Review

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Nanomaterials for Targeting Liver Disease: Research Progress and Future Perspectives

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Abstract

Liver disease is a significant global health issue that affects the liver and contributes to approximately 2 million deaths worldwide each year. Although treatment options including surgery and medication are available, effective treatment remains a challenge because of limitations of the traditional drug-delivery methods, such as uneven and nonspecific drug distribution, which lead to negative effects on healthy tissues and a reduction in drug bioavailability. Nanotechnology provides a promising solution for targeted drug delivery to the liver, which has unique anatomical and physiological structures that render it an ideal target for nanomedicine. Several categories of nanomaterials, including inorganic nanomaterials, polymer nanomaterials, and multifunctional nanoparticles (NPs), have been studied as potential agents for targeting this organ in the context of liver diseases. Using surface modification and functionalization, nanomaterials can be selectively targeted to liver tissue or hepatocytes, thus delivering drugs, and enhancing their efficacy while minimizing their side effects. Nanomaterials exhibit numerous benefits; however, their stability and toxicity pose potential risks to living organisms result in adverse effects, such as protein adsorption, and inflammation. Despite the challenges inherent to the development of nanomaterials, ongoing research and development have a great potential for the liver-targeted treatment of liver diseases through the use of nanotechnology. In this review, we first describe the nanomaterials used to target liver diseases, i.e., metallic NPs, ceramic nanomaterials, micelles, polysaccharides, liposomes, dendrimers, carbon nanotubes, and multifunctional NPs. Moreover, the mechanisms for nanomaterials target liver disease are discussed. Finally, this review discusses the current challenges and prospects for future research directions in this field.

Keywords: nanomaterials; liver disease; targeting; drug delivery; treatment

Introduction

Liver diseases, such as hepatitis, cirrhosis, and hepatocellular carcinoma (HCC), represent a notable worldwide health concern. Liver disease is one of the top 10 causes of death worldwide, with approximately 2 million deaths attributed to it every year [1]. The liver is one of the most important organs in the human

body and plays a crucial role in metabolism, detoxification, synthesis, and storage. However, unhealthy lifestyles, environmental pollution, and genetic factors contribute to the growing prevalence of liver disease, rendering it a serious public health problem [2].

Despite the existence of various treatments for liver diseases, such as surgery and medication, the effective treatment of these conditions remains a challenge. Surgical treatment of liver disease may lead to postoperative complications, such as liver failure, bleeding, and infection, which can have negative effects on patient recovery and survival [3]. Although medication for liver disease is safer than surgery, it often has significant side effects, and the traditional drug-delivery methods still have limitations. Using the traditional drug-delivery methods, the drugs are often not delivered specifically to the site of liver disease, leading to an uneven and non-specific distribution of the drugs in the body [4, 5]. Consequently, drugs may have negative effects on healthy tissues, leading to additional side effects, and they may be metabolized or excreted by the liver, which reduces their bioavailability [6]. The development of targeted drug-delivery systems provides a new approach to solving these problems. Nanotechnology has become a promising tool for targeted drug delivery, with the liver being an ideal target in this context [7], because this organ is the main site of drug metabolism and clearance and has a unique anatomical and physiological structure, which allow the effective delivery of drugs [8]. Moreover, by tailoring them to specific types of liver disease, nanomaterials can selectively transport therapeutic agents to particular liver cells, such as hepatic stellate cells (HSCs) in the case of liver fibrosis or hepatocytes in the case of hepatitis B virus (HBV) infection and HCC. A drug-delivery system based on nanotechnology can enhance drug efficacy and reduce toxicity by increasing drug accumulation in the liver and minimizing drug exposure in other organs [9]. Furthermore, they offer remarkable advantages compared with conventional surgery and medicine because of their distinct size and surface characteristics. These attributes encompass: ① shielding the therapeutic agent, especially nucleic acids, against premature degradation; ② averting premature clearance and elimination by the reticuloendothelial system (RES) and the kidneys; ③ diminishing the accumulation of therapeutic agents in non-hepatic tissues, thereby limiting undesirable organ toxicities; ④ encouraging liver-cell-specific penetration and uptake; ⑤ surmounting drug-resistance mechanisms [10–13].

Extensive research is carried out to explore the potential of nanomaterials for targeting liver disease [14]. These materials have the potential to provide improved drug-delivery systems [15, 16], visualization agents [17, 18], and treatment tools [19, 20] for liver disease. Various types of nanomaterials have been studied for targeting liver disease, including metallic nanoparticles (NPs), ceramic nanomaterials, micelles, polysaccharides, liposomes, dendrimers, carbon nanotubes (CNTs), and multifunctional NPs. Superparamagnetic iron oxide nanoparticles (SPIONs) have been developed as a potential therapeutic modality for the treatment of HCC by employing targeted-therapy and hyperthermia-therapy techniques [21–23]. Polymer-based NPs possess an extensive range of applications because of their synthetic flexibility, which enables the precise modulation of their physicochemical properties, including size, charge, and controlled release [24]. Moreover, they are particularly suited for the introduction of surface modifications, such as liver-cell-specific receptor ligands. For targeted intrahepatic delivery, they have been widely employed for this purpose [25]. For example, chitosan-based NPs, which are biodegradable and loaded with chemotherapeutic agents, such as glycyrrhizin and norcantharidin, were embellished with lactose [26] or galactose (Gal) [27] to direct them toward the asialoglycoprotein receptor (ASGPR), which is overexpressed on the membrane of HCC cells. Polymer-based delivery platforms have been studied for the treatment of various liver diseases during these achievements [13]. CNTs have good physical and chemical properties and are widely used for targeted therapy and the imaging of liver cancer [28]. Multifunctional NPs, with multiple functions (such as drug delivery, imaging, and photothermal therapy (PTT)) have also been studied for the treatment of liver cancer [29]. By altering the surface of these materials, targeted delivery can be achieved, thus enabling improved hepatocyte targeting and drug release and minimizing toxic effects. For instance, hepatocyte-specific targeting of NPs can be achieved via surface modification of antibodies targeting HCC cells [30].

Thus, nanotechnology is a promising avenue for developing solutions for targeted drug delivery to the liver. With continued research and development, the use of nanomaterials for liver disease therapy and imaging is poised to revolutionize the field of medicine. In this review, we explored the liver-disease-targeting potential of various nanomaterials, including metallic NPs, ceramic nanomaterials, micelles, polysaccharides, liposomes, dendrimers, CNTs, and multifunctional NPs (Fig. 1). Furthermore, the mechanisms for nanomaterials target liver disease are discussed. Finally, the current challenges, and prospects for future research directions in this domain are considered.

Metallic Nanoparticles

Metallic NPs exhibit unique physical and chemical characteristics in their nanoscale manifestation, in contrast to their bulk form. Investigations of metallic NPs have primarily centered on gold and silver NPs, because of their biocompatibility [31]. Gold NPs have gained a significant attention in biomedical research because of their ease of synthesis, functionalization, and remarkable optical and photothermal characteristics [32]. This type of NP serves as a photothermal agent by inducing local hyperthermia, as a result of their ability to absorb and scatter visible laser light, leading to the eradication of cancerous cells [33]. Furthermore, silver NPs have exhibited a remarkable antimicrobial activity [34]. Biologically synthesized silver NPs, which are known for their biocompatibility, stability, enhanced solubility, and high-yield production without aggregation, have been extensively investigated [35]. Ahmadian et al. [36] concluded that silver NPs may have the potential as a treatment option for HCC based on their *in vitro* study using HepG2 cells, which demonstrated cytotoxic effects and the upregulation of pro-apoptotic factors. Gold NPs are submicron colloidal particles that are typically dispersed in aqueous solutions that have unique properties that make them potential candidates for therapeutic applications. Notably, gold NPs have exhibited antiangiogenic properties by inhibiting heparin-binding growth factors, including bFGF and VEGF165 [37]. Recent studies have shown that sequestering hepatic cancer cells in gold NPs can augment their sensitivity to chemotherapeutic agents, such as cisplatin, doxorubicin (DOX), and capecitabine, thus highlighting the potential of gold NPs as a cancer treatment [38]. In addition, gold NPs are reportedly non-cytotoxic and do not display antiproliferative

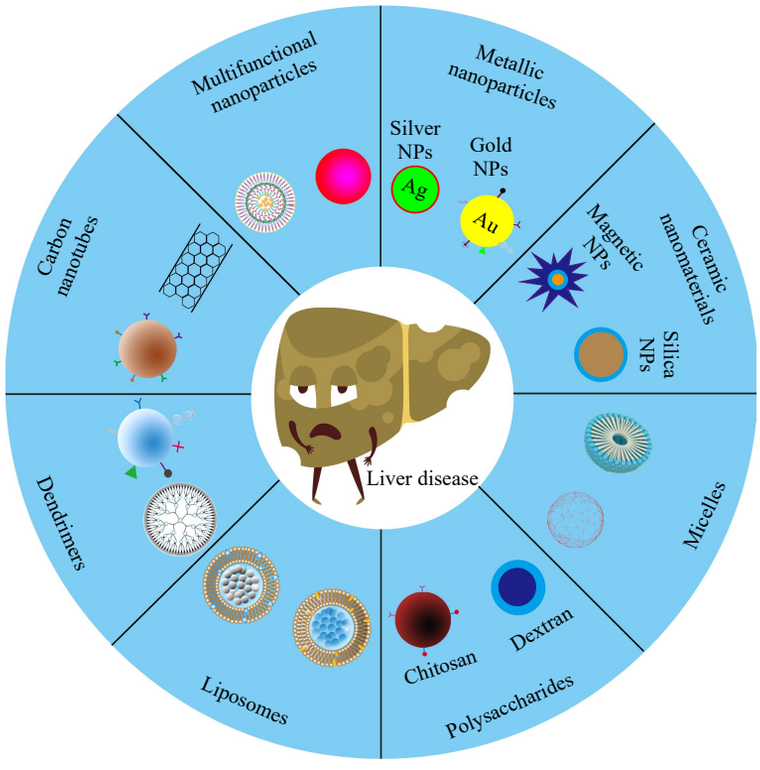

Fig. 1 Schematic diagram of the different NPs that are used to target liver disease and the different effects exerted by them on liver disease.

characteristics when assessed using the Hep3B HCC cell line [39].

