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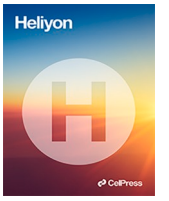

Review article

Recent advances of novel targeted drug delivery systems based on natural medicine monomers against hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC), the most prevalent type of liver cancer, is often diagnosed at an advanced stage. Surgical interventions are often ineffective, leading HCC patients to rely on systemic chemotherapy. Unfortunately, commonly used chemotherapeutic drugs have limited efficacy and can adversely affect vital organs, causing significant physical and psychological distress for patients. Natural medicine monomers (NMMs) have shown promising efficacy and safety profiles in HCC treatment, garnering attention from researchers. In recent years, the development of novel targeted drug delivery systems (TDDS) combining NMMs with nanocarriers has emerged. These TDDS aim to concentrate drugs effectively in HCC cells by manipulating the characteristics of nanomedicines, leveraging receptor and ligand interactions, and utilizing endogenous stimulatory responses to promote specific nanomedicines distribution. This comprehensive review presents recent research on TDDS for HCC treatment using NMMs from three perspectives: passive TDDS, active TDDS, and stimuli-responsive drug delivery systems (SDDS). It consolidates the current state of research on TDDS for HCC treatment with NMMs and highlights the potential of these innovative approaches in improving treatment outcomes. Moreover, the review also identifies research gaps in the related fields to provide references for future targeted therapy research in HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for 90 % of cases and ranking as the fifth most prevalent malignant tumor globally. It is estimated that in 2020, there were approximately 905,677 new cases of liver cancer worldwide, resulting in 830,180 deaths. The mortality rate is comparable to the incidence rate, and liver cancer has become the third leading cause of cancer-related deaths. It is projected that by 2040, over 1.2 million individuals will die from liver cancer [1]. For early-stage HCC patients without metastasis, surgical resection is the most effective treatment. However, HCC often presents with subtle symptoms, leading to late-stage diagnosis and missed opportunities for surgical intervention. Consequently, most patients opt

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for chemotherapy [2]. Unfortunately, first- and second-line chemotherapeutic agents like sorafenib, lenvatinib, ramucirumab, and regorafenib, while killing cancer cells, also result in severe neurotoxicity, cardiotoxicity, and liver and kidney dysfunction. This poses significant physical and psychological challenges for patients [3].

To address this issue, the development of drugs with greater targeting precision, better efficacy, and fewer side effects has become a crucial goal. Natural medicine monomers (NMMs), a natural treasure trove that cannot be ignored, have attracted widespread attention. NMMs are characterized by fewer adverse reactions, higher stability, easier metabolism, lower risk of residues, and good drug compatibility. In addition, for the treatment of HCC, NMMs have shown many advantages in improving patients' quality of life, delaying the progression of HCC, improving patients' immune function, preventing tumor recurrence and metastasis, and enhancing sensitivity to chemotherapeutic agents. It has been reported that about half of the small molecules approved for the treatment of cancer from 1940 to 2014 are NMMs or their derivatives [3]. Some popular anticancer drugs, such as vinblastine, vincristine, paclitaxel (PTX), docetaxel, topotecan, and irinotecan, are also derived from NMMs. Various NMMs such as coptisine, betulinic acid, PTX, silymarin, silibinin, apigenin, curcumin (Cur), isoginkgetin, artesunate, solamargine, sanguinarine, quercetin, cantharidin, cucurbitacin I, cucurbitacin E, and toosendanin have demonstrated anti-HCC effects through different mechanisms [4–18]. These mechanisms include inhibiting specific pathways, inducing apoptosis and autophagy, mitochondrial dysfunction, glycolysis inhibition, enhancing antioxidant defense mechanisms, mediating ferroptosis and cuproptosis, targeting disruption of the endoplasmic reticulum, inducing an immune-stimulated tumor microenvironment (TME), impairing lysosomal function, and disrupting the cytoskeleton. Exploring NMMs to treat HCC has become a research hotspot, and its potential value will inevitably be fully utilized in the future. The chemical structures of commonly used NMMs for the treatment of HCC are depicted in Fig. 1.

Furthermore, some NMMs have shown potential for combination therapy with conventional chemotherapeutic drugs. For example, oleanolic acid overcomes HCC cell resistance to cisplatin and reduces hepatotoxicity [19]. Rhein enhances the antitumor effect of doxorubicin (DOX) by affecting mitochondrial energy metabolism [20]. However, challenges remain due to the poor water solubility and low bioavailability of certain NMMs, such as tanshinone IIA and Cur, which hinder their clinical applications. Additionally, compounds like camptothecin (CPT), gallic acid, and quercetin are susceptible to hydrolysis or oxidation, further complicating their

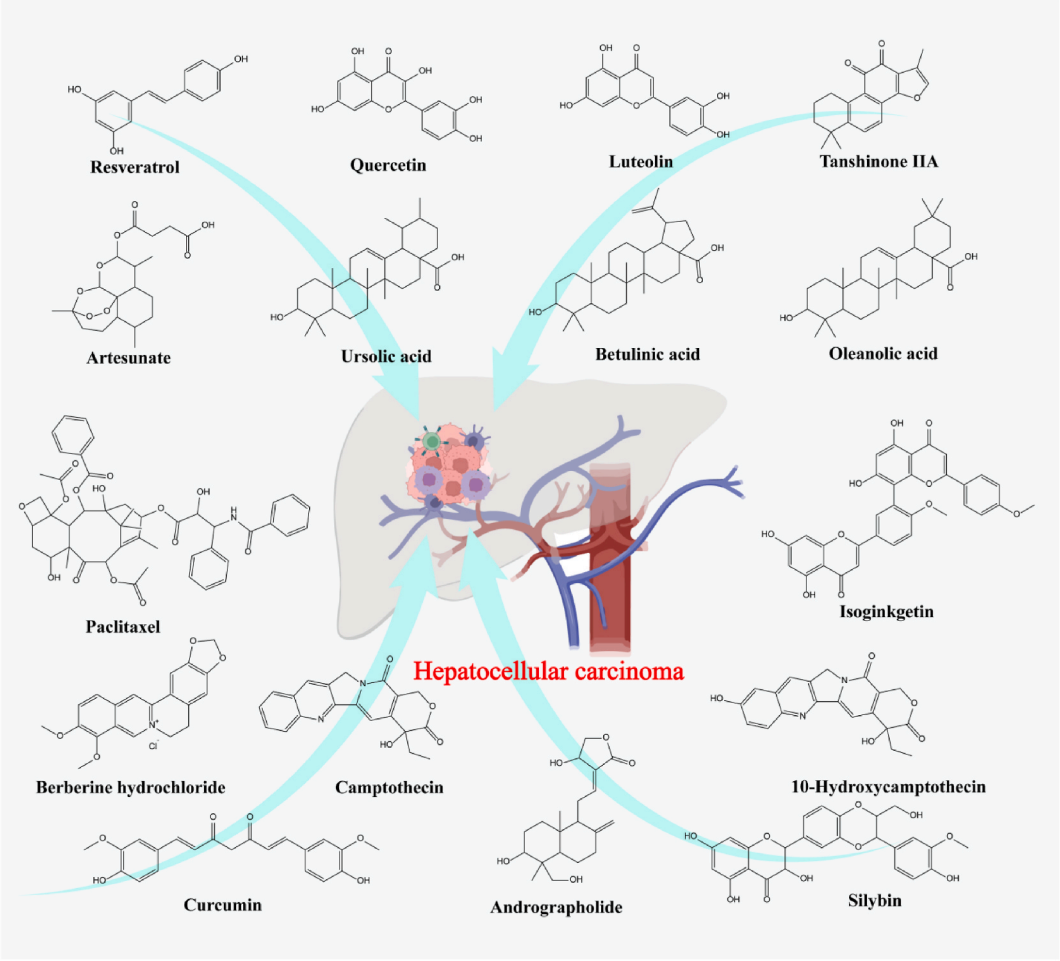

Fig. 1. Chemical structures of common NMMs used in the treatment of HCC.

use.

To overcome these obstacles and achieve precise delivery of NMMs, the combination of nanomedicine technology and NMMs has gained attention. Nanomedicines possess characteristics such as small size and large surface area, enabling the enhancement of solubility, stability, and controllability of NMMs through various methods like adsorption, dissolution, and encapsulation. Targeted drug delivery systems (TDDS) based on nanomedicine can concentrate the drug specifically at the site of the lesion, reducing non-specific toxic side effects on normal tissues. This approach holds promise for HCC treatment. Research on TDDS for HCC treatment has been ongoing for over a decade, with a significant increase in related studies in the past five years, particularly in the delivery of NMMs as loading drugs. However, it is important to acknowledge that the development of NMMs drugs for targeted HCC treatment is still in its early stages, and most findings are limited to preliminary cellular and animal experiments.

To advance the research and development of NMMs for targeted HCC treatment, this paper provides a systematic review of the literature, focusing on three main aspects: passive TDDS, active TDDS, and stimuli-responsive drug delivery systems (SDDS). Active TDDS refers to systems based on different receptors on the surface of HCC cells, while SDDS includes magnetic-responsive preparations, pH-responsive preparations, and thermosensitive preparations. By exploring these avenues, the aim is to accelerate the progress of NMMs-based therapies for HCC treatment.

