



Nanoparticles Drug Delivery System in Targeted Therapy of Hepatocellular Carcinoma

Xinyuan Kong¹, Zirui Zhang¹, Hongyu Tang², Yihang Chen³, Juan Li^{2,#}

¹Jilin University School of Pharmaceutical Sciences, Jilin University, Changchun, Jilin 130021, China

²CAS Key Laboratory for Biomedical Effects of Nanomaterial and Nanosafety, Institute of High Energy Physics, Chinese Academy of Sciences (CAS), Beijing 100049, China

³School of Life Science, Beijing Institute of Technology, Beijing 100049, China

Abstract: This article presents a comprehensive overview of the application of nanoparticles drug delivery system in the detection and treatment of Hepatocellular Carcinoma (HCC). The nanoparticles drug delivery system, endowed with exceptional physical and chemical features, including remarkable drug-carrying capacity, precise targeting abilities, and visualization capabilities, offer promising new avenues for addressing HCC. Nanomaterials are important components of nano-drug delivery systems. Their utilization in HCC therapy, along with the advantages and disadvantages of various nanomaterials, including lipid, polymer, inorganic, biological macromolecular nanomaterials, exosomes and also hybrid nanoparticles, are thoroughly discussed. Our review identifies lipid nanoparticles as widely utilized bioactive nanocarriers in cancer treatment, with polylactic acid, a pioneering biodegradable polyester polymer, showing significant application potential. Additionally, hybrid nanoparticles, which combine the advantages of individual nanoparticles while mitigating their drawbacks, are poised to play a critical role in the targeted therapy of HCC. Additionally, the article delves into the targeting and release mechanisms of nanoparticles drug delivery system, encompassing passive targeting, active targeting, stimulus-responsive nanocarrier targeting, and specific types of it like pH stimulus-responsive nanocarriers. Despite their immense potential in HCC treatment, nanoparticles drug delivery system still faces numerous challenges, such as safety concerns, drug stability issues, and inadequate fundamental research for widespread application. As these challenges are gradually overcome, nanotechnology will open up new horizons for HCC diagnosis and treatment, leading to the development of more precise diagnostic tools and therapeutic strategies. Overall, the research on targeted nanoparticles drug delivery system therapy for HCC is entering an exciting new era filled with both opportunities and challenges.

Keywords: Nanoparticles drug delivery system; Nanomaterials; Hepatocellular carcinoma; Targeted therapy; Drug release.

Introduction

HCC is a major global health concern that ranks third in terms of cancer-related fatalities globally, approximately 18% of people worldwide have it^[1]. As a result, innovative and effective treatment strategies are urgently required. Among them, the use of targeted therapy with nanoparticle drug delivery systems has emerged as a promising option. Aristolochic acid, aflatoxins, and various dietary contaminants constitute a subset of the hazardous elements contributing to HCC development, alongside persistent hepatitis B and C infections, alcoholism, metabolic disturbances in the liver, notably nonalcoholic fatty liver disease, and numerous other factors^[2]. The Barcelona Clinic of Liver Cancer (BCLC) algorithm categorizes HCC patients into five clinical

stages: very early (BCLC 0), early (BCLC A), intermediate (BCLC B), advanced (BCLC C), and terminal (BCLC D), which is a widely accepted staging system^[3]. The selection of treatment methods varies depending on the stage. Existing treatment methods include liver transplantation, surgical resection, intra-arterial therapies, ablation, radiotherapy, systematic therapies, etc.

The primary aggressive treatment for HCC is surgical removal, yet up to 80 percent of patients face a significant risk of liver tumor recurrence after undergoing this procedure^[1]. Furthermore, timely access to suitable organs for transplantation remains challenging. Intra-arterial therapy is commonly used to treat intermediate stage HCC by directly injecting particles (with or without chemotherapeutic agents) into the tumor's blood vessels^[1]. However, chemotherapy's effectiveness is hindered by resistance to drugs, absence of specificity, and significant adverse reactions^[4]. Additionally, chemotherapy's cytotoxic can cause systemic damage, and radiation may also adversely affect normal tissues or organs. Hence, it is a significant challenge to create novel therapeutic approaches that target the liver and early detection methods^[4]. Nanomedicine combines the benefits of conventional chemotherapy, such as its clear effectiveness, with those of small molecule inhibitors or monoclonal antibodies, which offer specific therapy^[5]. Recently, there has been exploration into util-

Correspondence: Juan Li. E-mail: lijuan@ihep.ac.cn. Address: University of Chinese Academy of Sciences, CAS Key Laboratory for Biomedical Effects of Nanomaterial and Nanosafety, Institute of High Energy Physics, Chinese Academy of Sciences (CAS), Beijing 100049, China.

