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Review

The use of nanotechnology to combat liver cancer: Progress and perspectives

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ABSTRACT

Liver cancer is one of the most common cancers worldwide and is also one of the most difficult cancers to treat, resulting in almost one million deaths per year, and the danger of this cancer is compounded when the tumor is nonresectable. Hepatocellular carcinoma (HCC) is the most common type of liver cancer and has the third highest mortality rate worldwide. Considering the morbid statistics surrounding this cancer it is a popular research topic to target for better therapy practices. This review summarizes the role of nanotechnology in these endeavors. Nanoparticles (NPs) are a very broad class of material and many different kinds have been used to potentially combat liver cancer. Gold, silver, platinum, metal oxide, calcium, and selenium NPs as well as less common materials are all inorganic NPs that have been used as a therapeutic, carrier, or imaging agent in drug delivery systems (DDS) and these efforts are described. Carbon-based NPs, including polymeric, polysaccharide, and lipid NPs as well as carbon dots, have also been widely studied for this purpose and the role they play in DDS for the treatment of liver cancer is illustrated in this review. The multifunctional nature of many NPs described herein, allows these systems to display high anticancer activity *in vitro* and *in vivo* and highlights the advantage of and need for combinatorial therapy in treating this difficult cancer. These works are summarized, and future directions are presented for this promising field.

1. Introduction

Cancer is well known to be one of the leading causes of death worldwide, with millions of new cases being reported each year. [1] One particularly difficult type of cancer is liver cancer, which is the sixth most diagnosed cancer (906,000 cases) and third leading cause of cancer deaths worldwide (~830,000 deaths). [2] The incidence and mortality of this cancer are especially common in Asian and North African countries. [2] Hepatocellular carcinoma (HCC) is the most common type of liver cancer and is difficult to detect before the formation of tumors which leads to increased treatment difficulty. [3] The 5 year survival rate for liver cancer patients is about 20% overall (34% for localized and 3% for distant cases). [4] Survival rates are greatly increased if the liver is able to be operated on or transplanted, but in many cases, this is not possible. When resection is not possible there are a few options for therapy which will slow the progression of the cancer but does not often send the cancer into remission. [5] Chemotherapy, for HCC patients, involves infusion of the chemotherapeutic into the hepatic artery, which is designed to limit side effects to the rest of the body. [6] When cancer drugs are delivered this way, a significant portion of the dose will be broken down by the healthy liver cells, reducing the effective dose to the tumor cells. Even with this reduction of the chemotherapeutic in the rest of the body, side effects for this treatment (*e.g.* hair loss, nausea, fatigue) are still common. [6] Targeted therapy has shown promise in recent years and involves the inhibition of kinases which help tumors grow or increase their blood supply. [5] Targeted drugs approved for liver cancer in recent years include sorafenib and Lenvatinib. [7] Immunotherapy has also emerged as a promising option for liver cancer treatment. This process involves targeting a protein (*e.g.*, programmed cell death protein 1) on T cells or the corresponding binder on cancer cells which stops the cancer's ability to evade immune response. [8] Targeted and immune therapy have improved the treatment capability compared to the more established chemotherapy and radiation, but this improvement can be measured in months and all patients do not respond to these treatments. [9,10]. For this reason, there is a large need for better therapy options for liver cancer patients who cannot undergo surgery.

To address this issue many researchers have turned to the field of nanotechnology. This term was first used in 1974 by Norio Taniguchi

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(nano-technology) and then again by K. Eric Drexler (nanotechnology) in 1981. [11,12] While various types of inorganic nanoparticles have been used for many centuries, mostly in art, there has been a strong scientific thrust towards nanotechnology research only in the 40-50 years since this term was coined. Within this fast-growing field, there are many different material shapes such as spheres, sheets, and tubes, but the general term used for these materials is "nanoparticle" (NP) which can be defined as a material which has at least one dimension less than 100 nm. [13] This is a very wide class of materials which may include particles composed of inorganic materials such as precious metals, metal oxides, various inorganic salts, and silica. [14] Many carbon-based NPs have been developed including polymeric NPs, micelles, liposomes, lipid NPs, and more recently, carbon dots (CDs). Furthermore, NPs have been developed with specialized structures such as upconversion NPs, metal organic frameworks (MOFs), and Janus NPs (a NP which surface has distinct regions with differing physical properties). The exceedingly wide variety in this field illustrates the diversity of applications for nanotechnology. In the 21st century, nanomedicine has become a promising branch of nanotechnology. [15–17] This growth has been especially pronounced in areas of medicine where traditional methods are less than ideal, such as cancer treatment, or where therapeutics are being outpaced by sickness, such as is the case for antibiotic-resistant bacteria. [18,19] Some NPs possess inherent therapeutic effects and almost all types of NPs can act as a carrier in a drug delivery system (DDS). These traits have led to the explosion of research relating to NPs as the vehicle for a DDS for the treatment of cancers. [20–23]

DDSs have received a great deal of investigation in recent years as the promise of nanomedicine has increased. A typical DDS can have three components: a carrier, targeting ligand, and therapeutic species. In some cases, these three components may be combined into fewer than three compounds or particles (*e.g.* if the NP is the therapeutic itself). [24] The carrier is commonly a particle which is capable of encapsulating or binding the therapeutic species, and furthermore, binding can be achieved electrostatically or covalently. [25] To increase the efficiency of DDSs it is necessary to incorporate a means of targeting the desired area in the body. There are two general types of targeting: active and passive. [26] Active targeting involves the incorporation of a chemical species which will have a special affinity for the target site. For instance, folic acid has been used to target cancer cells and tumors because many cancers such as breast, colorectal, and liver cancers are known to overexpress folic acid receptors in their cell membrane. [27–29] Passive targeting is related to the circulation of the DDS in the body, which involves keeping the DDS in the bloodstream long enough to be carried to the desired location. This is often done by coating with polyethylene glycol (PEG) to reduce the likelihood of the body's immune system responding to the DDS as a foreign substance. [30] For both passive and active targeting, key complications which need to be addressed are specificity and selectivity. Active targeting can target the specific cells in a region of the body but delivering the DDS to the specific area or organ that needs to be treated is not trivial. Similarly, passive targeting can ensure the system will stay in the bloodstream and be carried throughout the body but will generally not provide a mechanism to selectively target cancer cells. [31] An effective DDS which could potentially be used to treat liver cancer in humans will ensure that both specificity and selectivity concerns are addressed, which can be done by coupling passive and active targeting methods.

The use of a selective DDS for treatment of liver cancer is highly beneficial as it reduces the toxicity of the therapy as well as potentially facilitating targeting of the affected area. NPs represent a unique material which, depending on their properties, commonly accumulates in the liver when introduced *in vivo*. [32] This is true for many different types of nanoparticles, however depending on size and charge, some may accumulate in the kidneys and spleen as well. [33] Fig. 1A shows a general diagram for blood flow though the body and illustrates the ability of NPs to be carried to the liver and also the importance of tailoring their properties to avoid damaging other organs. The blood

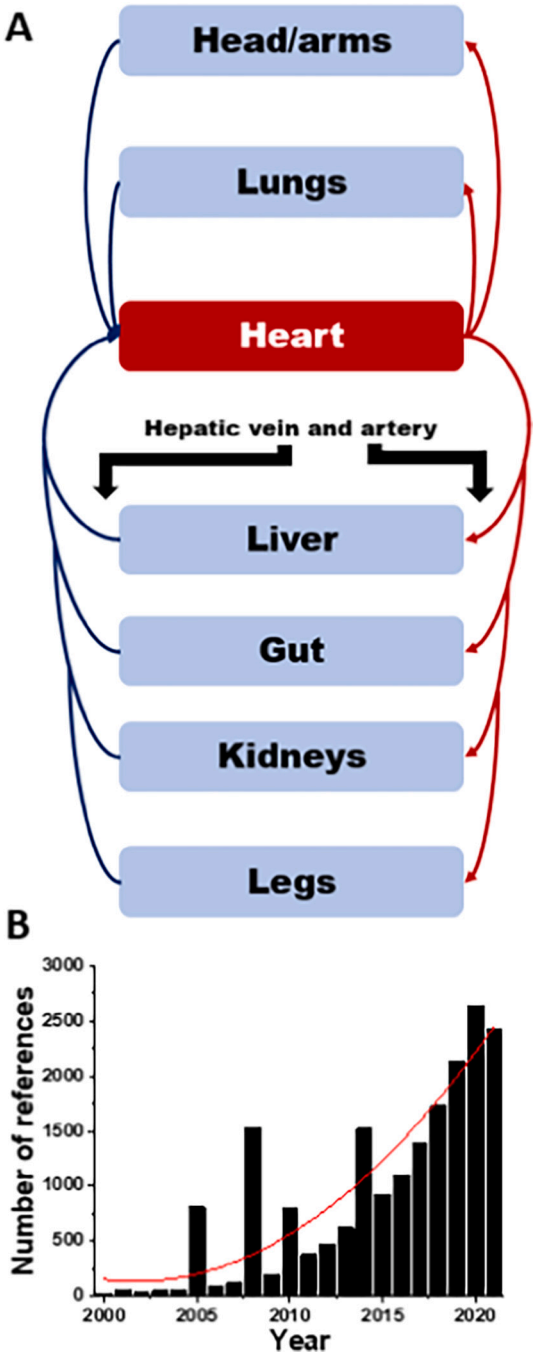

Fig. 1. (A) Schematic of blood flow through the body. (B) Chart showing the number of references per year based on the "nanoparticles", "liver cancer", and "hepatocellular carcinoma" google scholar search. The fitted curve is a second order polynomial with R^2 value of 0.81.

coming from the heart should reach the liver before the kidney (Fig. 1A), but since the entire blood supply does not pass through the liver, it is optimal for a DDS targeting liver cancer to avoid being trapped in the kidneys. As a general trend, particles with a hydrodynamic diameter greater than 6-8 nm will avoid being filtered by the kidneys and a vast majority of the particles will go to the liver. Similarly, negatively charged nanoparticles avoid the kidneys and accumulate in the liver, but neutral and cationic particles are more likely to be processed and excreted by the kidneys. [33] Based on this, as a general rule, a DDS designed to target the liver should possess a hydrodynamic diameter of 6-8 nm and be anionic in nature. This will enable the system to pass

through the kidneys but will be "caught" by the liver.

Passive targeting of the liver enables NPs or NP-based DDSs to accumulate at the cancerous organ, but care must then be taken to target the cancer cells so that the liver will not be unnecessarily compromised. Due to the different metabolic properties of the cancer cells, there will be some receptors that will be overexpressed in cancer *versus* normal cells. [34] Some ligands which have receptors which are overexpressed in liver cancer are glycyrrhetinic acid, transferrin and folate. [27,29,35–37] Some other receptors which are relevant to liver cancer are the asialoglycoprotein (ASGPR) and P-glycoprotein 1 (CD44) receptors. [38,39] As previously discussed, the correct design of a nanoparticle can lead to accumulation in the liver and then these ligands could be used as a targeting agent to specifically target cancer cells over normal liver cells. As will be discussed in this review, a wide variety of NPs can be selected to accommodate this modification.

Even though most classes of nanoparticles have been known and studied for 50 years or more, they have not been applied in nanomedicine until much more recently. [40] As an example of this, Fig. 1B shows the increase over the last 20 years of references which appear using the keywords "nanoparticles", "liver cancer", and "hepatocellular carcinoma". In 2000, there were less than 50 such references compared to almost 2700 in 2020. This robust growth shows the promise of the burgeoning field of nanomedicine. Considering the unique ability of nanoparticles to passively target the liver as previously discussed, this trend should continue to accelerate in future years. The current difficulties in detecting liver cancer at an early stage and the related poor prognoses compel focused attention on this promising area. It is our goal for this review to extensively describe the current efforts in this field and help to focus ensuing work on the areas which show the most promise for future treatment of liver cancer in humans. A summary of recent strategies for using nanotechnology to address liver cancer has been compiled and can be found in Tables 1 and 2. Expanded versions of these tables can be found online in the electronic supplementary material (**Tables S1** and **S2**).

2. Metal NPs

2.1. Precious metal NPs

2.1.1. Gold NPs

Gold NPs, commonly called colloidal gold, are among the most studied and well-known NP. [141] They have been prepared and used for centuries but have been well characterized only in the last 100 years due to microscopy developments. Their most common method of production is reduction of a soluble gold salt such as chloroauric acid. [142] Commonly the reductant can serve as the capping agent as well, although this is not always the case. [143] Either way the capping agent is an important consideration for the development of a DDS from gold NPs, since a therapeutic and/or targeting ligand will need to be bound to the gold surface. [144] In a DDS, gold NPs can act as a carrier delivering drugs/genes to a specific area, but, due to their surface plasmon effect, they can also act as a photothermal therapeutic or an enhancer of radiation therapy. [145,146] These properties combined with their small size and typically anionic charge make them an obvious choice on which to base a DDS for liver cancer.