2. Passive TDDS

Passive targeting refers to the natural tendency of drug-loaded particles to accumulate effectively at tumor sites due to physiological and pathological differences between tumor tissue and normal tissues. These differences arise from factors such as incomplete tumor blood vessels and lymphatic vessels due to the rapid proliferation of tumor cells. As a result, drug particles that enter tumor tissue through blood vessels have difficulty flowing back through lymphatic vessels, leading to an enhanced permeability and retention (EPR) effect [21] (Fig. 2). This effect allows drug particles to stay in the tumor tissue for a longer duration. Researchers have explored passive targeting strategies using nanoparticles. For example, Zhao et al. developed a nanodrug called Nano-Fe-GSS by conjugating ginsenosides with nanoparticles composed of a Fe core and Fe_3O_4 shell using (3-aminopropyl)trimethoxysilane [22]. Magnetic resonance imaging demonstrated that Nano-Fe-GSS exhibited auto-liver targeting characteristics, passively accumulating in the liver of mice and maintaining a significant drug concentration for at least 4 h. This approach demonstrates the potential of passive targeting for specific organ delivery.

The passive targeting of drugs is also influenced by the phagocytosis activity of the reticuloendothelial system. After entering the body, nanoparticles are rapidly cleared by macrophages in this system, ultimately reaching the lysosomes of Kupffer cells in the liver. Due to the abundance of Kupffer cells in the liver, drug-loaded nanoparticles can accumulate and exert their effects in this organ. The liver endothelial wall has capillary sinusoids with fenestrations of 100–200 nm, making it difficult for nanoparticles larger than 250 nm to reach the liver. On the other hand, nanoparticles smaller than 100 nm are easily cleared by phagocytosis. Therefore, nanoparticles within the size range of 100–200 nm are more likely to be retained in the liver [23]. However, controlling the precise size of drug particles in most nanoparticles remains challenging.

The surface charge of nanoparticles can also influence their passive targeting. Anionic components present on the inner membranes of cancer cells, such as phosphatidylserine, anionic phospholipids, glycoproteins, and proteoglycans, result in a negatively charged

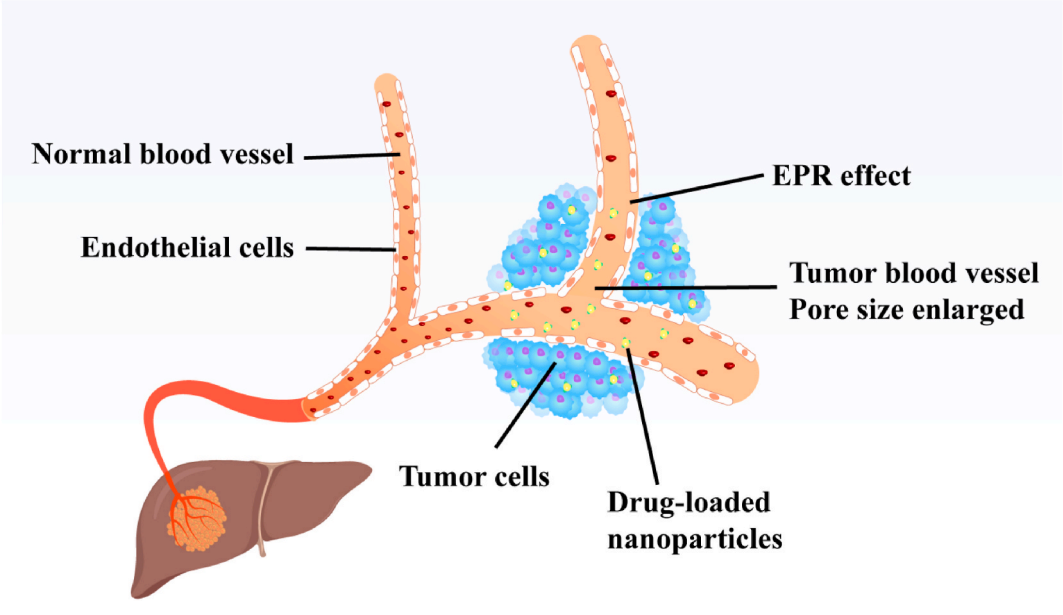

Fig. 2. Schematic diagram of TDDS for the treatment of HCC through passive targeted drug delivery.

surface on cancer cells [24]. This enhances the electrostatic interactions with positively charged nanoparticles. Modulating the surface charge of nanoparticles can improve their delivery to tumor target sites. For instance, a team developed cationic resveratrol (RV) solid lipid nanoparticles (RV-*c*-SLN) with a size of 139.27 nm [25]. The concentration of RV-*c*-SLN in tumor tissue was 1.4 times and 2.6 times higher than that of RV solid lipid nanoparticles and RV solution, respectively. This resulted in a more pronounced anti-tumor effect, while the distribution of RV-*c*-SLN in the heart, kidneys, and lungs was lower.

Passive targeting, driven by physiological and pathological characteristics, holds promise for improving drug delivery to tumor sites. It can be achieved through strategies such as leveraging the EPR effect, targeting specific organs, and modulating nanoparticle size and surface charge. These approaches offer potential for enhancing the therapeutic outcomes of drug-loaded nanoparticles in cancer treatment.

3. Active TDDS

The concept of active targeting, which involves the selective destruction of diseased cells while sparing healthy cells, was initially proposed by Nobel laureate Ehrlich in 1906, who referred to it as the “magic bullet." In active TDDS, three key components are involved: the targeting ligand, carrier, and drug. In comparison to normal cells, HCC cells exhibit an increased expression of certain molecules and proteins on their surface, which serve as receptors for interacting with ligands present in the TDDS (Fig. 3). This interaction facilitates the internalization of the drug. Some commonly targeted receptors for HCC cells include the asialoglycoprotein receptor (ASGPR), glycyrrhetinic acid receptor (GAR), cluster of differentiation 44 (CD44), folate receptor (FR), transferrin receptor (TfR), and others (Table 1).

3.1. Asialoglycoprotein receptor (ASGPR)-based active targeting

The ASGPR plays a specific role in recognizing and binding molecules containing galactose (Gal) and N-acetylgalactosamine residues. Clathrin facilitates the endocytosis of glycoproteins bound to the receptor, leading to their separation within acidic endocytic vesicles and subsequent degradation in lysosomes [26]. ASGPR is not expressed during fetal development but becomes rapidly

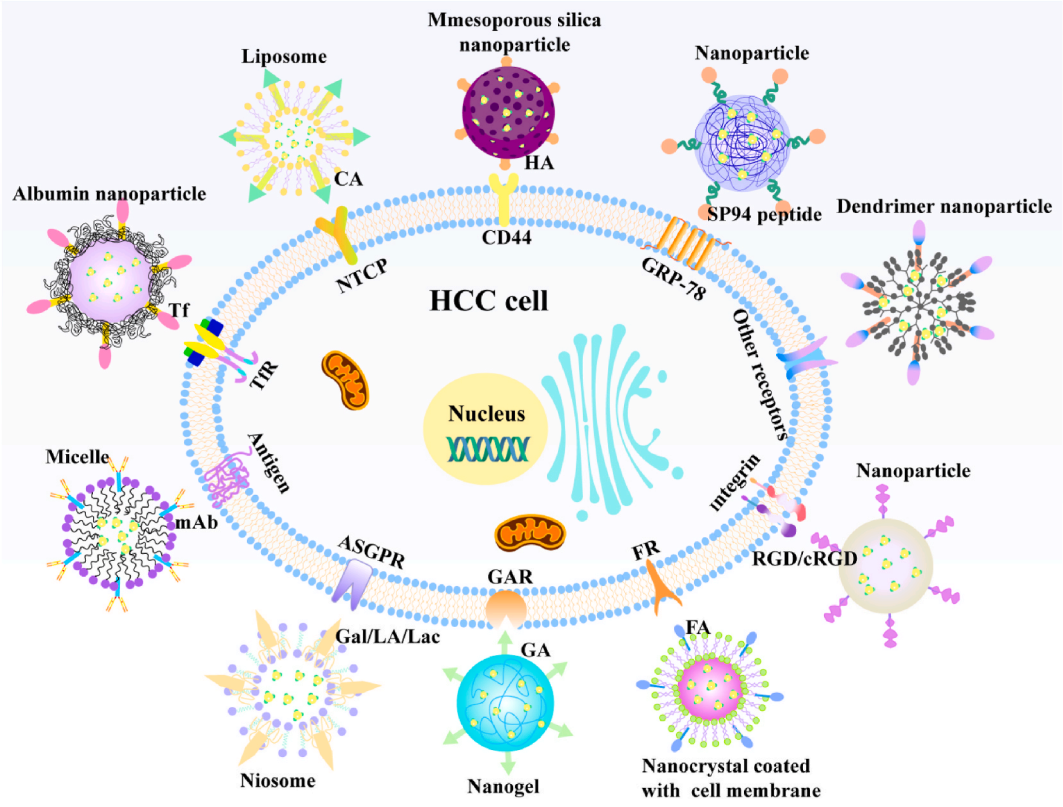

Fig. 3. Summary of active TDDS with ligands for the treatment of HCC by targeting overexpressed receptors on HCC cells.
Abbreviations: ASGPR, asialoglycoprotein receptor; Gal, galactose; LA, lactose; Lac, lactobionic acid; GAR, glycyrrhetinic acid receptor; GA, Glycyrrhetinic acid; FR, folate receptor; FA, folic acid; RGD, Arginyl-Glycyl-Aspartic acid peptide; cRGD, cyclic Arginyl-Glycyl-Aspartic acid peptide; GRP-78, glucose regulated protein-78; CD44, cluster of differentiation 44; HA, hyaluronic acid; NTCP, sodium taurocholate cotransporting polypeptide; CA, cholic acid; TfR, transferrin receptor; Tf, transferrin; mAb, monoclonal antibody.

Table 1
Customized active TDDS developed for different types of HCC receptors.