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izing nanoparticle drug carriers in the field of radiotherapy for potential advancements. Tong^[6], etc, for example, developed and synthesized a kind of multi-functional mesoporous silica nanoparticles (MSN) boron agent, specifically for boron neutron capture therapy (BNCT) in treatment of HCC. Paradigms in nanoparticles drug delivery system offer promising prospects for the detection and therapy of HCC.

The utilization of nanoparticle drug delivery systems has been expanded to encompass tumor therapy, medication administration, and disease diagnosis. As an important part of nano-drug delivery system, nanomaterials undertake many functions. In the field of diagnosis, nanomaterials can be utilized to modify sensor surfaces, enhancing the detection sensitivity for specific biomarkers. They also act as imaging agents for diagnostic imaging. Therapeutically, nanomaterials can be tailored with targeting ligands like antibodies or aptamers, enabling precise drug delivery to tumor sites and mitigating non-specific toxicity and chemotherapy resistance^[7]. These carriers are typically composed of macromolecules such as inorganic materials, polymers, and lipids^[8], offering fine-tuned regulation of particle attributes, and flexibility in payload and surface modification. Polymer-based nanocarriers facilitate precise manipulation of particle properties and simplify surface customization. Inorganic nanocarriers have unique electrical, magnetic and optical properties suitable for theranostic applications. Lipid-based carriers excel in bioavailability and formulation simplicity^[9]. Nevertheless, these nanomaterials also have limitations, which will be subsequently elaborated upon. Nanodrugs have the ability to precisely target specific sites and deliver drugs via active targeting. Surface modification of

nanobiomaterials with peptides, proteins, small molecules, and polymers enables targeted delivery of immune therapeutics to specific cell types, including hepatoma and immune cells^[9]. Furthermore, stimuli-responsive polymeric nano-delivery systems facilitate precise drug release, enhancing therapeutic efficacy while minimizing adverse effects on healthy cells^[10]. The review by Xier Pan et al. emphasized nanomaterials have demonstrated the ability to counteract the immunosuppressive microenvironment in HCC^[9]. Roland Böttger et al. described the research progress of liposomes as a kind of nanomaterials for liver targeting^[8]. Besides, the purpose of this review is to provide a broad and inclusive summary of the various nanomaterials utilized for treating HCC, examining their respective strengths and weaknesses. It will also explore the targeting and release mechanisms of nanoparticles drug delivery system, offering predictions on the potential challenges and application prospects of nanoparticles drug delivery system in the identification and management of HCC.

Various nanomaterials for precise therapeutic intervention in HCC

A variety of nanoparticles have been investigated for the therapy of HCC, and they can be classified according to the material composition, including lipid nanoparticles (LNPs), polymer nanoparticles (PNPs), inorganic nanoparticles, biological macromolecular nanomaterials, exosomes, etc. This section will introduce these nanoparticles as well as their advantages and disadvantages, and provide a brief statement of related research, see Fig. 1.