First, gold NPs as carriers will be considered. Tomuleasa et al. used ascorbic acid as a reducing/capping agent to form gold NPs and connected various chemotherapeutics with this functionality. [51] In 2016, Shaat et al. capped gold NPs with branched polyethyleneimine (PEI) to improve biocompatibility and create a positive surface charge to electrostatically bind siRNA. [48] This system effectively delivered siRNA to Huh-7 liver cancer cells and the authors showed the capability of silencing the c-Myc gene which is an important factor in tumor proliferation. [147] The use of peptides to target cancer cells has also been explored. Scrimin and coworkers used a thiol based linker to attach a peptide sequence present in the hepatitis B virus-PreS1 protein to gold NPs surface. [46] This system displayed 6 times higher uptake in HepG2 cells over bare gold NPs showing the strong capability of targeting ligands. Xue et al. used gold NPs to deliver miR-375 for cancer treatment (AuNP-miR-375). [45] miR-375 is a tumor suppressor naturally produced in the body, but its production is commonly downregulated in HCC. [148] This approach constitutes replacement therapy by introducing miR-375 to the HCC cells. After 3 weeks of treatment with the gold NPs-miR-375 complex in FVB/n and BALB/c nude mice there was a tumor mass reduction of over 40%. After uptake by cancer cells, AuNP-miR-375 escapes from the endosome and lysosome and mature miR-375 is released to the cytoplasm allowing for the gene expression (Fig. 2A). Gold NPs have also been used as an immunotherapeutic delivery agent as shown by Tian and coworkers. [49] Here they coupled antibody SM5-1 to their NPs to target membrane protein p230 which is overexpressed in HCC. This system showed tumor growth inhibition rates up to 40% in mice and displayed significant improvement over SM5-1 alone.

Interesting effects were also observed by using novel bio-reductants. Rajeshkumar used *Enterococcus* sp. bacteria to reduce gold atoms into NPs. [47] These displayed dose-dependent anti-cancer activity against HepG2 and A549 cells. The author believed the bio-reduction led to enhanced cell uptake followed by gold atom interaction with cellular proteins inducing cell death. In 2018, Khandanlou et al. used extract from *Backhousia citriodora* to prepare their gold NPs. [43] In addition to antioxidant properties, these displayed activity against HepG2 cells with an IC_{50} value of 108.21 μg. This was believed to be due to the introduction of anti-proliferative molecules from *B. citriodora* into the cell as well as gold atom-protein interaction. Bio-reductants provide a facile method for functionalizing gold NPs, but it can be difficult to understand the anticancer activity due to the complex matrix from the plants used.

The role of surface charge has been investigated by Choi and Joo. [41] Here, gold NPs were capped with various polymers/capping molecules to produce positive (bPEI), negative (lipoic acid), and neutral (PEG) surface charges. The positively charged displayed the highest cellular uptake by the HepG2-C3A cells, however all three NPs exhibited toxicity towards the cells and the LC_{50} value for positive and neutral NPs was comparable. These two particles showed evidence of inducing oxidative stress and all three systems suppressed *Cytochrome P450 3A4* activity which is an important element of the cells' defense against foreign molecules. The enhanced uptake of positive particles is most likely due to the negative charged cell surface, but there does not seem to be a large correlation between surface charge and anti-cancer activity. As discussed in the introduction, negatively charged NPs are more likely to accumulate exclusively in the liver, and this work shows the potential favorability of cationic particles to penetrate cancer cells.

As previously mentioned, gold NPs possess the ability to have their surface plasmon properties used for photothermal or radiation therapy. To this end, Mocan et al. prepared gold NPs which were capped with bovine serum albumin (BSA). [50] BSA capping produced a selective internalization of these gold NPs in liver cancer cells over normal liver cells by targeting the *albondin* (GP60) receptor. After incubation these cells were irradiated with a 2 W, 808 nm laser and the resulting cell response was dependent on dose and irradiation time. The maximum cell death produced in HepG2 cells was 52.3% upon irradiation (compared to 22.0% for normal liver cells). In 2018, photothermal therapy was combined with delivery of a drug (5-fluorouracil) by Badr and coworkers to create a dual action DDS (Fig. 2B). [42] Without laser irradiation the DDS was more potent against HepG2 cells than 5-fluorouracil alone indicating the benefits of drug delivery, but when the radiation was applied (532 nm, 200 mW) an additive effect was observed, and the combined therapy was much more effective than the drug alone. In a similar direction, Guo et al. used gold NPs to enhance radiation therapy. [44]. Without radiation, the NPs exhibited some toxicity towards H22 and HepG2 cells through the disruption of normal protein function by the gold particle. Radiation was applied from ^{137}Cs with doses between 0 and 4 Gy. The sensitizer enhancement ratio was calculated to be 1.2-1.3 for this system which is competitive with what

Table 1
Description of strategies using inorganic NPs for treatment of liver cancer.

Nanoparticle (NP)	Preparation	Cellular Model	Cancer Targeting	Anticancer Mechanism	Reference
Gold NPs	Carbonate reduction/capping	HepG2-C3A	–	Cationic cellular uptake/oxidative stress	[41]
	Chitosan reduction	HepG2	–	5-fluorouracil delivery/photothermal therapy	[42]
	B. citriodora reduction	HepG2, MCF-7	–	Introduction of anti-proliferative molecules	[43]
	Citrate reduction/PEG-SH capping	HepG2, H22	–	Gold-protein interaction/Radiotherapy	[44]
	Citrate reduction/conj. w/ miR-375	HepG2, HepB3	–	miR-375 replacement therapy	[45]
	NaBH4 reduction/octylamine capping	HepG2	Peptide conjugation	Cell uptake through peptide conjugation	[46]
	Bioreduction w/ *Enterococcus* sp.	HepG2, A549	–	Gold atom-intercellular protein interaction	[47]
	Citrate reduction	Huh-7	–	c-Myc gene silencing by siRNA	[48]
	Citrate reduction	HCC-LM3-fLuc, HepG2	SM5-1 targets membrane proteins	Immunotheraphy, conjugation with SM5-1	[49]
	Citrate reduction/BSA capping	HepG2, HepB5	GP60 receptor uptake	Photothermal therapy	[50]
	Aspartic acid reduction/drug capping	resistant HepG2	–	Conj. w/ cisplatin, doxorubicin, or capecitabine	[51]
Silver NPs	Bioreduction w/ *O. corniculata*	HT29	–	Induction of apoptosis	[52]
	Citrate/NaBH4 reduction	HepG2	–	ROS formation/apoptosis induction	[53]
	Bioreduction w/ *P. granatum*	HepG2	–	Disruption of intercellular proteins	[54]
	Bioreduction w/ *E. eugeniae*	HepG2	–	Apoptosis through caspase expression	[55]
Platinum NPs	NaBH4 reduction/peptide capping	HepG2	Peptide conjugation	Release of Pt (II) ions	[56]
	Bioreduction	HepG2	–	Apoptosis through caspase expression	[57]
Iron Oxide NPs	–	HepG2, Huh-7	–	Magnetic field induces lysosomal leakage	[58]
	Co-precipitation/capping w/ galactose, PEI	Hepa1-6	Passive liver targeting	Delivery of si-RNA	[59]
	Co-precipitation, thermolysis	HepG2	–	Magnetic hyperthermia	[60]
	Incubation	Huh-7	ASGPR targeting	Imaging only	[61]
	Thermolysis/encapsulation with sorafenib	HepG2	–	Delivery of sorafenib	[62]
	Sonication	Hep3B	Folate receptor	Delivery of doxorubicin	[63]
Zinc Oxide NPs	Bioreduction by *M. tenacissima*	Hep-2	–	Membrane disruption/ ROS production	[64]
	Reduction by protein	HepG2	Glucan binding protein	ROS production	[65]
Arsenite NPs	Double emulsion/ polymer capping	Huh-7, Bel-7402	–	Induction of pyroptosis through caspase 3	[66]
	Encapsulation of ZnAsOx in SiO2 matrix	MHCC97L, Hep3B	–	Delivery of As (III) to induce apoptosis	[67]
	Embeddment of As2O3 into silica NPs	SMMC-7721	Folate receptor	Delivery of As (III) to induce apoptosis	[68]
Hafium Oxide NPs	Proprietary	–	Tumor accumulation	Increased energy deposit of radiation therapy	[69]
Alumina NPs	Precipitation/ capping with hyaluronic acid	SMMC-7721	CD44 receptor	Delivery of paclitaxel	[70]
Calcium NPs	Precipitation/encapsulation of Gd	HepG2, BEL-7402	Peptide conjugation	Imaging only	[71]
	Emulsion mixture/precipitation	SMMC-7721, A549	–	Delivery of Beclin I siRNA and FTY720	[72]
	Emulsion mixture/precipitation	HepG2	–	Delivery of sorafenib and miR-376	[73]
	Emulsion mixture/precipitation	HepG2, HepG2/ADR	–	Delivery of doxorubicin and miR-375	[74]
Silica NPs	Silica NPs capping w/ polymers/ lactose	HepG2	Lactose conjugation	Delivery of doxorubicin	[75]
	Precipitation/sorafenib loading	H22	–	Delivery of sorafenib/photothermal therapy	[76]
	Purchased	HepG2, SMMC7721, PLC, BEL-7402, QGY7703	–	Gene regulation by silica NPs	[77]
	Purchased/coated with CAR-T cell membrane	Huh-7, SK-HEP-1	T cell membrane	Photothermal therapy	[78]
	Silica deposition on MNPs	HepG2	MRI guidance	Suicide gene delivery/magnetic hyperthermia	[79]
	Silica NPs capping w/ polymers/ lactose	HepG2	Lactose conjugation	Delivery cisplatin	[80]
	Precipitation /coating with lipids	HepG2, Hep3B, Huh7, HepG2/ADR		Delivery of doxorubicin and miR-375	[81]
	Precipitation	HepG2	Glycyrrhetinic acid conjugation	Delivery of curcumin	[82]
	Emulsion mixture/precipitation	HepG2	Redox repsponsive	Co-delivery of cetuximab and doxorubicin	[83]
	Precipitation/ursolic acid loading	HepG2	pH sensitivity	Delivery of ursolic acid	[84]
	Precipitation/encapsulation in alginate	HepG2	Peptide conjugation	Delivery of doxorubicin	[85]
Selenium NPs	Reduction with ascorbic acid	HepG2	Galactose conjugation, pH responsive	Delivery of doxorubicin	[86]
	Reduction with ascorbic acid	HepG2	Folate receptor	Delivery of HES5-siRNA	[87]
	Reduction with ascorbic acid	HegG2, HepG2215	Folate receptor	Delivery of baicalin	[88]

(*continued on next page*)

Table 1 (*continued*)

Nanoparticle (NP)	Preparation	Cellular Model	Cancer Targeting	Anticancer Mechanism	Reference
Hydroxyapatite NPs	Co-precipitation/substitution with selenium	HCCLM9	–	Calcium deposition in tumor	[89]
	Precipitation	HCC	–	Physical damage to cell structure/release of ions	[90]
Upconversion NPs	Multi-step yolk-shell synthesis	HepG2	–	Phothermal therapy, codelivery of doxorubicin and HCPT	[91]
	Hydrothermal/ Polymer and antibody capping	BEL-7404	EpCAM conjugation	Photodynamic therapy, delivery of mitoxantrone	[92]
Janus NPs	Multi-step	HepG2, H22	pH/light sensitivity	Photothermal therapy, sequential delivery of doxorubicin and docetaxel	[93]
MOF NPs	Zeolitic imidazolate covered in cancer cell membrane	HepG2, HCT116, MCF-7	Cell membrane camouflage, pH sensitivity	Delivery of dihydroartemisinin and Fe(II)	[94]

has been reported for other cancers. The ability of gold to enhance radiation dose is a unique capability which can could potentially be combined with delivery of a chemotherapeutic. The *in vivo* use of gold's surface plasmon properties needs to be studied in depth as there would be significant challenges to implement this therapy in large animals.

2.1.2. Silver/platinum NPs

Many of the main considerations involved with gold NPs can be applied to silver or platinum NPs. One exception is the significantly lower toxicity resulting from gold ion release compared to silver/platinum ions. [142,149] This results in inherent toxicity from the silver and platinum NPs and so makes targeting an important factor. Another difference is the infrequent use of the surface plasmon resonance of the silver and platinum NPs compared to the gold analogues. This is particularly true for platinum as this absorption band is typically around 215 nm. [150] Despite the potential shortcomings of these systems there has been some interesting work done recently in this area.

Silver NPs are commonly prepared through bio-reduction in an attempt to reduce their inherent toxicity. Benelli and coworkers used an extract from *E. eugeniae* (earthworms) to form silver NPs. [55] These displayed an IC_{50} value of 25.96 μg/mL against HepG2 cells. Nuclear DNA staining made it clear that the NPs were inducing apoptosis, and this was believed to be caused by initiating the caspase-3 signaling pathway. Saratale et al. used a different bio-reductant, extract from *Punica granatum*, in their 2018 study. [54] These NPs inhibited HepG2 cell growth by over 90% at 200 μg/mL. The authors showed the ability of these NPs to inhibit α-amylase and α-glucosidase activity, so it was hypothesized that inhibition may occur through interaction with intracellular proteins. In 2019, researchers used *Oxalis corniculate* to reduce silver ions to NPs. [52] These displayed advanced activity against cancer cells over normal fibroblast cells (L-929). This selectivity was thought to be due to the enhanced metabolism of the cancer cells enabling them to uptake the particles at a faster rate due to the molecules from the plant extract coating the surface. Ahmadian et al. prepared silver NPs through a more traditional citrate/$NaBH_4$ method. [53] These exhibited toxicity towards liver cancer cells in a dose and incubation time dependent manner. They presented multiple mechanisms for this activity including production of reactive oxygen species (ROS), apoptosis induction through enhanced caspase expression, and upregulating Bax (a pro-apoptotic protein).