Therapeutic agents	ligands	Matched receptors	Size (nm)	Delivery vehicles	References
Apigenin	Gal	ASGPR	129.0	Poly (lactic-*co*-glycolic acid) nanoparticles	[28]
Oleanolic acid	Gal	ASGPR	210.45 ± 9.96	Galactosylated chitosan-modified liposomes	[29]
Echinacoside	Gal	ASGPR	200	Galactose and poly (ethylene glycol) diglycidyl ether conjugation mesoporous silica nanoparticles	[30]
CPT	Gal	ASGPR	100	Galactose decorated trimethyl chitosan-camptothecin prodrug nanoparticles	[31]
Apocynin	Gal	ASGPR	224.29 ± 3.27	Galactosylated chitosan-coated poly (D,L-lactide-*co*-glycolide) nanoparticles	[32]
Oridonin	Gal	ASGPR	92.90, 102.90, 83.70	Chitosan-graft-poly (N-isopropylacrylamide) nanogels	[33]
Tanshinone IIA	Gal	ASGPR	53.72	Cholesteryl hemisuccinate and cholesterol niosomes	[34]
CPT	LA	ASGPR	114.40	CPT-S-S-LA nanoparticles	[35]
Ursolic acid	Lac	ASGPR	150	Polyamidoamine-G_0 dendrimers	[36]
HCPT	Lac	ASGPR	85	Lipid-poly (ethylene glycol) nanoparticles	[37]
PTX and DOX	Lac	ASGPR	148.7 ± 13.8	Bovine serum albumin nanoparticles	[38]
PTX	Lac	ASGPR	200	Lac-polyethylene glycol-PTX nanoparticles	[39]
CPT	Lac	ASGPR	91.0 ± 1.8	IR780-Lac/CPT-S-S-CPT co-assemble nanoparticles	[40]
PTX	Pullulan	ASGPR	198.3	Phospholipid and Pluronic F68 complex nanoparticles	[41]
Cur	Angelica polysaccharide	ASGPR	194.5	Arachidonic acid/angelica polysaccharide-azobenzene-ferrocene polymer micelles	[42]
Ferulic acid	GL	GAR	107.2 ± 3.08	Valeric modified chitosan nanoparticles	[48]
PTX	GL	GAR	203.4 ± 1.4, 111.9 ± 1.0, 147.1 ± 2.9	O-carboxymethyl chitosan nanoparticles	[49]
Cur	GA	GAR	171.6	Red blood cell membrane encapsulated GA-angelica polysaccharide nanomicelles	[51]
Cur	GA	GAR	–	Supramolecular hydrogels based on short peptides	[52]
Berberine hydrochloride	GA	GAR	–	Nano graphene oxide in-situ thermosensitive hydrogel	[53]
Andrographolide	GA	GAR	126.47 ± 3.74	Poly (ethylene glycol)-poly (lactic-*co*-glycolic acid) micelles	[54]
Artesunate	GA	GAR	88	Polyethyleneglycol-poly (d,l-lactic-*co*-glycolic)acid nanoparticles	[55]
HCPT	GA	GAR	135.55 ± 2.76	Nanoliposomes modified with and TAT peptide	[56]
Murrayafoline A	GA	GAR	103.49 ± 4.17	Cholesterol-poly (ethylene glycol)-glycyrrhetinic acid liposomes	[57]
Celastrol	GA	GAR	165.67 ± 2.27	Carboxymethyl chitosan-thioketal-rhein polymeric micelles	[58]
Isoginkgetin and DOX	HA	CD44	–	Manganese-doped mesoporous silica nanoparticles	[63]
Berberine and DOX	HA	CD44	300 × 100	Rod-like Janus magnetic mesoporous silica nanoparticles	[64]
PTX and DOX	Folate	FR	218.3 ± 11.2	Vesicle	[69]
RV	FA	FR	102.1 ± 4.9	Human serum albumin nanoparticles	[70]
Berberine	FA	FR	< 250	Janus gold mesoporous silica nanocarriers	[71]
PTX	FA	FR	200	Mesoporous hollow carbon nanospheres	[72]
Protocatechuic Acid	FA	FR	17 ± 2.08	Graphene Oxide Nanocomposite	[73]
CPT	Folate	FR	102 ± 9	Polylactic-*co*-glycolic acid hybrid nanoparticles	[74]
PTX	FA	FR	230 ± 2.10	HCC cell membrane encapsulated nanocrystals system	[77]
Cur	Tf	TfR	132.16 ± 1.37	Methoxy-polyethylene glycol-poly (d,L-Lactide) polymeric Micelles	[83]
Carnosic acid	Tf	TfR	97.06	Liposomes	[84]
Erianin	Tf	TfR	88.63	Liposomes	[85]
PTX and vorinostat	Tf	TfR	195	Albumin with PEGylated lipid bilayers	[88]
PTX	RGD peptide	Integrin	124.6 ± 7.7	Polydopamine poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate) nanoparticles	[93]
PTX	RGD peptide	Integrin	138 ± 3	PEGylated Poly (lactide-*co*-glycolide) nanoparticles	[94]
Cur	RGD peptide	Integrin	10–20	2-chlorotrityl chloride resin peptide nanofiber	[95]
Tanshinone IIA	Cyclic RGD peptide	Integrin	190 ± 42	Methoxypolyethylene glycol-polylactic-*co*-glycolic acid-poly-L-lysine nanoparticles	[96]
Silybin and DOX	CA	NTCP	97.03 ± 2.17	Distearoylphosphatidylethanolamine-polyethylene glycol-cholic acid-modified liposomes	[99]
PTX and bufalin	CA	NTCP	114.63 ± 1.56	Methoxy poly (ethylene glycol)-cholic acid/D-α-Tocopherol polyethylene glycol 1000 succinate micelles	[100]

(*continued on next page*)

Table 1 (*continued*)

Therapeutic agents	ligands	Matched receptors	Size (nm)	Delivery vehicles	References
PTX	HBsAg preS1 protein	NTCP	50	Methacryloyloxyethyl phosphorylcholine-co-*n*-butyl methacrylate-co-*p*-nitrophenylcarbonyloxyethyl methacrylate micelles	[102]
HCPT	Myrcludex B	NTCP	125	Liposomes	[104]
Cryptotanshinone	SP94 peptide	GRP78	144.7 ± 6.53	Poly (ethylene glycol)-poly (lactic-*co*-glycolic acid) nanoparticles	[109]
Cur and RV	SP94 peptide	GRP78	< 200	Nanoparticles co-assembled with amphiphilic lipids, cholesterol and 1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[maleimide (polyethylene glycol)-2000]	[110]
PTX	Anti-GPC3 mAb YP7	GPC3	–	Albumin nanoparticles	[113]
CPT	CD147 mAb	CD147	102	CD147-polyethylene glycol-b-polyphosphoester	[114]
PTX	HAb18 F $(ab')_2$	CD147	175.51 ± 60.31	Poly (lactic-*co*-glycolic acid) nanoparticles	[115]
Luteolin	PD-L1 Ab	PD-L1	159.3 ± 7.45	Stealth poly (lactic-*co*-glycolic acid)/liposomes nanoparticles	[117]
Oxymatrine	FH peptide	Tenascin-C	125.30 ± 0.96	Liposomes	[120]
PTX	aptamer L5 (TLS9a)	Hsp70	232.8 ± 16.72	Aptamer L5 (TLS9a)-functionalized polymeric nanoparticles	[122]
HCPT	Lysine	Amino acid transporters	71.4 ± 9.4	Hydroxyethyl starch-10-hydroxy CPT micelles	[124]
Cur	Triphenylphosphine bromide	–	208.3 ± 5.2	Chitosan-g-poly-(N-3-carbobenzyloxy-L-lysine) nanomicelles	[127]
Cur	Triphenylphosphonium	–	56.8 ± 21.5	Polyamidoamine dendrimer	[128]
Rhein and DOX	Rhein	–	80	Rhein-DOX nanogel	[129]
PTX	Pullulan and FA	ASGPR and FR	130–170	Disulfide-crosslinked pullulan nanoparticles	[130]
Ursolic acid	FA and pectin	ASGPR and FR	105.72 ± 6.94	Pectin-eight-arm polyethylene glycol-based nanoparticles	[131]
Cur	Angelica polysaccharide and GA	ASGPR and GAR	171.6	Angelica polysaccharide nanomicelle encapsulated with the membranes from red blood cells	[132]
Cur and combretastatin A-4 phosphate	GA and Gal	ASGPR and GAR	150	Liposomes	[133]
Cantharidin	GA and folate	GAR and FR	78.01 ± 1.03	Solid lipid nanoparticles	[134]
Cur and aprepitant	GA and HA	GAR and CD44	117.40 ± 0.62	Liposomes	[135]
Berberine and diosmin	Lac and FA	ASGPR and FR	208.3 ± 0.23	Casein micelles	[136]
Quercetin and sorafenib	Lac and GA	ASGPR and GAR	169.0 ± 1.5, 230.2 ± 1.7	Lactoferrin shell-oily core nanocapsules	[137]
RV and Sulfasalazine	FA and Lac	ASGPR and FR	276.8 ± 6.6	Amphiphilic maltodextrin-ursodeoxycholic acid micelles	[138]
CPT	CA and HA	NTCP and CD44	15 ± 2	Fe_3O_4-graphene oxide coated with β-cyclodextrin-cholic acid-HA polymer	[140]

Abbreviations: ASGPR, asialoglycoprotein receptor; Gal, galactose; LA, lactose; Lac, lactobionic acid; GAR, glycyrrhetinic acid receptor; GA, Glycyrrhetinic acid; FR, folate receptor; FA, folic acid; RGD, Arginyl-Glycyl-Aspartic acid peptide; cRGD, cyclic Arginyl-Glycyl-Aspartic acid peptide; GRP-78, glucose regulated protein-78; CD44, cluster of differentiation 44; HA, hyaluronic acid; NTCP, sodium taurocholate cotransporting polypeptide; CA, cholic acid; TfR, transferrin receptor; Tf, transferrin; mAb, monoclonal antibody; PTX, paclitaxel; CPT, camptothecin; HCPT, Hydroxycamptothecin; DOX, doxorubicin; Cur, curcumin; RV, resveratrol; Hsp, heat shock protein.

expressed after birth on the basolateral (sinusoidal) membranes of hepatic parenchymal cells [27]. Galactose-based nanoparticles loaded with drugs such as NMMs have been extensively studied for targeted therapy in HCC [28–32]. For example, a research team developed drug-loaded nanogels consisting of oridonin with galactosylated chitosan grafted onto poly (N-isopropylacrylamide) (Gal–CS–*g*-PNIPAm) [33]. These nanogels, compared to non-galactose-modified ones, exhibited increased toxicity to HepG2 cells and higher antitumor activity with increasing Gal substitution. The Gal grafting and modification onto the copolymer backbone allowed for enhanced targeting to HepG2 cells, as the hydrophilic Gal group at the outermost part of the nanoparticles facilitated binding to ASGPR, resulting in more efficient targeted drug delivery.