Furthermore, metallic NPs hold promise for the early diagnosis of HCC. An extensive body of literature is available on serological biomarkers for the timely diagnosis of HCC [40, 41]. Nevertheless, a restricted number of such biomarkers are currently employed for nano-based detection, thus creating an opportunity to develop systems that can significantly enhance HCC diagnosis [42]. Although alpha-fetoprotein (AFP) remains the primary HCC biomarker and has undergone phase 5 validation, recent studies have identified several other potential biomarkers, such as glypican-3, osteopontin, Golgi-protein 73, and PIVKA [43]. An electrochemical method for detecting AFP has been developed that utilizes an AFP aptamer for detection [44]. This method utilizes aptamers, which are short single-stranded nucleic acids with the ability to bind specifically to targets [45]. The surface of the electrode is enhanced with gold–platinum NPs, to augment its electrical conductivity. It is then layered with reduced graphene oxide, chitosan, and a redox mediator, followed by the integration of AFP aptamers, to provide specificity for the target analyte. Although this technique is moderately sensitive to interference from other proteins, it exhibits an adequate sensitivity to detect AFP at low concentrations [44]. Metallic NPs have been utilized for the electrochemical detection of glypican-3 using two similar methodologies; one technique employed gold NPs [46], whereas the other employed platinum–palladium structures [47]. The electrode surfaces were modified by covalently bonding nanomaterials in the presence of either reduced graphene oxide, hemin [46], or ferrocene [47], as redox mediators. Moreover, the glypican-3-specific aptamer was immobilized by cross-linking. The aptasensor yielded a reduction in the differential-pulse voltammetry oxidation peak of the redox mediator upon introduction of glypican-3, thus allowing detection. Although the platinum–palladium nanostructure method displayed a superior linear correlation coefficient and enhanced stability, it exhibited a lower sensitivity compared with the gold NP approach.

PTT is a novel technique that utilizes photothermal converters to convert light energy into heat, thus inducing local tumor ablation [48]. In the context of HCC treatment, comprehensive investigations have been conducted to address the challenges associated with the selective uptake of photothermal agents by tumor cells, high photothermal conversion efficiency, and excellent biosafety. Metallic and metal sulfide NPs are acknowledged as proficient photothermal agents; however, their biotoxicity can be worrisome. To alleviate this concern, they can be encapsulated, or modified. For example, gold nanorods can be enclosed within nanocapsules composed of either graphene oxide NPs or mesoporous silica shells, to improve their safety and photothermal conversion efficiency [49, 50]. Wen et al. [51] synthesized a hybrid nanomaterial, MGO@CD-CA-HA, by enclosing a polymer consisting of β-cyclodextrin, cholic acid, and hyaluronic acid (CD-CA-HA) into FeO-graphene oxide (MGO), which resulted in a remarkable photothermal conversion efficiency and multi-targeting potential for HCC [52].

Ceramic Nanomaterials

Ceramic materials, mostly consisting of metal oxides, are commonly considered as biomaterials. Ceramic materials mainly comprise silica and magnetite [53]. Ceramic NPs with a porous or hollow configuration have emerged as a propitious replacement for organic systems in several biomedical applications. In particular, magnetite and silica NPs have been extensively investigated as nanocarriers for drug-delivery applications for the treatment of liver cancer. Among them, silica NPs are particularly promising as they possess desirable characteristics for functionalization with diverse groups, thereby facilitating the loading of various anticancer drugs.

Silica NPs have been the subject of intensive examination for various biomedical applications. Nevertheless, it has been observed that crystalline silica NPs can be toxic by leading to chronic obstructive pulmonary disease [54]. In contrast, amorphous silica NPs are extensively utilized in biomedical applications, especially for controlled drug delivery and multimodal imaging [55]. Silica NPs exhibit exceptional characteristics that are favorable for *in vivo* applications [56, 57]. These traits encompass a hydrophilic surface that is conducive to extended circulation, a versatile silane chemistry for surface functionalization, excellent biocompatibility, ease of large-scale synthesis, and

cost effective NP production. Furthermore, mesoporous silica NPs are acknowledged for their precise and regulated size, porosity, morphology, and steadfastness. The distinctive properties of silica NPs render them an excellent contender for drug-delivery applications. The presence of porosity in silica NPs greatly enhances the drug-loading capacity by effectively trapping drugs within the pore channels [58]. In contrast, nonporous silica NPs are also employed in drug delivery and have demonstrated a significant potential in targeted molecular imaging, thereby aiding in early diagnosis. These advances have resulted in their successful translation into human clinical trials [59].

In recent years, various tumor-targeted delivery systems modified with the SP94 peptide have emerged. These delivery systems encompass protocells based on mesoporous silica NPs with supported lipid bilayers [60, 61], bacteriophage MS2 virus-like particles [62], and an HCC targeting probe (99mTc/188Re-HYNIC-SP94) that is utilized for imaging and therapy [63]. The multivalent binding of the SP94 peptide affords a substantially greater avidity for human HCC in contrast with other cell types, such as hepatocytes, endothelial cells, peripheral blood mononuclear cells, B lymphocytes, or T lymphocytes, with a 10 000-fold disparity [64]. The remarkable specificity of the SP94 peptide for HCC, combined with enhanced delivery of multi-component payloads, facilitates a precise discrimination between normal and targeted tissues. Thus, the SP94 peptide is an outstanding model for studying the mechanisms of active tumor targeting [60]. Andreou et al. [65] developed gold NPs coated with silica using a chemical reduction route and a modified Stöber approach, with incorporation of a Raman reporter, to serve as a contrast agent for the intraoperative detection of HCC in mice using the surface-enhanced Raman scattering (SERS) functionality. The deposition of the silica layer was accomplished using a non-toxic method, which prevented the aggregation of NPs. These particles were used to identify HCC by selectively accumulating in non-tumorous regions of the liver, thus providing a clear visualization of tumor margins. The SERS technique exhibited a superior sensitivity and photostability compared with fluorescence methods, and it effectively discerned smaller tumors compared with intraoperative magnetic resonance imaging (MRI). However, the paucity of clinically accessible Raman imaging apparatuses represents a significant drawback of this approach.

SPIONs have been effectively used for both diagnostic [66] and therapeutic [67] purposes. The composition of SPIONs includes a magnetic core encapsulated within a coating agent, thus conferring the ability to be maneuvered via an external magnetic field, thereby demonstrating immense potential for targeted drug-delivery applications. Moreover, because of their superparamagnetic nature, magnetic NPs can function as an effective contrast agent for MRI. Diverse physical and chemical synthesis methods can be employed to produce magnetic NPs, which can subsequently be functionalized with inorganic or organic ligands to enhance their stability [68]. Because of their exceptional stability and versatility, magnetic NPs represent an ideal nanomaterial for drug delivery and diagnosis [69]. An MRI detection approach for HCC has been established using the cytoplasmic expression of AFP and surface glypican-3, which are overexpressed on tumor cells compared with healthy cells. Antibodies against these biomarkers were immobilized on ultra-small SPIONs with a diameter of 5 nm through the establishment of amide bonds, resulting in the formation of modified SPIONs (SAG). These nanomaterials were utilized for MRI of HCC cells and compared with SPIONs that were functionalized only with antibodies against AFP (SA) or glypican-3 (SG), respectively. To examine the accumulation of carriers within tumor cells, Prussian blue staining assays and *in vitro* MRI experiments were conducted. SAG exhibited the highest Prussian blue staining intensity and the greatest reduction in T2 values during MRI, suggesting that dual functionalization is superior in detecting HCC compared with single functionalization. This technique offers significant advantages [66].

Cytokines are a diverse class of signaling molecules that comprise interferons, chemokines, lymphokines, and interleukins, which are vital for regulating the growth and activation of immune cells [70]. More than 200 distinct cytokines have been identified that participate in cell signaling, with specific cytokines, such as interleukin 7 (IL-7) and IL-12, currently undergoing clinical and preclinical evaluations [71, 72]. However, the systemic delivery of cytokines as monotherapies is frequently associated with dose-limiting toxicities, which

hinders the application of unmodified cytokines as a cancer therapy [73]. In response to this drawback, researchers have looked to nanotechnology as a means to enhance the safety, pharmacokinetics, and therapeutic efficacy of systemically administered cytokines, among other parameters. The amalgamation of hyperthermia and gene therapy is founded on the capacity of hyperthermia to trigger immunogenic cell death and improve the transfection of plasmids encoding cytokines, resulting in the localized release of cytokines that can regulate the tumor microenvironment (TME). One of the strategies employed in this context involves the amalgamation of protamine-modified SPIONs, which are capable of inducing magnetic hyperthermia, with plasmids encoding tumor necrosis factor (TNF). Because of the elevated temperature caused by the alternating magnetic field, these NPs exhibited a high transfection efficiency. In a mouse xenograft model of HCC, this nanocarrier yielded favorable and complementary antineoplastic outcomes [74].

Micelles

Micelles are part of the class of amphiphilic colloids that are characterized by a size range of 10–100 nm. These entities consist of two distinct units: hydrophilic and hydrophobic groups that compose amphiphilic/lipid molecules, which then assemble to form micelles [75]. The hydrophobic core of micelles offers protection to drugs against degradation, whereas the hydrophilic shell prevents opsonization. The use of micellar carriers is regarded as a highly auspicious approach to augmenting the solubility of lipophilic compounds while simultaneously extending their systemic circulation time. For instance, in a study aimed at developing a natural anticancer therapy, curcumin (Cur) was conjugated with Gum Arabic (GA), a highly water-soluble polysaccharide, to form nanomicelles. The conjugation of GA with Cur significantly improved the solubility and stability of Cur at a physiological pH compared with its free form. In addition, a cellular internalization investigation revealed that the GA–Cur conjugate effectively delivered the drug to the cytoplasm of HepG2 cells because of the targeted effectiveness of the Gal groups present in GA [76].