As has been observed silver NPs provide multiple actions against cancer cells, however they often lack specificity. Their cytotoxicity has been studied against multiple organisms and are often toxic to normal, healthy cells as well, although occasionally to a smaller degree. [151] Their mechanisms of actions (ROS production, silver ion release, protein interaction, *etc.*) are not capable of discerning between healthy and cancerous cells and so any strategy involving drug delivery would demand a strong targeting strategy. Furthermore, therapies involving ROS formation are creating a risk of secondary tumor formation. [152] For these reasons, silver NPs are not strong candidates for drug delivery in biological systems.

Platinum NPs are perhaps an obvious choice to base a DDS on for treatment of cancer considering the ubiquitous use of cisplatin in cancer therapy. Medhat et al. prepared platinum NPs by incubating hydrogen hexachloroplatinate with bacterial strains for bioreduction. [57] These NPs displayed an IC_{50} value of 10.3 μM compared to 26.5 μM for cisplatin showing the increased efficacy over the chemotherapeutic. In their investigation with swiss albino rats, not only was higher anticancer activity observed for platinum NPs over cisplatin, but the measured parameters for liver function were much closer to control for platinum NPs indicating reduced side effects. These NPs seemed to have a similar mechanism of action as cisplatin indicating release of Pt (II) ions from the NPs may occur. To further increase selectivity, Wennemers and coworkers prepared platinum NPs and coated them with a peptide selected using a combinatorial library (H-Lys-(Pro-Gly-Lys)$_2$-NH_2). [56] Platinum NPs selectivity to oxidative environments was used to convert the neutral platinum atoms to the cation (Fig. 3A). This enhanced selectivity enabled increased cytotoxicity towards HepG2 cells over cisplatin and sorafenib, while showing a marked increase in cell viability towards normal cell lines (AML-12) over the same chemotherapeutics. These also showed the ability to selectively target HepG2 over a wide variety of other cancer cells (Fig. 3B). The highly oxidative environment inside the HepG2 cells compared to the other cancer/non-cancer cells appeared to be the main contribution to the excellent activity against the liver cancer cells. Platinum NPs are a more promising candidate than silver NPs for drug delivery, however, there is much work to be done to prove a significant improvement of the efficacy to side effect ratio over cisplatin *in vivo*.

2.2. Metal oxide NPs

This section covers a wide range of materials formed from the oxides of several metals. Although metal oxide NPs have been used in a wide variety of applications such as sensing and catalysis, they are less commonly applied to drug delivery as pure materials. [153,154] Despite this they possess potential in this area since they can act as a therapeutic themselves, carry another therapy as a ligand, and some could also act as a magnetic resonance (MR) imaging agent. These intriguing possibilities are discussed below.

2.2.1. Iron oxide NPs

Iron oxide NPs are most commonly prepared through coprecipitation, but they can also be prepared through high temperature treatment of iron/oxygen containing organic precursors. [155] Their magnetic properties are desirable for imaging or magnet-mediated drug delivery as both common oxidation states of iron (+2/+3) are capable of being ferromagnetic. [156] In addition to the aforementioned uses of iron oxide NPs' magnetic properties, this property can also be used to induce hyperthermia and use heat as a therapeutic against liver cancer. [157] The applications based on magnetism plus the more typical carrier ability of iron oxide NPs make it a compelling material for the treatment of liver cancer *in vivo*.

Table 2
Description of strategies using carbon-based NPs for treatment of liver cancer.

Nanoparticle (NP)	Preparation	Cellular Model	Cancer Targeting	Anticancer Mechanism	Reference
PEG NPs	Nanoprecipitation with PEG derivative	HepG2	anti-GPC3 conjugation	Delivery of sorafenib	[95]
	Micelle self-assembly/peptide grafting	BEL-7402	RGD peptide conjugation	Delivery of verapamil and mitoxantrone	[96]
PLGA NPs	Stepwise self-assembly	Hep3B, SK-Hep1	Peptide conjugation	Delivery of sorafenib	[97]
	Polymer cross-linking	Hep G2, HL-7702 cells	Conjugation of lactobionic acid, biotin	Delivery of 10-hydroxycamptothecin and apoptin	[98]
	Double emulsion/solvent evaporation	SMMC-7721, LO2	Lactose acid conjugation	Delivery of As(III)	[99,100]
	Single-step nanoprecipitation	Hep3B, HCC1, SK-Hep1, JHH-7	CXCR4 targeting peptide	Delivery of sorafenib and selumetinib	[101]
	Nanoprecipitation with PLGA copolymer	HepG2	–	Delivery of genistein	[102]
PEG/PLGA NPs	Nanoprecipitation/ drug encapsulation	HepG2, Huh7, SMMC-7721	LFC131 peptide conjugation	Delivery of sorafenib and metapristone	[103]
	Nanoprecipitation/ prodrug encapsulation	Hep3B	–	Delivery of SN38	[104]
	Nanoemulsion/solvent evaporation	SMMC-7721	Conjugation of anti-AFP	Delivery of brucine	[105,106]
	Nanoprecipitation/ drug encapsulation	BEL-7402	iRGD peptide conjugation	Delivery of vandetanib	[107]
	Ultrasonic emulsification/solvent evaporation	HepG2, HCa-F cells	–	Delivery of emodin	[108]
	Nanoprecipitation/ capping with dopamine	HepG2	Galactosamine conjugation	Delivery of docetaxel	[109]
	Solvent diffusion/antibody conjugation	HepG2	Anti-VEGF conjugation	Imaging only (Embedded Gd complex)	[110]
Polysaccharide NPs	Dialysis/sonication method	HepG2	–	Delivery of doxorubicin	[111]
	Nanoprecipitation	H22, HepG2	Galactose from pectin/folic acid conjugation	Delivery of dihydroartemisinin	[112]
	Sonication/crosslinking pullalan	SMMC-7721	Folic acid conjugation/GSH responsive	Delivery of paclitaxel	[113]
	Nanoprecipitation	HepG2	Targeting of ASGPR w/ galactose	Delivery of doxorubicin	[114]
	Nanoprecipitation/dialysis	HepG2	Glycyrrhetinic acid conjugation	Delivery of doxorubicin	[115]
Other polymers	Nanoprecipitation/PEG capping	HepG2	Lactobionic acid conjugation/ GSH responsive	Delivery of 10-hydroxycamptothecin and siBcl-2	[116]
	Oxidative polymerization	Hep3B	SP94 peptide conjugation	Photothermal therapy	[117]
	Nanoprecipitation	Hep3B, HepG2, C3A, SK-HEP-1	–	Delivery of DNA	[118]
	Nanoprecipitation/dialysis	HepG2, Hepa-1.6	Glycyrrhetinic acid conjugation	Delivery of doxorubicin and shRNA	[119]
Chitosan/Chitin NPs	Tripolyphosphate cross-linking	SMMC-7721	Galactose conjugation	Delivery of triptolide	[120]
	Ionic crosslinking	HepG2	–	Delivery of honokiol	[121]
	Nanoprecipitation	H22, LO2, SMMC-7721	Biotin conjugation	Delivery of plasmid DNA	[122]
	Dialysis	H22, HU7,	–	Delivery of adriamycin	[123]
	Tripolyphosphate cross-linking	HepG2	–	mRNA apoptotic gene expression	[124]
Lipid NPs	Thin-film dispersion/ultrasound emulsification	SMMC-7721	Hyaluronic acid incorporation	Delivery of 10-hydroxycamptothecin	[125]
	Encapsulation of doxorubicin w/ lipid film	SK-HEP-1	SP94 peptide conjugation	Delivery of doxorubicin	[126]
	Encapsulation of drugs w/ lipid film	HepG2	iRGD peptide conjugation	Delivery of doxorubicin and sorafenib	[127]
	Emulsion microfluidics	HepG2	–	Delivery of doxorubicin and curcumin	[128]
Carbon Dots (CDs)	Hydrothermal pyrolysis/emulsion in lipid CaPO4 NPs	HepG2	pH sensitivity	Delivery of doxorubicin	[129]
	Hydrothermal pyrolysis of Mn(III) acetylacetonate	HepG2	–	Restrains migration for adjuvant therapy	[130]
	Pyrolysis/assembly of individual CDs	HepG2	Peptide conjugation	Photothermal therapy generated hyperthermia	[131]
	Pyrolysis/incorporation in liposomes	HepG2	Mannose conjugation	Targeted imaging only	[132]
	Pyrolysis of berberine	HepG2, HL-7702	–	Delivery of berberine-like structure	[133]
	Pyrolysis of glycine/Gd complex	HepG2	–	Increased efficiency of radiotherapy	[134]
	Microwave-mediated	HepG2	pH sensitivity	Delivery of doxorubicin	[135]
Chemotherapeutic NPs	Electrostatic spray	SMMC-7721	–	Delivery of paclitaxel	[136]
Albumin NPs	Nanoprecipitation/desolvation	HepG2	Galactose conjugation	Delivery of curcumin	[137]
	Emulsion/homogenization	HepG2	Lactose conjugation	Delivery of doxorubicin and paclitaxel	[138]
Peptide NPs	Self-assembly/solution mixing	Huh7	Conjugation of lactobionic acid	Delivery of miRNA-199a-3P	[139]
Vesicle NPs	Extraction of vesicles from milk	Hep3B, LCSC	–	Delivery of siRNA	[140]

The dual potential of iron oxide NPs was exhibited by Maeng et al. with a nanosystem including doxorubicin as a therapeutic and folate as a targeting ligand. [63] These NPs were able to reduce tumor size in rats' livers significantly more than a treatment of doxorubicin alone. Furthermore, the location of the DDS was able to be determined through the use of MR imaging. More recent chemotherapeutics have been used in conjunction with iron oxide NPs as Denora and coworkers incorporated sorafenib into their DDS. [62] In this case, phospholipids were used to coat the NPs and encase the sorafenib, and magnetic force was shown to increase the uptake of the particles to HepG2 cells,

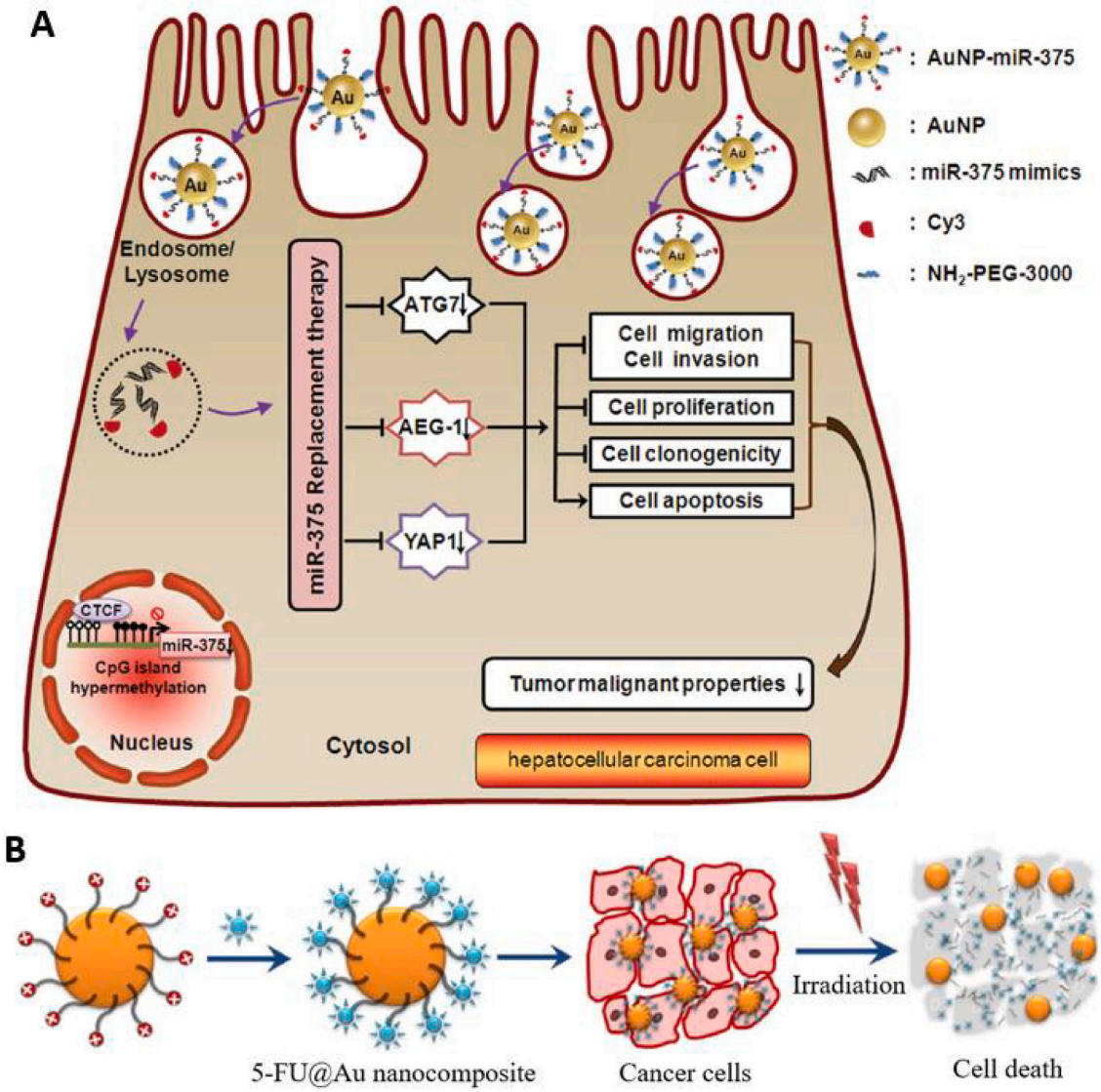

Fig. 2. (A) Schematic diagram of gold NPs delivering miR-375 for replacement therapy in HCC (miR-375 is downregulated in HCC cells, replaced by this system), used from Ref. 45 with permission from Impact Journals. (B) Illustration of the treatment of cancer cells with 5-FU@ gold NPs for chemo-photothermal therapy, reprinted with permission from Ref. 42 from Elsevier.

