Hindawi
Journal of Nanomaterials
Volume 2022, Article ID 7798919, 8 pages
https://doi.org/10.1155/2022/7798919

Review Article

Recent Advances in Drug Delivery Nanocarriers for Targeting Hepatocellular Carcinoma

Shanshan Wang, Qianzhou Lv, and Xiaoyu Li

Department of Pharmacy, Zhongshan Hospital, Fudan University, Shanghai 201203, China

Correspondence should be addressed to Xiaoyu Li; lixiaoyulxb@163.com

Received 25 May 2022; Revised 11 July 2022; Accepted 13 July 2022; Published 25 July 2022

Academic Editor: Abdelwahab Omri

Copyright © 2022 Shanshan Wang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Hepatocellular carcinoma (HCC) is among the primary drivers of cancer-related death globally, owing to the ineffectiveness of treatments in intermediate and terminal stages—an issue that drug delivery therapy techniques are expected to address. Drug delivery that works therapeutic techniques necessitates the use of efficient and safe drug carriers, and recent improvements in drug delivery nanocarriers have had a significant impact on HCC targeted delivery. These nanocarriers, including liposomes, micelles, nanocapsules, polymers, exosomes, and inorganic nanoparticles, are accompanied by favorable unique properties such as small particle size, good biocompatibility and biodegradability, low immunogenicity, sustained and controlled release capacity, unique optical, magnetic and heat properties, high drug loading efficiency, and easy surface modification with targeting ligands. Moreover, studies have shown that these nanocarriers can achieve passive targeting or active targeting effect, which improves the therapeutic efficacy of drugs and decreases their side effects. In this paper, we provide a brief overview of some latest studies about nanocarriers for targeting HCC.

1. Introduction

One of the most common types of the primary tumor, hepatocellular carcinoma (HCC), has risen to become the world's fourth-biggest cause of cancer mortality [1, 2]. Patients with HCC have a 5-year overall survival rate of just 10-18% [3]. Up to now, surgical resection, liver transplantation, radiofrequency ablation, transarterial chemoembolization, and systemic drug therapy have been considered to be main treatment strategies for HCC. Among all of these treatment strategies, surgical approaches are the curative measures at the early stage [4]. Unfortunately, the majority of HCC patients are diagnosed in the intermediate or terminal phases when systemic drug treatment is typically a viable therapeutic choice. However, a major disadvantage of these drugs (including doxorubicin, oxaliplatin, gemcitabine, irinotecan, docetaxel, and gene drugs) is their lack of selectivity to HCC cells or tissues, which may result in insufficient drug accumulation within tumor and substantial intrinsic toxicity to normal tissues [5]. Furthermore, HCC cells' multidrug resistance to chemotherapy drugs can also result in tumor recurrence and dismal efficacy of recent chemotherapies. Therefore, the development of novel strategies that may overcome the abovementioned challenges has become a crucial topic in HCC therapy researches.

In recent years, the rapid development of nanocarrier-based drug delivery therapeutic approaches has become a way to improve therapeutic efficacy while lowering the toxicity of systemic medication treatment. These nanocarrier-based drug delivery systems utilize various forms of nanomaterials as carriers for loading chemotherapy drugs or gene drugs and delivering these drugs to a specific binding site of HCC cells, in which drugs can be triggered release. Superior to conventional therapy, these drug delivery systems are highly versatile: (1) Their small size makes them easier to penetrate tissues and passively target HCC cells [6]. (2) Their multifunctional modification, especially for binding the specific molecule on the surface of HCC cells, allows high drug concentration in the tumor site [7]. (3) Their higher specific surface area and extraordinary biodegradable, optical, heat, and magnetic properties also make them ideal candidates in HCC treatment and diagnosis [8–10]. (4) Some nanocarriers have great capacity to improve the

bioavailability of hydrophobic drugs [11]. (5) Some of them bring excellent characteristic of drug controlled release [12]. (6) Certain novel nanocarriers are useful in reversal of tumor multidrug resistance [13]. (7) They can avoid being cleared by the immune system [14]. (8) Some of smart nanocarriers can load two or more substances, such as chemotherapy drugs, imaging agents, and gene drugs [15]. All of these advantages highlight the promising nanocarrier-based drug delivery systems in improving HCC treatment. In these systems, the structure of the nanocarrier plays an incredible role, which determines the form of drug loading, such as physical adsorption or chemical conjugation. Hence, a wide array of drug delivery nanocarriers, including liposomes, micelles, nanocapsules, polymers, exosomes, and inorganic nanoparticles, which are usually modified with HCC-specific ligands or antibodies for targeting tumor site, have continued to spring up.

In spite of many merits and applications in HCC treatment and diagnosis, there are few review articles focusing on the role of various forms of nanocarriers in improving HCC treatment outcomes. In this paper, we hope to offer a basic overview of various nanocarriers and their applications in delivering drugs to HCC. Specifically, this review has summarized the characteristics of various nanocarriers and presented representative examples of the nanocarriers for targeting HCC to supplement previous studies. By such an article, our main objective is to deepen our knowledge for exploiting HCC drug delivery systems and serve as a paradigm for further HCC treatment.

2. HCC-Targeted Drug Delivery Nanocarriers

2.1. Liposomes. Consisting of hydrophobic bilayer membrane and an internal aqueous cavity, liposomes are considered bilayer vesicles [16]. Along with the unique amphiphilic structural components, various hydrophobic or hydrophilic drugs could be encapsulated in bilayer membrane or entrapped inside the internal core of the liposome, respectively. These liposomes have been proven to possess good biocompatibility and biodegradability, low toxicity, and low immunogenicity [17]. These properties have made liposomes catch intensive attention as ideal carriers for delivering drugs. To enhance the delivery of therapeutic medicines to tumors, the surface of liposomes could be modified with a variety of functional groups as targeting ligands, including folate, transferrin, ^{D}T7 peptide, RGD peptide, and antibodies [18–22].