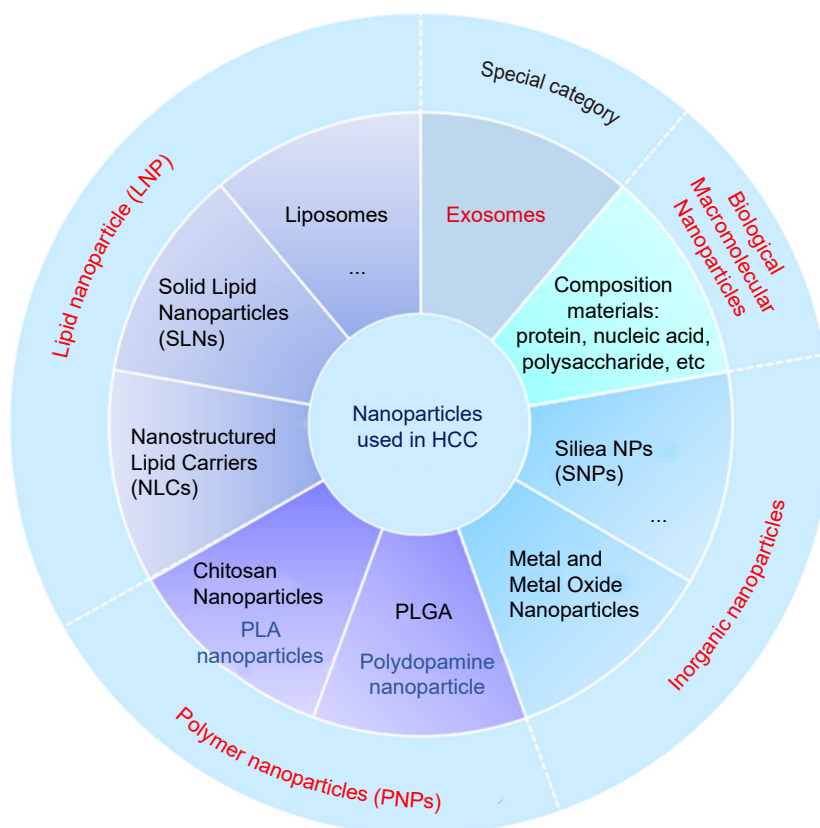


Fig. 1. Classification of nanoparticles used in HCC.

Lipid Nanoparticle

LNPs are widely used as bioactive nanocarriers for treating tumors^[11]. Liposomes, nanostructured lipid carriers (NLCs), and solid lipid nanoparticles (SLNs) are widely prevalent, each show remarkable properties^[12]. LNPs, for instance, demonstrate robust stability and high drug encapsulation abilities are simple to formulate, allowing for cost-effective large-scale production^[11].

Liposomes

LNPs typically range from 50 to 200 nm in size and are mainly composed of phospholipids and cholesterol^[13]. Liposomes have been extensively researched as delivery systems due to their biocompatibility and ability to degrade naturally^[12]. Phospholipids can form spherical lipid bilayers with their hydrophobic tails, allowing them to encapsulate drugs within liposomes, and this protective feature shields the encapsulated cargo from degradation by the immune system, making liposomes advantageous for their biocompatibility and improved targeting efficiencies^[13]. They possess the capability to encapsulate a diverse range of drugs, including those that are hydrophobic and hydrophilic in nature^[14]. The preparation methods of nano-liposomes mainly include film method, emulsification method, ultrasonic method, and membrane evaporation method. Zhang Y^[15] et al. developed a targeted liposome-polycation-DNA (LPD) complex nanoparticle system, demonstrating its effectiveness in delivering RNA to tumor sites, thereby enhancing the immune response against HCC for antitumor therapeutic outcomes. Nano-liposome encapsulation technology has many advantages. However, nanoliposome encapsulation technology also faces some challenges, such as the complexity of preparation methods, stability, toxicity and immunogenicity of nanoliposome. Therefore, the preparation method, application field and safety of nano-liposome encapsulation technology need to be further studied and explored in the future.

Solid Lipid Nanoparticles

SLNs are used for delivering drugs, consisting of solid natural or synthetic lipids like lecithin and triacylglycerol as carriers. These particles encapsulate drugs in the lipid core and have a size range of 10-1000 nm. They possess benefits like regulated drug release, precise targeting, enhanced drug stability, substantial drug loading capacity, and minimal toxicity. SLNs can transport both hydrophilic and lipophilic drugs. Nonetheless, they also come with some limitations, such as moderate drug-loading capacity and the possibility of drug expulsion caused by crystallization during storage^[16]. Rahman M^[17] et al. developed cationic SLNs loaded with resveratrol (RV-c-SLNs) and demonstrated its favorable antitumor activity by in vivo, in vitro, and biochemical studies.

Nanostructured Lipid Carriers

A novel type of LNPs, known as NLCs, are created by blending liquid and solid lipids to form a mixed lipid matrix. To overcome the constraints of SLNs, NLCs were devised. They boast a superior drug-loading capacity and hinder drug expulsion during storage by inhibiting lipid crystallization, thanks to the inclusion of liquid lipids in their formulation^[12]. NLCs can accommodate both hydrophilic and hydrophobic drugs, offering similar advantages

to SLNs. However, there are still some drawbacks, such as the easy excretion of lipids after undergoing polymorphic transformation within the nanocarrier matrix and low efficiency in drug loading^[18]. Eman M.M. Shehata^[19] et al. created NLCs loaded with positively charged PIP, which were then coated with pectin to produce novel pectin-coated NLCs (PIP-P-NLCs) for targeting HCC. The P-NLCs under development exhibited enhanced cytotoxicity and cellular internalization compared to their non-targeted counterparts^[19]. In addition to the aforementioned three, microemulsion, nanoemulsion, phytosomes, lipid-coated nanoparticles, and nanoassemblies are also beneficial in the treatment of HCC.