The uptake and storage of vitamin A (VA) in HSCs is predominantly mediated by low-molecular-mass plasma proteins known as retinol-binding proteins (RBPS) that facilitate its transport and storage. These proteins are accountable for capturing and retaining about 80% of the VA deposited in the human body. VA, upon its release from HSCs, is first sequestered by RBPs. Subsequently, it binds to RBP receptors situated on the surface of HSCs, which culminates in its internalization and intracellular storage [77]. Hence, VA-modified nanocarriers can be tailored to specifically target the RBP present on the membranes of HSCs, thereby enabling the selective delivery of anti-fibrotic agents to the desired cell population. In a study reported by Qiao et al. [78], a low-concentration method was employed to create core-shell polymer micelles (PVMs) using a VA-modified polymer micelle strategy. These PVMs were then loaded with Silybin and the small interfering RNA-siCol1α1, to generate Silybin/siCol1α1 co-loaded core-shell polymer micelles (CGPVMs). The CGPVMs produced a positively charged surface with a small size and exhibited a negligible cytotoxicity and hemolytic activity *in vitro*. Furthermore, *in vivo* studies indicated that they were well tolerated in mice, without inducing hepatotoxicity, or inflammatory responses. Significantly, the CGPVMs exhibited a remarkable accumulation in the fibrotic liver and specifically targeted the activation of HSCs. Compared with the singular employment of chemical-drug-loaded PVMs (CPVMs) or gene-drug-loaded PVMs (GPVMs), the use of CGPVMs yielded a superior effectiveness in reducing type I collagen synthesis and ameliorating liver fibrosis. Thus, the use of nanocarriers for the co-delivery of chemical and genetic drugs in combined therapy has demonstrated a significant and desirable therapeutic effect, thus offering a promising direction for the future treatment of liver fibrosis.

The use of Pluronics is a noteworthy example of successful micelle assembly for drug-delivery purposes. With a size ranging from 10 to 100 nm, Pluronic micelles are compact and ideal for injection, thereby promoting their accumulation at the liver cancer site [79]. In a specific investigation, a biocompatible and multifaceted nanosystem was synthesized by amalgamating Pluronic F68 with hematoporphyrin (HP) and DOX. This NP system manifested a core-shell nanostructure in which DOX was complexed with HP via intermolecular forces to form the hydrophobic core. The HP/DOX nanocomplex surface was coated with Pluronic F68,

which is a non-ionic amphiphilic triblock polymer composed of a hydrophobic poly (propylene oxide) (PPO) block and two hydrophilic poly (ethylene oxide) (PEO) blocks, thus creating a hydrophilic shell. That study demonstrated that HPDF micellar NPs enhanced the biostability of both HP and DOX, thus leading to improved delivery targeting the tumor site and synergistic effects stemming from the combination of sonodynamic therapy and chemotherapy.

Polysaccharides

Naturally occurring polymers, such as chitosan, and dextran, exhibit a remarkable biocompatibility and multifunctionality, thus allowing a further structural refinement to facilitate the loading of diverse drug types. Chitosan, a linear biopolyaminosaccharide, is derived from the alkaline deacetylation of chitin and is considered to be the second most abundant biopolymer in nature after cellulose [80]. Conversely dextran is a complex branched polysaccharide that has been widely utilized in drug-delivery applications because of its exceptional biocompatibility and multifunctionality. The inherent functional groups situated along the chitosan molecule, particularly the —OH, and —NH2 groups, play a substantial role in conferring its functional attributes and responsiveness to various drug moieties. Moreover, the naturally hydrophilic exterior of chitosan can counteract the phagocytic action of macrophages *in vivo*, thus prolonging its retention time in the blood circulation [81].

Chitosan has wide-ranging applications in the fabrication of hepatoma-targeted NPs with diverse particle sizes, to investigate the *in vitro* and *in vivo* anticancer potency of these nanoconjugates against human liver cancer cells [82]. Their anti-tumor activity in cancerous mice was found to be strongly associated with the size of the generated NPs. The observed correlation can be attributed to the greater capacity of larger NPs for drug entrapment and the preferential uptake of 100-nm particles, in contrast to smaller counterparts by the cells. The low water solubility of chitosan at the physiological pH presents a formidable obstacle in the development of a readily employable form of this agent. As a result, the solutions formed are highly viscous and display a significant chitosan chain aggregation. Low-molecular-mass chitosan has emerged as a viable solution to mitigate the challenges stemming from the poor solubility of chitosan in water at the physiological pH, as well as its high viscosity and pronounced aggregation in drug-delivery applications. The distinctive properties of chitosan have bolstered its adaptability in the realm of drug delivery. In particular, low-molecular-mass chitosan NPs have been synthesized that encapsulated DOX and exhibited a sufficient cytotoxicity against human hepatic cancer cell lines *in vitro* [83]. It is believed that chitosan NPs inhibit HCC by either inhibiting tumor angiogenesis through the inhibition of the vascular endothelial growth factor receptor II [84] or via the stimulation of the p53 pathway [85].

To improve the bioavailability and therapeutic efficacy of Cur, dextran NPs have been utilized as a drug carrier to encapsulate the substance. In HepG2 cells, the NPs exhibited a higher efficacy compared with pure Cur, with cytotoxicity increasing at higher drug concentrations within the dextran NPs. These findings indicate that dextran NPs may represent a safer and more efficient mode of Cur delivery to the liver [86]. In a separate investigation, magnetite NPs were enveloped with a multifaceted bioactive layer using dextran. The dextran sheath acted as a facilitator of the adhesion of crocin, a vital bioactive constituent derived from the stigma of the saffron flower, as a natural medication for HCC. Both *in vitro* and *in vivo* analyses revealed the significant potential of this nanocarrier platform for treating HCC compared with pure crocin molecules [87].

Liposomes

Liposomes are a widely used type of nano drug carrier that comprises one or more spherical or ovoid particles consisting of a lipid bilayer [88]. They have been extensively studied as a nanomaterial for targeting liver disease and have yielded promising results regarding drug delivery [89]. Liposomes can be selectively targeted to liver tissues through surface modification and functionalization [90], thereby increasing drug concentration locally and reducing side effects in other parts of the body. Furthermore, liposomes can modulate the rate and mode of drug release [91], enhance drug bioavailability and stability, and prolong the half-life of the drugs in the body. Liposomes are commonly used for drug

delivery and imaging in studies targeting liver disease [92]. Moreover, specific targeting ligands, such as antibodies [93], nucleic acids [94], and proteins [95], can be attached to the surface of liposomes to achieve a more precise targeting delivery.

The application of liposomes in the treatment of liver disease focuses on two main areas. First, they can be used for targeted delivery to liver tissues or hepatocytes via surface modifications. For instance, surface modifications with antibodies [96] or heparins [97] that target liver cancer cells can achieve targeted therapy against this type of cancer. Second, liposomes can also be used to package and deliver water- and fat-soluble drugs, to improve their efficacy, and reduce side effects. Water-soluble drugs can be encapsulated in the interior of liposomes [98], whereas lipid-soluble drugs can be encapsulated in their bilayer membrane [99]. Recent research has shown promising applications for liposomes in drug-delivery systems targeting liver disease. For example, studies have demonstrated that the encapsulation of drugs targeting HCC in liposomes can increase the concentration of the drugs in the liver and improve their efficacy against HCC [100]. Furthermore, liposomes can be utilized in vaccine preparation to enhance immune efficacy and reduce toxic side effects [101].

In recent years, several research groups have investigated the potential of liposomes for the treatment of acute liver injury. Those researchers achieved this by modifying the surface properties of liposomes to increase their affinity and selectivity toward damaged liver cells. For instance, some teams have successfully attached glycosyl molecules with hepatocyte affinity to the surface of liposomes, which improves their recognition and targeting of damaged hepatocytes [102, 103]. Moreover, Zhang et al. used a cyclodextrin–liposome supramolecular nanocomponent as a treatment for acute liver injury [104]. The results of that study showed that the cyclodextrin–liposome supramolecular nanocomponent has the dual effect of dissolving drugs and removing toxins, thus representing a promising treatment for liver injury [104].

Liposomes targeting hepatitis can be tailored to target hepatitis viruses specifically by incorporating specific surface modifications. For instance, several research teams have successfully conjugated antibodies or oligonucleotide probes with specificity for HBV [105] and hepatitis C virus (HCV) [106] onto the surface of liposomes, thereby enabling them to efficiently recognize and target the viruses present within hepatocytes. In turn, Xu et al. [107] constructed a novel liver-targeted baicalin (BA) liposome to promote the bioavailability and antiviral capacity of this agent. The results showed that apolipoprotein A1 (ApoA1)-modified liposomes (BAA1) significantly enhanced the uptake and specific distribution of BA cells in the liver [107]. Moreover, Lee et al. [108] showed that promethrin-modified liposomes were effective in reducing the viability of activated HSCs, but not of control cells. In three different mouse models of liver fibrosis, intravenous administration of promethazine-modified liposomes significantly reduced the areas of fibrosis. In addition, in a bile duct ligation (BDL) mouse model, treatment with Promelittin-modified liposomes improved overall survival, as shown in Fig. 2.