Ligand modifications not only enable specific liver targeting but also allow for responsive drug release at the tumor site. Cholesteryl hemisuccinate, a pH-sensitive membrane excipient with lipophilicity and membrane stability, has been used in the construction of galactose-modified tanshinone IIA niosomes (Gal-pH-Tan IIA-NSVs) [34]. In vitro experiments demonstrated that Gal-pH-Tan IIA-NSVs exhibited increased cytotoxicity, apoptosis induction, and proliferation inhibition in HCC cells (Huh7, HepG2) compared to colon and ovarian cancer cells. The acidic environment accelerated the release of tanshinone IIA, enhancing its therapeutic effects on HCC cells. Similarly, Gal–CS–*g*-PNIPAm nanogels also demonstrated pH-responsive drug release behavior, exhibiting significant

cytotoxicity to HepG2 cells at lower pH levels [33].

Lactose (LA), a disaccharide composed of glucose and galactose, has been utilized in the construction of redox-responsive target prodrugs. For instance, CPT-S-S-LA, a prodrug consisting of lactose-conjugated CPT via a disulfide bond, effectively accumulated at the tumor site and released active CPT through a sulfhydryl-disulfide bond exchange chemical reaction mediated by glutathione [35]. This approach targeted HCC cells specifically, enhancing the anti-tumor efficacy while minimizing damage to normal tissues. Lactobionic acid (Lac) has demonstrated excellent targeting properties in HCC when connected with dendrimers, liposomes, albumin, and other delivery carriers [36–39]. A study modified the photosensitizer IR-780 with Lac to create an amphiphilic molecule (IR780-LA). Through co-assembly with disulfide-modified CPT-ss-CPT prodrugs, IR780-LA/CPT-ss-CPT nanoparticles were formed, exhibiting active targeting to HCC cells and responsive release of CPT in the presence of glutathione [40]. The inclusion of the photosensitizer IR-780 enabled photothermal therapy in combination with drug therapy, and it also served as a fluorescent agent for in vivo imaging to guide tumor treatment.

Polysaccharides, known for their biodegradability, low cost, and compatibility, have attracted interest in drug delivery systems. Pullulan polysaccharide, for instance, has been utilized in a PTX-loaded composite nano-core (phospholipid/Pluronic F68) with a pullulan nano-shell [41]. This system exhibited excellent targeting and accumulation abilities in HCC cells, effectively inhibiting tumor growth and angiogenesis. Angelica polysaccharide, with its higher affinity for ASGPR due to increased Gal content and unique spatial structure, has also been used. Researchers linked angelica polysaccharides to ferrocene via azobenzene and modified the side chains with arachidonic acid, resulting in an amphiphilic polymer that self-assembled into micelles capable of loading the hydrophobic drug Cur [42]. The use of azobenzene as a hypoxia-sensitive bond allowed for the reactive release of Cur in the hypoxic microenvironment of HCC, synergistically enhancing the anti-tumor effects.

ASGPR is one of the most extensively studied receptors for HCC targeting, characterized by a wide range of ligands and a high number of binding sites. However, ASGPR activity and quantity are often reduced in HCC pathological states, with reported variations in ASGPR expression levels among patients [43]. Therefore, ASGPR-targeted delivery strategies should be combined with corresponding ASGPR diagnosis, emphasizing the importance of individualized therapy and precision medicine in ASGPR-dependent anti-HCC approaches. Further research on natural polysaccharides is necessary, as they exhibit high affinity for HCC cells and possess desirable properties for TDDS, but only a few natural polysaccharides have been identified to have natural affinity for HCC cells without additional modifications.

3.2. GAR-based active targeting

Glycyrrhizic acid (GL) and glycyrrhetinic acid (GA), the main active constituents of licorice, have been found to exhibit high affinity for receptors in the liver. In 1986, researchers demonstrated this high affinity, and subsequent studies by Negishi et al. confirmed that GA can bind reversibly and saturably to cell membrane components of rat liver homogenates [44]. These membrane receptors on hepatocyte membranes, collectively referred to as “GAR", specifically bind to GA and GL [45,46]. The amphiphilic structural characteristics of GA and GL allow for interactions with cholesterol or phospholipids on the cell membrane, making them suitable targeting ligands for HCC cells. Chitosan, a natural cationic polysaccharide, possesses multiple binding sites that enable drug loading through chemical cross-linking, electrostatic adsorption, and other methods. Chitosan-based nanomaterials for intravenous administration have gained interest due to N-acylated chitosan derivatives exhibiting slower clotting rates and improved antithrombotic properties compared to natural chitosan [47]. Researchers prepared GL-modified ferulic acid chitosan valerate nanoparticles by modifying chitosan with valeric acid [48]. These GL-modified nanoparticles showed the highest accumulation in the liver, reaching 13.34 % ID/g of the total injected dose after 6 h of injection. Non-GL-modified nanoparticles, in contrast, did not exhibit significantly different accumulation in the liver, kidney, and spleen, at 4.19 % ID/g, 5.88 % ID/g, and 5.03 % ID/g, respectively. Another study evaluated GL-modified O-carboxymethyl chitosan nanoparticles with different degrees of substitution as HCC targeting delivery vehicles and found that various degrees of GL substitution had similar targeting efficiency on HCC cells, possibly due to factors such as ligand shielding, receptor saturation, and increased hydrophilicity after GL modification [49].

Both GA and GL can bind to GAR. In one study, hepatocytes were co-incubated with glucuronic acid solution, and the uptake of GL-modified liposomes by hepatocytes was not reduced, demonstrating the key role of GA in binding to GAR [50]. A team prepared GA-modified Cur nanomicelles (GACS-Cur) using angelica polysaccharide as carriers and then encapsulated them with red blood cell membranes to confer bionic properties (GACS-Cur@RBCm) [51]. GA acted as a targeting ligand for preferential delivery of GACS-Cur@RBCm to HCC sites, where GACS-Cur@RBCm disintegrated upon exposure to the stimulation of a high concentration of glutathione in the TME. Compared with hyaluronic acid (HA) nanomicelles, GACS-Cur@RBCm combines the immunotherapy of angelica polysaccharides with the targeted delivery of Cur, which enhances the interaction between antigen-presenting cells and T cells and improves the ability of T cells and NK cells to kill the target cells, resulting in higher anti-HCC efficiency and targeting ability. GA-modified hydrogel, liposomes, and nanoparticles have also demonstrated effective targeting of human HCC cells [52–58].

Although the specific receptor proteins that bind to GA and GL have not been definitively identified, and some concerns and limitations remain in the aforementioned studies, GA and GL continue to exhibit promising potential in the treatment and targeting of HCC.

3.3. CD44-based active targeting

CD44 is a non-kinase transmembrane glycoprotein initially identified on lymphocytes. It is minimally expressed in normal hepatocytes but often overexpressed in various HCC cells, correlating with HCC cell proliferation and migration [59,60]. CD44 serves as a

common receptor for molecules such as HA, osteopontin, collagen, and fibronectin. HA, one of the most common ligands of CD44, can interact with CD44, and the strength of interaction increases with the molecular weight of HA. However, reversible interaction is limited to smaller HA molecules (<10 kDa) [61,62].

In recent years, nanotechnology has emerged as a promising approach for the treatment and diagnosis of HCC. Inorganic nanomaterials, known for their biocompatibility and high drug loading capacity, have gained attention in HCC treatment. Examples include mesoporous silica nanoparticles, mesoporous hollow alumina nanoparticles, and graphene oxide. Researchers developed an HA-conjugated and manganese-doped mesoporous silica nanoparticle loaded with isoginkgetin and DOX (HM@ISO@DOX) for HCC treatment [63]. The presence of HA on the surface of HM@ISO@DOX prevents drug leakage and actively targets CD44 on HCC cell surfaces. The nanoparticles degrade in the presence of hyaluronidase, glutathione, H_2O_2, and the weakly acidic TME, enabling responsive drug release. Additionally, the highly reactive Mn ions (Mn^{3+} and Mn^{4+}) in the nanoparticles are reduced to Mn^{2+}, triggering an Mn^{2+}-mediated Fenton-like reaction that generates reactive oxygen species (ROS). These ROS induce autophagic cell death in tumor cells. Compared to spherical nanoparticles, researchers also developed rod-like HA-functionalized Janus magnetic mesoporous silica nanoparticles for the delivery of berberine and DOX [64]. These nanoparticles exhibit stronger magnetic properties, are better internalized by tumor cells, and show enhanced tumor site accumulation, potentially attributed to their unique architecture and reduced interference between components, as well as decreased uptake by macrophages in the reticuloendothelial system.