Polymer Nanoparticles

Polymer nanoparticles (PNPs) encompass various polymeric structures such as dendrimers, polymer micelles, nanospheres, and more. PNPs have many excellent properties, such as outstanding physical characteristics, elevated specific surface area, and favorable compatibility with living organisms. But PNPs have stability problems: such as instability, easy hydrolysis and autooxidation. There are also risks of particle aggregation and toxicity. Chitosan and PLGA are one of the most leading natural and synthetic polymers used, respectively^[20,21], as described below. Moreover, PLA NPs are also a kind of common nanoparticles used in research for the treatment of HCC.

Chitosan Nanoparticles

Chitosan, a polysaccharide that is naturally abundant, is derived from the partial deacetylation of chitin, which is found in the exoskeletons of insects and crustaceans. It possesses a linear aminopolysaccharide structure (poly-1,4-D-glucosamine)^[4,22]. The presence of amino groups in weakly acidic environments causes the polymer to become a polycation, enabling it to interact with negatively charged surfaces such as cell membranes^[23-25]. Therefore, it has an affinity for negatively charged biofilms and selectively accumulates in tumors. Some researchers have claimed that chitosan itself has anticancer properties against HCC cells, and Qi^[26] et al. were among the pioneering researchers to show the effectiveness of chitosan NPs in inhibiting tumor growth. However, further studies are needed to confirm this. Chitosan NPs may be susceptible to protein adsorption in the blood, resulting in particle agglomeration and rapid clearance, which limits their long-term circulation application in vivo. This also presents a challenge in the realm of tumor-targeted therapy.

PLGA

Poly (lactic-co-glycolic acid) (PLGA) consisting of lactic acid and glycolic acid monomers, which is a degradable functional macromolecular organic compound. PLGA NPs offer excellent drug solubility and stability^[27]. In the process of biodegradation, it decomposes into monomers, glycolic acid, and lactic acid. These substances are subsequently metabolized by the body, undergoing the Krebs cycle, and ultimately eliminated as carbon dioxide and water. So its systemic toxicity to biological systems is negligible^[27]. However, PLGA NPs may undergo drug burst release, and excessive drug release may cause toxicity.

PLA nanoparticles

Poly(lactic acid) (PLA), also referred to as polylactide, is a pioneering biodegradable polyester polymer derived from lactic acid polymerization. PLA NPs hold great potential in drug delivery systems, improving drug efficacy by facilitating targeted release. Additionally, they can be tailored for bioimaging and diagnostics purposes, incorporating fluorescent or magnetic labels. Ma^[28] et al. explored the potential of SM5-1-conjugated PLA nanoparticles loaded with 5-fluorouracil (5-FU) for targeted HCC imaging and treatment. Their research showed that PLA-5FU-SM5-1 NPs outperformed PLA-5FU and 5-FU individually in inhibiting tumor growth. In summary, these PLA-based NPs offer a promising avenue for HCC diagnosis and therapy through targeted drug delivery and imaging.

Polydopamine nanoparticles

Polydopamine (PDA) NPs, biomimetic structures made from dopamine monomers, demonstrate outstanding biocompatibility and biodegradability. Dopamine oxidation initiates self-polymerization, resulting in PDA formation. Leveraging PDA's pH sensitivity, researchers have enhanced drug stability and controlled release for HCC treatment. For instance, Wu^[29] et al. synthesized Folic Acid-modified PDA-taxol-loaded Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) NPs, a pH-responsive system designed to boost targeted HCC therapy.

Inorganic Nanoparticles

Within biomedicine, inorganic NPs, including metals, semiconductors, and metal oxide NPs, have garnered significant attention as therapeutic candidates due to their tunable size, unique optical & electrical attributes, magnetic & catalytic properties, and good biocompatibility^[30]. A brief introduction to the commonly used types will be given below.

Metal and Metal Oxide Nanoparticles

Currently, there is a considerable amount of focus and interest on copper oxide nanocomposites because of their unique chemical and physical properties. These composites are recognized for their specific characteristics like suitable redox potential, enhanced specific surface areas, exceptional electrochemical activities, and improved stability in solution^[31]. Currently, gold, silver, platinum and other metal materials are being studied in the form of NPs for the therapy of HCC. For example, silver nanoparticles show the effective antibacterial properties^[31]. Platinum NPs demonstrate significantly higher cytotoxicity compared to bulk platinum^[32]. Due to their distinct characteristics, such as a high surface area-to-mass ratio and enhanced reactivity, Pt NPs have been swiftly acknowledged as potential nanomedicines for the treatment of different cancer types using chemotherapy^[33]. But metal and metal oxide NPs may have toxic effects on organisms. The size, shape, surface modification and other factors of NPs can also affect their toxicity and biocompatibility.