The surface of HSCs expresses the mannose-6-phosphate (M6P)/insulin-like growth factor (IGF)-II receptor, which is a versatile receptor that modulates cellular growth and lysosomal-targeting functions. Recent studies have indicated that the expression of the M6P/IGF-II receptor is increased on the surface of activated HSCs during liver fibrosis [109]. *In vivo* studies have revealed the capacity of the M6P/IGF-II receptor to specifically detect M6P groups that are integrated into proteins. This trait has facilitated the creation of an M6P-modified nanocarrier platform that selectively delivers anti-liver fibrosis drugs to HSCs. Luk et al. [110] formulated liposomes comprising 18β-glycyrrhetinic acid that were subsequently modified with M6P and human serum albumin (HSA). Subsequently, these liposomes were administered to Wistar rats displaying CCl4-induced liver injury. Rats treated with M6P-HSA loaded with 18β-glycyrrhetinic acid exhibited noteworthy reductions in serum indices of liver injury, such as glutamic-pyruvic transaminase (ALT) and glutamic-oxalacetic transaminase (AST), as well as liver fibrosis compared with those treated only with 18β-glycyrrhetinic acid. Furthermore, Sirius red staining revealed a marked improvement in collagen deposition within the liver tissue, indicating a significant reduction in the degree of liver fibrosis in the model rats. It has been postulated that liver injury triggers the activation of the Hedgehog signaling pathway, thereby stimulating the transdifferentiation

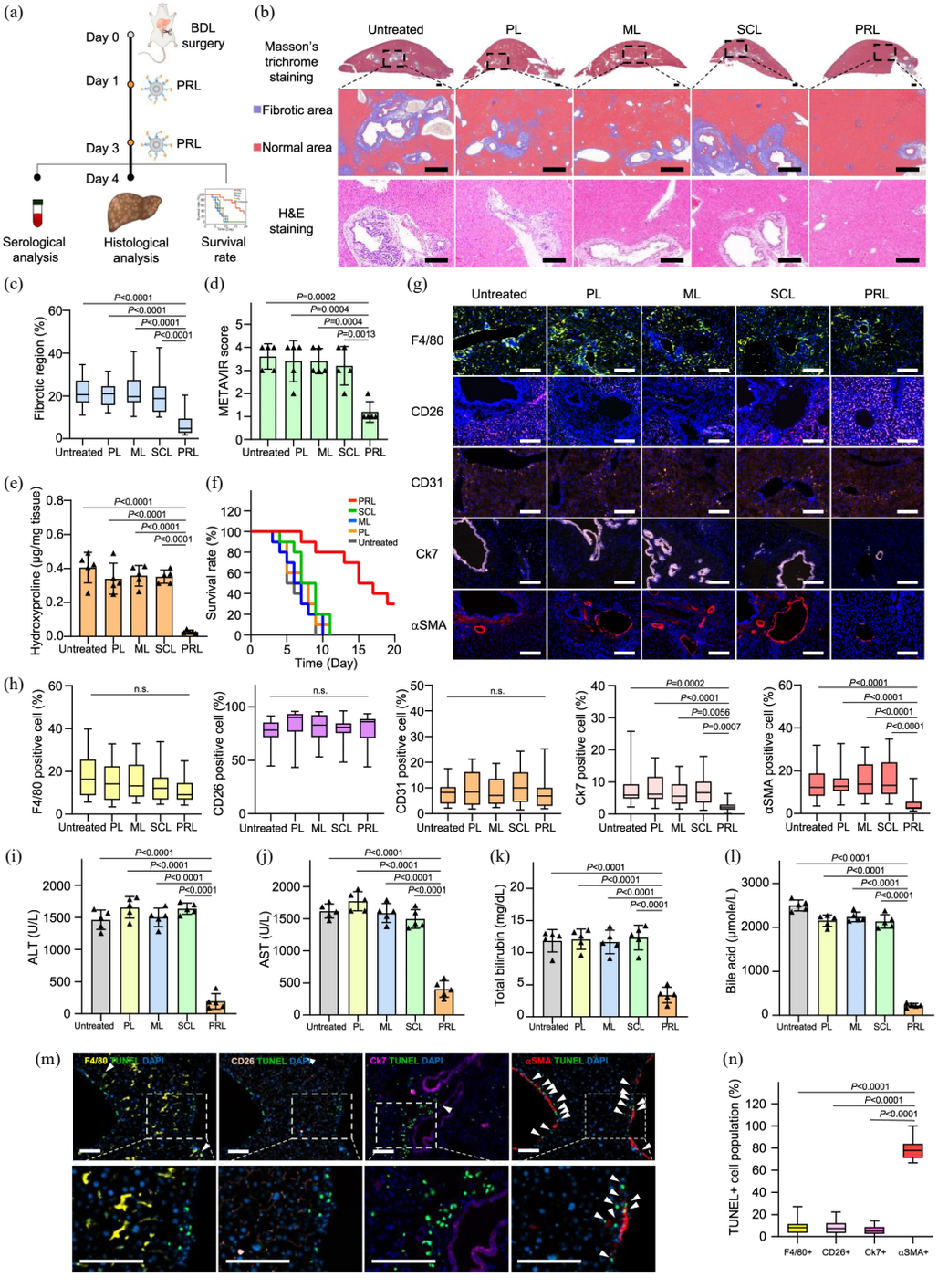

Fig. 2 (a) On days 1 and 3 after BDL surgery, mice were intravenously administered 1 mg/kg of the different drug-loaded liposomes. On day 4, liver tissues were extracted, and further analyzed. **(b)** The top panel shows representative Masson's trichrome-staining in BDL-induced fibrotic liver. The lower panel shows pseudocolored images obtained by InForm 2.2.1 analysis, distinguishing fibrotic regions (blue) from normal tissue (red). The bottom panel shows representative H&E staining in BDL-induced fibrotic liver treated with various liposomes. Scale bar: 50 μm. **(c)** Quantification of the connective tissue area, as calculated from whole images of the stained liver based on five randomly selected fields per sample. Significant differences were assessed using a one-way ANOVA with Tukey's test. In the box plots, the boxes indicate the 25th–75th percentile with the median, and the whiskers indicate the minimum–maximum range. **(d)** Severity of the liver fibrosis in each group, as assessed using the METAVIR scoring. Significant differences were assessed using a one-way ANOVA with Tukey's test. The results are presented as the mean ± S.D. **(e)** Collagen content of fibrotic liver samples, as measured using hydroxyproline assays. Significant differences were assessed using a one-way ANOVA with Tukey's test. The results are presented as the mean ± S.D. **(f)** Survival rates of mice with BDL-induced disease after treatment with the various liposome formulations. **(g)** Mice with BDL-induced disease were treated with various liposomes. One day after the administration of the last dose, liver tissues were frozen-sectioned and stained with antibodies against F4/80 (for macrophages), CD26 (hepatocytes), CD31 (endothelial cells), Ck7 (cholangiocytes), and αSMA (aHSCs) [108]. Copyright © 2022, Nature Research.

of HSCs into active myofibroblasts. Nevertheless, the utilization of smoothened inhibitors has been demonstrated to effectively impede this pathway, thereby affording hepatoprotection. Chai et al. [111] have recently shown the efficacy of arginine-glycine-aspartic acid (RGD)-labeled liposomes loaded with oxymatrine (OM) in targeting and suppressing HSC activation, by leading to apoptosis, and ameliorating carbon tetrachloride-induced liver fibrosis. Rats with fibrosis that were treated with OM exhibited a noteworthy decrease in serum alkaline phosphatase levels compared with the group that did not receive the treatment. Moreover, the expression of genes related to fibrosis, such as matrix metalloproteinase-2 (MMP-2), tissue inhibitor of MMP-1, and type I procollagen, was significantly downregulated. These experimental results imply that the effectiveness of OM in enhancing HSC viability and apoptosis was augmented by RGD. In turn, Du et al. [112] conducted an independent study to examine the targeting ability of a novel drug carrier consisting of sterically stable liposomes modified with the cyclic peptide RGD in relation to recombinant human interferon (IFN)-α1b in BDL rats subjected to biliary tract ligation. Upon incubation with HSCs or hepatocytes, the cyclic peptide RGD displayed selectivity for binding to activated HSCs. Moreover, liposomes modified with RGD exhibited an approximately 10-fold greater accumulation in HSCs obtained from BDL rats than did unmodified liposomes. The localized administration of a cyclic peptide-containing RGD sterically stable liposome (CRGD-SSL) resulted in a marked reduction in HSC proliferation compared with the BDL control group. Furthermore, there was a significant downregulation of the mRNA expression of type I and type III collagen. Serum liver function indices, including ALT, and AST levels, were decreased in the model rats. These findings demonstrated that CRGD-SSL is a potent drug carrier that selectively targets activated HSCs and significantly enhances the efficacy of drug therapy for liver fibrosis. In summary, this liposome preparation provides a novel method for targeting drug carriers in the treatment of liver fibrosis, and exhibits potential for clinical application.

Liposomes can be further targeted to liver cancer tissue through surface modification, which increases drug concentrations in the liver cancer tissue and reduces side effects in other parts of the body. It is widely recognized that ASGPR is highly expressed on the membrane of liver cells, with a density of 500 000 ASGPRs per liver cell, thus surpassing its expression in other tissues [113]. ASGPR exhibits a cluster effect in recognizing structures that contain Gal or acetylgalactosamine groups, thus showing a specific recognition ability [114]. Hence, NPs carrying drug payloads or biomolecules that are engineered with Gal and acetylgalactosamine show promise for achieving hepatic targeting and mitigating toxicity in non-targeted tissues [115]. Cur has been reported to be capable of inducing apoptosis in cancer cells through the lysosomal pathway. Nevertheless, its low selectivity constrains its utilization in the treatment of HCC. Because of the lysosome-targeting ability of morpholine groups, Gal, morpholine groups, and Cur have been incorporated into a low-toxicity dual-targeting liposome. For example, Wang et al. [115] prepared Gal-morpholine-modified liposomes (Gal-Mor-LPs) loaded with Cur and compared them with conventional liposomes (LPs) and Gal-modified liposomes (Gal-LPs). Their findings revealed that the hepatic-targeting capabilities of the liposomes *in vitro* and *in vivo* adhered to the sequence of Gal-Mor-LPs > Gal-LPs > LPs. The internalization of Gal-Mor-LPs was competitively suppressed by Gal, thus providing evidence that Gal-modified liposomes enter liver cancer cells through a pathway mediated by the ASGPR. Gal-Mor-LPs exhibited a superior lysosome-targeting efficacy compared with LPs and Gal-LPs because of the attraction of the acidic lysosomes to the basic morpholine group in Gal-Mor-LPs. The *in vivo* tumor-suppressive effect of the preparations followed the trend of Gal-Mor-LPs > Gal-LPs > LPs > free Cur, thus verifying the capacity of liver and lysosome dual-targeting carriers to increase the anti-tumor potency of Cur. Moreover, *in vivo* studies showed that Cur -loaded liposomes modified with Gal and morpholine segments exhibited an excellent biocompatibility.