Recently, Tang and coworkers developed a ^{D}T7 peptide-modified liposome to encapsulate docetaxel with the aim of local delivery to HCC [20]. Herein, ^{D}T7 peptide was first attached to the surface of the liposome, and then the docetaxel was encapsulated into the already prepared ^{D}T7 peptide-modified liposome by the same procedure. On the membrane of HCC cells, the transferrin receptor is abundantly expressed, which could mediate ^{D}T7 peptide-modified liposomes to accumulate in the tumor site, thereby boosting the drug's absorption by tumor cells. *In vitro* and *in vivo* experiments stated that the docetaxel-loaded^{D}T7 peptide-modified liposome showed significant antitumor activity in HCC cells and subcutaneous HCC xenograft models. Apart from chemotherapy drugs against HCC, some liposomes were also applied to deliver gene drugs. Liu et al. synthesized a GP73 antibody-modified liposome which could deliver HSVtk/GCV suicide gene and target the transfection of the carrier selectively to the tumor cells by recognition of the GP73 protein, which was overexpressed on the HCC cell membrane [22]. Results demonstrated that the HSVtk/GCV suicide gene was expressed selectively in HCC cell lines and it has greatly slowed the growth of HCC xenograft tumors with the use of targeted liposomes (Figure 1). To the best of our knowledge, the FDA has authorized a few drug-loaded liposomes that have been used in HCC clinical studies. (https://www.clinicaltrials.gov/ct2/home). For example, in order to increase intratumoral doxorubicin concentration for the same systemic dosage, a phase I clinical study employed a specifically developed lyso-thermosensitive liposomal to deliver doxorubicin to HCC. These preclinical and clinical studies have revealed the feasibility of liposome as an HCC-targeted drug delivery nanocarrier.

2.2. Polymeric Micelles. Polymeric micelles are fabricated using self-assemblage of amphiphilic polymers dispersed in a suitable solvent, thus retaining a unique set of properties such as low toxicity, high stability, biomembrane permeability, excellent biocompatibility, and longer circulation time [23]. Compared with conventional surfactant micelles, polymeric micelles are more stable, attributed to their low critical micelle concentration. As reported, the core-shell structure is the characteristic of the polymeric micelles, with an outer hydrophilic layer and an interior hydrophobic core, which is able to accommodate both hydrophilic and hydrophobic drugs, thereby possessing high drug loading potential [24, 25]. Furthermore, polymeric micelles have a particle size of roughly 10-100 nm, which can promote the enhanced permeation and retention (EPR) effect as well as the permeability of endothelial cells [24]. Because of the merits of polymeric micelles mentioned above, several pieces of researches have been conducted to evaluate the potential of polymeric micelles for encapsulation and delivery of therapeutic medicines that target HCC.

In a study by Anwar and colleagues, amphiphilic maltodextrin-based micelles with lactobionic acid (LA) and folate as dual-targeted ligands were constructed for HCC treatment [26]. In this research, sulfasalazine was conjugated with maltodextrin backbone via tumor-cleavable ester. And resveratrol, another chemotherapeutic agent within the hydrophobic core, was physically entrapped. Assisted by LA and folate, the polymeric micelle could target HCC cells through asialoglycoprotein receptors (ASGPR) and folate receptors mediated cellular internalization. The authors demonstrated dual-targeted micelles were preferentially internalized by HCC cells in comparison to nontargeted micelles. Moreover, the *in vivo* evaluation on HCC bearing mice demonstrated dual-targeted micelles could efficiently inhibit tumor growth, indicating their promising application in HCC treatment. Taken together, as a feasible and effective nanocarrier, polymeric micelles may hold the ability to deliver therapeutic medicines to HCC.

2.3. Nanocapsules. Nanocapsule is another novel drug delivery nanocarrier with a hollow structure, comprising an oil core circumvented by the membrane [27]. These hollow container systems have been mostly used to carry and store hydrophobic

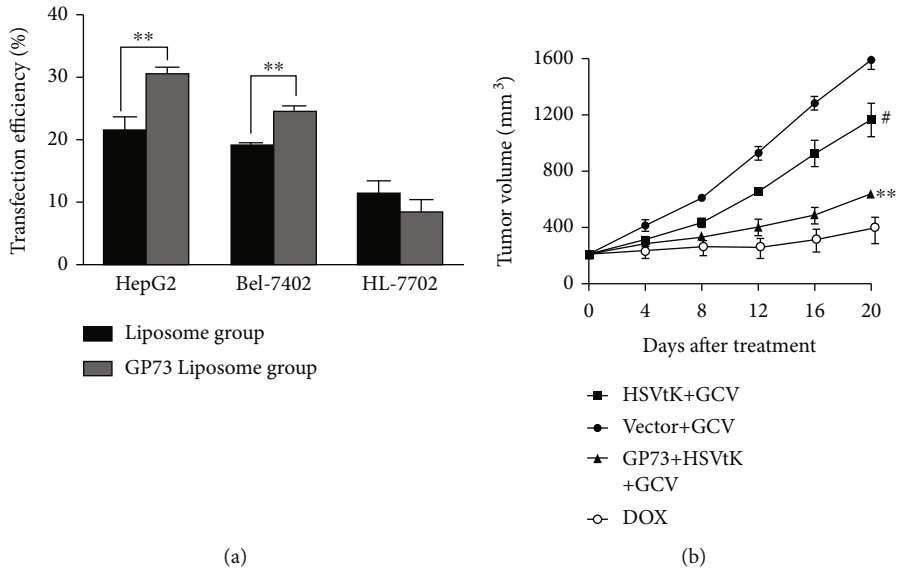

Figure 1: (a) HSVtk/GCV suicide gene transfection efficiency (%) of liposome group and GP73 liposome group in HCC cells (HepG2 cells and Bel-7402 cells) and normal hepatic cells (HL-7702 cells), respectively. (b) Tumor volume of HepG2 xenograft tumor-bearing mice after treatment of GP73-HSVtk transfection liposome (GP73+HSVtk+GCV) and other control groups. Copyright (2019) ELSEVIER.