interestingly without affecting cell viability (a control without sorafenib present). While this concept is promising, the use of magnet-guided delivery *in vivo* introduces further complications as care must be taken that the magnetic nanoparticles do not cause damage to healthy tissue in the body. Biomolecules have also been delivered as therapeutics with iron oxide NPs. In 2018, Yang et al. developed a DDS which delivered siRNA to the liver of tumor bearing mice. [59] The siRNA chosen was able to target tyrosine-protein kinase Met, the receptor for the hepatocyte growth factor, which plays an important role in the proliferation of HCC. The authors found that the NPs shielded the siRNA from serum degradation, increasing the half-life in the blood. This system was able to reduce tumor volume by ~60%. The ability to deliver more than organic molecules is an important ability as investigation of peptides, RNA, and other biomolecules is currently being extensively investigated. [158,159]

Further work regarding imaging with iron oxide NPs was performed by Liang et al. [61] In this study a near-infrared active dye (IR-783) was incorporated with the iron oxide NPs to create a dual imaging material utilizing MR imaging and fluorescence imaging. To create specificity, a polymer (Gal—P_{123}) was added to the surface of the NP which targeted the asialoglycoprotein receptor which is overexpressed by hepatocellular carcinoma cells. The biofluorescence imaging revealed localization of the system mainly in the liver/tumor and kidneys with increased specificity arising from the incorporation of Gal-P_{123} (GPC@IR783-Fe_3O_4). This targeted approach also yielded greater than 5× signal enhancement over IR783-Fe_3O_4 from the MR images.

The magnetic properties of iron oxide NPs can also be exploited to utilize the particles as therapeutics themselves. Maity and coworkers developed NPs which were used to induce hyperthermia in HepG2 cells. [60] Different surfactants were used to produce NPs which were biocompatible, water stable, and shows high magnetization values. From these objectives 3,4-diaminobenzoic acid was shown to be the best surface molecule as it displayed a killing efficiency of 88%. This was achieved by applying an alternating magnetic field with an amplitude of 10.9 kA/m and a frequency of 751.51 kHz which compelled the internalized NPs to generate heat which produced the cell death. Translation of this concept to *in vivo* systems would require an *in vivo* targeting mechanism or localized exposure to the magnetic field to contain the hyperthermic effect to the liver. A similar approach, with a different mechanism of action, was used by Dejneka and coworkers in 2019 (Fig. 3C). [58] The NPs in this case (super paramagnetic iron oxide NPs, SPIONs) induced lysosomal leakage which was induced by application

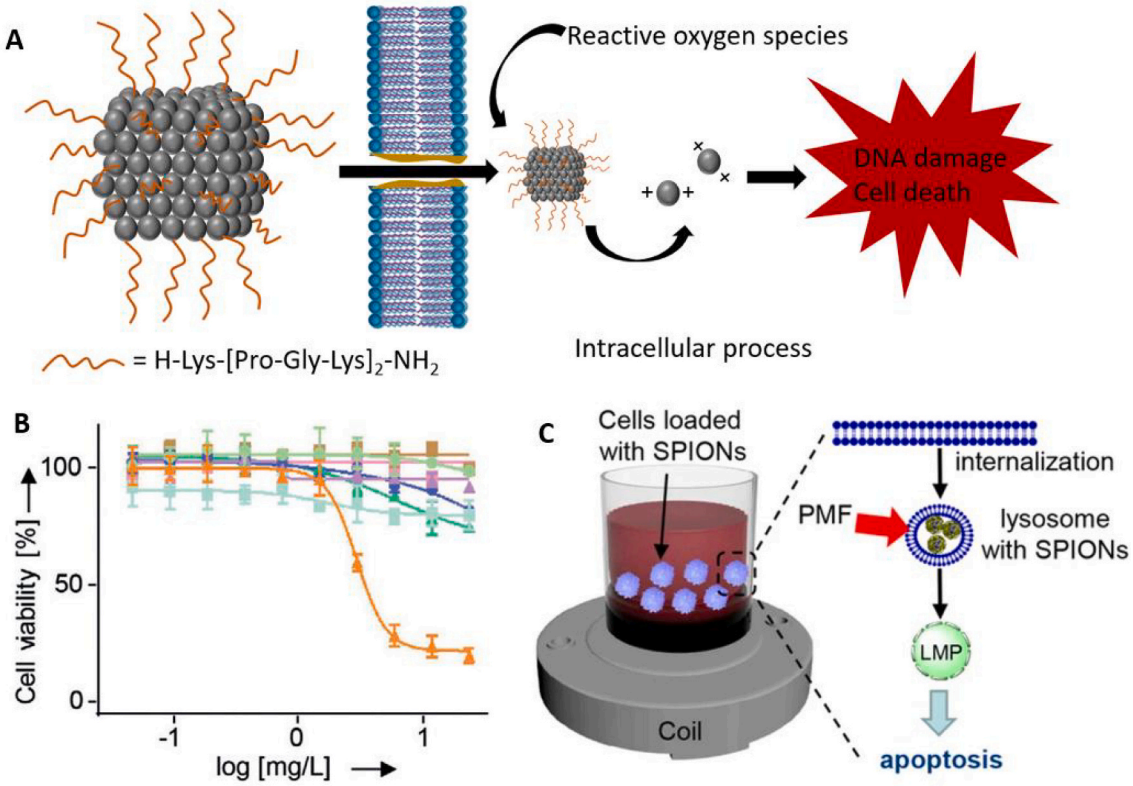

Fig. 3. (A) Schematic showing the ability of platinum NPs to induce toxicity in oxidative cells through release of Pt (II) ions. (B) Viability of human cancer cells treated with platinum NPs: HepG2 (dark orange), HT-29 (light green), MCF-7 (rose), HeLa (lilac), PC3 (brown), A431 (blue), A549 (turquoise), A2780 (green), used with permission from Ref. 56 from John Wiley and Sons. (C) Diagram showing the potential for iron oxide NPs (SPIONs) to remotely induce apoptosis, reprinted with permission from MDPI from Ref. 58.

of a pulsed magnetic field. The authors estimated that a force of 500 pN was needed to produce this leakage which led to mitochondrial damage and apoptosis. This strategy was further validated by a 3D cell model meant to mimic *in vivo* systems, but again, care must be exercised when applying this type of therapy in biological systems to localize the effect to the cancerous region.

The diversity of capabilities makes iron oxide NPs an intriguing material on which to base a DDS. Most of the systems discussed here utilize a polymer to increase biocompatibility, but the ability of these NPs to act as a carrier, imaging agent, and therapeutic illustrates the potential ability of this class of material to provide combinatorial therapy. The main drawback for iron oxide NPs is related to biocompatibility and clearance from the body, issues which have not been fully addressed in the literature.

2.2.2. *Other metal oxide NPs*

In addition to iron oxide NPs, there has been several other NPs composed of metal oxides which have been shown to have potential in the treatment of liver cancer. Alumina NPs were generated by Gao et al. to deliver paclitaxel to cancer cells *in vitro* and *in vivo*. [70] These were coated with hyaluronic acid to increase cellular uptake through the P-glycoprotein 1 receptor and it was also shown that this coating allowed paclitaxel to achieve a slower release from the hollow alumina NPs.

Several examples of arsenite NPs use for HCC treatment have been reported recently. Duan and coworkers prepared arsenite NPs using a double emulsion method to encapsulate As_2O_3 in a polymer shell. [66] Delivery of As_2O_3 cancer cells was believed to activate caspase 3 which cleaved the GSDME gene triggering pyroptosis (Fig. 4A). The As_2O_3 NPs showed enhanced efficacy over treatment with As_2O_3, indicating enhanced efficiency of therapy from the NP form of the compound. In 2019, Shan and coworkers developed arsenite based NPs encapsulated in silica which showed 2-3 times more efficacy (based on IC_{50}) values than treatment with arsenic trioxide alone. [67] These display exciting potential due to their ability to prevent tumor formation *in vitro* and initiation *in vivo* by reducing markers for stemness and epithelial-mesenchymal transition. A histological analysis of the organs in BALB/c nude mice after treatment showed that a majority of NPs accumulated in the tumor and liver, but some did accumulate in other sensitive areas such as the heart and lungs (Fig. 4B). The same researchers expanded on this nanosystem by incorporating iron oxide, in addition to arsenite, in the silica shell of the NP in order to incorporate an imaging functionality and attached folate to the surface of the NP as a targeting ligand (Fig. 4C). [68] Release profiles showed the As (III) ion release was much more effective in acidic pH values compared to neutral pH, which is favorable for targeted release in cancer cells. The addition of folate to the surface of the NPs showed a significant enhancement of cytotoxicity towards SMMC-7721 cells (IC_{50} = 0.36 μM) compared to the PEG coated NPs (IC_{50} = 1.46 μM). The incorporation of iron oxide allowed MR imaging of the NPs *in vivo*. This multifunctional DDS is very promising, but further studies are needed to focus the NP delivery to the liver alone to reduce harmful effects to other organs.

Zinc oxide NPs are another example of a metal oxide which has been tested against liver cancer cells, although the mechanism of action is much different than the previous examples. Iswarya et al. prepared zinc oxide NPs through a bioreduction method, utilizing a 3-glucan binding protein to reduce Zn ions and coat the surface of the NPs to increase their cellular uptake. [65] The reduction in viability of HepG2 cells after treatment with these NPs was believed to be due to membrane permeation which facilitated protein and nucleic acid leakage leading to cell death. The use of zinc oxide NPs was further explored in 2019 by Yu and coworkers. [64] ROS production and membrane permeation were important factors in the anticancer activity of these NPs. These effects combined to upregulate proapoptotic proteins and downregulate anti-apoptotic proteins. The mechanisms of membrane permeation and ROS

