent to hepatocytoma cells [89]. Modifying the surface of NPs can provide specific targeting ligands that allow NPs to control drug delivery to HCC with better therapeutic efficacy. Nanoparticles based delivery of anticancer drugs can improve solubility, reduce the dose and frequency of therapy and, above all, reduce the undesirable toxicities accompanied with antitumor drugs [90]. In addition, the delivery of nanoparticles, a combination of different anti-cancer drugs, can be loaded, making it a promising tool for the treatment of HCC.

Toma *et al*. [91] prepared superparamagnetic iron oxide nanoparticles (SPIONs) coated with polyvinyl alcohol (PVP) for delivery of sorafenib, which exhibited a higher loading capacity for sorafenib and long-term drug effect. The cytotoxicity of sorafenib with PVA/SPIONs has shown greater efficacy against cancer than that of free sorafenib alone. Karimia *et al*. [92] developed κ-carrageenan-crosslinked magnetic chitosan nanoparticles of sunitinib with high drug loading efficiency and a controlled release profile for effective management of HCC. Gao *et al*. [93] have evaluated hollow alumina nanoparticles functionalized with hyaluronic acid loaded with paclitaxel (PAC) (HMHA-NP). *In vitro* cellular uptake of PAC-HMHA-NP was significantly high and *in vivo* studies have shown better anti-tumor activity by PAC-HMHA-NP than nonfunctionalized PAC-MHA-NP and pure PAC.

Zhao R *et al*. [94] prepared a pH-sensitive mesoporous silica nanoparticle for co-administration of sorafenib and ursolic acid. The prepared nanoparticles were decorated with chitosan and lactobionic acid (MSN-CS-LA nanocarriers) to target of ASGPR in hepatocellular carcinoma cells. The study showed better bioavailability of the drug and effective targeting and synergistic cytotoxicity. *In vivo*, compared with UA or SO alone, the nanocomplex significantly reduced the tumor burden in hepatocellular carcinoma (HCC). Mathilde *et al*. [95] developed nanoparticles of human serum albumin loaded with doxorubicin with high loading capacity (88%) to inhibit the *in vivo* growth of human hepatocarcinoma cells, the study showed significant growth inhibition. W. Ni *et al*. [96] prepared nanoparticle of biotin-/lactobionic acid modified poly (ethylene glycol)-poly (lactic-co-glycolic acid)-poly (ethylene glycol) (BLPP) copolymer for co-delivery of curcumin and 5-

fluorouracil to enhance the treatment of hepatocellular carcinoma. The cytotoxicity study in animals and hepatoma Hep G2 cell line showed higher cellular uptake and a synergistic anticancer effect. W. Gao *et al*. [97] prepared human serum albumin (HAS) nanoparticle surface modified with grafted folic acid for loading sorafenib (FA-HAS-SRF-NPs). *In vitro* study in the hepatocellular BEL-7402 showed enhanced cytotoxicity and increased safety in the normal liver LO2 cells. *In vivo*, the prepared nanoparticles showed effective antitumor activity toward nude mice bearing xenograft tumors without systemic toxicity.

4.2 Liposome based nanocarriers

Liposomes are a colloidal nanovesicle with phospholipid bilayer membrane, which have the ability to encapsulate various hydrophilic anticancer agents in their aqueous core and hydrophobic cytotoxic agents in their hydrophobic outer membrane [98]. Liposomes are effective nanocarriers for delivering many therapeutic drugs, they are biocompatible, biodegradable, and, because of their non-immunogenic properties, have a safe and effective therapeutic potential for clinical applications [99]. Many liposomal formulations of antineoplastic chemotherapy drugs have been approved for clinical use and are commercially available in the market, such as, Doxil® doxorubicin encapsulated in PEG-liposome, which is the first nano-drug product approved by FDA for clinical use [100]. PEGylated liposome has been widely used as a nanocarrier to improve the effectiveness of chemotherapy and is clinically effective with reduced toxicity [89]. Recently, research works focus on surface engineering by modifying the surface with ligands with different functional groups to achieve ligand binding. Targeted ligands enable specific targeting of tumor sites by targeting the liposome towards specific receptors that overexpressed in hepatoma cell, like folate receptor [101], CD-44 receptor [102], and transferrin receptor [103,104].

Shah *et al*. [105] prepared doxorubicin-loaded palmitoylated arabinogalactan (PAG) liposomes. *In vitro* cytotoxicity study in HepG2 cell lines showed higher antitumor activity by PAG liposomes as compared to the non-PAG liposomes. A better pharmacokinetic profile was observed by PAG liposomes as compared to the non-PAG liposomes. *T.* Wang *et al.* [106] prepared liposome for co-delivery of doxorubicin and lovastatin, the *in vivo* study in H22 mice model *mice* hepatoma demonstrated that the co-loaded Doxorubicin-Lovastatin liposomes effectively inhibit the growth of the tumor with reducing toxicity.