drugs. Aside from excellent drug encapsulation, nanocapsules have other prerequisites for successful antitumor drug delivery such as good biodegradability, sustained and controlled release of the payloads, and sufficient blood circulation time [28].

Recently, cationic lipid nanocapsules have yielded encouraging results for drug delivery. A novel cationic lipid nanocapsule was developed by Yang and colleagues to increase the therapeutic efficacy of Bmi1 siRNA in the removal of HCC stem cells [13]. The nanocapsule was formed by blending two reverse microemulsions with a cationic lipid layer and a highly soluble cis- diamminedichloroplatinum (II). The results of *in vitro* and *in vivo* experiments illustrated Bmi1 siRNA-loaded nanocapsules could induce a strong apoptotic signal in the cisplatin-resistant tumor, implying these nanocapsules could be used to address the multidrug-resistance issue of tumors.

Except for lipid nanocapsules, some protein shell nanocapsules were also developed. In another study, the group of Abdelmoneem proven *in vitro* and *in vivo* tumor cellular uptake efficiency of a series of lactoferrin- (LF-) coated protein shell-oil core nanocapsules [12]. These nanocapsules, using LA or glycyrrhetinic acid (GA) as targeted ligands, were able to deliver two hydrophobic anti-HCC medicines, sorafenib, and quercetin (Figure 2). The dual drug-loaded nanocapsules were physicochemically characterized and found to have a size distribution of below 300 nm, a positive surface charge, and higher drug encapsulation. Also, the targeted nanocapsules showed sustained release for both anti-HCC drugs and excellent physical stability in particle size. Furthermore, the targeted nanocapsules showed high hemocompatibility and serum stability. These results further demonstrated that nanocapsules were promising nanocarriers for drug delivery to HCC.

2.4. Polymers. Polymers are the fourth nanocarrier platform that is ubiquitously used in delivery strategy for drugs in order to ameliorate HCC therapy. They are classified as natural existing polymers (chitosan, alginate, and gelatin) and synthetic ones (dendrimer polyamide-amine (PAMAM), polyethylenimine (PEI), poly(lactic-co-glycolic acid) (PLGA), and poly-lysine (PLL)) [29–35]. Polymers are typically prepared through various techniques including solvent evaporation, emulsion polymerization, precipitation, and interfacial polymerization [36]. One of noteworthy characteristics of the polymers is that they can be easily modified with targeting ligands due to the abundant external functional groups. Furthermore, polymers are reported to possess high drug loading capability, controllable structure, strong stability, and temporally controlled drug release [37, 38]. These specific properties provide polymer advantages in acting as nanocarriers. The group of Li developed a cell-penetrating peptide-modified aptamer (ST21) linked to histidine- (H_3R_5-) polyethylene glycol (PEG) to produce a ST21-H_3T_5-PEG-based nanosystem, in which two types of anti-HCC drugs, miRNA-195 and fasudil, were loaded via electrostatic interaction and transmembrane electrochemical gradient, respectively, forming ^{fasudil}ST21-H_3T_5-PEG_{miR195} [39]. Using HCC cells (SK-Hep-1), as well as normal hepatic cells ($L0_2$), a cellular internalization experiment showed that^{fasudil}ST21-H_3T_5-PEG_{miR195} efficiently accumulated in SK-Hep-1 cells in comparison to $L0_2$ cells, which verified the HCC targeting ability of the nanosystem. Moreover, the authors found that ^{fasudil}ST21-H_3T_5-PEG_{miR195} triggered rapid and remarkable cytotoxicity in SK-Hep-1 cells. This further clarified the feasibility of polymers as effective drug delivery carriers. Some other polymers, especially cationic polymers, such as PAMAM, PEI, PLGA, PLL, and their derivatives, have been widely used to encapsulate gene drugs and increase gene transfection efficiency. Cao et al. attempted to deliver plasmid DNA to nuclei of HCC cells using some targeting modified PEIs (glycyrrhizin acid- (GL-) PEI and GA-PEI) to enhance the selectivity and gene expression of pDNA [40]. These PEI-based systems showed excellent specificity to HCC cells, low toxicity, and high transfection efficiency. The