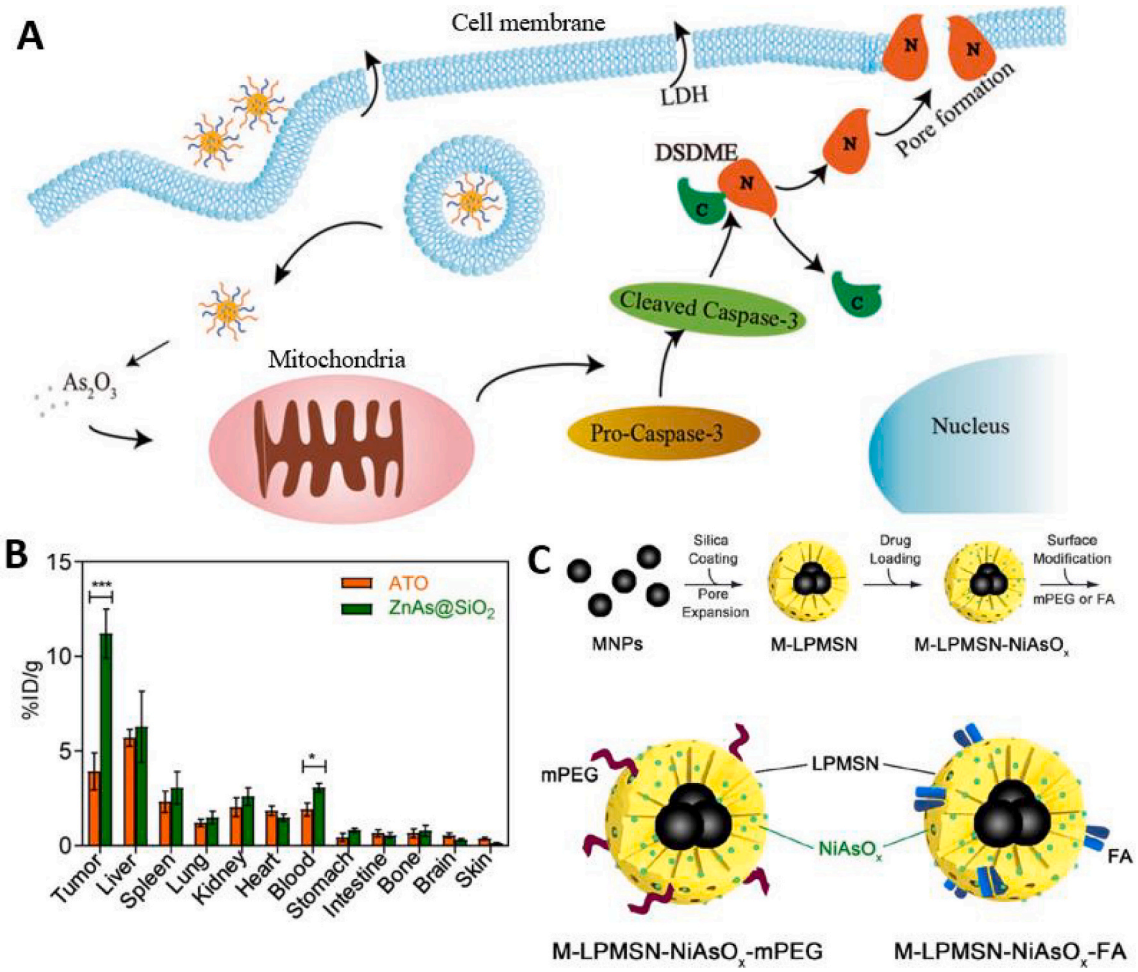

Fig. 4. (A) Mechanisms of pyroptosis induced by As_2O_3-NPs in HCC, reprinted from Ref. 66 with permission from Nature Publishing Group. (B) Biodistribution of arsenic cations in mice 24 h post-intravenous injection of arsenic trioxide (ATO) and $ZnAs@SiO_2$ NPs ($n = 3$), reprinted from Ref. 67 with permission from Ivyspring International Publisher. (C) Schematic diagram of the assembly of M-LPMSN-$NiAsO_x$ nanoparticles. Spherical MNPs (black) were coated with a silica shell (yellow). $NiAsO_x$ (green) was then loaded inside the porous silica structure. M-LPMSN-$NiAsO_x$ nanoparticles were further coated with mPEG (purple) or folic acid (FA, blue), used from Ref. 68 with permission from IOPscience.

production are effective in producing cell death, but as mentioned for silver NPs there must be great care given in these situations to target the desired area as these are not selective processes. For this reason, zinc oxide NPs are not widely researched for this purpose.

The last metal oxide which will be discussed is hafnium oxide NPs. These are used in conjunction with radiotherapy to increase the radiation dose at the site of the tumor to enhance the efficacy of the therapy. Maggiorella et al. have shown that this effective radiation dose can be enhanced by 15% compared to radiation alone. [160] This is achieved by the high electron density of the hafnium nucleus which enhances absorption of the radiation at the treated site. Marill et al. showed that the dose enhancement can be predicted based on the local nanoparticle concentration. [161] This type of treatment has recently been explored in clinical trials for several cancers, including HCC. [69,162,163] Clinical trial NCT02721056 was terminated after determining the highest dose with acceptable toxicity (RP2D) for intratumoral injection and a separate phase II trial is being designed. Clinical trial NCT02379845 for soft tissue sarcoma was completed in April 2021 and this study showed that the use of hafnium oxide NPs doubled the rate of a pathological complete response over radiotherapy alone (16% to 8%, respectively). [163] This same system is also currently recruiting for a phase 1 study related to mouth cancer (NCT01946867).

As is apparent from this section, diverse metal oxides result in quite varied approaches to treating liver cancer. The challenges for these materials lie in producing a selective and specific therapy which will not result in the harmful side effects typically associated with cancer therapy. Some researchers have overcome this by including a targeting ligand and the use of nanoparticles (as opposed to free molecules or compounds) seems to intrinsically enhance delivery to appropriate targets. Iron oxide NPs are particularly promising as they have the ability to act as a carrier, therapeutic, and imaging agent. A final concern for metal oxide NPs involves clearance of the DDS from the body. This could be potentially solved through design of the NP size and charge, but it is an important consideration to increase biocompatibility.

2.3. Other inorganic NPs

2.3.1. Calcium based NPs

Calcium NPs have been widely investigated since calcium is widely present in the human body. Zhao et al. developed calcium carbonate NPs which were coated in a cationic lipid coating. [73,74] This NP design generated a pH sensitive effect which was sensitive to the tumor microenvironment, a biodegradable NP, and increased circulation time by escaping clearance by the reticuloendothelial system. These NPs were used to deliver microRNA-375 (miR-375), which is downregulated in HCC, in conjunction with doxorubicin [74] or sorafenib. [73] This strategy increased the concentration of chemotherapeutic in the tumor, liver, and spleen, relative to treatment with the drug alone, and

decreased the amount of drug being delivered to the heart, lungs, and other organs. Cytotoxicity was increased *in vitro,* and mice treated with the DDS showed reduce tumor volume without reducing the body weight of the mice. Wu et al. also combined RNA and a small molecule for HCC treatment. [72] In this case, a calcium phosphate (CaP) core was used with a lipid shell to deliver Beclin 1 siRNA and fingolimod (FTY720). The siRNA in this case was used to reduce autophagy by the cancer cells which increased sensitivity to FTY720. Fluorescence imaging of treated mice showed that most of the DDS was delivered to the liver and tumor compared to the kidneys, and the combined system showed more efficacy *in vitro* and *in vivo* than delivery of the siRNA or FTY720 alone. This shows the promise of combinatorial therapy and the potential of these NPs to effectively deliver the two compounds. CaP NPs have also been used as imaging agents by incorporating gadolinium, an MRI active nucleus. [71] This delivery method was able to vastly increase the concentration of Gd in the tumor, liver, and kidneys in mice compared to treatment with a free Gd complex. When a targeting peptide was attached (A54), Gd concentration was further enriched in the tumor indicating this may be a good tool for early diagnosis of HCC, although the high concentration of NPs in the kidneys shows the need for further optimization (Fig. 5A). The system displayed no side effects in mice further displaying the promise as a diagnostic tool, although the system could be extended as a treatment method with incorporation of a therapeutic as previously discussed.

A different material involving calcium which has been researched for treatment of liver cancer is hydroxyapatite NPs. Bauer et al. used a precipitation method to create needle-like NPs which were 20 nm wide and 100 nm long. [90] These were shown to have uptake in HCC cells by clathrin-mediated endocytosis and the toxic effect of the NPs was thought to be due to physical damage to the cells from the needle-like structure as well as release of ions from the NP which reduced potassium concentration in the cells. Zhang and coworkers used a similar method with the exception of doping with selenium ions to replace some calcium atoms in the structure of the hydroxyapatite NPs. [89] Interestingly, these NPs did not reduce tumor volume in mice compared to a control and simple hydroxyapatite NPs, but they did increase survival and health of the mice at 36 days. This was thought to be due to the release of selenium ions in the liver and kidney which improved organ function. This may be an important strategy to combine with a separate therapeutic to ameliorate side effects and improve survival rates in cancer patients.

Calcium complexes overall show promise for the development of DDS for liver cancer treatment. Calcium-based NPs show strong biocompatibility and the ability to incorporate multiple compounds to achieve diverse functionality. The susceptibility of calcium-based NPs to pH is a limitation for some systems but could potentially be exploited for selective release of drugs in cancer cells. These studies compel further work to optimize a DDS for potential future use in humans.

2.3.2. Selenium based NPs

Selenium was mentioned in the previously discussed hydroxyapatite NPs as a potential promoter of organ health in the process of liver cancer

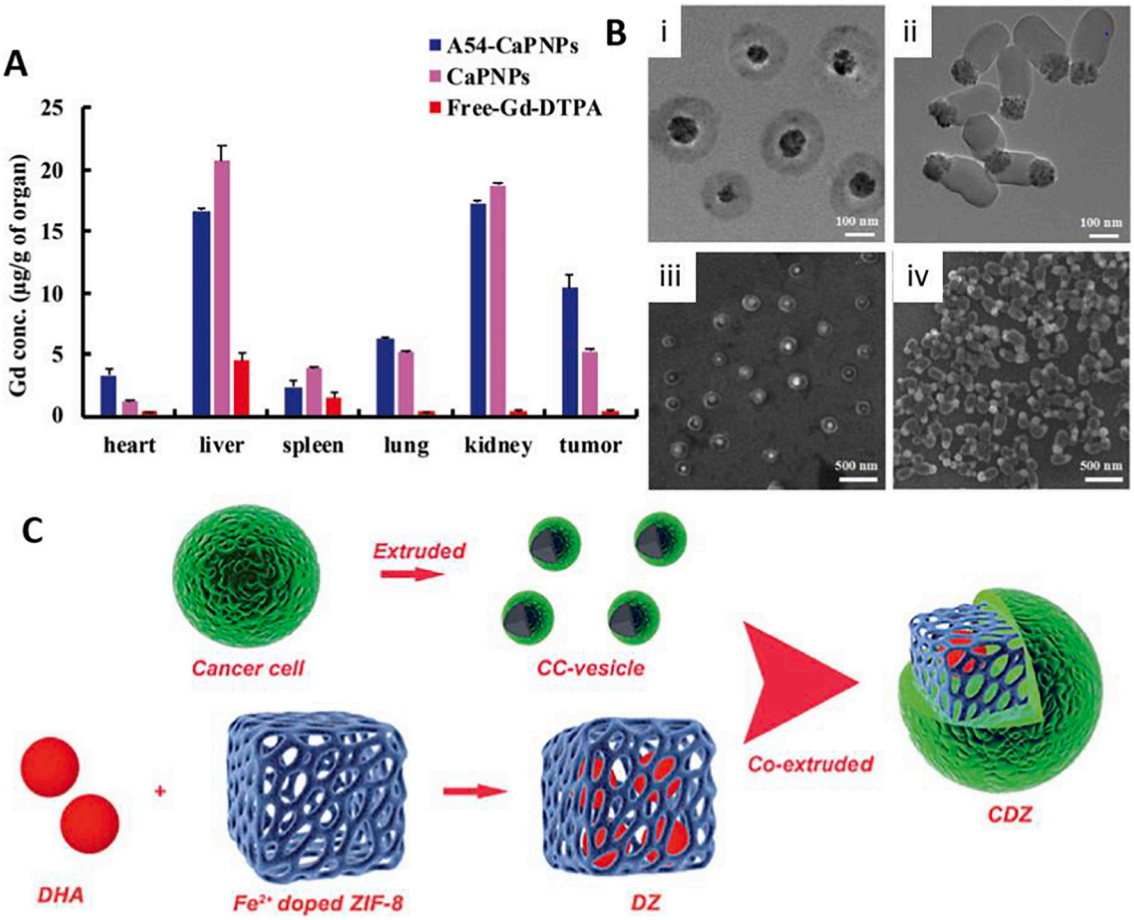

Fig. 5. (A) *In vivo* biodistribution of Gd (III) ions in mice bearing BEL-7402 tumors at 1 h post administration of peptide conjugated A54-CaPNPs, CaPNPs and free gadopentetic acid (Gd-DTPA), used from Ref. 71 with permission from The Royal Society of Chemistry. (B) Characterization of different magnetic silica NPs (MSNs): (i) TEM and (iii) SEM images of the spherical MSNs and (ii) TEM and (iv) SEM images of the rod-like MSNs, used from Ref. 79 with permission from Elsevier. (C) Schematic illustration of cancer cell membrane-camouflaged pH-sensitive and ferrous ion-doped MOF nanoparticles loaded with dihydroartemisinin (DHA), reprinted from Ref. 94 with permission from The Royal Society of Chemistry.

treatment. Primarily selenium-based NPs have also been studied as drug carriers for treatment of HCC. Fang et al. used ascorbic acid as a reducing agent to prepare selenium NPs which encapsulated baicalin and they capped the surface with folic acid as a targeting group. [88] Baicalin is a traditional Chinese medicine which has been used for the treatment of hepatitis B, which could be an important factor in some liver cancer patients as the hepatitis B virus is thought to increase the risk of liver cancer. The NPs showed 4× uptake in HCC cells compared to normal liver cells (L02) due to the increase expression of folate receptors and displayed enhanced toxicity to the HCC cells as well ($IC_{50} \sim 20$ μM, approximately 5× lower than for L02 cells). These NPs were shown to target the lysosome of cells and were also able to downregulate intracellular ROS expression. Zhu and coworkers used a similar approach to deliver doxorubicin to cancer cells, with the exception of using galactose as a targeting ligand. [86] These displayed pH dependent release of doxorubicin and reduced cell viability in HepG2 cells to 25% at 16 μg/mL. In contrast, the DDS without doxorubicin displayed over 95% cell viability in the same cell line at the same concentration. This nanosystem showed similar efficacy *in vivo* with no apparent harmful effects to the heart and other important organs. The same authors used selenium NPs for delivery of siRNA as well. [87] In this case HES5-siRNA was used as it can silence the HES5 gene which can inhibit tumor growth.

As a carrier, selenium NPs can deliver both small molecules and RNA to tumor sites and there is also a suggestion that release of selenium ions at the delivery area can mitigate harmful effects from any therapeutic. However, the inorganic surface is not easily manipulated, so selenium would best be used by integration into another DDS (*e.g.*, polymeric NPs) to replicate the mitigation effect without the need for drug encapsulation in selenium.