Silica Nanoparticles

Silica NPs (SNPs), especially non-crystalline ones, are commonly utilized in the medical field for transporting chemother-

apy drugs and multimodal imaging agents^[34]. The high drug loading efficiency of SNPs is attributed to their ability to encapsulate drugs within their pore channels^[11]. Research by In-Yong Kim MS^[34] and colleagues revealed that identical SNP formulations elicited diverse responses across different cell lines of the same type. Notably, HepG2 cells exhibited minimal sensitivity to SNP toxicity, whereas NIH/3T3 cells were highly susceptible^[34]. It is hypothesized that cytotoxicity stemming from SNPs exposure is significantly influenced by oxidative stress and ROS-induced DNA damage, which may arise from nanoparticle distribution and accumulation within cellular compartments^[35].

Other Inorganic Nanoparticles

Inorganic nanomaterials possessing exceptional photothermal conversion abilities, like selenium, black phosphorus nanosheets, and graphene oxide, can potentially facilitate multi-modal synergistic therapy, bolstering HCC treatment efficiency^[36]. Additionally, Ji^[37] et al. capitalized on this by deploying cancer cell-macrophage hybrid membrane-cloaked copper sulfide NPs for photothermal-chemotherapy against HCC. This strategy enhanced the synergistic impact of photothermal therapy (PTT) and chemotherapy on hepatoma cells through homotypic targeting.

Biological Macromolecular Nanoparticles

Biomacromolecular nanomaterials consist of proteins, nucleic acids, polysaccharides, and other compounds. Albumin NPs modified by various substances are the most frequently utilized biomacromolecular nanomaterials for the therapy of HCC. The natural origin and versatility of albumin make it a perfect choice for drug delivery applications^[11]. Three key technologies for drug delivery have been established: conjugating low-molecular-weight drugs with exogenous or endogenous albumin, fusing them with bioactive proteins, and encapsulating drugs within albumin NPs^[38]. The researchers used Biguanides decorated albumin NPs loading nintedanib^[39], arsenite-loaded albumin NPs^[40], sorafenib and doxorubicin loaded microbubble-albumin NPs complex^[41], etc., to synergistically enhance the treatment of HCC.

Exosomes

Exosomes, minute nanovesicles with a phospholipid bilayer, originate from the separation of intracellular polyvesicles from cell membranes and are subsequently released into the extracellular milieu^[42]. Exosomes facilitate the transfer of biologically active substances from one cell to another, influencing the microenvironment and immune system through a range of biomolecules including proteins, RNA, and DNA^[43-45], and the cellular mechanisms involving genetics and epigenetics^[46]. Recent studies underscore exosomes' pivotal role in HCC progression and dissemination, with their cargo also serving as clinical diagnostic and therapeutic tools. Tumor-derived exosomes harbor cancer-associated serological markers, notably miRNAs, enabling early HCC detection^[47]. However, while several investigations have explored the exosome-liver cancer link, the underlying mechanisms governing liver cancer formation via exosomes remain inadequately probed^[48].

Hybrid nanoparticles

Non-hybrid nanocarriers face challenges related to stability and targeting. To overcome these limitations, hybrid NPs (HNPs) comprising two or more materials or excipients are synthesized. This approach leverages the advantages of individual nanocarriers while addressing their limitations^[49]. Different types of HNPs, like lipid-polymer, inorganic, metal-organic, and hybrid carbon nanocarriers, have been utilized for cancer diagnosis and therapy. HNPs exhibit improved loading capacity, release profiles, cellular entry, and cytotoxicity in vitro and in vivo compared to non-hybrid counterparts. For instance, Xu^[50] et al. developed a Doxorubicin-embedded copper diethyldithiocarbamate-functionalized layered double hydroxide HNP for HCC-targeted therapy, showcasing promising applications in cancer treatment.

Diverse targeting methods on nanocarries for precise therapeutic in HCC

There have been at least three categories of NPs utilized to diagnose or treat HCC: passive targeting, active targeting, and stimuli-responsive NPs targeting^[51].