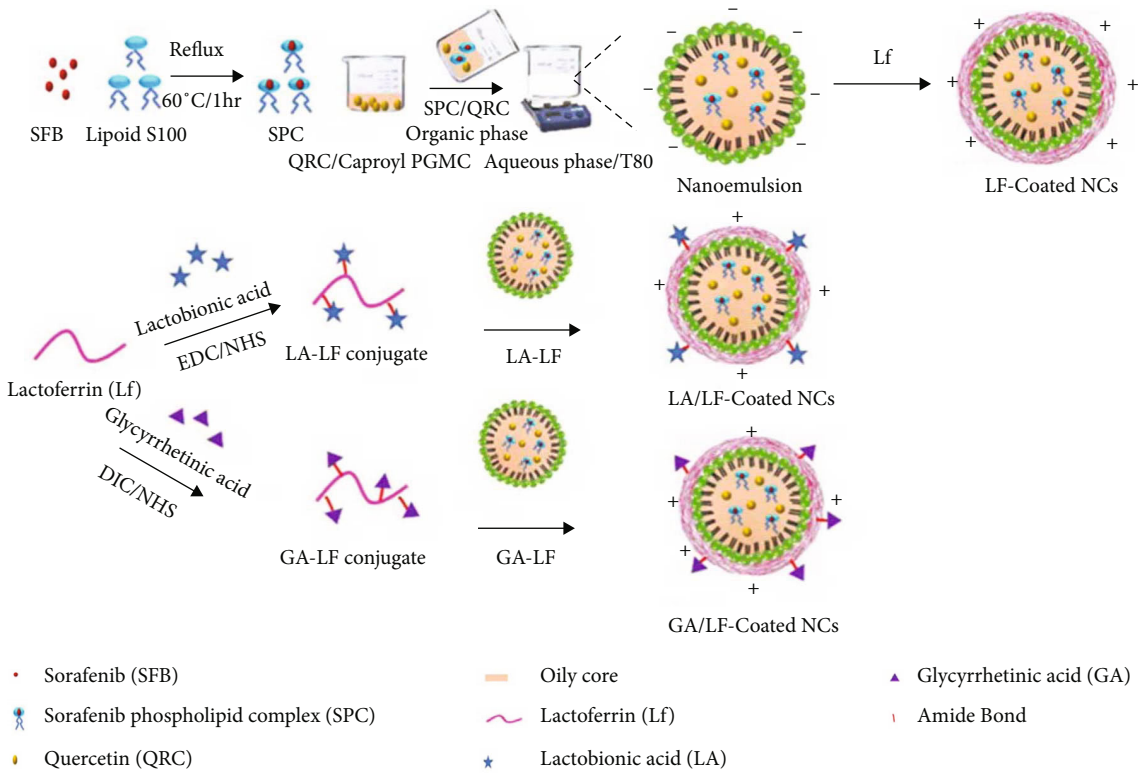

Figure 2: Schematic description of the preparation of LF-coated nanocapsules (NCs). Copyright (2019) ACS publications.

Table 1: Representative drug delivery nanocarriers for targeting HCC.

Nanocarrier	Surface modification	Targeting site	Payload	Reference
Liposomes	^{D}T7 peptide	Transferrin receptor	Docetaxel	[20]
	GP73 antibody	GP73 protein	HSVtk/GCV suicide gene	[22]
Polymeric micelles	LA and folate	ASGPR and folate receptor	Sulfasalazine and resveratrol	[26]
Nanocapsules	N/A	N/A	Bmi1 siRNA	[13]
	LA or GA	ASGPR or GA receptor	Sorafenib and quercetin	[12]
Polymers	ST21	N/A	miRNA-195 and fasudil	[39]
	GL and GA	GA	Plasmid DNA	[40]
Exosomes	Apo-A1	SR-B1 receptor	miR-26a	[48]
Inorganic nanoparticles	PEI	N/A	HNF4α-encoding plasmid	[52]
	CS/PEG	N/A	Doxorubicin	[55]

above results have suggested the polymer-based nanocarrier is a new perspective for drug delivery.

2.5. Exosomes. Exosomes, naturally occurring nanosized lipid membrane vesicles (40-100 nm), are generated from different sorts of cells, including cancer cells [41]. They can carry lipids, proteins, nucleic acids, or small molecules specifically targeting the receptor molecules of recipient cells, which exhibits strong effects on recipient cells through intercellular communication [42]. Ever-increasing researches demonstrated that exosomes had exhibited momentous functions in HCC cells' proliferating, invading, and spreading [43, 44]. Surprisingly, some modified exosomes are capable of being utilized against HCC mainly due to their cargo capacity. They have been used as prospective delivery vectors for a wide range of gene therapeutic agents and small molecular drugs. Recently, some downregulated miRNAs in HCC, such as miR-26a, have been proved to induce HCC cell apoptosis specifically [45–47]. An Apo-A1-modified exosome was fabricated by inducing Apo-A1 overexpression in HEK293 cells and then isolating intracellular exosomes [48]. The prepared Apo-A1-modified exosomes were loaded with miR-26a via electroporation and easily taken up into HCC cells through SR-B1 receptor-mediated endocytosis, resulting in inhibition of tumor growth and metastasis. In addition to above-mentioned, the miRNA downregulation in HCC cell-derived exosomes could also lead to enhanced tumor cell sensitivity to chemotherapy drugs [49–51]. In general, so many attempts were exerted to prove

that exosomes could be used to carry a number of drugs to HCC cells and improve the sensitivity of chemotherapy drugs. Based on these, exosomes seem to show a major promise as HCC-targeted drug delivery nanocarriers.

2.6. Inorganic Nanoparticles. In addition to organic nanoparticles, inorganic nanoparticles, including silica, carbon, gold, and magnetic nanoparticle, have also generated some considerable interest for HCC therapy in recent years [10, 52–54]. When considered collectively, they present a number of common characteristics in physical and chemical properties, including ideal biocompatibility, high stability under physiological conditions, low immunogenicity, unique optical, magnetic, and heat properties, easily tunable size, and modified surface. More importantly, either by noncovalent binding or by covalent interaction, drugs could be encapsulated and delivered by these inorganic nanoparticles.