2.3.3. Silica NPs

Silicon is a widely used element for semiconductors, but it has also found use in drug delivery in recent years. Silicon dioxide is quite cheap as it is ubiquitously found in nature and is essentially non-toxic, although inhalation of fine silica particles can result in varying health problems. [164,165] Silica's use in nanomedicine is almost entirely limited to mesoporous silica NPs (MSNs) as they possess small pores (2-30 nm) which are capable of entrapping and carrying small molecules. [166] Wu and coworkers developed MSNs through a precipitation method which trapped doxorubicin in the pores, and then they entrapped the particles in a shell of alginate. [85] These were coupled with a K_4YRGD peptide to facilitate selectivity to HepG2 cells. A similar method was used to deliver ursolic acid which exhibited a pH sensitive and sustained release. [84] Delivery of curcumin [82], doxorubicin again [75], and co-delivery of cetuximab and doxorubicin [83] has been achieved in recent years using various targeting ligands to improve selectivity. Interestingly, the co-delivery system showed redox responsive properties, as glutathione molecules in cancer cells triggered the release of cetuximab. [83] Xue et al. also used a codelivery strategy using MSNs to deliver doxorubicin and miR-375 (microRNA known to induce apoptosis in HCC cells). [81] This system showed efficacy in several cell lines including, significantly, drug resistant HepG2 cells. Activity against these resistant cells was observed due to the ability of the miR-375 to downregulate control of the drug efflux pumps in the cells. Researchers have also used a more traditional therapeutic, platinum, with MSNs. [80] In this case the metal atom was introduced into the MSNs as cisplatin (IV) as a prodrug which could be reduced to platinum (II) in the cancer cells and so reduce undesired toxicity. Dong and coworkers used a joint silica/iron oxide NPs for combination of magnetic and carrier properties. [79] The author reported spherical and rod-like NPs (Fig. 5B) where the two components were oriented differently. The rod-like NPs showed higher drug-loading capability, faster drug-release, and improved gene delivery with the aid of an electromagnetic field. The preceding examples show the strong capability of MSNs to act as a drug carrier, but they are also able to be used as a therapeutic themselves.

In 2019, Niu et al. showed that commercially acquired silica NPs were able to exhibit enhanced toxicity towards HCC cells, whether they were drug resistant or not. [77] To achieve photothermal therapy with silica NPs, Ma et al. embedded IR780 in MSNs and coated the NPs with a CAR-T cell membrane to achieve a biomimetic system with specific targeting. [78] The CAR-T cell membrane produced excellent targeting ability, with a majority of IR780 being found in the tumor and liver and almost none in the heart. Chang and coworkers used a similar photothermal approach combined with delivery of sorafenib. [76] Mice treated with this combinatorial approach showed drastically reduced tumor size and a 100% survival rate over the course of the 24-day study. In 2019, a core-shell NP was used with MSNs as a core coated in a shell of gold to develop a similar chemo/photothermal therapeutic approach. [167]

Silica NPs show strong capability as a carrier of small molecules and biomolecules. Their mesoporous structure allows for this property and also can exhibit a controlled release based on pH or reductive stimuli. Additionally, their ability to produce combinatorial therapies is promising, particularly for resistant strains of liver cancer.

2.3.4. Special structure NPs

In addition to the general classes of inorganic NPs discussed above there are several types of NPs which have a specialized structure and/or function which have been used as anticancer agents against HCC. In 2020, Xiao et al. used a MOF NP composed of a zeolitic imidazolate framework for this purpose. [94] This MOF structure was doped with Fe (II) ions and encapsulated dihydroartemisinin (DHA) (Fig. 5C). Targeting cancer cells was enabled by embedding the NP in a cancer cell membrane to create a biomimetic system. When the NP reached the low pH microenvironment of the cancer cell or tumor site, the release of DHA was compelled which interacted with Fe^{2+} to generate ROS which created the anticancer effect. This strategy achieved over 90% tumor inhibition and the cancer membrane surface enabled high selectivity to liver cancer tumors *in vivo*. Multifunctional Janus NPs were developed for dual drug delivery, photothermal therapy, and MR imaging. [93] This nanosystem was sensitive to NIR light which not only facilitated photothermal therapy, but, coupled with the pH properties of cancer cells, allowed for sequential release of doxorubicin and docetaxel. These again showed greater than 90% tumor inhibition in mice with no obvious side effects to the animal. The location of the Janus NP was able to be tracked through MR imaging and due to its selectivity is a promising tumor imaging agent.

Upconversion NPs have also been shown capable of generating a multifunctional DDS for liver cancer treatment. Tang and coworkers generated $NaYF_4$:Yb,Er upconversion NPs and coupled them with a cell adhesion molecule antibody as well as mitoxantrone. [92] This system is capable of imaging through MR and upconversion luminescence. Additionally, the NIR sensitivity enabled generation of $^1O_2$ for photodynamic chemotherapy. Combined with the release of mitoxantrone this system shows promise as a combinatorial therapeutic, as tumor growth in mice was not only inhibited but reduced effectively to zero volume. In 2020, a similar strategy was used to co-deliver hydroxycamptothecin and doxorubicin. [91] This dual-drug delivery was coupled with the commonly used photothermal capability of upconversion NPs and MR and luminescence imaging to demonstrate a multimodal anticancer tool. Similar to the previously discussed study, this system showed the capability to reduce tumor volume to almost zero *in vivo*. The multiple potential pathways of these NPs to be used as a therapeutic compels further studies to maximize their efficacy and ensure biocompatibility in the short and long term.

The diverse elements and types of NPs described in the sections above illustrates the numerous pathways nanotechnology can address the issue of liver cancer therapy. Strengths and weaknesses of these various approaches will be evaluated in the conclusions and future outlook section at the end of this review.

3. Carbon based NPs

This section will discuss carbon-based, mostly organic, NPs and their proven potential for the treatment of HCC *in vitro* and *in vivo*. The NPs presented will obviously be less elementally diverse, but carbon-based materials have the potential to be highly biocompatible and biodegradable, which compensates for the lack of multifunctionality, as most (but not all) carbon-based NPs are used as carriers only. Despite this restricted capability, many NPs in this category show enormous potential as the foundation for a DDS to treat liver cancer.

3.1. Polymeric NPs

3.1.1. Polyethylene glycol (PEG) NPs

PEG is perhaps the most ubiquitous polymer as it is commonly used as a laxative or excipient in the medical field and its chemical uses include as a hydrophilic coating, polar stationary phase, and as a protein linker, among others. [168] It is has shown utility in DDS for inorganic NPs as it can be coated onto the surface of a NP to increase circulation time in the blood. [169] Due to its simplicity of structure, it is often modified to some degree when used as the basis for a DDS as is the case for most of the research discussed in this section. Tang et al. developed NPs with PEG as a scaffold, and entrapped sorafenib as a therapeutic, while conjugating anti-*glypican 3* as a targeting ligand. [95] This system resulted in a tumor reduction of more than half compared to treatment with sorafenib alone. This DDS was shown to downregulate induced myeloid leukemia cell differentiation protein (Mcl-1) resulting in polymerization of membrane proteins which induced apoptosis. Furthermore, ROS production was also enhanced, and this indicates a synergistic mechanism between ROS production and apoptosis induction. The synergistic possibilities from a PEG-based DDS were also exhibited by Duan and coworkers. [96] In this case RGD peptide-modified PEG was precipitated in the presence of mitoxantrone followed by coating with calcium and phosphate ions and verapamil (Fig. 6A). This system showed a sequential release of drugs as mitoxantrone was released more slowly from the core (this release was triggered by the lower pH of cancer cells and the release of calcium and phosphate ions) than verapamil from the surface. The multiple components of this system allowed toxicity to be observed against multidrug resistant (MDR) cancer cells by slowing efflux of the chemotherapeutics. While this is a promising approach, this system needs optimization as significant accumulation of the DDS components was observed in the brain and lungs. Overall, PEG has shown the capability of producing promising drug delivery properties, but other polymers have been used more frequently for this purpose.

3.1.2. Poly (lactic-co-glycolic acid) (PLGA) NPs

PLGA is FDA approved for numerous medicals applications due to its biocompatibility and biodegradable properties. It can be prepared with the lactic and glycolic acid units randomly throughout the polymer or as a *co*-block polymer. This capability for modification allows versatility of PLGA depending on the application. [170] A *star*-shaped PLGA copolymer was used to prepare NPs which acted as a carrier for genistein which showed greater drug release and cellular uptake than the DDS based on the linear polymer. [102] The use of a targeting ligand may make this approach more viable moving forward, but the effect of the shape of the polymer is interesting and was attributed to increased hydrophobicity from the star-shaped form. In 2019, Feng et al. prepared a

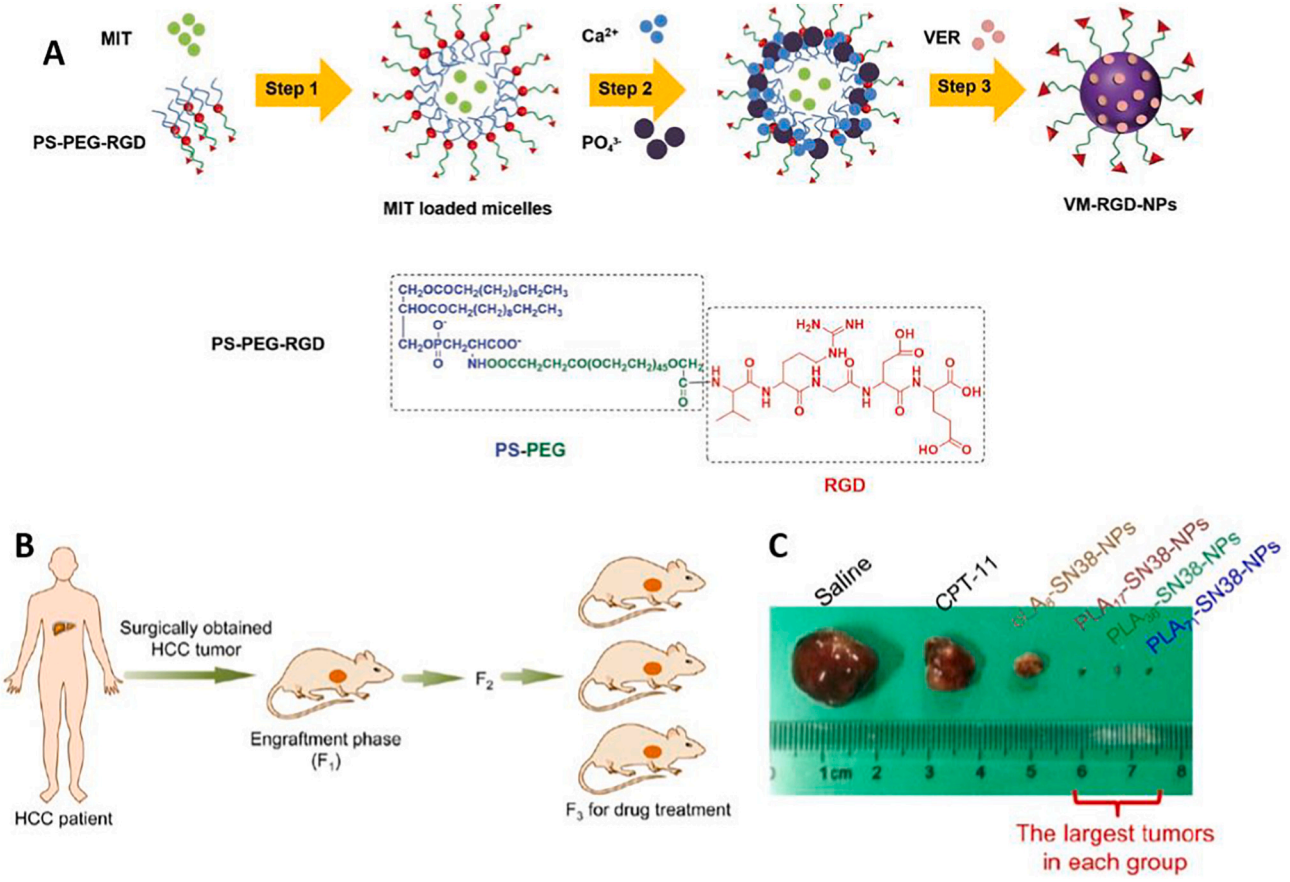

Fig. 6. (A) Multifunctional core-shell VM-RGD-NPs for treatment of MDR hepatocellular carcinoma, reprinted from Ref. 96 with permission from John Wiley and Sons. (B) Protocol for the establishment of a human HCC PDX tumor model in Balb/c nude mice. (C) Representative images of excised tumors from a Hep 3B cancer cell-derived xenograft nude mouse model using SN38-containing polymeric NPs, reprinted from Ref. 104 with permission from Ivyspring International Publisher.