Passive Targeting

Passive targeting relies on the natural affinity of certain molecules or cells for specific targets within the body. Unlike active targeting, which involves the use of external agents to direct the delivery system, passive targeting allows for a more natural and spontaneous interaction between the therapeutic agent and the diseased tissue. The fundamental principle behind passive targeting is the inherent differences in the vasculature and permeability of healthy and diseased tissues. One instance involves the frequent occurrence of enhanced permeability and retention (EPR) effects in tumor blood vessels, resulting in the preferential accumulation of large molecules and NPs within the tumor for a prolonged duration compared to normal tissues^[52]. The debate over the existence and significance of EPR effects has been a topic of contention in recent years, with the variability of EPR among various tumors raising doubts about its applicability^[53]. Passive targeting has several advantages, including its simplicity, cost-effectiveness, and lack of the need for external energy sources or specialized equipment. However, it also has limitations, such as the inability to precisely control the distribution of the therapeutic agent and the potential for nonspecific accumulation in other tissues. By harnessing the natural affinity of certain molecules or

cells for specific targets within the body, passive targeting allows for the precise delivery of therapeutic agents directly to diseased tissues, while minimizing off-target effects. While it has its limitations, the simplicity, cost-effectiveness, and potential for clinical translation of passive targeting make it an important and ongoing area of research and development.

Active Targeting

Active targeting is a strategy that aims to maximize the delivery of therapeutic agents to specific cells or tissues while minimizing nonspecific interactions with healthy cells. This approach is particularly important in diseases that require precise delivery of drugs to affected areas, such as cancer. Active targeting is frequently employed for HCC, where the drug delivery system's surface markers or ligands bind to specific receptors on the target cell, leading to conformational changes^[54-56]. By using ligand (such as peptides, proteins, adaptation and antibody) to surface modification of NP, these ligands selectively with over expression in tumor specific antigens or receptors interactions, thus enhance the NP to the target cells^[57].

Membrane Receptor and Protein Targeting

The Table 1 provides a brief description of part of molecules that are overexpressed in HCC cells and can be used in active-targeted delivery systems.

Enhanced active targeting ligands HCC

Ligands that exhibit the ability to enhance active targeting possess unique properties that allow them to effectively bind to specific receptors or biological markers, thereby facilitating precise and efficient delivery of therapeutic agents or other bioactive molecules. The Table 2 shows the classification and a brief introduction of ligands that can enhance active targeting of NPs and can be applied to the therapy of HCC.

Stimuli-responsive nanoparticles for targeted delivery

Stimuli-responsive NPs target cells by adjusting their movement with external (e.g., magnetic fields, ultrasound) or internal (e.g., pH, tissue environment) stimuli, ensuring precise drug delivery^[54,58]. The potential of stimuli-responsive NPs in HCC treatment is promising, as they are capable of reacting to stimuli

Table 1. Molecules that are overexpressed in HCC cells and can be used in delivery systems with active targeting^[51].

Name	Category of Affiliation	Sites of Expression
Asialoglycoprotein receptor (ASGP-R)	a receptor that relies on calcium for activation	The expression of this protein is limited to the surface of liver cells.
Glypican-3 (GPC3)	This proteoglycan belongs to the glypican family and is categorized as a heparan-sulfate.	It is overexpressed in cell membrane and cytoplasm of HCC cells.
Glycyrrhetic acid receptor (GAR)	-	surface of HCC cells.
Transferrin receptor (TFR)	homodimeric transmembrane glycoprotein	The expression of this gene is predominantly observed in HCC tissue and cell lines derived from colon cancer.
Receptor for somatostatin (SSTR)	receptor coupled with G-protein	Broadly present in brain, gut, kidneys, immune cells, & glands.
Cluster of differentiation CD44	surface glycoprotein	Variant isoforms of CD44 are expressed by tumor cells.

Table 2. Ligands that can enhance the active targeting of NPs and can be applied to the treatment of HCC^[51].