For instance, silica nanoparticles are adopted as one of the most well-studied drug delivery nanocarriers, especially mesoporous silica nanocarriers. In an attempt to make silica nanoparticles more stable as drug carriers, their surface could be coated with polymer or other inorganic materials for loading drugs. Recently, Tsai et al. reported a PEI-modified mesoporous silica nanocarrier which denoted a well-ordered porous structure, adjustable porosity and dimension, a high surface area, and pore volume [55]. The nanocarriers loaded with gene drugs (HNF4α-encoding plasmid) on the surface and chemotherapeutic drugs (cisplatin) inside the pore have exhibited extraordinary ability in reducing the tumorigenic capacity of HCC cells. In addition, a lot of other studies altogether cemented the fact that the silica-based nanocarrier had been identified as a potential vector [53, 56, 57]. Recent years also witnessed a rapid growth of the application of magnetic nanoparticles. Due to the magnetic property, magnetic nanoparticles have successfully been employed as the MRI contrast agents, as well as the magnetic force-guided drug vectors in cancer therapy. For instance, Wu and coworkers constructed a magnetic, pH-sensitive system using magnetic nanoparticle Fe_3O_4 for doxorubicin delivery [58]. The Fe_3O_4 was coated with chloride chitosan and subsequently coupled with amount of PEG (Fe_3O_4@CS/PEG) to favor Fe_3O_4 with pH-sensitive, passive target, and long circulation. The data of cytotoxicity study in HCC cells clarified that the doxorubicin-loaded Fe_3O_4@CS/PEG revealed high anticancer ability, which made the decorated Fe_3O_4 a prominent drug carrier for HCC treatment. In addition to silica and magnetic nanoparticles, some gold and carbon nanoparticles such as gold nanorods, gold nanorices, carbon nanotubes, and graphene oxide also get considerable attention in delivering drugs to HCC cells because of their good performance [52, 54, 59–61]. Therefore, we strongly believe that the development of the inorganic nanoparticle-based systems is an effective way in HCC therapy.

Table 1 summarizes several exemplary drug delivery nanocarriers for HCC treatment.

3. Challenges and Future Prospects

Various nanocarriers have been introduced with their characteristics and applications in HCC targeting drug delivery and demonstrated huge promise for enabling HCC therapy. However, there are still a few challenges for researchers to address:

(1) Owing to high physicochemical stability, surface modification, and unsuitable particle size, some nanocarriers have difficulties in eliminating from the bloodstream, which may increase systemic toxicity and organic impairment [62]

(2) The intracellular transduction of many nanocarriers from endosomes to cytosol is tough, resulting in insufficient drugs accumulating in targeted cells [63]

(3) Even though nanocarriers have shown a lot of advantages for HCC treatment in preclinical studies, especially reducing the systematic toxicity, long-term biological security assessment to human health still could be a bottleneck for clinical application [64]

(4) Experimental rodent models were often utilized to assess the anticancer activities of nanocarrier-based drug delivery systems. However, only a small percentage of positive results of animal models could be replicated in clinical trials

Of course, with the development of novel nanocarriers and the further study of tumor microenvironment, experimental animal models, the mechanism of antitumor drug action, and the behavior of nanocarriers in human body, we believed that nanocarrier-based drug delivery systems could push through all kinds of obstacles and have broad prospects in the field of HCC therapy. In addition, the potential impact on the world economy and the safety hazard of these nanocarriers may prompt the establishment of special regulations in the future.

4. Conclusions

HCC is among the most frequent types of cancer. A variety of nanocarrier-based drug delivery methods for targeting drugs to HCC cells have been developed in order to maximize drug accumulation in the tumor site while reducing intrinsic toxicity to normal tissues and tumor multidrug resistance. These nanocarrier-based drug delivery strategies have clearly concentrated on nanocarrier selection and engineering. The facts displayed in this article demonstrated the potential of various nanomaterials as nanocarriers and revealed their advantages over conventional therapeutic techniques. Some researchers have proposed that nanocarriers, mainly including liposomes, micelles, nanocapsules, polymers, exosomes, and inorganic nanoparticles, can package and specifically deliver multiple chemotherapy drugs or gene drugs, revealing excellent anti-HCC efficiency *in vitro* and *in vivo*. Besides, some HCC targeting drug delivery nanocarriers attached with certain pH-, heat-, or magnetic-sensitive function groups can also affect the release site and release rate of therapeutic drugs. Unfortunately, despite the fact that the unique and diverse features of these nanocarrier-based drug carriers are opening up new avenues for HCC therapy, most formulations have not been

clinically tested and further approved by the FDA. This serves as a reminder that the technique has a long way to go, and some additional in-depth researches are needed before these systems can be used in clinics.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Shanshan Wang wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgments

This work was sponsored by the grants from the National Natural Science Foundation of China (82003278), Shanghai Sailing Program (18YF1403900), the Natural Science Foundation of Shanghai (16ZR1428000), and Shanghai Key Clinical Specialist Construction Projects (shslczdzk06504).

References

[1] N. D. Parikh and A. Pillai, "Recent advances in hepatocellular carcinoma treatment," *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association.*, vol. 19, no. 10, pp. 2020–2024, 2021.

[2] D. I. Tsilimigras and T. M. Pawlik, "Prognostication in hepatocellular carcinoma: is it a burden or a ticket?," *British Journal of Surgery.*, vol. 108, no. 4, pp. 337–339, 2021.

[3] S. Qin, Z. Ren, Z. Meng et al., "Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial," *The Lancet Oncology.*, vol. 21, no. 4, pp. 571–580, 2020.

[4] L. Mocan, "Multimodal therapy for hepatocellular carcinoma: the role of surgery," *European Review for Medical and Pharmacological Sciences.*, vol. 25, no. 13, pp. 4470–4477, 2021.

[5] M. Cervello, M. R. Emma, G. Augello et al., "New landscapes and horizons in hepatocellular carcinoma therapy," *Aging-Us*, vol. 12, no. 3, pp. 3053–3094, 2020.