PLGA/sorafenib core and coated with a phospholipid and PEGylated peptide specific to *glypican 3*. [97] The specificity provided by the peptide allowed most of the DDS to locate in the liver tumor (or liver) of mice and the system showed strong *in vivo* activity. This DDS, and many previously discussed, used sorafenib as the therapeutic as it is FDA approved to treat HCC, however it has been shown the cells can evade the sorafenib treatment by dimerizing RAF kinases and activating ERK signaling. [101] To avoid this, a PLGA NP was developed which encapsulated sorafenib and selumetinib (AZD6244), an MEK inhibitor which provided a dual mechanism against HCC cells. This system exhibited higher toxicity to HCC cells and tumor reduction, but more importantly may reduce the possibility for development of resistance to sorafenib. Another dual delivery was developed by Wei and coworkers who incorporated 10-hydroxycamptothecin and apoptin (a small protein which induces apoptosis) into PLGA NPs. [98] Lactobionic acid and biotin were used to target cancer cells, but an extra dimension of targeting capability was added by incorporating polylysine in the DDS as a nucleus targeting ligand. This tumor reduction from this system was very promising indicating that a high level of targeting capability is highly beneficial for future approaches.

An inorganic therapeutic was combined with PLGA in 2018 by Song et al. by encapsulating arsenic trioxide in PLGA NPs. [99,100] Through lactose acid conjugation some degree of targeting was achieved, but the combination of increased antitumor activity and reduced side effects over treatment with arsenic trioxide alone was not as significant compared to the enhanced properties obtained using the organic therapeutics discussed above. Attention will now be turned to studies which utilized PEG and PLGA in a DDS.

3.1.3. PEG/PLGA NPs

PEG-PLGA copolymers have been frequently used for the purpose of treatment of HCC, which is unsurprising as both are commonly used and FDA approved for different applications. Researchers have utilized this copolymer to generate NPs which have been used to deliver docetaxel [109], emodin [108], vandetanib [107], and brucine [105,106] for treatment of HCC *in vitro* and *in vivo*. A dual delivery system was developed by Jia and coworkers which incorporated sorafenib and metapristone, again to overcome and prevent drug resistance. [103] This DDS illustrated a burst release as 40-50% of the drugs were released within a few hours, but then developed a slow, sustained release as another 30% was released over the course of 10 days. A prodrug strategy was used by Wang et al. in an attempt to further limit harmful side effects in cancer therapy. [104] In this case, an anticancer molecule, SN38, was conjugated to polylactide and embedded in PEG/PLA NPs. This system displayed remarkable promise as tumor volume was reduced to almost zero and there was 100% survival of treated mice 90 days post-administration (Fig. 6B, C). The chain length of the polylactic acid used to create the NPs had some effect as the longest chain length (71) displayed the highest efficacy. The delayed release created by the prodrug approach and embedment of the drug in a NP most likely creates this performance. This is an intriguing model to follow for future systems to achieve sustained release.

Most work regarding polymeric systems are focused on treatment of liver cancer, but an early diagnosis of HCC can greatly affect the prognosis. In an effort to potentially achieve this detection, Zhang and coworkers used a copolymer to encapsulate a gadolinium complex for MR imaging. [110] Tumor selectivity was obtained for these NPs through conjugation to anti-VEGF, whose antigen is expressed to a greater degree in cancer cells and this system showed promise for the early detection of HCC. These simple polymers, PEG, PLGA, or some combination of the two, have shown promise as carriers of therapeutics, particularly when used in a combinatorial approach.

3.1.4. Other polymers

While PEG and PLGA are the most commonly used polymers for drug delivery, others have also been used with success in *in vivo* studies. Green and coworkers utilized poly(beta-amino ester) to create NPs which were shown to be capable of carrying DNA to treat HCC in a non-viral gene therapy approach. [118] In a co-culture model and *in vivo* these NPs were shown to be able to specifically transfect liver cancer cells over normal hepatocyte cells, illustrating the potential of DDS to facilitate gene therapy for cancer treatment. Poly(ethylenimine) was used to generate NPs decorated with glycerhettinic acid to co-deliver shRNA (shAkt1) and doxorubicin. [119] In addition to the apoptosis induced by doxorubicin, autophagy was enhanced by the RNA leading to increased activity over the DDS with doxorubicin alone. In 2020, Li et al. used a polymeric approach to develop a redox-responsive system to carry hydroxycamptothecin and siRNA (siBcl-2). [116] Similar to the previous study, a dual approach was used, but this time the siRNA silenced the anti-apoptotic gene. Jin et al. used polypyrrole to create a system for the diagnosis and treatment of HCC. [117] Diagnosis was achieved by attachment of a liver cancer selective peptide (SP94) which facilitated tumor accumulation and the system could be imaged by monitoring the fluorescence of the incorporated indocyanine green dye. Treatment with this system was achieved by laser induced photothermal therapy. The multi-functionality of this system and the potential to improve efficacy even further by incorporation of a therapeutic, shows the high potential for polymers as materials for DDS.

3.1.5. Polysaccharide NPs

Polysaccharides are the most abundant carbohydrate and are commonly manipulated into NPs through cross linking the sugar components or through self-assembly techniques. Some polysaccharides, such as pullalan have been shown to have intrinsic liver targeting capability, making them an ideal candidate for *in vivo* drug delivery to the liver. [171] Wang and coworkers used a polysaccharide from *Angelica sinensis* to self-assemble nanoparticles containing doxorubicin through a sonication/dialysis method. [111] These showed sustained, pH dependent drug release of doxorubicin and HepG2 cells were targeted through the asialoglycoprotein receptor which recognizes the sugar monomers such as galactose. *In vivo* this nanosystem showed enhanced tumor inhibition over doxorubicin alone, while showing no significant difference in the body weight of mice compared to the control. This illustrates the targeting capability of NPs based on saccharides.

In 2018, pullalan was crosslinked, loaded with paclitaxel, and decorated with folic acid as a targeting ligand. [113] This system not only displayed the targeting capability expected from the use of pullalan and folic acid, but also incorporated lipoic acid into the crosslinking of pullalan, and the disulfide bond of lipoic acid allowed for a redox responsive DDS which was sensitive to enhanced glutathione concentration. This system showed remarkable liver/tumor targeting and showed tumor reduction capabilities with reduced side effects compared to paclitaxel. Lei and coworkers also used a polysaccharide/folic acid targeting approach by preparing NPs based on pectin and conjugated to dihydroartemisinin and hydroxycamptothecin, molecules commonly used in the treatment of malaria and cancers, respectively (Fig. 7). [112] This system showed sustained release of both drugs, and the presence of two targeting mechanisms and two therapeutics allowed for strong *in vivo* performance as H22 tumor bearing mice showed a survival rate enhancement of 80% after 30 days of treatment compared to control mice and mice treated with the chemotherapeutics alone. Polysaccharide NPs in general are a promising material based on the asialoglycoprotein receptor targeting of the sugar monomers and have displayed versatility to be able to incorporate multiple targeting and therapeutic approaches.

3.1.6. Chitin and chitosan-based NPs

Chitin is a type of polysaccharide based on glucose and also incorporates nitrogenous side chains. It is the primary component of arthropods' exoskeletons and has been used for various applications in humans as well as agriculture. Chitosan is a derivative of chitin as it is prepared by treating chitin with a base (*e.g.*, hydroxide). [172] As a type

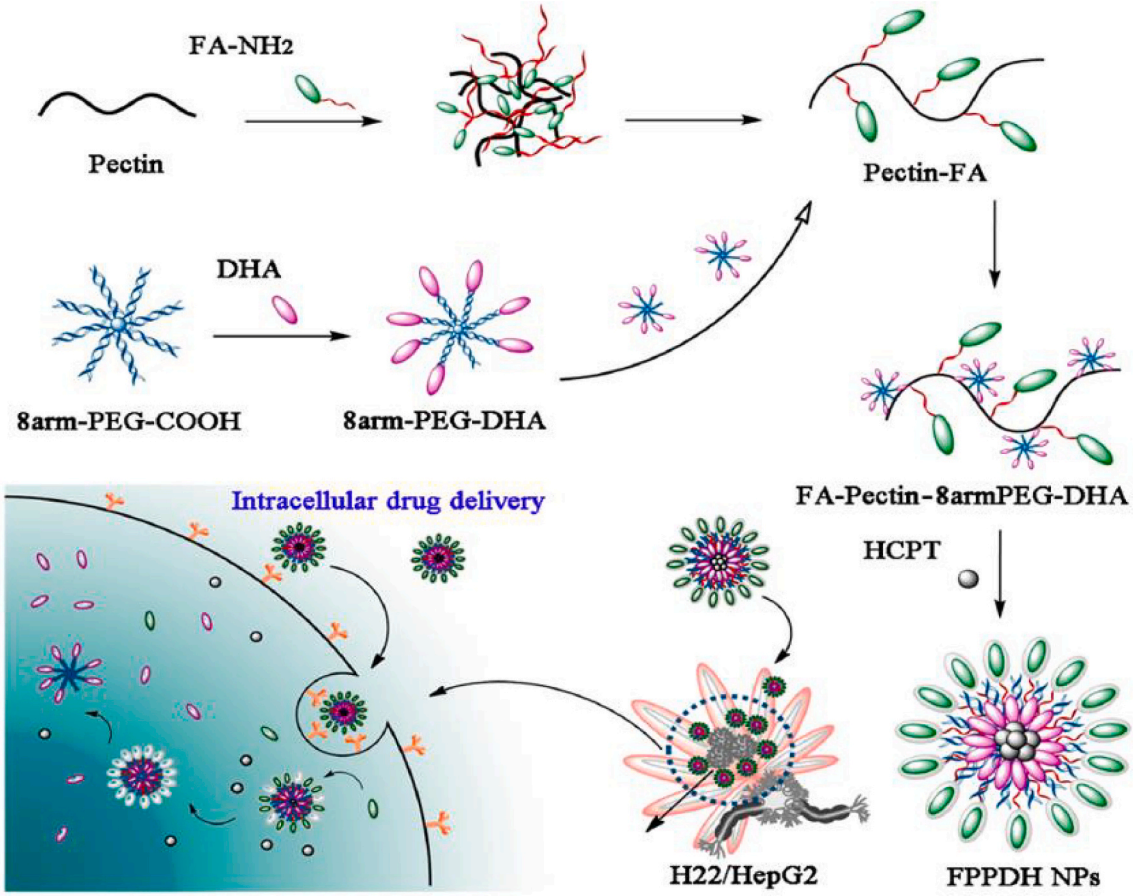

Fig. 7. (A) Schematic design for the pectin-based NPs and a diagram of these NPs dual targeting of liver cancer cells *via* folate receptors and asialoglycoprotein receptor protein. The chemotherapeutics delivered are dihydroartemisinin (DHA) and hydroxycamptothecin (HCPT), reprinted from Ref. 112 with permission from American Chemical Society.

of polysaccharide, drug delivery strategies typically follow the strategies detailed in the last section. Chitin/chitosan NPs have been used as the basis for DDS to carry doxorubicin and honokiol. [121,123] Loutfy et al. used chitosan NPs to delivery mRNA coding for apoptotic genes (caspase 3). [124] In 2019, Webster and coworkers utilized chitosan NPs conjugated with galactose to deliver triptolide to treat HCC in mice. [120] Hou and coworkers used the immune-stimulating properties of chitin to deliver plasmid DNA to generate an immune response towards HCC cells. [122] This cooperation of chitin with DNA may be an important concept to optimize and build upon for future work.

3.2. Lipid NPs

NPs comprised of lipids are often used in DDSs since many drugs are hydrophobic and can be easily entrapped in the non-polar environments of the lipid NP core. [173] Yang and coworkers prepared lipid NPs which encapsulated doxorubicin and curcumin. [128] These showed different release profiles, as doxorubicin show logarithmic release and curcumin's was more linear, and this creates the potential for synergistic and sustained therapy. A similar strategy was used to co-deliver sorafenib with doxorubicin, and specificity was created in this case by surface decoration with iRGD peptides which enabled strong *in vivo* performance. [127] A high level of targeting to the liver/tumor in mice was also obtained from attaching the SP94 peptide to lipid NPs containing chemotherapeutics. [126] A stimuli responsive approach was developed by Zhao et al. by preparing lipid NPs encapsulating 10-hydroxycamptothecin combined with focused ultrasound. [125] After mice were treated with the lipid-based DDS, ultrasound waves were focused on the desired area, in this case the liver, which induced the release of the anticancer drug. This additional level of targeting allows for further protection against undesired side effects. Lipid NPs are mostly limited to acting as carriers in DDS but have been shown to be effective in this capacity. Surface engineering of these NPs is vital, not only for targeting purposes, but also to facilitate the release of drugs from their hydrophobic core.

3.3. Carbon dots (CDs)

CDs are a relatively new class of nanoparticle which has shown great promise in areas such as bio-imaging, sensing, and drug delivery. This is because CDs display excellent optical properties, biocompatibility, and ease of surface modification. CDs are small, carbon-based nanoparticles which typically have a size between 1 and 10 nm. [174] They commonly exhibit excitation-dependent emission with the strongest intensity in the blue region of light. CDs' emission in blue and green wavelengths commonly possess high quantum yields, of photoluminescence but in longer wavelengths such as orange and red the quantum yield for CDs remains quite low. [175,176] The surface of CDs usually possesses simple organic functional groups such as carboxylic acids, alcohols, and amines. [177,178] This functionality allows ligands to be conjugated through simple organic coupling reactions. CDs with carboxylic acid groups are commonly conjugated to molecules with amines through an amide bond. Other strategies have also been adopted to take advantage of different functional groups. [179] The optical properties, surface functionalization, and size of CDs creates the large potential for use as a DDS for treatment of liver cancer.