Category	Name	Molecules to Target	Pros and Cons
Saccharide-based ligands	Lactobionic acid (LA)	ASGP-R	Small dimensions, excellent permeability, and cost-effectiveness; Comparatively less specificity, simple to synthesize and modify.
	Hyaluronic acid (HA)	CD44	
	Pectin	ASGP-R	
Vitamin-based ligands	Folate	Folate receptor	-
	Biotin (vitamin B7)	Biotin receptor	
	Retinoic acid (RA)	RA receptor- α (RAR α)	
	Dehydroascorbic acid (DHAA)	GLUT1	
Antibody-based ligands	anti-EGFR/EGFRv III mAb(9B9mAb)	EGFR/EGFRv	High specificity and affinity; Large size, poor permeability, potential immune genicity, costly.
	anti-VEGF mAb (Sc7269)	VEGF	
	anti-CD44 antibody	CD44	
			
Peptide-based ligands	Arginine-Glycine-Asparagine (RGD)	Integrin- α v β 3	Moderate size, easy synthesis and manipulation, high affinity and specificity; Prone to proteolysis.
	Gerbich GE11	EGFR	
	Fibroblast growth factors (FGFs)	FGFRs	
	heptapeptide sequence (MQLPLAT)	FGFR	
Aptamer-mediated ligand	CL4: 5'GCCUUAGUAAACGU GCUUUGAUGUCGAU UCGACAGGAGGC-3'	EGFR	Good solubility and non-immunogenic permeability; Rapid clearance and degradation.
	A15: 5'-CCCUCCUACAUA GGG-3'	CD133	
Transferrin-based ligands	Transferrin (TF)	TFR1	-
		TFR2	

within the tumor microenvironment (TME), leading to the release of their cargo^[59]. Stimuli-responsive NPs further enhance the specificity and efficacy of targeted delivery by allowing for precise control over the release of drugs at the site of action. In the review^[59] by Seyedeh Setareh Samaei et al., the stimulation-responsive liposomes have been used to treat HCC, including liposomes that are sensitive to pH, redox, and light. These liposomes have the capability to transport drugs into the TME in order to enhance the therapeutic effectiveness.

The controlled release of drugs of various nanosystem for precise therapeutic intervention in HCC

The controlled release of drugs through nanosystems allows for sustained and localized therapy, ensuring maximum efficacy with minimal side effects. These systems are created to react to particular environmental signals present in the TME, like pH levels or enzyme concentrations, causing the drugs to be released precisely at the required location. This targeted approach not only improves therapeutic outcomes but also enhances patient compliance and quality of life. This section will present information on stimulus-responsive nanomedicine and its corresponding release mechanisms. Stimuli-responsive NPs can be used to control the release of drugs, leading to improved drug effectiveness and reduced harm to healthy cells^[10]. They're classified as single or multiple stimulus-responsive, and exogenous or endogenous

based on function and action pathways^[10]. The Fig. 2. illustrates the detailed categorization of individual Stimuli-responsive NPs.

The multiple-response stimuli approach can incorporate a mix of endogenous, exogenous, or both types of stimulus-responsive NPs^[10]. For example, scientists have investigated pH-responsive NPs as a potential treatment for HCC. These NPs are designed to respond to changes in pH levels, allowing them to target and release chemotherapy drugs specifically at tumor sites. Tumor and inflamed tissues tend to have a lower pH compared to healthy tissue and blood, making this targeted drug delivery system effective^[11]. This observation led to the creation of nanocarriers capable of responding to natural and abnormal pH levels in the body, leading to targeted drug release in cancer cells^[60]. The primary categories of pH-sensitive NPs include liposomes, polymers, and SNPs^[11]. In addition, redox-, magnet- and light-sensitive NPs also occupy a place in the therapy of HCC research.

Conclusion

This review introduces various nanomaterials for the therapy of HCC and their advantages and disadvantages, including LNPs, PNPs, inorganic NPs, biological macromolecule NPs, exosomes and hybrid NPs. As well as the targeting and release mechanisms and research status of NPs drug delivery system for the therapy of HCC in various current studies are introduced. With the continu-