[6] J. F. Liu, Z. Lan, C. Ferrari et al., "Use of oppositely polarized external magnets to improve the accumulation and penetration of magnetic nanocarriers into solid tumors," *ACS Nano*, vol. 14, no. 1, pp. 142–152, 2020.

[7] M. A. Abdelmoneem, M. Mahmoud, A. Zaky et al., "Dual-targeted casein micelles as green nanomedicine for synergistic phytotherapy of hepatocellular carcinoma," *Journal of Controlled Release*, vol. 287, pp. 78–93, 2018.

[8] Z. Shen, B. Li, Y. Liu et al., "A self-assembly nanodrug delivery system based on amphiphilic low generations of PAMAM dendrimers-ursolic acid conjugate modified by lactobionic acid for HCC targeting therapy," *Nanomedicine-Nanotechnology Biology and Medicine.*, vol. 14, no. 2, pp. 227–236, 2018.

[9] M. T. Hasan, E. Campbell, O. Sizova et al., "Multi-drug/Gene NASH therapy delivery and selective hyperspectral NIR imaging using chirality-sorted single-walled carbon nanotubes," *Cancers*, vol. 11, no. 8, p. 1175, 2019.

[10] X. Chi, R. Zhang, T. Zhao et al., "Targeted arsenite-loaded magnetic multifunctional nanoparticles for treatment of hepatocellular carcinoma," *Nanotechnology*, vol. 30, no. 17, p. 175101, 2019.

[11] M. I. Anik, M. K. Hossain, I. Hossain, A. M. U. B. Mahfuz, M. T. Rahman, and I. Ahmed, "Recent progress of magnetic nanoparticles in biomedical applications: a review," *Nano Select.*, vol. 2, no. 6, pp. 1146–1186, 2021.

[12] M. A. Abdelmoneem, M. A. Elnaggar, R. S. Hammady et al., "Dual-targeted lactoferrin shell-oily core nanocapsules for synergistic targeted/herbal therapy of hepatocellular carcinoma," *Acs Applied Materials & Interfaces.*, vol. 11, no. 30, pp. 26731–26744, 2019.

[13] T. Yang, Y. Chen, P. Zhao et al., "Enhancing the therapeutic effect _via_ elimination of hepatocellular carcinoma stem cells using Bmi1 siRNA delivered by cationic cisplatin nanocapsules," *Nanomedicine-Nanotechnology Biology and Medicine.*, vol. 14, no. 7, pp. 2009–2021, 2018.

[14] S. Hossen, M. K. Hossain, M. K. Basher, M. N. H. Mia, M. T. Rahman, and M. J. Uddin, "Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: a review," *Journal of Advanced Research*, vol. 15, pp. 1–18, 2019.

[15] M. I. Khan, M. I. Hossain, M. K. Hossain et al., "Recent progress in nanostructured smart drug delivery systems for cancer therapy: a review," *ACS Applied Bio Materials*, vol. 5, no. 3, pp. 971–1012, 2022.

[16] H. Tamam, J. Park, H. H. Gadalla et al., "Development of liposomal gemcitabine with high drug loading capacity," *Molecular Pharmaceutics*, vol. 16, no. 7, pp. 2858–2871, 2019.

[17] Y. Cheng, P. Zhao, S. Wu et al., "Cisplatin and curcumin coloaded nano-liposomes for the treatment of hepatocellular carcinoma," *International Journal of Pharmaceutics*, vol. 545, no. 1-2, pp. 261–273, 2018.

[18] M.-C. Liu, L. Liu, X.-R. Wang et al., "Folate receptor-targeted liposomes loaded with a diacid metabolite of norcantharidin enhance antitumor potency for H22 hepatocellular carcinoma both in vitro and in vivo," *International Journal of Nanomedicine*, vol. 11, pp. 1395–1412, 2016.

[19] W. Zhang, F. Peng, T. Zhou et al., "Targeted delivery of chemically modified anti-miR-221 to hepatocellular carcinoma with negatively charged liposomes," *International Journal of Nanomedicine*, vol. 10, pp. 4825–4836, 2015.

[20] J. Tang, Q. Wang, Q. Yu et al., "A stabilized retro-inverso peptide ligand of transferrin receptor for enhanced liposome-based hepatocellular carcinoma-targeted drug delivery," *Acta Biomaterialia*, vol. 83, pp. 379–389, 2019.

[21] W. Fei, Y. Zhang, S. Han et al., "RGD conjugated liposome-hollow silica hybrid nanovehicles for targeted and controlled delivery of arsenic trioxide against hepatic carcinoma," *International Journal of Pharmaceutics*, vol. 519, no. 1-2, pp. 250–262, 2017.

[22] C. Liu, C. Wen, X. Wang et al., "Golgi membrane protein GP73 modified-liposome mediates the antitumor effect of survivin promoter-driven HSVtk in hepatocellular carcinoma," *Experimental Cell Research*, vol. 383, no. 1, article 111496, 2019.

[23] S. Patil, V. Ujalambkar, A. Rathore, S. Rojatkar, and V. Pokharkar, "Galangin loaded galactosylated pluronic F68 polymeric micelles for liver targeting," *Biomedicine & Pharmacotherapy*, vol. 112, article 108691, 2019.

[24] B. Li, M. Cai, L. Lin et al., "MRI-visible and pH-sensitive micelles loaded with doxorubicin for hepatoma treatment," *Biomaterials Science*, vol. 7, no. 4, pp. 1529–1542, 2019.

[25] J. Zhang, A. Froelich, and B. Michniak-Kohn, "Topical delivery of meloxicam using liposome and microemulsion formulation approaches," *Pharmaceutics.*, vol. 12, no. 3, p. 282, 2020.