CDs are traditionally used as carriers of chemotherapeutics through covalent conjugation. [180,181] Zeng et al. used an electrostatic conjugation with CDs and doxorubicin to create a pH dependent DDS.

[135] Due to the small size of CDs, they were able to localize, in mice, almost exclusively in the tumor, liver, and kidneys, with a large majority of the fluorescence intensity observed in the liver cancer tumor. The electrostatic nature of the conjugation creates a degree of cancer selectivity, since the more acidic microenvironment of cancer cells will compel dissociation between the CDs and drug molecule. Care must be exercised for electrostatic systems, as this relatively weak attraction may be disrupted in the blood or healthy cells. Another strategy involving CDs which are active against cancer is through direct pyrolysis of an organic therapeutic. Some CDs have been shown to retain structural features of their precursors and so retain the ability of the precursor molecule. [182] A general structural hypothesis for these types of preparations for CDs is shown in Fig. 8A. In 2018, berberine, a molecule with some anticancer activity was directly pyrolyzed to create CDs. [133] These CDs, without further treatment were able to mainly localize in the tumor and liver in mice (Fig. 8B) and showed higher efficacy *in vitro* and *in vivo* over treatment with berberine with no obvious side effects (Fig. 8C). This strategy shows a great deal of promise, as it allows the therapeutic to localize in the liver based on the size properties of CDs, but further optimization is needed to selectively target cancer cells.

A common approach used to prepare CDs is heteroatom doping. Wang and coworkers prepared Mn (III) doped CDs which displayed temperature dependent fluorescence and the ability to restrain migration of cancer cells, displaying the possibility for use in adjuvant therapy. [130] Gadolinium has also been used as a dopant in CDs to enhance radiation therapy and enable tumor MR imaging. [134] These studies show the versatility of CDs as, even though a carbon-based NP is not expected to have much activity, they can incorporate different organic or inorganic components to make a useful DDS.

The versatility of CDs is further highlighted by their incorporation into other nanosystems. Guan et al. used CDs as a fluorescent tag and incorporated them into liposomes decorated with mannose for cancer specific imaging. [132] In 2020, researchers encapsulated CDs and doxorubicin in lipid calcium phosphate NPs to create a pH dependent release of the chemotherapeutic with imaging capabilities due to CDs photoluminescence. [129] Xu et al. observed an interesting result when they manipulated CDs to self-assemble. [131] This assembly was done my lowering the pH of CDs solution and collecting the precipitate that formed, which showed a particle size approximately 5-6 times larger than the individual CDs. The assembled CDs displayed enhanced absorption above 600 nm which was used to treat cancers cells with the photothermal effect. Selectivity towards HepG2 cells was created through peptide conjugation and the induced hyperthermia was able to selectively kill the cancer cells in a co-culture with L02 cells (normal liver cells). This method along with the other possible uses of CDs to treat liver cancer, shows the significant possibility of CDs to create a DDS capable of combinatorial therapy.

3.4. Other carbon-based NPs

Other strategies have been used to develop carbon-based NPs which do not fit into the above categories. Xu and coworkers converted the

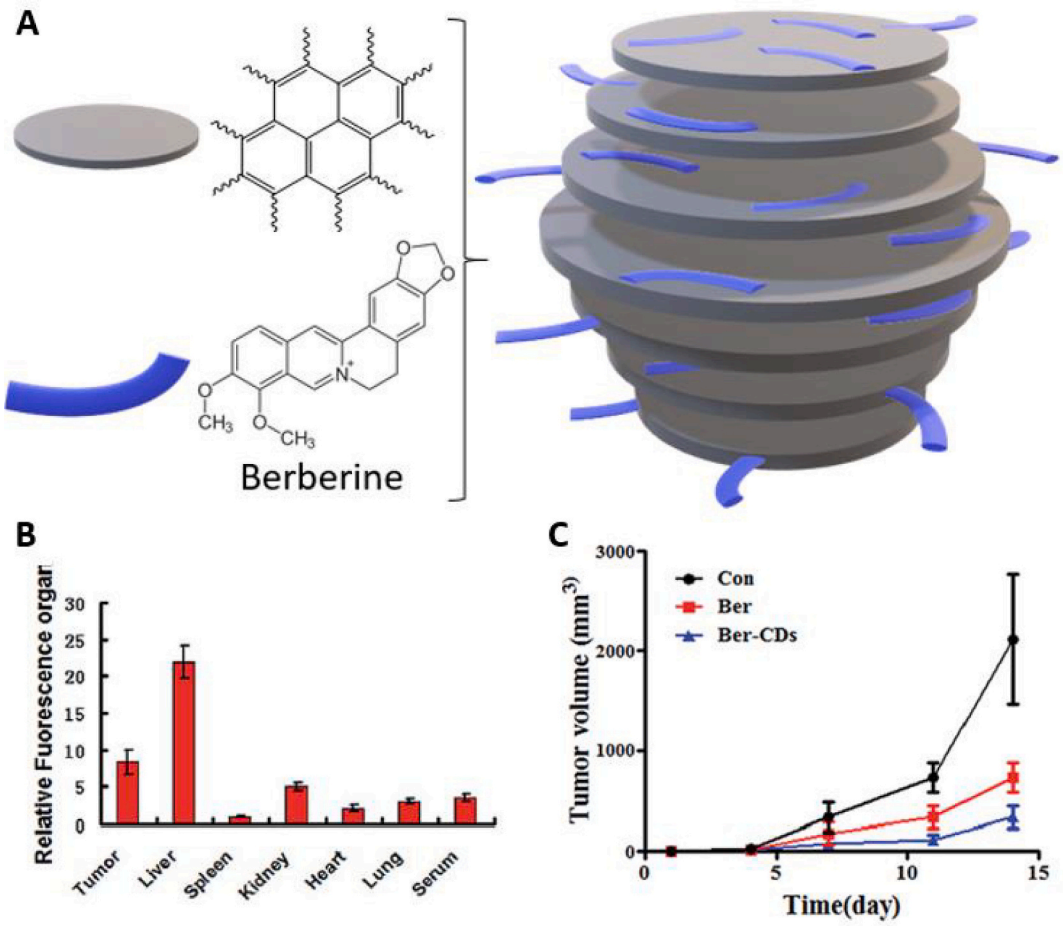

Fig. 8. (A) Graphical representation of the formation of CDs from chemotherapy molecules, in this case berberine. (B) Biodistribution of Ber-CDs based on the fluorescence intensity of the organ or serum. Each bar represents the mean ± standard deviation, $n = 6$. (C) Tumor volume from mice after administration of Ber or Ber-CDs. Each bar represents the mean ± standard deviation, n = 6, and $^*P < 0.05$ *vs.* the control group, #P < 0.05 *vs.* Ber group, reprinted from Ref. 133 with permission from The Royal Society of Chemistry.

chemotherapeutic, paclitaxel, into 90 nm sized NPs through electrostatic spray. [136] These NPs showed greater efficacy against liver cancer cells than did a typical sample of paclitaxel, potentially helping to overcome solubility issues typically associated with some chemotherapeutics. Varshney et al. used a dipeptide (arginine, α,β-dehydrophenylalanine to self-assemble NPs for the delivery of microRNA (miR-199a-3p). [139] Conjugation of lactobionic acid allowed for increased cellular uptake and this system showed significant tumor reduction while not effecting the body weight of mice. Larger biomolecules such as BSA have been used create DDSs which can deliver therapeutics such as curcumin, doxorubicin, and paclitaxel with success. [137,138] These systems have the advantage of using a commonly present protein which can increase the circulation time of this system *in vivo*. In 2020, Patel and coworkers used an even larger biological structure by isolating 100-200 nm vesicles from milk and using them to deliver siRNA for treatment of liver cancer. [140] These achieved activity against liver cancer *in vitro* and *in vivo* with a very low degree of cytotoxicity or side effects to mice. NPs have been produced from silk-derived proteins, sericin and fibroin, which have been used in creating DDSs for many types of cancer. [183] The diverse systems mentioned in this section illustrate the wide potential of carbon-based systems to act against liver cancer, particularly biomimetic systems.

4. Conclusion and future outlook

This review has endeavored to show the promising ability of nanotechnology in the fight against liver cancer. An extensive summary of specific research articles has been presented in **Tables 1** and **2** and a brief summary of the most important NPs is given in Table 3 showing the roles and specific considerations for each system. This discussion was broken into two main sections: inorganic and carbon-based NPs. Among inorganic NPs, several display multifunctional capabilities including, gold (acting as a photothermal therapeutic and carrier), iron oxide (MR imaging agent, photothermal therapeutic, and carrier), and silica NPs (multifunctional therapeutic and carrier). Other such as platinum, silver, and arsenic NPs rely heavily on release of metal cations. Some nanosystems can also act as a radiation therapy enhancer (hafnium oxide, upconversion, and gold NPs). Conversely, carbon-based NPs most commonly act as a carrier unless there is a separate inorganic component integrated in the DDS. This one dimensionality does not reduce the promise of these materials, however, as many carbon-based systems are capable of carrying multiple therapeutics and can easily be functionalized with a targeting ligand. Furthermore, many carbon-based systems are biodegradable, and they are less likely to produce undesired or unforeseen side effects.

As mentioned above, many of the NPs discussed in this review act as a carrier. Among the chemotherapeutics used in these studies, doxorubicin is the most commonly used by far, although sorafenib and paclitaxel are used with some frequency as well. Many works seek to incorporate traditional remedies which have not been approved for liver cancer (*e.g.*, honokiol, hydroxycamptothecin, and berberine). Additionally, many promising studies have been published relating to the delivery of biological molecules, including DNA and several types of RNA.

An important part of many DDSs is the targeting ligand which will enable cancer selectivity. The most commonly targeted receptors are folate (ligand of folic acid) and asialoglycoprotein receptor (ligands consisting of sugars) receptors. A high level of specificity has been obtained by the use of specific peptides as well. Some studies have augmented the targeting capabilities of their system through the use of stimuli-responsive elements. These typically respond to a low pH or reducing environment to release their cargo in cancer cells more specifically. There are many promising strategies currently explored for this objective.

Moving forward it is important to combine the most successful elements of these discussed DDS. Many of the most successful strategies discussed here utilized a combinatorial approach, either through multiple chemotherapeutics or through the use of different therapeutic strategies. The therapeutic strategies which show the most promise for the future are delivery of chemo/immunotherapeutics, delivery of RNA, photothermal therapy, and radiation enhancement. Systems which can utilize more than one of these approaches have been proven to have a strong effect against liver cancer *in vitro* and *in vivo* and these should be optimized in the future. Regarding the types of therapeutics delivered, attention should be devoted to therapeutics which have been approved by the FDA in more recent years, such as Lenvatinib and pembrolizumab. In the DDSs explored in the future, targeting mechanisms need to be incorporated. The unique capability of some nanosystems to passively target the liver should be combined with the active targeting that has been demonstrated many times in this review. Additionally, several CRISPR-Cas NP systems have achieved liver targeting and this is a promising future avenue to explore gene editing for liver cancer treatment. [184–186] With time and effort the different components used to create DDSs can be refined and optimized to create a viable and effective treatment for liver cancer which clinicians can then begin to explore in humans.

Table 3
Summary of the capabilities, advantages, and disadvantages of the most important NPs.

Nanoparticle	Roles in DDS	Advantage	Disadvantage
Gold	Drug carrier, photothermal therapy, radiation enhancer	Easily prepared Multifunctional	Accumulation of NPs *In vivo* limitations for the use of light
Platinum	Therapeutic through Pt(II) release	Easily prepared Similar to standard treatment	Highly toxic One-dimensional
Iron oxide	Drug carrier, hypothermia induction, MR imaging	Multiple therapy pathways MR imaging/ targeting	Toxicity Accumulation of NPs Physical damage from magnetic guidance
Calcium	Drug carrier	Biocompatible	One dimensional
Silica	Drug carrier, photothermal therapy	Versatile platform	Potentially toxic Accumulation of NPs
Selenium	Drug carrier, amelioration of side effects	Capability of mitigating side effects	One dimensional Non-facile modification
Upconversion	Drug carrier, photothermal therapy	Strong photothermal therapy capability	Potentially toxic More difficult preparation
Polymeric	Drug carrier	Excellent drug carrier Biodegradable Stimuli responsive	Potentially premature leakage of cargo
Polysaccharide	Drug carrier, targeting ligand	Biodegradable Inherent targeting of ASGPR	Potentially premature leakage of cargo
Lipid	Drug carrier	Carrier of hydrophobic drugs	One dimensional High need for surface engineering
Carbon dots	Drug carrier, fluorescence imaging	Easily modified surface Imaging capabilities Liver targeting	Need for covalent attachment of drugs
Biological	Drug carrier, targeting nature	Biocompatible Targeting capabilities	Difficult preparations

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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Appendix A. Supplementary data

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