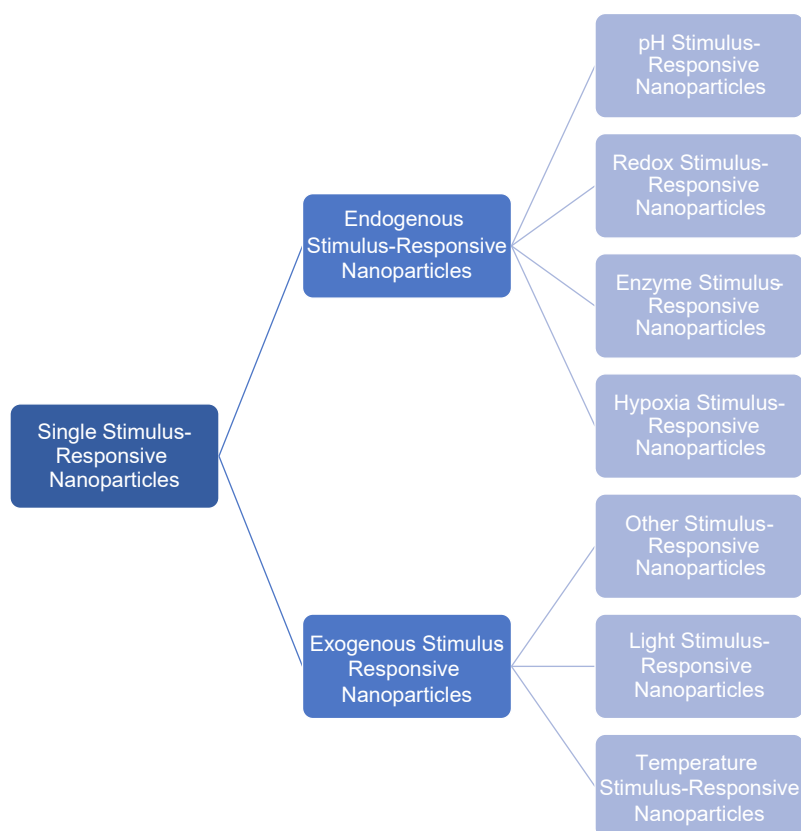


Fig. 2. Classification of single stimulus-responsive NPs.

ous development of nanotechnology, the potential of NPs drug delivery system in the diagnosis and treatment of HCC has received increasing attention. The advantages of NPs drug delivery system include high drug delivery ability, precise targeting ability and visualization ability, etc., which provide a new means for HCC therapy.

However, in the clinical application process, nanomedicines for HCC treatment still encounter numerous challenges. Firstly, the tumor microenvironment restricts the penetration and accumulation of nanomedicine at the tumor site, leading to inefficient drug delivery. Secondly, the long-term accumulation of nanomedicines in vivo may result in drug tolerance and toxicity issues. Thirdly, achieving sustained and stable drug release at the tumor site to improve therapeutic effects is a crucial issue in nanomedicine research and development. Finally, identifying biomarkers related to the occurrence and progression of HCC is essential for better predicting the therapeutic effect of nanomedicines in order to enhance their efficacy. In conclusion, while nanomedicine holds great potential for treating HCC, there are still numerous challenges that need to be overcome.

Therefore, it is necessary to further study the biocompatibility of NPs drug delivery system to reduce their side effects on human body, develop new drug encapsulation technologies to improve the stability of drugs, and strengthen basic research to understand the behavior and mechanism of NPs drug delivery system in vivo. As these problems are gradually solved, nanotechnology will bring new opportunities to treat HCC. Beyond existing treatments, nanotechnology is poised to transform emerging therapies like surgical nanorobots, immunotherapy, gene, cell, and re-

generative medicine^[61]. Furthermore, it promises to personalize treatments and enable real-time therapy monitoring. Hence, nanomedicine is expected to become a cornerstone in the future diagnosis and treatment of HCC. In general, the research on the targeted therapy of HCC with NPs drug delivery system is entering a new stage full of opportunities and challenges.

Abbreviations

5-FU, 5-fluorouracil; ASGP-R, asialoglycoprotein receptor; BCLC, Barcelona Clinic of Liver Cancer; BNCT, boron neutron capture therapy; DHAA, dehydroascorbic acid; FGFs, fibroblast growth factors; GAR, glycyrrhetic acid receptor; GPC3, glypican-3; HA, hyaluronic acid; HCC, hepatocellular carcinoma; HNPs, hybrid nanoparticles; LA, lactobionic acid; LNPs, lipid nanoparticles; MSN, mesoporous silica nanoparticles; NLCs, nanostructured lipid carriers; NPs, hybrid nanoparticles; PDA, Polydopamine; PLA, Polylactic acid; PLGA, Poly (lactic-co-glycolic acid); P-NLCs, pectin-coated NLCs; PNPs, Polymer nanoparticles; PTT, photothermal therapy; RAR α , RA receptor- α ; RV-c-SLNs, cationic SLNs loaded with resveratrol; SLNs, solid lipid nanoparticles; SNPs, Silica nanoparticles; SSTR, receptor for somatostatin; TF, transferrin; TFR, transferrin receptor; TME, tumor microenvironment.

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Conflict of interest

The authors declare no conflict of interest here.

Authors' contributions

XYK: Data curation, Investigation and Writing – original draft. ZRZ: Data analysis. HYT: Formal analysis. YHC: Resources, Formal Analysis. JL: Conceptualization, Funding acquisition, Supervision, and Writing – review & editing.

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