CD44 is generally considered to be overexpressed in various HCC cells, such as SMMC-7721 cells and MHCC97-H cells. However, the exact expression of CD44 in different HCC cells remains unclear. Recent research has shown that CD44 mRNA expression is almost absent in HepG2 cells but approximately 20-fold higher in Huh7 cells compared to HepG2 cells. Moreover, the uptake of liposomes by these HCC cell types was evaluated, revealing significant differences in the uptake of HA-modified versus unmodified liposomes in Huh7 cells but not in HepG2 cells [65]. Therefore, the use of HA as a ligand in TDDS may not be applicable to HepG2 cells. The therapeutic targeting of CD44 in HCC may have limitations depending on individual patients, and future clinical treatments should consider combining CD44 targeting with individual diagnoses of HCC patients.

3.4. FR-based active targeting

Folate, a vital nutrient involved in DNA replication, is essential for the survival of all living cells, particularly rapidly dividing cells. Folate receptor (FR) is a transmembrane glycoprotein, typically linked by glycosylphosphatidylinositol, with a molecular weight of 38–40 kDa [66]. It mediates the endocytosis of folate and its derivatives. FR exists in three main forms: FR-α, FR-β, and FR-γ. While FR, especially FR-α, is expressed at low levels in most tissues, upregulation of FR expression has been observed in various human solid tumors, including liver, lung, breast, and ovarian cancers. This upregulation serves to meet the folate requirements of rapidly dividing cells under conditions of low folate availability [67,68].

Folic acid (FA), a small molecule ligand for FR, has been widely utilized in the development of targeted drugs for HCC [69–74]. However, none of these FA-modified drugs have been approved for clinical use thus far. FA-modified liposomes have demonstrated efficacy in increasing hepatic uptake compared to non-modified liposomes. However, FA ligands can also accelerate the clearance of liposomes [75]. Plasma proteins in circulation have gained attention as influential factors affecting the efficiency of targeted drug delivery, as they can specifically bind to drug nanoparticles, inactivating targeting ligands or inducing adverse immune responses. IgM, in particular, is considered a key plasma protein that regulates the performance of FA-functionalized nanoparticles in vivo. IgM binding to drug nanoparticles leads to their rapid clearance and enhances uptake by liver macrophages [76]. To prolong the circulation time of FA-targeted drug delivery systems, researchers have modified FA on the surface of SMMC-7721 cell membranes and developed PTX nanocrystal particles (FCPN) coated with SMMC-7721 HCC cell membrane [77]. Compared to other groups, the PTX concentration in the FCPN group decreased more slowly, indicating a longer systemic circulation time. This approach partially overcame the drawback of rapid clearance associated with FA-functionalized nanoparticles. The unique protein composition and homologous aggregation on the membrane surface of SMMC-7721 cells were leveraged to confer stronger targeting ability to FCPN based on FA ligand targeting.

The exploration of FA-modified TDDS remains ongoing. While several drugs have demonstrated good safety profiles in phase I clinical trials, various challenges have emerged in subsequent clinical trials, including adverse events [78] and failure to achieve the desired therapeutic effect [79]. These challenges may be closely linked to factors such as variations in immunoglobulin levels between species. Additionally, the differences among patients are also crucial considerations in the clinical translation of FA-modified TDDS.

3.5. TfR-based active targeting

Transferrin (Tf) is a glycoprotein responsible for iron transport. It is produced primarily in the liver and has a serum half-life of approximately 8 days [80,81]. Tf receptors (TfR) include TfR1 and TfR2, both of which are type II transmembrane glycoproteins. In human HCC cells, the expression of Tf and TfR2 is down-regulated, while TfR1 expression levels are significantly up-regulated [82]. This indicates a potential targeting opportunity for Tf-based drug delivery systems in HCC. Researchers have explored the use of Tf as a targeting ligand in TDDS for HCC.

To investigate the targeting effect of Tf-modified TDDS, Kumari et al. prepared Tf-modified polymeric micelles loaded with Cur (Tf-PPC) [83]. They examined the cellular uptake and cytotoxicity of Tf-PPC in HeLa cells and HepG2 cells, which overexpress TfR, and compared them to NIH-3T3 control cells. The results demonstrated that Tf-PPC exhibited higher cellular uptake and cytotoxicity in the tumor cells overexpressing TfR compared to non-targeted micelles without Tf modification. There was no difference observed between Tf-PPC and non-targeted micelles in NIH-3T3 control cells. This suggests that Tf can act as a targeting ligand in TDDS for HCC.

Researchers have made various attempts to construct Tf-based TDDS. For example, Liu et al. encapsulated carnosic acid in liposomes and modified them with Tf (Tf-LP-CA) [84]. Tf-LP-CA exhibited significant targeting to HCC cells, reduced mitochondrial membrane potential, and promoted mitochondrial-mediated apoptosis of HCC cells. Similarly, Tf-modified liposomes loaded with erianin demonstrated enhanced targeting to HCC cells through Tf receptor-mediated endocytosis [85]. This improved efficacy against HCC by modulating immunity.

Albumin, the major protein component of serum, has been utilized as a drug carrier due to its preferential phagocytosis by tumor endothelial cells via the gp60-mediated endocytosis pathway [86]. Abraxane®, an albumin-bound formulation of PTX, became the first successful albumin-based drug delivery system approved by the Food and Drug Administration (FDA) [87]. However, limitations such as hypersensitivity reactions, side effects, and poor pharmacokinetic characteristics remain. Efforts to develop novel drug delivery systems to improve stability, safety, and pharmacokinetic behavior of drugs are crucial. Ruttala et al. encapsulated albumin PTX/vorinostat nanoparticles within a Tf-modified PEGylated lipid bilayer (Tf-L-APVN) to improve biodistribution and pharmacokinetic characteristics [88]. Tf-L-APVN prolonged circulation time, increased stability, and controlled release of PTX and vorinostat. It effectively reduced the migration capacity of tumor cells and showed excellent synergistic effects in the treatment of solid tumors.

Overall, the utilization of Tf as a targeting ligand in TDDS holds promise for the treatment of HCC. By specifically targeting TfR-overexpressing cells, Tf-based TDDS can enhance drug delivery and improve therapeutic outcomes in HCC treatment.

3.6. Integrin-based active targeting

The integrin family of membrane receptors plays a crucial role in intercellular adhesion, signaling, and cell migration. Integrins are composed of α and β subunits linked by non-covalent bonds, and to date, 24 different combinations of integrins have been identified [89]. These receptors are poorly expressed on normal cells but are highly expressed on the surface of many solid tumor cells and neovascular endothelial cells in tumor tissue [90]. Integrins act as signaling molecules, mechanotransduction molecules, and key components of cell migration [91].

The receptor specificity of integrins is determined by the combination of α and β subunits, and approximately half of the integrin receptors bind to extracellular matrix proteins via the arginine-glycine-aspartate (RGD) tripeptide motif. The RGD sequence was described as a highly conserved minimal integrin recognition sequence within fibronectin [92]. Integrin recognition of their ligands, particularly the αvβ3 integrin, has been extensively explored for targeted delivery in HCC [93–96]. RGD peptides, which specifically interact with integrins, have garnered significant interest due to their excellent targeting ability, non-toxicity, and non-immunogenicity.

Cyclic RGD (cRGD) peptides have emerged as a hot topic in research. They are 30 times more stable than linear RGD peptides within the pH range of 3–7. cRGD peptides with two disulfide bonds exhibit approximately 20 and 200 times greater affinity for integrin αvβ3 compared to cRGD peptides with a single disulfide bond and linear RGD peptides, respectively [97]. Wang et al. utilized cRGD as a targeting ligand to construct tanshinone IIA-loaded nanoparticles (TNPs) [96]. In vivo fluorescence imaging demonstrated that the TNPs primarily accumulated in tumor and liver tissues 2 h after injection. The TNPs significantly extended the lifespan of HCC mice, with a 79.2-fold and 2.5-fold increase compared to the free tanshinone IIA group and the non-targeted nanoparticle group, respectively. Additionally, the TNPs effectively inhibited the development of HCC.

Overall, the specific recognition of integrins, particularly the αvβ3 integrin, with their ligands, such as RGD peptides, holds great potential for targeted delivery in HCC. The utilization of cRGD peptides as targeting ligands improves stability and enhances the affinity for integrin αvβ3, thereby enabling efficient and effective delivery of therapeutic agents to HCC cells.

3.7. Sodium taurocholate co-transporting polypeptide (NTCP)-based active targeting

In 1991, the NTCP gene was cloned for the first time, revealing its role in facilitating the sodium-dependent uptake of mostly bound bile acids by hepatocytes [98]. The specific expression of NTCP in liver tissues is crucial for the enterohepatic circulation of bile acids. Cholic acid (CA), a primary bile acid synthesized in the liver, is biocompatible and non-toxic. Researchers have utilized the liver-targeting properties of CA for the development of TDDS in HCC [99].

Liu et al. synthesized an amphiphilic copolymer of CA linked to monomethyl ether poly (ethylene glycol) and prepared polymeric micelles encapsulating the anticancer drug PTX (PTX/PCTm) and the natural product Bufalin (BF) (BF/PCTm) [100]. The micelles showed higher uptake by HepG2 cells compared to the free drug after 2 h of culture, indicating their enhanced cellular internalization. In vivo imaging also demonstrated the liver-targeting ability of the micelles. The combination of PTX and BF in the targeted micelles exhibited potent tumor inhibition and lower systemic toxicity compared to non-targeted drugs or single-drug targeted formulations. To introduce liver targeting capabilities to poly (lactic acid-*co*-glycolic acid) nanoparticles, Zhang et al. incorporated synthetic poly-[3-(4-vinylbenzonate)-7, 12-dihydroxy-5-cholan-24-oic acid], which actively targeted the liver site [101].