4.3 Carbon nanotube-based nanocarriers

Carbon nanotubes are cylindrical hydrophobic tubes made of carbon atoms with a diameter of approximately 1-4 nm and length 1-100 nm. depending on the number of graphene layers nanotube can be single-walled nanotube or multiwalled carbon nanotubes [107]. Carbon nanotubes are widely applied for cancer diagnosis and therapy due to its unique features [108]. Moreover, carbon nanotubes

have a unique physicochemical architecture that can be functionalized chemically on its surface by modifications or bounding with different targeting ligands to make them a promising platform for active targeting of tumor cells [109].

Z. Ji *et al*. [110] prepared chitosan modified single-walled carbon nanotubes loaded with doxorubicin, chitosan layer was bounded with folic acid for targeting folate receptor highly expressed in cancer liver cells. The *in vitro* and *in vivo* studies in HCC cell line SMMC-7721 showed that the DOX/FA/CHI/ SWNTs are much more effective in inhibition cancer cells than free DOX. X. Qi *et al*. [111] developed galactosylated chitosan-grafted oxidized carbon nanotubes loaded doxorubicin, the *in vitro* studies in HepG2 cells showed that the prepared doxorubicin carbon nanotubes were more efficient tumor targeting and higher cellular uptake.

4.4 Lipid nanoparticulate carrier

Particulate carriers (solid lipid nanoparticles, and nanostructured lipid carriers) have received much attention for the loading of antitumor drugs for the treatment of various types of cancers [112]. Nanoparticulate are desirable as carriers of active drugs because they have a high carrying capacity, longer circulation time and, facilitate the selective accumulation of tumors due to the effect of increased permeability and retention (EPR) or active targeting [113]. Lipid nanoparticulate can improve oral bioavailability, control the release and, target the anticancer with better physical stability [114]. Lipid nanoparticulate carriers are a promising candidate for anticancer targeting of the liver by lymphatic delivery [115]. NLCs show superior stability and loading capacity profile to overcome possible drawbacks and limitations of SLNs [116]. Various anti-cancer drugs have been encapsulated either in SLN or in NLC.

L. Tunki, *et al*. [117] prepared sorafenib loaded solid lipid nanoparticle conjugated with polyethylene glycol (PEGylated) galactose as a delivery carrier for HCC. Sorafenib loaded ligand conjugated nanoparticles show superior cytotoxicity, intracellular uptake and, apoptotic activities on HepG2 cells when compared with the free drug or non-ligand nanoparticle. *In vivo* studies in BALB/c mice show ligand conjugated SLN resulted in superior pharmacokinetic profile and better targeting of the liver by nanoparticles.

Harshita *et al*. [118] prepared paclitaxel-loaded nanostructured lipid carrier (PTX-NLC). PTX-NLCs showed higher antitumor activity than commercial formulation (Intaxel®) on the HepG2 cell line. The bioavailability of paclitaxel from PTX-NLCs was better than from PTX suspension. In another study, M.L. Bondì *et al*. [119] prepared nanostructured lipid carriers for delivery of sorafenib, the *in vitro* studies showed that sorafenib loaded into NLC had more growth inhibition than that of free drug.

4.5 Polymeric micelles based nanocarriers

Polymeric micelles are colloidal structures that contain amphiphilic copolymers. They have a hydrophobic core responsible for the uptake of water-insoluble drugs and a hydrophilic shell that ensures good stability drugs from the physiological environment [120]. The diameter of the polymeric micelles is less than 100 nm. Due to their range of nanometer sizes, their ability to self-assemble, stability, their ability to dissolve and transport hydrophobic drugs, polymeric micelles offer an attractive option for delivery of cytotoxic drugs to HCC [121]. High stability, low toxicity, and sustained release of the incorporated drug are the major advantages of polymeric micelles over surfactant-based micelles [122].

Fan *et al*. [123] prepared polymeric micelles-based gelatin functionalized with glycyrrhetinic acid for delivery of doxorubicin (DOX-GA-GEL) polymeric micelles. The *in vivo* studies with HepG2 cell lines have shown higher cellular uptake and cytotoxicity than DOX-HCl. *In vivo* study in mice with orthotopic H22 tumor have demonstrated the targeted ability and stronger tumor inhibition of GA-GEL-2 micelles to liver tissue compared with the free DOX. Su *et al*. [124] formulated micelles loaded with sorafenib for improved water solubility and enhanced anticancer activity, as observed through inhibition of tumor growth in the HepG2 tumor cells *in vivo*.