Liposomes represent the most clinically advanced non-viral gene-delivery system, with the approval of ONPATTRO by the US Food and Drug Administration and European Medicines Agency in 2018 for treating hereditary transthyretin (TTR)-mediated amyloidosis, which is a liver disease [116]. Consequently, ONPATTRO has become the first liver-targeting nanomaterial to gain regulatory approval. Several liposomal drugs for liver diseases have advanced to clinical trials, in addition to those

already in clinical use. SMARTICLES® are amphotericliposomescomposedofamixtureofpalmitoyl oleoyl phosphatidylcholine, DOTAP, 1, 2-dimyristoylglycerol-3-hemisuccinate, and cholesterol. MTL-CEBPA, the first SMARTICLES® drug under clinical investigation, delivers a small activating RNA (saRNA) to enhance the expression of the transcription factor and tumor suppressor CCAAT/enhancer-binding protein-alpha (CEBPA) for the treatment of HCC [117]. A phase I clinical trial is currently in progress (NCT02716012). BMS-986263, a retinoid-conjugated lipid NP, carries the HSP47 siRNA and is designed for the treatment of hepatic fibrosis by targeting HSCs [118]. Its formulation consists of a cationic lipid (*O*,*O*′-ditetradecanoyl-*N*-(α-trimethylammonioacetyl) diethanolamine chloride (DC-6-14), which facilitates nucleic acid binding), as well as cholesterol and DOPE (at a 4:3:3 molar ratio). BMS-986263 is presently undergoing a phase 2 clinical trial (NCT03420768) targeting patients with advanced liver fibrosis [119]. Although liposomal drugs that undergo clinical trials may appear promising, not all of them progress to clinical use, and some fail in clinical trials. An example of this is the use of SMARTICLES® technology to deliver the tumor-suppressing microRNA-34 (MRX34) for human HCC therapy [120]. Despite the fact that this phase 1 trial (NCT01829971) provided proof-of-concept evidence for microRNA-based cancer therapy, it was prematurely terminated because of serious immune-mediated adverse effects, which resulted in four deaths [23]. Celsion performed a phase 3 trial (NCT02112656) evaluating the efficacy of ThermoDox® (a thermosensitive liposomal formulation of DOX) combined with radiofrequency ablation (RFA) as a treatment for HCC. However, in February 2021, the company declared the termination of the study as there was no "convincing evidence or rationale to warrant further monitoring of patients for overall survival." [121]

Dendrimers

Dendrimers are highly branched and three-dimensional macromolecules that have a vast array of promising applications in the field of nanotechnology. In the context of nanomaterial research for liver disease, dendrimers present an attractive option. Unlike liposomes, dendrimers can be customized to achieve a better targeting by modifying their surface chemical functional groups. By altering their structure and surface modifications, dendrimers can be optimized for improved hepatocyte targeting and drug release [122]. For instance, studies have demonstrated that the introduction of specific functional groups, such as phosphate [123], cysteine [124], or glucose [125] groups, can enable dendrimers to target hepatocytes. Several studies have demonstrated that dendrimers can be targeted to the liver by being taken up by hepatocytes [126]. This targeting can be achieved through chemical modification of the dendrimer's surface. In addition, several studies have shown that dendrimers can be stabilized in the liver and can gradually release the drug over time [127]. This release behavior can be modulated by the cavity structure located within the dendrimer.

Dendrimers offer the ability to precisely target and treat hepatocytes through controlled branching structures and surface chemical modifications. For instance, researchers can incorporate targeting molecules, such as antibodies, onto the surface of dendrimers to enable the selective recognition and treatment of HCC cells [128]. Dendrimers achieve a high affinity for the diseased area by exploiting their specific structure and chemistry, with a highly branched three-dimensional structure that provides a large surface area to increase their affinity for targeting cells. Materials such as polylactic acid (PLA) can afford a high affinity and good biocompatibility with diseased tissues via the variation of their molecular mass and chemical modifications [129]. Moreover, the large molecular size and high surface area of dendrimers allow them to carry more drugs, to improve treatment efficiency. The modification of the structure and surface chemistry of dendrimers has been shown to yield a better hepatocyte targeting and drug release [130], thus further enhancing their potential as a targeted drug-delivery system. Dendrimers [131] can be used for targeted delivery by binding to receptors or ligands located on the surface of the target cells via the multiple functional groups present on their branched structure. For example, when a Gal molecule is modified on the surface of a dendrimer, it can bind to the ASGPR on the surface of hepatocytes, thus enabling targeted delivery to hepatocytes [132]. Furthermore, dendrimers can achieve a precise targeted delivery through molecules such as targeted ligands and antibodies that bind to receptors in the

diseased region of the liver.

Hołota et al. [133] mixed carbosilane copper metal dendrimers containing chloride ligands and nitrate ligands with the commercially available conventional anticancer drugs DOX, methotrexate (MTX), and 5-fluorouracil (5-FU), respectively, to form a possible therapeutic system for liver cancer cells. DOX, MTX, and 5-FU are more effective against HCC cells when coupled with copper metal dendrimers. This combination significantly reduced HCC cell viability compared with that observed for non-coupled drugs or dendrimers (Fig. 3(a)). In turn, Grześkowiak et al. [134] designed a platform based on photothermally active polydopamine (PDA) NPs for loading chemotherapeutic drugs and targeting cancer cells. These NPs exhibit a high efficacy for near-infrared photothermal conversion and allow the loading of drugs that inhibit the growth of cancer cells when specifically targeted for release (Figs. 3(b)–3(h)).

Carbon Nanotubes

Carbon nanotubes (CNTs) are a type of nanomaterial composed of carbon atoms that possess unique electronic, mechanical, and optical properties. Because of their excellent biocompatibility and biodegradability, they are widely used in the biomedical field, particularly for the targeted therapy [135] and imaging of liver diseases [136]. CNTs have emerged as a promising nanomaterial for the passive targeting of hepatocytes because of their high specific surface area and reactive surface groups. The negative charge of CNTs also enables them to adsorb cationic substances and form complexes that can be targeted to the diseased liver tissue [137]. CNTs offer the advantage of achieving targeted delivery to hepatocytes via surface modification, as well as the release of therapeutic drugs using various labeling techniques, such as fluorescent [138] and nucleic acid [139] labeling. Previous studies have shown that CNTs can effectively deliver anticancer drugs and generate a thermal effect upon irradiation with near-infrared light, leading to an increased inactivation of liver cancer cells [140]. Moreover, the use of CNTs for targeted therapy reduces adverse effects and enhances drug efficiency, rendering them a promising option for liver cancer treatment [141].

CNTs have been extensively researched for their potential applications in targeted liver disease therapies [141], imaging [142], and local thermal therapy [143]. For targeted therapy, the surface of

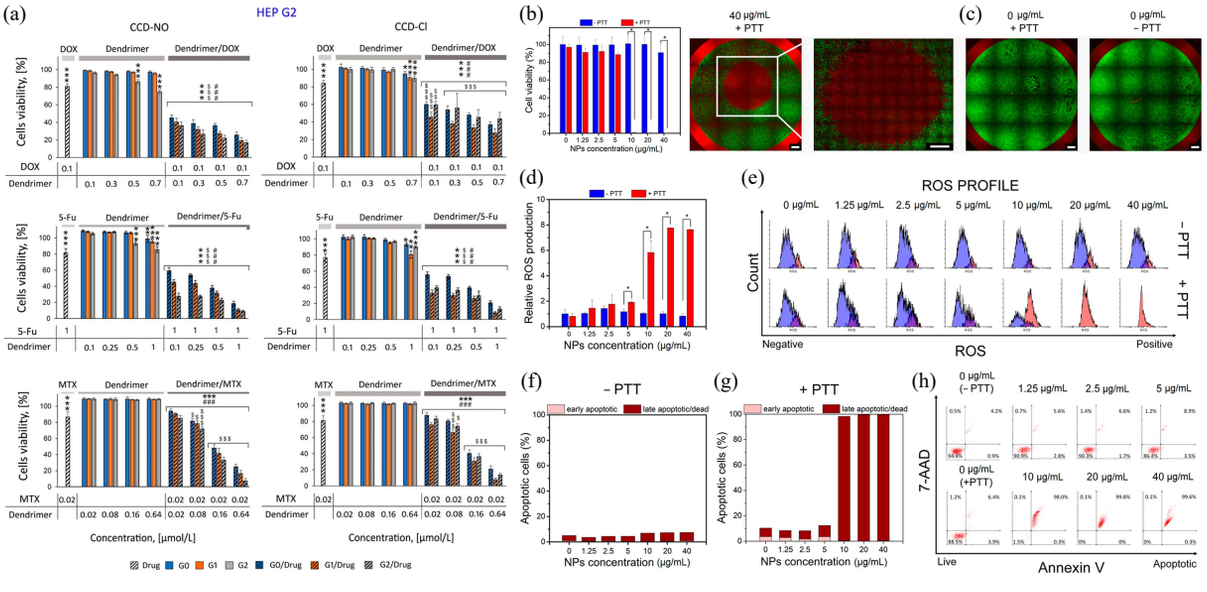

Fig. 3 (a) Cytotoxicity profiles of anticancer drugs, copper dendrimers, and their (dendrimer/drug) complexes toward HEP G2 cells. MTT assay: incubation time, 72 h in phosphate saline buffer (10 mmol/L, pH = 7.4). The results are the mean ± SD from a minimum of three independent experiments. Statistically significant differences vs. the control: * $P < 0.05$, ** $P < 0.01$, *** $p < 0.001$; vs. the free drug: \$ $P < 0.05$, \$\$\$ $P < 0.001$; and vs. the free dendrimer: ### $P < 0.001$ [133]. Copyright © 2023, MDPI. Viability assay of HepG2 cells after 5 min of heat treatment in the presence or absence of different concentrations of PDA-loaded NPs ((b)–(h)). **(b)** Results of the WST-1 cell viability assay. **(c)** Fluorescence microscopy images; Calcein-AM staining of live cells (green); PI staining for dead cells (red). Scale bar, 1000 μm. **(d)** Relative reactive oxygen species (ROS) production and **(e)** ROS profiles evaluated by flow cytometry (blue: ROS-negative cells; red: ROS-positive cells). **(f, g)** Percentages of cells in different phases and **(h)** apoptosis profile evaluated by flow cytometry. Statistically significant differences are indicated by an asterisk (*) for $P < 0.05$ [134]. Copyright © 2021, MDPI.

CNTs can be chemically modified with specific molecules that target hepatocytes. For instance, by modifying the surface receptors of CNTs, they can be directed toward the receptors located on the surface of cancer cells, thus enabling the targeted treatment of liver cancer [144]. In imaging, CNTs possess unique optical properties that can be used for liver cancer imaging [145]. By introducing fluorescent dyes or metals on the surface of CNTs, they can emit specific light signals in the infrared and near-infrared range, which can be utilized for imaging liver cancer. CNTs can also serve as a local thermal therapy for liver cancer by converting infrared light into thermal energy based on their excellent photothermal conversion properties [146]. Therefore, CNTs can be used not only as drug carriers for targeted therapy, but also as potential candidates for local heat therapy for liver cancer.