NTCP also serves as a functional receptor for hepatitis B virus (HBV) entry into hepatocytes. PTX-loaded micelles modified with the hepatitis B surface antigen preS1 protein (PTX/PMBN-preS1) were developed for targeted drug delivery to human hepatocytes [102]. After 4 h of administration, the PTX/PMBN-preS1 group exhibited excellent targeting to tumors with 8-fold higher levels of PTX compared to PTX alone. Furthermore, Myrcludex B (myrB), a lipopeptide that specifically recognizes and binds NTCP, has been approved for marketing and inhibits the functional HBV receptor [103]. A team developed liposomes co-modified with TAT peptide, MMP2-cleavable peptide, and myrB (PPP-LIPs) for encapsulation of hydroxycamptothecin (HCPT, a chemotherapeutic agent) and targeted delivery to HCC cells [104]. In vivo imaging and cell uptake studies confirmed the enhanced uptake of PPP-LIPs in the liver and HCC cells, leading to improved antitumor effects compared to commercially available injectable formulations of HCPT.

Although progress has been made in the development of TDDS for HCC, there are limitations, such as the majority of drugs being administered via injection rather than orally. However, CA possesses a unique transport system in the body, making it one of the few carriers for oral liver-targeted drug delivery. Thus, NTCP serves as a key receptor for the study of oral liver-targeted TDDS.

3.8. Glucose regulated protein-78 (GRP78)-based active targeting

GRP78 is a 78 kDa protein that tends to accumulate on the cell membrane of tumor cells [105]. Jiang et al. recently identified GRP78 as a membrane receptor for the HCC targeting peptide SP94 [106]. SP94 is a novel peptide derived from a phage display peptide library and exhibits specific targeting toward human HCC cell lines. The affinity of SP94 to human HCC cells is 10,000 times higher than that to various normal cells, including hepatocytes, endothelial cells, monocytes, B lymphocytes, and T lymphocytes [107]. This high selectivity allows SP94 to distinguish human HCC cells from normal cells and minimize damage to healthy tissues.

SP94-mediated TDDS have demonstrated the potential to enhance anti-tumor efficacy by improving the pharmacokinetic properties and tissue distribution of drugs in vivo, leading to increased drug accumulation in tumors [108]. Nie et al. developed poly (ethylene glycol)-poly (lactic-*co*-glycolic acid) nanoparticles (PEG-PLGA NPs) loaded with cryptotanshinone and modified with SP94 peptide [109]. Due to the significant affinity difference between SP94 peptide for HepG2 cells and normal hepatocytes, PEG-PLGA NPs were able to be actively targeted to HepG2 cells and achieved a 98.8 % uptake rate. Compared with the non-targeted group, PEG-PLGA NPs slowly released cryptotanshinone within 48 h and significantly increased the apoptosis rate of HepG2 cells. The results of in vivo experiments also demonstrated that PEG-PLGA NPs have good targeting effect and anti-tumor activity, and do not cause toxicity to the organism. Another study formed liposomes by self-assembling resveratrol and Cur with lipid materials and modifying the surface of nanoparticles with SP94 [110]. The EPR effect and the highly selective targeting effect of SP94 peptide caused the nanoparticles to aggregate at the tumor site, which did not show any obvious abnormality in the blood and various organs. It further demonstrated the safety of SP94 peptide as a targeted ligand. However, further research is needed to fully explore the potential of SP94 peptide in HCC-targeted drug delivery.

3.9. Specific antigen-based active targeting

Glypican-3 (GPC3) is a proteoglycan expressed at elevated levels in more than 70 % of HCC patients, making it a promising biomarker and target for HCC treatment [111]. Monoclonal antibodies (mAb) such as YP7 have been developed that specifically recognize GPC3 and exhibit high specificity for HCC cells [112]. Researchers have coupled these antibodies with photosensitizers IR Dye700DX® to form antibody-photosensitizer conjugates (APC), and conjugated IRDye800CW® with Nab-PTX to form nanodrugs [113]. APC exerts therapeutic agent activity only in the presence of membrane-bound target cells in the presence of GPC3 and has no effect on adjacent normal cells. Upon exposure to near-infrared light, APC leads to disruption of membranes and necrotic cell death based on the combination of photoinduced ligand exchange and ROS, resulting in a ''super-enhanced permeability and retention'' effect, which leads to a rapid increase in vascular permeability, an approach known as photoimmunotherapy. Photoimmunotherapy allows for the rapid accumulation of Nab-PTX in high concentrations at the tumor site, which is an attractive approach for cancer treatment.

CD147 is a transmembrane glycoprotein involved in various processes in HCC, including invasion, metastasis, and apoptosis. Antibodies targeting CD147 have been incorporated into polymer-based drug delivery systems, such as antibody-drug conjugates (CD147-CPT NPs) [114]. The CD147-CPT NPs actively recognize CD147 glycoproteins overexpressed in HCC cells and accumulate on the tumor surface, responsively releasing CPT in response to the stimulation of high glutathione concentrations in the TME. Similarly, HAb18G/CD147, a member of the CD147 family, is highly expressed in HCC cells and tissues. The HAb18G/CD147 mAb has been used for the treatment of primary liver cancer. Researchers have developed PTX nanoparticles co-modified with HAb18F $(ab')_2$ and a cell-penetrating peptide, resulting in enhanced targeting, improved endocytosis, and significant anti-HCC effects [115].

Programmed cell death ligand 1 (PD-L1) is expressed on the surface of tumor cells and plays a role in immune escape [116]. PD-L1 antibodies have been used to modify liposomes loaded with luteolin (L-PD-SP/Ls) [117]. L-PD-SP/Ls of 159 nm enhanced drug uptake by HCC cells through passive targeting and active targeting with PD-L1 and limited tumor growth by interfering with the mitochondrial pathway of tumor cells. Humanized mAbs targeting programmed cell death 1 and PD-L1, such as nivolumab, pembrolizumab, atezolizumab, and avelumab, have been approved and demonstrated significant antitumor efficacy in clinical applications. These approaches demonstrate the potential of antibody-based targeting strategies for HCC treatment, utilizing specific antigens expressed on the surface of HCC cells to improve drug delivery and enhance therapeutic outcomes.

3.10. TME-based active targeting

TME plays a critical role in tumor development and progression. The TME consists of various cellular and non-cellular components, including tumor cells, immune cells, stromal cells, extracellular matrix, cytokines, and chemokines [118]. Disruptions in the signaling pathways within the TME caused by tumor-secreted cytokines can promote tumor growth.

Neutrophils are an essential part of the innate immune system and have been shown to influence tumor progression. When tumors occur, neutrophils are rapidly activated by inflammation and TME at the tumor site and metastasize to the tumor tissue. Zhang et al. developed neutrophil membrane-coated hypocrellin B nanoparticles (NM-HB NPs) that retain the functionality of neutrophils [119]. These nanoparticles can evade immune clearance and actively accumulate in the TME. In combination with Photodynamic therapy, the enhanced EPR effect also further contributed to the accumulation of NM-HB NPs in the TME, demonstrating significant tumor

suppression by promoting ROS production and inducing mitochondrial dysfunction.

Cancer-associated fibroblasts (CAFs) are a major component of the TME and have emerged as potential therapeutic targets. Hepatic stellate cells can undergo epithelial-mesenchymal transition to become CAFs in HCC. Guo et al. designed cysteine-terminated FH peptide (CFH) modified oxymatrine liposomes (CFH/OM-L) to specifically target CAFs [120]. The high affinity of CFH for tenascin-C, which is overexpressed in CAFs, enables targeted delivery of oxymatrine to CAFs. Moreover, CAFs can competitively phagocytose nanoparticles with tumor cells, creating a favorable environment for deep nanoparticle penetration. CFH/OM-L reprogram the TME by reversing epithelial-mesenchymal transition, inactivating CAFs, promoting M1 tumor-related macrophage polarization, and activating natural killer cells. This strategy inhibits tumor metastasis while preserving the viability of CAFs. These studies highlight the importance of understanding and targeting the cellular and non-cellular components of the TME to develop effective therapeutic strategies for cancer treatment.

3.11. Other receptors-based active targeting

Heat shock proteins (Hsp) are a group of proteins that are upregulated in response to cellular stress and play important roles in cellular processes, immune response, and tumor development. In particular, Hsp70 is highly expressed in HCC tissues [121]. Chakraborty et al. utilized the specific binding affinity of aptamer L5 (TLS9a) to Hsp70 and developed polymeric nanoparticles loaded with PTX functionalized with aptamer L5 (PTX-NPL5) [122]. Compared to the non-targeted drug Abraxane®, PTX-NPL5 showed specific accumulation and retention in the liver of HCC rats, induced apoptosis in HCC cells through the mitochondrial pathway, and exhibited minimal toxicity to normal hepatocytes. This targeted delivery system based on Hsp70 and aptamer L5 demonstrated promising therapeutic effects in HCC.

Another potential target in HCC is Hsp90α. Deoxyelephantopin (DET) has been found to directly bind to Hsp90α and induce mitochondrial dysfunction and oxidative stress in HCC cells [123]. However, the poor solubility and low oral bioavailability of DET limit its clinical application. Developing a targeted drug delivery system using the specific binding properties of DET to Hsp90α could be a promising strategy to overcome these limitations.