4.6 Dendrimer based nanocarriers

Dendrimers are highly branched three-dimensional synthetic macromolecules of various size (10-100 nm) [125]. The typical architectural structure of dendrimers includes a core, monomer branches, and functional surface groups, in which branching units are arranged around the central core, so, dendrimers are candidates for different ligands and allow transport of a wide variety of drugs. [126] The modification of the chemical synthesis of the dendrimers improves the pharmacokinetics and the biocompatibility of the carrier and gives it promising properties for its use as a new carrier in the treatment of cancer [89,127]. Maria *et al*. [128] prepared poliamidoamine dendrimer (PAMAM) loaded with sorafenib to target asialoglycoprotein receptor (ASGP-R). The prepared dendrimer functionalized with lactobionic acid as a ligand. *In vitro* studies conducted in HepG2 and HLE cell lines have shown a higher uptake ability of dendrimer in ASGPR expressing hepatoma cell line HepG2 than in non-expressing HEL cells. *In vivo* cytotoxicity studies have shown that sorafenib loaded with dendrimer exhibits superior and long-lasting antitumor activity due to the kinetic release with delayed-release. Yousef *et al*. [129] prepared dendrimers anchored to galactosamine and loaded with curcumin. *In vivo* cellular uptake of curcumin from dendrimer-galactosamine on the HePG2 cell line was significantly enhanced.

5. Recent updates on the drugs approved for HCC treatment

US Food and Drug Administration (FDA) has approved several drugs for use in patients with liver cancer [130]. In this clinical-stage, the systemic treatment for HCC with the multikinase inhibitor sorafenib is the most common treatment option [131]. Also, several Immune checkpoint drugs are under development in phase 1, phase 2, and phase 3 trials, such as durvalumab, tremelimumab, atezolizumab, bevacizumab and, tivantinib have shown significant positive results in clinical phase 1 and 2. However, clinical studies in phase 3 trials are required to confirm their efficacy for use in HCC [132–134].

6. Challenges with HCC treatment and future opportunities

Morbidity and mortality rates of HCC are significantly higher due to complexity that demands the development of an effective targeting therapeutic approach for treatment and prevention of HCC [150]. Despite of this, the design of an effective nanocarrier system for HCC targeting faces challenges and only a few nanotherapeutic formulations have entered clinical trials [151,152]. Despite advances in nanotechnologies for targeting of nanocarrier containing chemotherapeutic agents, yet many challenges and limitations are remaining. Toxicity is a major safety concern for applications of nanocarriers in clinical trials [153,154]. In addition, the accumulation of nanocarriers in the liver and their poor clearance rate causes high toxicity. The discovery of new ligands or targeting molecules needed to deliver nanocarriers to hepatoma cells is a major challenge [155,156]. For active targeting, the selection of the most suitable targeting agents "ligands" which are capable of binding the specific receptors expressed on the tumor cell surface is the prerequisite for the successful transport of nanocarriers to tumorous liver tissues for avoiding systemic toxicity [153,157,158].

7. Authors Insight on the Topic

Currently, the growing interest in the field of HCC diagnosis and nanocarrier based chemotherapy demonstrate a potential future scope for human application. Nanocarriers such as surface-engineered liposomes, nanoparticles, nanotubes, micelles, quantum dots, *etc*. are some of the nanocarriers that are considered potentially useful as drug delivery agents in the treatment of HCC. The incidence of HCC is related to many sophisticated factors and molecular mechanisms, so we should comprehensively consider when to fabricate and investigate novel nanocarriers loaded therapy for HCC targeting. The design of an ideal drug carrier still needs more research and continuous efforts to understand the exact molecular mechanism of various nanocarrier materials, their long-term possible hazards, so provide a safe and reliable treatment for HCC. The perfect HCC targeted nanocarrier based drug delivery system should be able to maintain the drug in the liver tissue and specifically identifying the hepatocarcinoma cells. Thus, ligand-based hepatic receptor targeted drug delivery systems are expected to play a significant role in HCC diagnosis and treatment. In the present, nanocarrier-based cancer-targeting therapy will face many challenges, such as surface engineered modification,

multireceptor targeting, and drug loading efficacy, toxicology, immunotoxicology, biocompatibility testing, and, stability testing. The emerging nanocarriers chemotherapy targeting techniques will be theranostic, with a multifunctional capability of simultaneous diagnosis and therapy.

8. Conclusions

Most traditional strategies for treating hepatocellular carcinoma experience poor targeting ability. Thus, it has taken increasing attention by the researchers for the exploration of new targeting receptors, ligands, and nanostructured systems to ensure efficient delivery of chemotherapeutic agents for the HCC treatment. Several studies in the literature reports mainly on animal or cell line models have shown the HCC-selective targeting ability of the nanocarriers based on their binding affinity to the target ligands-receptors, which further require exploration of their safety and efficacy through clinical studies in patients with HCC.

Conflicts of interest

The authors declare no conflict of interest, financial or otherwise.

Nomenclature

CD274	Cluster of differentiation 274
C-Met	Tyrosine-protein kinase Met or hepatocyte growth factor receptor (HGFR)
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
FGFR	Fibroblast growth factor receptors
PD-1	Programmed cell death protein 1
PDGF-R	Platelet-derived growth factor receptors
PD-L1	Programmed death-ligand 1
VEGF-A	Vascular endothelial growth factor A
VEGFR	Vascular endothelial growth factor receptor

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