Several studies have demonstrated that CNTs have potential as biomarker probes for diagnosis and monitoring of liver diseases [147]. Moreover, they can be utilized for PTT in the context of treatment of liver disease, where the near-infrared light absorption by CNTs generates thermal effects that destroy liver cancer cells [140]. Hu et al. [148] developed a sensitive and specific multiplex immunoassay for the HCC, AFP, and Golgi protein 73 (GP73) biomarkers. Horse radish peroxidase and alkaline phosphatase were modified with click chemistry reactive groups, followed by self-assembly to form the enzyme aggregates HRPn and ALPn. CNTs were coupled to the enzyme aggregates and biomarker detection antibodies via a bio-orthogonal reaction, to form immunosensors for AFP and GP73, respectively. The nanosensors were highly characterized for the biomarkers of HCC, and their sensitivity could be adjusted according to practical needs, as shown in Fig. 4.

Multifunctional Nanoparticles

Multifunctional NPs have gained interest as a promising approach for the treatment of liver disease, and various types of NPs are under investigation for this purpose. Multifunctional NPs targeting liver disease, with functions such as drug delivery [149], imaging [150], and therapeutic monitoring [151], have emerged as a hot topic in nanomedicine

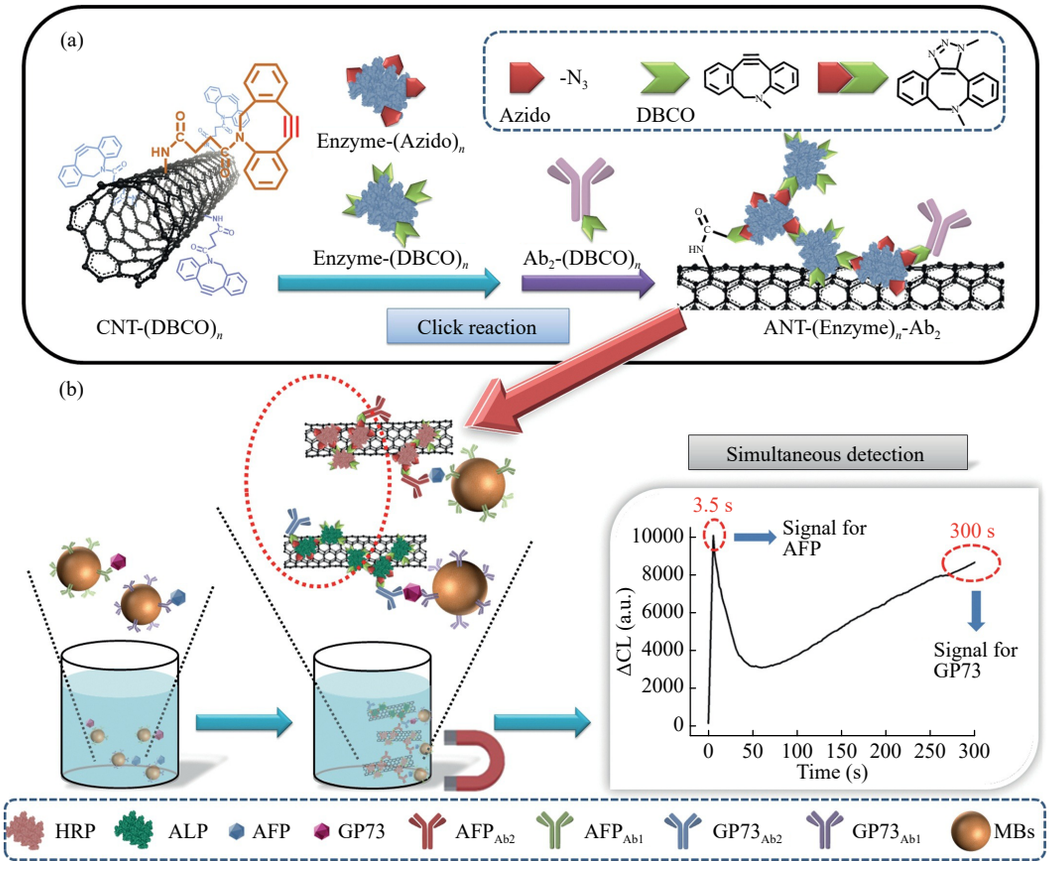

Fig. 4 Principle behind **(a)** the preparation of the nanosensors and **(b)** the simultaneous detection of AFP and GP73 [148]. Copyright © 2021, Elsevier.

research. The *in vivo* behavior and effects of multifunctional NPs in targeting liver disease are affected by several factors, including their size, shape, surface modifications, charging properties, and constituent materials [152]. These factors play a significant role in the biodistribution, metabolism, and toxicity of NPs *in vivo*. Furthermore, appropriate surface modifications can significantly improve the biocompatibility and targeting of NPs *in vivo*. For example, glycosylated surface modifications can enable the recognition of the particles and their uptake by Kupffer cells in the liver, leading to liver-targeted delivery [153]. However, the effects of multifunctional NPs *in vivo* are mainly related to their toxicity and immunogenicity [154]. Toxicity is one of the major limiting factors of the application of NPs, as excessive toxicity may lead to side effects and adverse reactions. Multifunctional NPs may cause adverse effects *in vivo*, such as inflammatory reactions, immune responses, and liver damage [155]. Therefore, it is crucial to assess the safety of multifunctional NPs to minimize their potential side effects and ensure their clinical translation.

The use of multifunctional NPs in the treatment of liver disease has gained a significant interest in recent years because of their unique properties. Multifunctional NPs are composed of multiple materials with multiple functions and applications, thus offering benefits such as strong targeting, easy control of drug release, and low side effects. Moreover, they have been widely studied in the field of nanomedicine for targeting liver diseases. Researchers have successfully functionalized and surface-modified multifunctional NPs to achieve a selective targeting to liver tissues and hepatocytes for the treatment of liver diseases. For instance, several multifunctional NPs can be targeted to diseased liver tissues by selectively targeting receptors on the surface of hepatocytes through receptor-mediated endocytosis [156]. Multifunctional NPs can also be used to treat different types of liver diseases by carrying different types of drugs, genes, or photosensitizers. Promising results have been reported, including the successful piggybacking of multifunctional NPs on chemotherapeutic drugs to treat liver cancer, with good anti-tumor effects and less toxic side effects [134]. Furthermore, multifunctional NPs have been used to treat liver diseases such as liver fibrosis via the piggybacking of genes [157]. Researchers are currently proposing multifunctional NPs with multiple therapeutic functions, which are expected to be an effective tool for the treatment of liver diseases in the future.

Multifunctional NPs are nanomaterials that possess multiple functions, which allow them to achieve multiple therapeutic effects simultaneously when targeting liver disease. These NPs perform the following key functions. ① Targeting: using surface modification and functionalization, multifunctional NPs can achieve a selective targeting of liver tissues and hepatocytes, thus enhancing the drug's local efficacy [158]. ② Drug carrier: multifunctional NPs serve as drug carriers by encapsulating the drug inside the particle, thereby enabling targeted drug release and reducing side effects in other tissues [159]. ③ Detection: these NPs can function as diagnostic or imaging agents for detecting or imaging liver disease and providing treatment options [160]. ④ Therapeutic response monitoring: multifunctional NPs can respond to the environment or detectors via changes in their morphology or structure and the translation of this response into a signal that controls drug release, thus facilitating therapeutic response monitoring and adjustment [161]. The research on multifunctional NPs for targeted liver disease therapy has experienced a significant progress. For instance, researchers have developed a multifunctional NP with a modified receptor on its surface for targeting the liver and encapsulating a therapeutic drug for liver cancer [162]. These particles can target liver cancer tissues precisely while releasing the drug and minimizing damage to other tissues. Moreover, these multifunctional NPs can be targeted and monitored using techniques such as MRI [163]. He et al. [164] constructed multifunctional NPs using poly(lactic acid-ethanolic acid)-ε-polylysine (PLGA-EPL) carriers for the co-delivery of 10-hydroxycamptothecin (HCPT) and apoptotic plasmid for the synergistic treatment of HCC. The multifunctional NPs exhibited a good targeting ability, as demonstrated by flow cytometry and confocal scanning laser microscopy analysis (Fig. 5).

Mechanisms Underlying the Targeting of Liver Disease by Nanomaterials

The mechanism for nanomaterials target liver disease is based on their specific properties and functions. Via appropriate surface modifications and