Transporters have also been explored as targets for TDDS. Amino acid transporters, which are upregulated in various cancers, exhibit high substrate selectivity and transport capacity. Li et al. synthesized lysine-modified hydroxyethyl starch-HCPT micelles that showed increased accessibility to HepG2 cells and achieved significant tumor inhibition [124].

Mitochondria-targeted drug delivery has gained attention due to the high activity and transmembrane potential of mitochondria in tumor cells [125]. Lipophilic cations, such as triphenylphosphonium, have been used to covalently link anticancer drugs or as probes for targeted delivery to mitochondria [126]. Cur-loaded nanomicelles and nanogels based on triphenylphosphonium have shown promising results in delivering drugs to mitochondria, reducing mitochondrial membrane potential, and promoting apoptosis in HCC cells [127,128]. However, the TDDS based on lipophilic cations designed to target mitochondria is more easily recognized by the reticuloendothelial system and accelerates drug clearance. Wu et al. utilized hydrogen bonding and π-π stacking interactions to enable self-assembly of rhein and DOX to form a negatively charged nanogel, which serves as a therapeutic agent as well as a component of TDDS [129]. In the acidic TME, the rhein-DOX nanogel can undergo charge reversal, and the positively charged rhein-DOX nanogel is more likely to bind to the mitochondrial membrane of tumor cells. Meanwhile, the unique nanofiber network structure of rhein-DOX nanogel coordinates the metabolic differences between rhein and DOX, reduces the cardiotoxicity of DOX, and significantly improves the efficacy of coordinated anti-HCC of rhein-DOX, which results in an in vivo tumor inhibition rate of 79.4 %. These studies highlight the potential of targeting Hsp, transporters, and mitochondria for the development of effective TDDS in HCC treatment.

3.12. Multi-TDDS

The efficiency and specificity of active targeting in TDDS can be limited by factors such as receptor saturation, non-specific distribution, and complexity of TME. To overcome these limitations, multi-targeted drug delivery systems (multi-TDDS) have been investigated, which involve modifying TDDS with multiple targeting ligands. Multi-TDDS often target some common receptors such as ASGPR, FR, and GAR. These systems have shown higher specificity in distribution, stronger anti-tumor effects, and lower toxicities compared to single-TDDS [130–135]. For example, Lac- and FA-modified casein micelles loaded with berberine and diosmin exhibited enhanced uptake by HepG2 cells and superior anti-tumor effects compared to single-targeted casein micelles [136]. Other multi-TDDS, such as protein shell oil nucleated nanocapsules and maltodextrin-ursodeoxycholic acid-based micelles, have also demonstrated improved targeting efficiency and anti-tumor effects [137,138].

However, it's important to note that increasing the number or type of ligands does not always lead to improved targeting and efficacy. In some cases, the interaction between multiple ligands can hinder binding to receptors, resulting in no significant advantage over single-TDDS [139]. Therefore, the design and optimization of multi-TDDS should consider the compatibility and synergy between different ligands. Furthermore, combining active targeting with other properties, such as magnetic response, can enhance the specific accumulation of drugs in the target tissue. For example, Wen et al. coated β-cyclodextrin-cholic acid-hyaluronic acid polymer on Fe_3O_4 graphene oxide to create a system that exhibited both active targeting and magnetic response properties [140]. This system showed significant accumulation of the drug in the liver and achieved remarkable anti-tumor effects.

In summary, multi-TDDS hold promise for improving the efficiency and specificity of drug delivery to HCC. The design and optimization of these systems should carefully consider the interaction between ligands, select appropriate targeting receptors, and explore the combination of active targeting with other beneficial properties to achieve optimal therapeutic outcomes.

4. SDDS

SDDS are designed to control the accumulation of drugs at specific target sites or facilitate their release at these sites using external or internal stimuli (Fig. 4). These stimuli can include magnetic fields, ultrasound, microwaves, pH, and temperature. By relying on external stimuli, such as magnetic fields, ultrasound, and microwaves, or internal stimuli like pH and temperature, SDDS offer a more scientific approach to drug delivery. These stimuli can be precisely controlled, allowing for accurate drug targeting and release at the desired location.

Compared to other drug delivery systems, SDDS have several advantages. They reduce the need for extensive ligand modifications, which can introduce uncertainty and potential side effects. This reduction in modification steps increases the safety and stability of the drug delivery systems. Moreover, the unique properties of stimuli-responsive carriers open up possibilities for combining drug therapy with diagnosis and thermotherapy for HCC. Overall, SDDS offer a scientific and controlled approach to drug delivery, enhancing safety, stability, and the potential for combination therapies in the treatment of HCC.

4.1. Magnetic-responsive preparations

Magnetic-responsive preparations use magnetic nanoparticles as carriers to target and concentrate drugs at the site of disease under the action of an applied magnetic field. Common magnetic nanomaterials include iron oxide, cobalt, nickel, manganese, and metal alloys, which have high magnetic responsiveness, good biocompatibility, and low toxicity. Magnetic-responsive preparations are widely used in biomedical and clinical research as they integrate drug and imaging components in the same drug delivery system, providing both diagnostic and therapeutic functions.

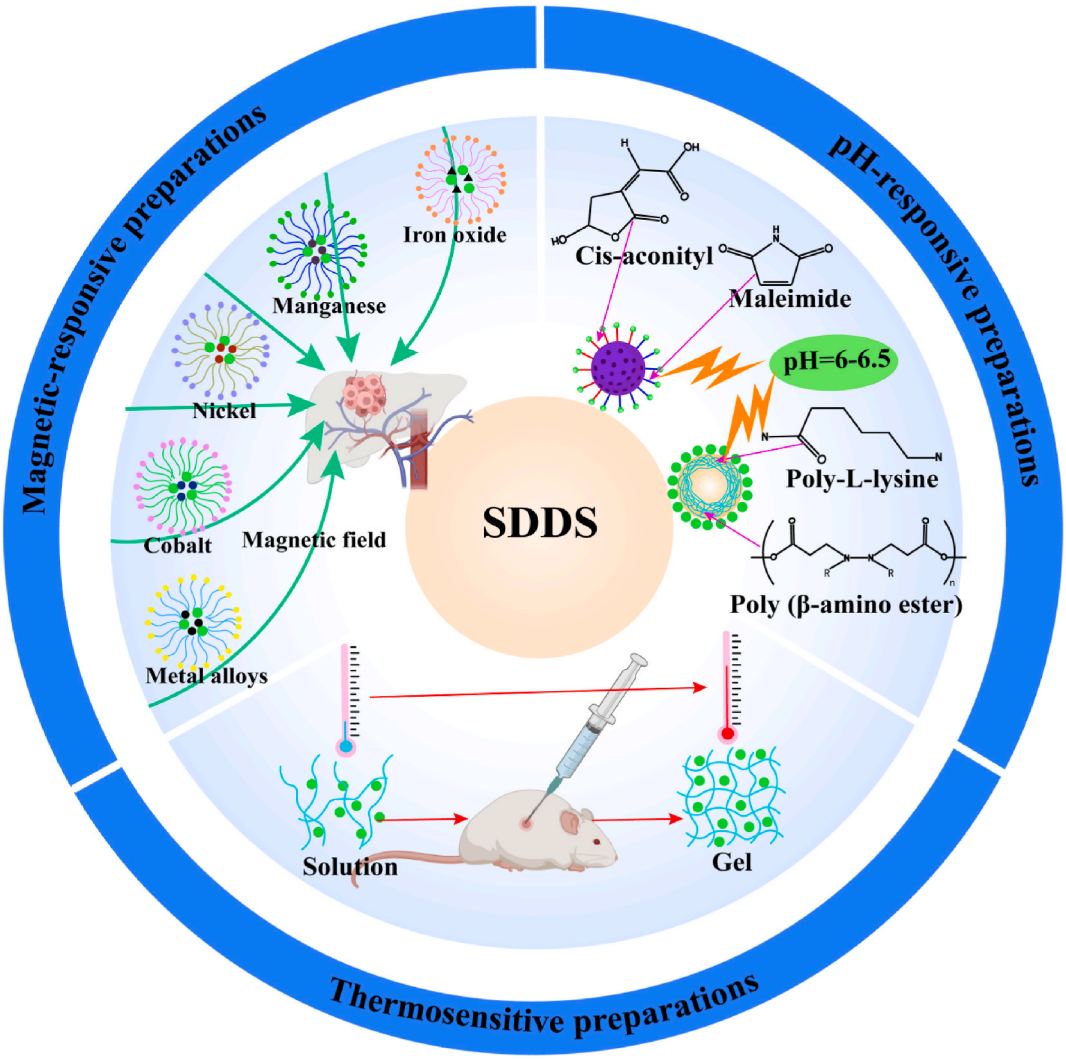

Fig. 4. Schematic diagram of the classification of SDDS.

Iron oxide nanoparticles are the most common magnetic nanocarriers and have been approved by the FDA for the treatment of iron deficiency, cancer diagnostics, and the construction of drug delivery platforms [141]. Superparamagnetic iron oxide nanomicelles loaded with quercetin were prepared using a thin film hydration method [142]. These nanomicelles exhibited aggregation and effectively suppressed the growth of HCC cells when exposed to a strong magnetic field generated by a neodymium-iron-boron magnetic disk. However, superparamagnetic iron oxide nanoparticles have the disadvantages of easily aggregating into nanoclusters, adsorbing proteins in the body, and being phagocytosed by mononuclear phagocytes in a liquid environment. Ibrahim et al. covered magnetic nanoparticles with polyethylene glycol and coated the outermost layer with crocetin to overcome the agglomeration of magnetic nanoparticles, resulting in a smaller magnetic nanoparticle size and greater magnetization strength [143]. In addition, the use of α-ketoglutaric acid-modified chitosan as a coating material for magnetic nanoparticles can also improve the stability of magnetic nanoparticles, prolong the cycle time and control the drug release [144].