[26] D. M. Anwar, S. N. Khattab, M. W. Helmy et al., "Lactobionic/folate dual-targeted amphiphilic maltodextrin-based micelles for targeted codelivery of sulfasalazine and resveratrol to hepatocellular carcinoma," *Bioconjugate Chemistry*, vol. 29, no. 9, pp. 3026–3041, 2018.

[27] J. M. Coelho, N. S. Camargo, R. Ganassin et al., "Oily core/amphiphilic polymer shell nanocapsules change the intracellular fate of doxorubicin in breast cancer cells," *Journal of Materials Chemistry B*, vol. 7, no. 41, pp. 6390–6398, 2019.

[28] B. Iyisan and K. Landfester, "Modular approach for the design of smart polymeric nanocapsules," *Macromolecular Rapid Communications*, vol. 40, no. 1, article e1800577, 2019.

[29] X. Lang, T. Wang, M. Sun, X. Chen, and Y. Liu, "Advances and applications of chitosan-based nanomaterials as oral delivery carriers: a review," *International Journal of Biological Macromolecules*, vol. 154, pp. 433–445, 2020.

[30] S. Yan, W. Wang, X. Li et al., "Preparation of mussel-inspired injectable hydrogels based on dual-functionalized alginate with improved adhesive, self-healing, and mechanical properties," *Journal of Materials Chemistry B*, vol. 6, no. 40, pp. 6377–6390, 2018.

[31] G. Piccirillo, M. V. Ditaranto, N. F. S. Feuerer et al., "Non-invasive characterization of hybrid gelatin: poly-l-lactide electrospun scaffolds using second harmonic generation and multiphoton imaging," *Journal of materials chemistry B.*, vol. 6, no. 40, pp. 6399–6412, 2018.

[32] D. Li, Y. Fan, M. Shen, I. Banyai, and X. Shi, "Design of dual drug-loaded dendrimer/carbon dot nanohybrids for fluorescence imaging and enhanced chemotherapy of cancer cells," *Journal of Materials Chemistry B*, vol. 7, no. 2, pp. 277–285, 2019.

[33] F. Hajifathaliha, A. Mahboubi, L. Nematollahi, E. Mohit, and N. Bolourchian, "Comparison of different cationic polymers efficacy in fabrication of alginate multilayer microcapsules," *Asian Journal of Pharmaceutical Sciences*, vol. 15, no. 1, pp. 95–103, 2020.

[34] S. Khaledi, S. Jafari, S. Hamidi, O. Molavi, and S. Davaran, "Preparation and characterization of PLGA-PEG-PLGA polymeric nanoparticles for co-delivery of 5-fluorouracil and chrysin," *Journal of biomaterials science Polymer edition.*, vol. 31, no. 9, pp. 1107–1126, 2020.

[35] E. Piedra-Arroni, F. Makni, L. Severac, J. L. Stigliani, G. Pratviel, and C. Bonduelle, "Smart poly(imidazoyl-l-lysine): synthesis and reversible helix-to-coil transition at neutral pH," *Synthesis and Reversible Helix-to-Coil Transition at Neutral pH. Polymers (Basel).*, vol. 9, no. 12, p. 276, 2017.

[36] K. M. El-Say and H. S. El-Sawy, "Polymeric nanoparticles: promising platform for drug delivery," *International Journal of Pharmaceutics*, vol. 528, no. 1-2, pp. 675–691, 2017.

[37] N. Avramovic, B. Mandic, A. Savic-Radojevic, and T. Simic, "Polymeric nanocarriers of drug delivery systems in cancer therapy," *Pharmaceutics.*, vol. 12, no. 4, p. 298, 2020.

[38] M. Alsehli, "Polymeric nanocarriers as stimuli-responsive systems for targeted tumor (cancer) therapy: recent advances in drug delivery," *Saudi Pharm J.*, vol. 28, no. 3, pp. 255–265, 2020.

[39] Y. Liu, X. Wu, Y. Gao et al., "Aptamer-functionalized peptide H3CR5C as a novel nanovehicle for codelivery of fasudil and miRNA-195 targeting hepatocellular carcinoma," *International Journal of Nanomedicine*, vol. Volume 11, pp. 3891–3905, 2016.

[40] M. Cao, Y. Gao, M. Zhan et al., "Glycyrrhizin acid and glycyrrhetinic acid modified polyethyleneimine for targeted DNA delivery to hepatocellular carcinoma," *International Journal of Molecular Sciences*, vol. 20, no. 20, p. 5074, 2019.

[41] Q. Han, H. Zhao, Y. Jiang, C. Yin, and J. Zhang, "HCC-derived exosomes: critical player and target for cancer immune escape," *Cell*, vol. 8, no. 6, p. 558, 2019.

[42] R. Chen, X. Xu, Y. Tao, Z. Qian, and Y. Yu, "Exosomes in hepatocellular carcinoma: a new horizon," *Cell Communication and Signaling: CCS*, vol. 17, no. 1, p. 1, 2019.

[43] H. Liu and B. Li, "The functional role of exosome in hepatocellular carcinoma," *Journal of Cancer Research and Clinical Oncology*, vol. 144, no. 11, pp. 2085–2095, 2018.

[44] X. Li, C. Li, L. Zhang et al., "The significance of exosomes in the development and treatment of hepatocellular carcinoma," *Molecular Cancer*, vol. 19, no. 1, p. 1, 2020.

[45] H. Hatakeyama, M. Murata, Y. Sato et al., "The systemic administration of an anti-miRNA oligonucleotide encapsulated pH- sensitive liposome results in reduced level of hepatic microRNA-122 in mice," *Journal of controlled release: official journal of the Controlled Release Society.*, vol. 173, pp. 43–50, 2014.