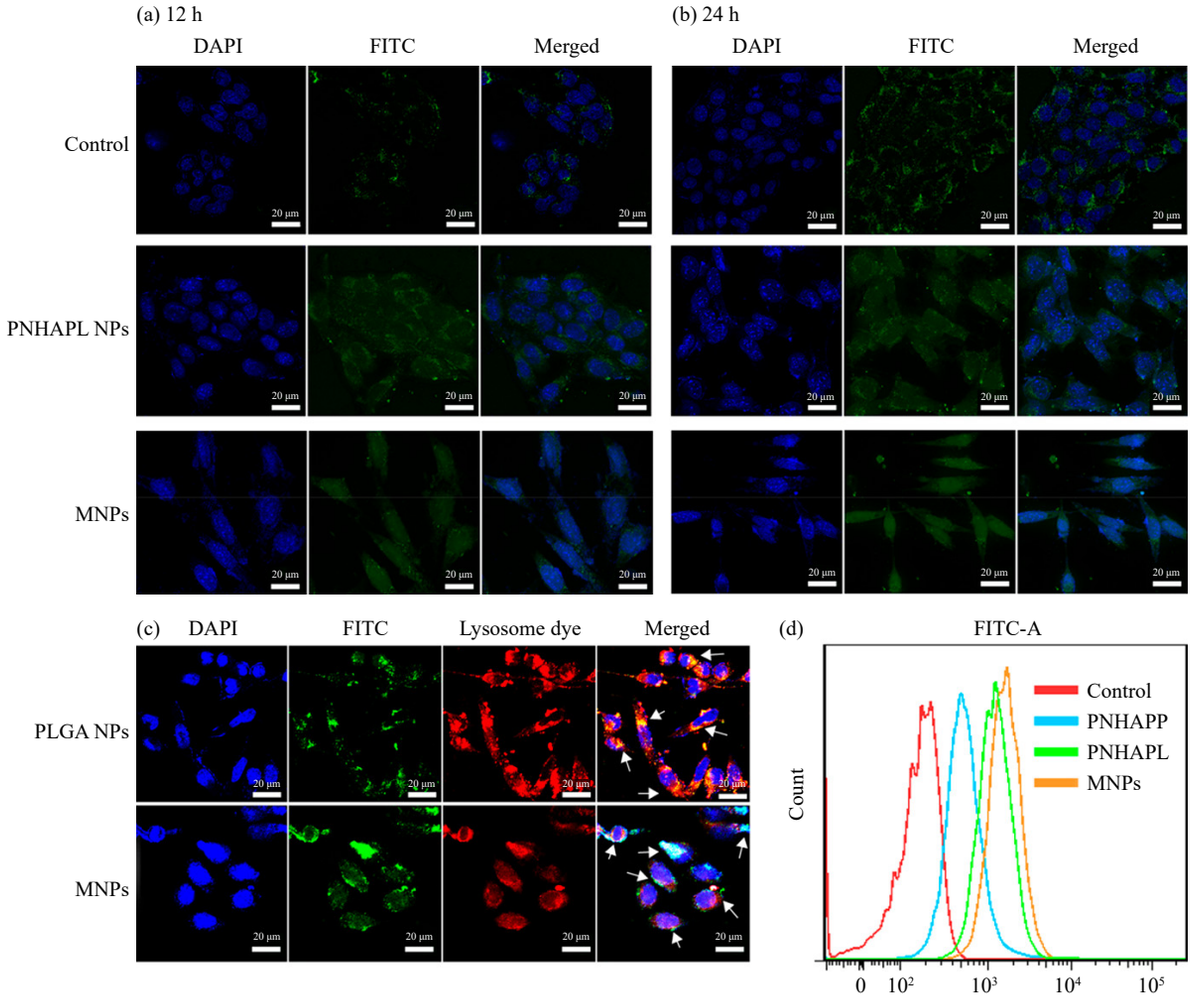

Fig. 5 Confocal laser scanning microscopy images of Hepa1–6 cells after incubation with PLGA NPs, PNHAPL NPs, and multifunctional NPs for **(a)** 12 h and **(b)** 24 h. **(c)** Confocal laser confocal images obtained after lysosomal staining of Hepa1–6 cells using a lysosome staining kit. **(d)** Flow cytometry of Hepa1–6 cells incubated with PNHAPP NPs, PNHAPL NPs, and MNPs for 12 h [164]. Copyright © 2021, American Chemical Society.

functionalization, nanomaterials can be selectively targeted to liver tissue or hepatocytes to deliver drugs or other therapeutic agents [165]. There are two ways in which nanomaterials can be targeted: passive targeting and active targeting. Passive targeting is achieved based on the physical and chemical properties of the nanomaterials, which can result in their accumulation in liver tissue or on cell membranes [166]. Nanomaterials can be passively targeted via static adsorption onto the cell membrane of liver tissue or by adsorption onto the surface of leukocytes [167]. The size and shape of nanomaterials can also affect their targeting properties. Smaller nanomaterials can penetrate into smaller blood vessels and vessel wall crevices, for better tissue penetration. In turn, active targeting involves specific molecular-recognition mechanisms to target nanomaterials to liver tissue or hepatocytes. For instance, NPs with ligand modifications on their surface for hepatic targeting can selectively bind to the corresponding receptors on the surface of hepatocytes, thus enabling active targeting [168]. Furthermore, NPs modified with liver-cancer-specific antibodies can bind to the corresponding antigens on the surface of liver cancer cells, thereby allowing the targeting of liver cancer [169].

Passive targeting

Passive targeting involves the use of the physical and chemical properties of the nanomaterials to target liver tissue or hepatocytes. Numerous nanomaterials are employed for passive targeting in the diagnosis or treatment of liver disease. Liposomes, in particular, have a unique chemical structure with a phospholipid bilayer that enhances their affinity to cell membranes, thus improving their targeting capabilities. Using endocytosis, liposomes can deliver drugs to the interior of hepatocytes, thereby avoiding degradation

by lysosomes and ensuring drug stability and efficacy [170]. The passive accumulation of liposomes in lesioned areas is attributed to their specific biological properties, such as prolonged wandering, and specific physiological and pathological features. For example, the microenvironment of the diseased liver area, which is characterized by hypoxia, acidification, and high permeability, promotes liposome accumulation and drug release [171]. Other factors, such as changes in potential, local blood flow, microvascular permeability, and inflammatory cell infiltration, also contribute to liposome targeting [172]. A negative charge can further promote liposome accumulation in areas of liver lesions [173]. Multifunctional NPs use their biological properties, such as size, surface charge, and morphology, to passively target hepatocytes. These NPs target diseased areas in the liver via mechanisms such as the enhanced permeability and retention (EPR) effect [174], receptor-mediated endocytosis [158], and pH responsiveness [175]. The EPR effect allows the accumulation of NPs in the diseased area by taking advantage of the increased vascular permeability and defects in the vessel wall caused by liver disease [174]. Receptor-mediated endocytosis occurs when NPs with specific receptor structures recognize receptors on the surface of hepatocytes and bind to the cell, to exert drug actions [158]. pH responsiveness refers to the ability of multifunctional NPs to automatically release drugs through responsive properties in different pH environments during the development of liver disease, to achieve a precise drug release [175]. Multifunctional NPs achieve a precise drug release by taking advantage of the intracellular acidic pH of liver cells and the diseased area during the development of liver disease.

Active targeting

The active targeting of nanomaterials to liver tissue or hepatocytes is achieved through specific molecular-recognition mechanisms (Fig. 6). The elevated surface-area-to-volume ratio of nanomaterials facilitates diverse functionalizations, which enable the integration of active targeting into nanotherapeutics. Active targeting has the potential to surpass the constraints of passive targeting. Liposomes are an effective drug-delivery system that can target hepatocytes by binding to specific

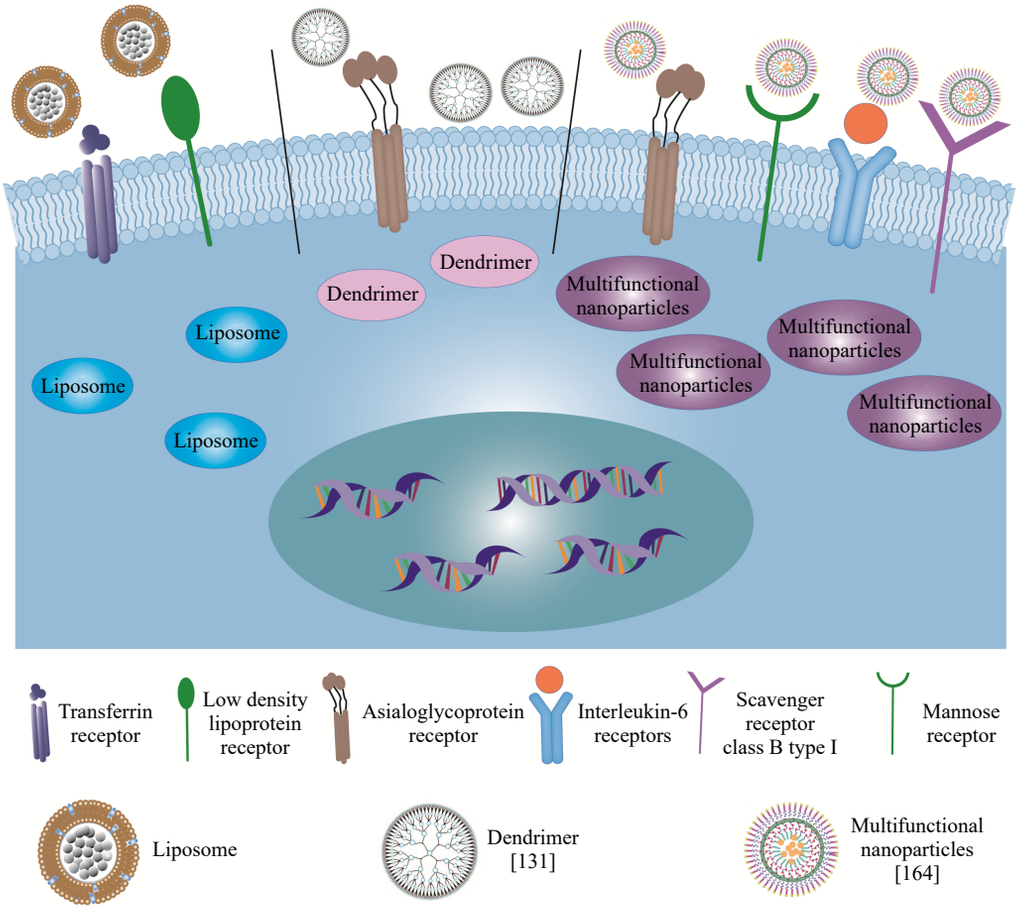

Fig. 6 NPs that target liver disease act on different receptors via active targeting.

receptors located on their surface. Liposomes can interact with hepatocyte membranes and molecules within hepatocytes via specific signaling pathways, to promote the phagocytosis and degradation of the drug by hepatocytes [176]. To achieve the targeting of areas of liver lesions, liposomes with altered surface properties can be used. Glycosylated liposomes can target overexpressed glycosylated receptors in the liver, such as glycosylated proteins on the surface of hepatocytes, to deliver drugs to the diseased area [177]. During the inflammatory response in the liver, receptors located on the surface of hepatocytes are altered, which offers the possibility of liposome targeting. For example, the inflammatory response leads to an accumulation of leukocytes and an increased expression of surface-adhesion molecules in the liver. These adhesion molecules can bind to receptors on the surface of liposomes, thus enabling liposome targeting. Several studies have shown that liver cells can target liposomes by recognizing and taking up liposomes. For example, receptors such as the low-density lipoprotein receptor (LDLR) [90] and transferrin receptor (TfR) [178] can interact with liposomes and participate in their mechanism of targeting diseased areas of the liver.