4.2. pH-responsive preparations

Weak acidity is one of the most typical microenvironmental features in tumor tissue, with a pH between approximately 6.5 and 6.8, and it is assumed that this weak acidity originates from the accumulation of lactate. Aerobic glycolysis in tumors results in increased lactate production, which is also known as the Warburg effect [145]. In addition, tumor cells also increase sodium-hydrogen exchangers [146], carbonic anhydrase-9 [147], and monocarboxylate transporter [148] to maintain weak acidity, resulting in an extra-tumoral pH between 6.0 and 7.0 and an intra-tumoral pH between 6.0 and 6.5.

The acidic TME is extremely attractive for the construction of drug delivery systems and many acid-unstable linkers have been extensively investigated, such as maleimide, *cis*-aconityl, and hydrazones [149]. Amide bonds have been reported to be used to covalently couple ursolic acid to the surface of silica-based mesoporous nanospheres and to encapsulate ursolic acid inside silica-based mesoporous nanospheres via non-covalent interactions to form a controlled release prodrug delivery system (UA@MSN-UA) [150]. At pH 5.5, UA@MSN-UA was more readily endocytosed by HepG2 cells, and rapid hydrolysis of the acid-unstable amide bond resulted in sustained release of UA@MSN-UA within the first 20 h. Zhang et al. developed a D-α-tocopheryl polyethylene glycol 1000-block-poly (β-amino ester) (TPGS-PAE) polymers nanoparticles ((D + C)/NPs) co-loaded with DOX and Cur [151]. The tertiary diamine fraction of poly (β-amino ester) is protonated in an acidic environment making the (D + C)/NPs pH-sensitive and rapidly releasing co-loaded drugs to inhibit cancer cell proliferation and angiogenesis.

The amine group of poly-L-lysine can be converted to a positively charged hydrophilic amino group under acidic conditions, which adsorbs nanoparticles to negatively charged tumor cell membranes and improves the uptake of Cur by human HCC Hep3B cells through electrostatic adsorption-mediated endocytosis [152]. In addition, the isoelectric point material N-Arginine-N-octyl chitosan reverses amino protonation in an acidic environment, reversing the negative charge on the nanodrug surface to a positive charge, disrupting lysosomes and effectively delivering HCPT to the tumor cytoplasm [153].

4.3. Thermosensitive preparations

Thermosensitive preparations are delivery systems that can sense temperature and release drugs in response. Thermosensitive hydrogels can be applied in the form of a flowing sol and undergo a rapid sol-gel phase change when stimulated by temperature change, which has the characteristics of fixed-point delivery, prolonging the local drug residence time, improving patient compliance, reducing systemic toxicity and side effects.

It has been reported that natural polymers such as collagen, chitosan, and polypeptide agarose, as well as synthetic thermosensitive polymers including poly (N-isopropylacrylamide) and poly (ethylene glycol)-based block polymers, can be modified or utilized as thermosensitive hydrogels [154]. For example, the PTX-loaded polypeptide hydrogel based on poly (γ-ethyl-L-glutamate)-poly (ethylene glycol)-poly (γ-ethyl-L-glutamate) can play a tumor inhibitory role for up to 3 weeks without causing significant organ damage [155]. Peng et al. constructed a thermosensitive injectable hydrogel (embelin/PECT gel) based on poly (ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-undecanone)-poly (ethylene glycol)-poly (ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-undecanone) loaded with embelin [156]. The anti-tumor effect of embelin was greatly improved, such that embelin/PECTgel containing 0.5 mg embelin was comparable to embelin solution containing 6 mg of embelin in HCC mice.

The unsatisfactory performance of single-SDDS in terms of biodistribution and delivery efficiency has led to the emergence of some dual-SDDS, such as thermosensitive magnetic liposomes loaded with HCPT that accumulate at the tumor site and responsively release HCPT in the presence of an external magnetic field and local heating, showing better targeting and antitumor activity, providing a reference for the inefficiency of commercially available HCPT injections [157]. Additionally, Santhamoorthy et al. developed a pH and temperature dual-responsive copolymer hydrogel system for the delivery of Cur using N-isopropyl acrylamide and acrylamide as comonomers [158]. A complete release of Cur was achieved within almost 4 h at pH 5.5 and 40 °C. It also showed good biocompatibility and cytotoxicity on a HepG2 cell line, laying the foundation for drug delivery to solid tumors.

5. Conclusion and perspectives

This paper provides a scientific review of novel TDDS for the treatment of HCC using NMMs. The researchers have designed and prepared various TDDS specifically tailored for HCC treatment, taking into consideration the unique characteristics of tumor pathology, overexpressed receptors on tumor cell surfaces, and the properties of nanocarriers themselves. To achieve more accurate treatment of HCC and minimize adverse reactions on normal liver cells, some researchers have designed various TDDS, which not only

can be specifically internalized by receptor proteins highly expressed on the surface of tumor cells but also possess the ability to degrade and responsively release drugs under special conditions such as enzymes, glutathione, H_2O_2, weakly acidic microenvironment, and hypoxic microenvironment. These TDDS have demonstrated excellent targeting ability for the liver at both cellular and animal levels, improving the therapeutic effects of NMMs while reducing cytotoxicity and side effects caused by non-specific drug distribution. Additionally, they have shown some potential in inhibiting multidrug resistance in HCC cells.

However, the paper identifies several gaps in the current research. While some receptor types on HCC cells have been targeted in TDDS, there are many highly recognized receptors that have not been developed for anti-HCC TDDS loaded with NMMs. These include epidermal growth factor receptor, low-density lipoprotein receptor, fibroblast growth factor receptor, scavenger receptor, mannose receptor, among others. Furthermore, most studies primarily focus on the number of receptors expressed in HCC cells and the affinity between ligands and receptors, with limited research on the effects of ligand-carrier binding sites or the spatial structure of ligands on the ligand-receptor affinity.

Moreover, the current TDDS loaded with NMMs predominantly concentrate on single-ligand targeting. However, individual variations among patients and pathological changes in the target site can significantly impact the number of receptors and the affinity between receptors and ligands, potentially leading to inefficient drug targeting. Therefore, the development of dual- or multi-ligand TDDS is crucial. Some scholars have also proposed the concept of targeted drug carriers loaded with multiple NMMs, akin to traditional Chinese medicine compound prescriptions, which could leverage the synergistic effects of different components against HCC while reducing the likelihood of drug resistance.

NMMs not only exhibit significant efficacy in HCC treatment but their unique structures and complex physicochemical properties also make them potential functional materials for TDDS assembly. Multiple NMMs can form nanoparticles ranging from 10 to 1000 nm through non-covalent interactions such as hydrogen bonding, van der Waals forces, π-π stacking interactions, hydrophobic interactions, electrostatic interactions, and coordination interactions. For example, ursolic acid and lentinan can interact with each other through hydrogen bonding and van der Waals forces to form nanoparticles [159]. The deprotonated sodium salt of rhein and rhein can form self-assembled hydrogels through π-π stacking and hydrogen bonding [160]. Additionally, natural flavonoids can form nanoparticles with photothermal effects by coordinating with Fe^{3+} [161]. This strategy, where NMMs serve as functional materials to construct TDDS, offers improved biodegradability, biocompatibility, and safety compared to synthetic nanomaterials. It holds promise as a novel natural drug nanoparticle carrier to potentially replace artificial nanomaterials.

It is observed that although some targeted drugs effectively accumulate in liver tumor sites, their efficacy is not significantly improved. This could be attributed to drug-loaded nanoparticles entering endosomes upon cellular entry. Endosomes contain various lyases in high concentrations, which can degrade the drug components and diminish the efficacy of the nanoparticles. Thus, the escape of endosomes represents a significant challenge that needs to be addressed. Additionally, when designing TDDS, it is crucial to consider the pharmacological effects of the loaded drugs. For instance, PTX promotes tubulin polymerization and inhibits cell division and proliferation, necessitating its delivery to the cytoplasm for optimal efficacy [162]. Therefore, targeted drugs should possess accurate targeting abilities to ensure cytoplasmic delivery.

In addition, enhancing the immune function of the body and improving the immune response in the TME as a unique advantage of NMMs holds significant promise in combination with TDDS. It has been reported that co-encapsulation of icaritin and DOX in nanoparticles has a synergistic effect in targeted therapy of HCC [163]. Icaritin, as an immunomodulatory drug, enhances DOX-induced immunogenic cell death, remodels the immunosuppressive TME, and triggers a robust immune memory response. The combination of auxiliary immune functions of NMMs with TDDS has become a potential direction for the treatment of HCC. In January 2022, icaritin capsules were approved by the National Medical Products Administration of China as an immunomodulatory agent for the treatment of advanced HCC based on positive results from Phase III clinical trials (NCT03236636, NCT03236649) [164,165], providing significant encouragement for the development of NMMs with auxiliary immune functions.

In conclusion, novel TDDS loaded with NMMs hold great potential for the treatment of HCC. However, to develop an ideal targeted drug, further research on TDDS and exploration of suitable carrier materials, receptors, and ligands are necessary. These efforts aim to provide safe and reliable treatment options for HCC patients.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Guanjie Ji: Writing – review & editing, Writing – original draft, Software, Data curation. **Yue Li:** Software, Formal analysis, Data curation. **Zhiyue Zhang:** Writing – review & editing, Formal analysis. **Hui Li:** Writing – review & editing, Supervision, Resources, Funding acquisition, Formal analysis. **Ping Sun:** Writing – review & editing, Supervision, Resources, Funding acquisition, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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