[46] J. Kota, R. R. Chivukula, K. A. O'Donnell et al., "Therapeutic microRNA delivery suppresses tumorigenesis in a murine liver cancer model," *Cell*, vol. 137, no. 6, pp. 1005–1017, 2009.

[47] A. Kheirolomoom, C. W. Kim, J. W. Seo et al., "Multifunctional nanoparticles facilitate molecular targeting and miRNA delivery to inhibit atherosclerosis in ApoE(-/-) mice," *ACS Nano*, vol. 9, no. 9, pp. 8885–8897, 2015.

[48] G. Liang, S. Kan, Y. Zhu, S. Feng, W. Feng, and S. Gao, "Engineered exosome-mediated delivery of functionally active miR-26a and its enhanced suppression effect in HepG2 cells," *International Journal of Nanomedicine*, vol. Volume 13, pp. 585–599, 2018.

[49] X. Fu, M. Liu, S. Qu et al., "Exosomal microRNA-32-5p induces multidrug resistance in hepatocellular carcinoma via the PI3K/Akt pathway," *Journal of Experimental & Clinical Cancer Research*, vol. 37, no. 1, p. 52, 2018.

[50] Y. Xu, F. Xia, L. Ma et al., "MicroRNA-122 sensitizes HCC cancer cells to adriamycin and vincristine through modulating expression of MDR and inducing cell cycle arrest," *Cancer Letters*, vol. 310, no. 2, pp. 160–169, 2011.

[51] G. Lou, X. Song, F. Yang et al., "Exosomes derived from miR-122-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma," *Journal of Hematology & Oncology*, vol. 8, no. 1, p. 122, 2015.

[52] L. Qin, D. Niu, Y. Jiang et al., "Confined growth of multiple gold nanorices in dual-mesoporous silica nanospheres for improved computed tomography imaging and photothermal therapy," *International Journal of Nanomedicine*, vol. Volume 14, pp. 1519–1532, 2019.

[53] Z. L. Kong, H. P. Kuo, A. Johnson, L. C. Wu, and K. L. B. Chang, "Curcumin-loaded mesoporous silica nanoparticles markedly enhanced cytotoxicity in hepatocellular carcinoma cells," *International Journal of Molecular Sciences*, vol. 20, no. 12, p. 2918, 2019.

[54] M. M. Elsayed, M. E. Mostafa, E. Alaaeldin et al., "Design and characterisation of novel sorafenib-loaded carbon nanotubes

with distinct tumour-suppressive activity in hepatocellular carcinoma," *International Journal of Nanomedicine*, vol. - Volume 14, pp. 8445–8467, 2019.

[55] P. H. Tsai, M. L. Wang, J. H. Chang et al., "Dual delivery of HNF4α and cisplatin by mesoporous silica nanoparticles inhibits cancer pluripotency and tumorigenicity in hepatoma-derived CD133-expressing stem cells," *ACS Applied Materials & Interfaces*, vol. 11, no. 22, pp. 19808–19818, 2019.

[56] F. Ji, H. Sun, Z. Qin et al., "Engineering polyzwitterion and polydopamine decorated doxorubicin-loaded mesoporous silica nanoparticles as a pH-sensitive drug delivery," *Polymers (Basel).*, vol. 10, no. 3, p. 326, 2018.

[57] J. Ye, R. Zhang, W. Chai, and X. Du, "Low-density lipoprotein decorated silica nanoparticles co-delivering sorafenib and doxorubicin for effective treatment of hepatocellular carcinoma," *Drug Delivery*, vol. 25, no. 1, pp. 2007–2014, 2018.

[58] J. Wu, X. Wang, B. Zhu et al., "pH-sensitive magnetic drug delivery system via layer-by-layer self-assembly of CS/PEG and its controlled release of DOX," *Journal of biomaterials science Polymer edition.*, vol. 31, no. 8, pp. 1057–1070, 2020.

[59] Y. Qu, F. Sun, F. He et al., "Glycyrrhetinic acid-modified graphene oxide mediated siRNA delivery for enhanced liver-cancer targeting therapy," *European Journal of Pharmaceutical Sciences*, vol. 139, article 105036, 2019.

[60] M.-H. Chan, C.-N. Lu, Y.-L. Chung et al., "Magnetically guided theranostics: montmorillonite-based iron/platinum nanoparticles for enhancing in situ MRI contrast and hepatocellular carcinoma treatment," *Journal of Nanobiotechnology*, vol. 19, no. 1, p. 308, 2021.

[61] H. Wu, H. Xing, M.-C. Wu, F. Shen, Y. Chen, and T. Yang, "Extracellular-vesicles delivered tumor-specific sequential nanocatalysts can be used for MRI-informed nanocatalytic therapy of hepatocellular carcinoma," *Theranostics.*, vol. 11, no. 1, pp. 64–78, 2021.

[62] P. P. Wyss, S. P. Lamichhane, A. Abed et al., "Renal clearance of polymeric nanoparticles by mimicry of glycan surface of viruses," *Biomaterials*, vol. 230, article 119643, 2020.

[63] R. Gonzalez-Pastor, Y. Hernandez, M. Gimeno et al., "Coating an adenovirus with functionalized gold nanoparticles favors uptake, intracellular trafficking and anti-cancer therapeutic efficacy," *Acta Biomaterialia*, vol. 134, pp. 593–604, 2021.

[64] P. G. Kremsner, P. Mann, A. Kroidl et al., "Safety and immunogenicity of an mRNA-lipid nanoparticle vaccine candidate against SARS-CoV-2," *Wiener Klinische Wochenschrift*, vol. 133, no. 17-18, pp. 931–941, 2021.