Receptor-mediated targeting, which is the most frequently researched method of active targeting, involves the use of specific receptors on the surface of hepatocytes, such as ASGPR [179], as targeting molecules. ASGPR is a receptor that specifically targets hepatocytes, and targeted NPs modified with ASGPR can be efficiently phagocytosed by hepatocytes and release the drug. In addition to ASGPR, the glycyrrhizin/glycyrrhetinic acid receptor can also be utilized in active-targeting strategies. Glycyrrhizin [180] and glycyrrhizinic acid [181], which are the primary bioactive compounds found in *Glycyrrhiza glabra*, can modify NPs to allow their recognition by receptors located on hepatocytes. This modification facilitates the uptake by hepatocytes through receptor-mediated endocytosis [182]. Furthermore, the mannose receptor, which is a transmembrane protein that is expressed on macrophages (such as Kupffer cells and endothelial cells), is a sugar receptor that has been leveraged to design cell-specific mannosylated NPs that actively target Kupffer cells [183]. Other ligand/receptor-mediated targeting strategies for hepatocytes include the use of the scavenger receptor class B type I [184], acetyl heparan sulfate proteoglycans [185], plasma membrane fatty acid transport proteins [186], IL-6 receptors [187], and immunoglobulin A binding proteins [188, 189]. To achieve active recognition and binding to areas of liver disease *in vivo*, surface modification, or functionalization of NPs is often required. For example, receptor ligands on the surface of NPs can be modified to achieve the targeting of liver tumor cells [190]. Thus, appropriate receptor-mediated modification of NPs can enable a preferential access to liver tumor cells, thus resulting in a more effective targeting.

Limitations of Nanomaterials

Nanomaterials have several limitations and drawbacks to their use have been reported. The small size and increased surface area of nanomaterials can cause friction and increased adhesion. Moreover, the chemical reactivity of nanomaterials can increase the production of ROS, thus resulting in oxidative stress, inflammation, and damage to DNA, proteins, and cell membranes, which contribute to toxicity. Furthermore, changes in the shape and size of nanomaterials can lead to different physical and chemical interactions, further complicating their use. The toxicity of nanomaterials depends on various factors, such as the surrounding environment, chemical composition, surface structure, and the presence of functional groups. After their introduction into the body, there may be unexpected reactions and interactions. Nanomaterials have the ability to cross cell membranes and even the blood–brain barrier by entering capillaries. In addition, biodegradable nanomaterials can be excreted from the body, whereas non-biodegradable, or slow-degrading nanomaterials can accumulate in the body and lead to inflammation. The cardiovascular toxicity of nanomaterials is dependent on their charge, with anionic nanomaterials being non-toxic and cationic nanomaterials having the potential to initiate hemolysis and blood clotting [53].

For the use of nanomaterials as targeting agents, it is crucial to evaluate their biocompatibility and toxicity, to ensure safe, and effective drug delivery to specific sites. The compatibility of nanomaterials is affected by several factors, including their shape, size, and surface characteristics, as well as the surrounding environment. This assessment is crucial to avoid complications and toxicity during drug

delivery. Moreover, nanomaterials possess the ability to both stimulate and suppress the immune system. Specifically, in terms of immunostimulation, nanomaterials have demonstrated adjuvant properties, which inhibit the formation of secondary tumors [191]. Gref et al. [192] reported that nanomaterials lacking surface modifications to prevent adsorption by opsonins (i.e., proteins that facilitate the clearance of foreign substances from the body via phagocytosis) are rapidly cleared by macrophages. Among the various polysaccharide nanomaterials available currently, PLGA has shown the highest level of biocompatibility because of its metabolites, lactic acid and glycolic acid [193].

The use of CNTs has been associated with various complications, including oxidative stress, alterations in cell morphology, platelet aggregation, and toxicity resulting from metal residues [191]. Furthermore, cationic NPs, such as gold NPs, have blood-clotting and hemolytic properties, and can traverse the blood–brain barrier [194]. In turn, metallic NPs, such as silver NPs, exhibit an enhanced toxicity, as they generate greater amounts of ROS and cause a lactate dehydrogenase leakage compared with other types of NPs. Studies involving silica NPs have revealed that they induce oxidative stress, stimulate inflammatory biomarkers, and exhibit hepatotoxic effects [193].

Future Prospects

With the rapid advancements reported in the fields of nanotechnology and biomedicine, the use of targeted nanomaterials for treating liver diseases is increasingly promising. However, to achieve even greater success, specific challenges, such as the toxicity, and stability of these nanomaterials, must be addressed. Moreover, the development of tailored and precise targeted nanomaterials for specific types of liver diseases is necessary, to enhance treatment outcomes. Anticipatedly, the employment of bispecific, or multispecific targeting methods for liver cancer cells, as described by Wang et al. [195], is expected to result in more-accurate targeting. However, we anticipate encountering challenges associated with variations in receptor activity and expression levels in human patients. To better identify receptors that are suitable for specific delivery, proteomics, and genomics analyses of receptor expression in target cells vs. other cells will be of great assistance. For example, the mannose receptor has been identified as a marker of the conversion of HSCs into stroma-producing myoblasts in hepatic fibrosis, making it a promising target for specific delivery to diseased cells [23]. It is expected that the use of such a system will result in an enhanced therapeutic efficacy while minimizing the risk of adverse effects in healthy cells. Consequently, analogous receptor–ligand interactions are likely to be investigated for diverse liver pathologies in the near future. Furthermore, as artificial intelligence (AI), big data, and intelligent technologies continue to evolve, targeted nanomaterials will be integrated with these advancements to provide more-intelligent and personalized solutions for treating liver diseases. In addition to novel therapeutic approaches and pharmaceuticals, the large volume of medical data can be scrutinized through big data analysis and AI techniques, to achieve the goal of personalized medicine, as demonstrated by numerous studies [196, 197]. IBM and the Memorial Sloan Kettering Cancer Center have collaborated to develop an AI-powered decision-making system known as Watson for Oncology (WFO) [198]. WFO has been trained for more than 4 years using the National Comprehensive Cancer Network guidelines and over 100 years of treatment experience. Its objective is to provide personalized treatment plans for individual patients by suggesting the optimal therapeutic schedule for them. In summary, targeted nanomaterials offer enormous potential as a new approach for the treatment of liver disease. With the ongoing development and enhancement of technology, targeted nanomaterials are expected to play an increasingly crucial role in the treatment of liver disease, thus providing better outcomes, and quality of life to patients.

Conclusion

Liver disease is a global health problem that affects millions of people worldwide. Although various treatment options are currently available, the effectiveness of these treatments is often limited, and many liver diseases remain incurable. In recent years, the development of targeted nanomaterials has shown great promise as a new approach for treating liver disease. Targeted nanomaterials are NPs designed to deliver drugs or therapeutic agents directly to the affected cells in the liver. These NPs can be

engineered to have specific properties, such as size, shape, and surface charge, which enable them to target specific cells or tissues in the liver. Furthermore, targeted nanomaterials can be designed to release drugs or therapeutic agents in a controlled manner, thus improving their efficacy, and reducing their side effects. One of the major advantages of targeted nanomaterials is their ability to overcome the limitations of traditional drug-delivery methods. For instance, many of the drugs used to treat liver disease have poor solubility or stability, which hamper their delivery to the target cells. Conversely, targeted nanomaterials can encapsulate these drugs and protect them from degradation, thus enabling them to reach the target cells in a more effective manner. However, the development and application of targeted nanomaterials for treating liver disease remains challenging. Metallic NPs, ceramic nanomaterials, micelles, polysaccharides, liposomes, dendrimers, CNTs, and multifunctional NPs are considered promising for targeting liver diseases. When these nanomaterials are combined with specific targeting ligands, the efficacy of liver disease treatment can be significantly enhanced. For example, the activated HSCs in liver fibrosis bears M6P, VA, and galactose, or acetylgalactosamine groups, which can be specifically recognized by ASGPR overexpressed on the liver cell membrane. However, one of the major concerns in this setting is the potential toxicity of these NPs. Although many studies have demonstrated the biocompatibility of targeted nanomaterials, there remains a need for further research to fully understand their toxicity profile and ensure their safety. Another challenge is the stability and clearance of these NPs from the body. Targeted nanomaterials can accumulate in the liver and other organs, potentially leading to long-term toxicity. Therefore, it is essential to design NPs that are stable and easily cleared from the body, to reduce the risk of long-term toxicity. Despite these challenges, the potential of targeted nanomaterials for treating liver disease is immense. Future developments in nanotechnology and biomedicine are expected to further enhance the effectiveness of these NPs for the treatment of liver diseases. The integration of AI and intelligent technologies is likely to enhance the efficacy and safety of targeted nanomaterials. AI has substantially augmented the precision and efficiency of the simulation and modeling of the *in vitro* pharmacokinetic and pharmacodynamic profiles of new drugs, thereby enabling the correlation of such data to forecast *in vivo* drug release and toxicity [199, 200]. For example, a proof-of-concept investigation showcasing the use of a series of 11 AI algorithms is reported to precisely predict the fractional release of drugs from a polymeric long-acting injectable drug formulation. In the future, the trained models derived from this study may be utilized to guide the design and development of comparable formulations [201, 202]. The main advantage of this approach lies in the acceleration of the design and development of drugs, resulting in the faster creation of drugs with better efficacy and lower toxicity to the human body. Therefore, this model can also be applied to the design of nanomaterials targeting liver diseases. In conclusion, targeted nanomaterials offer great potential as a new approach for treating liver diseases. Although several challenges remain to be addressed, the potential benefits of these NPs are immense. As research and development in nanotechnology and biomedicine continue to advance, it is likely that targeted nanomaterials will play an increasingly important role in the treatment of liver diseases by providing more-effective and personalized solutions to patients.

CRediT Author Statement

Yinghua Wu: data curation, investigation, conceptualization, writing–original draft, writing–review and editing. **Junfeng Zhang:** conceptualization, supervision, visualization, writing–review and editing. **Wen He:** data curation, supervision, visualization, writing–review and editing. **Chenchen Li:** project administration, resources, supervision, writing–review and editing. **Yanli Wang:** funding acquisition, project administration, resources, supervision, writing–review and editing.

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Conflict of Interest

The authors declare that no competing interest exists.

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