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Review Article

NANOTECHNOLOGY-DRIVEN THERAPEUTICS FOR LIVER CANCER: CLINICAL APPLICATIONS AND PHARMACEUTICAL INSIGHTS

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ABSTRACT

Hepatocellular carcinoma (HCC) represents a significant threat to global health and is responsible for significant mortality rates worldwide. Conventional treatment options such as surgery and chemotherapy have inherent limitations. To remedy these deficits, the development of novel therapeutic strategies is essential. Nanomedicines have shown promise in HCC treatment as they offer improved stability, controlled release, and increased drug loading capacity. This review explores the application of nanoconstructs in HCC treatment, including active and passive targeting strategies. In addition, liver cell targeting approaches, targeting moieties, and conjugation chemistry for surface functionalization are investigated. A compact overview of various therapeutic approaches to HCC treatment is also given.

Keywords: Hepatocellular carcinoma, Nanomedicine, Targeted drug delivery, Therapeutic nanoparticles, Liver cancer treatment, Diagnostic biosensors.

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INTRODUCTION

An estimated one million new cases of liver cancer are diagnosed each year, making it one of the leading causes of death worldwide. This problem is exacerbated by the lack of effective pharmacotherapies. Each year, approximately 800,000 people worldwide are diagnosed with liver cancer, and the mortality rate is over 90% [1,2]. Hepatocellular carcinoma (HCC), hepatic angiosarcoma, cholangiocarcinoma, and hepatoblastoma are among the subtypes of liver cancer, with HCC being the most common [2-5]. Effective drug delivery is hampered by the pathophysiology of HCC, which impairs normal liver function [2]. Poor prognosis, inadequate drug delivery, severe side effects, and lifelong immunosuppressive therapy after transplantation are the limitations of traditional HCC therapies such as chemotherapy, surgical resection, and radiotherapy [2,6,7]. Therefore, it is crucial to develop new and alternative approaches to the treatment of HCC.

With many advantages, such as increased drug stability, better absorption, especially in liver cells, reduced renal excretion, and reduced toxicity, the use of nanomedicines has revolutionized the treatment of liver cancer [2,3]. However, these nanomedicines have disadvantages, such as B. poor drug absorption due to aberrant tumor architecture that prevents the enhanced permeability and retention effect (EPR) [8-11]. Researchers have used targeting agents to alter the surface of nanoparticles (NPs) to overcome these limitations and make it easier to deliver the active moiety to the intended site of action [8]. Both active and passive targeting techniques can be used to specifically treat the liver. For nanocarriers to accumulate and remain in their intended location, passive targeting requires changing their surface area, size, and tissue properties. Conversely, active targeting identifies receptors on the surface of target cells through the conjugation of ligands to the nanocarrier surface [12,13]. Numerous receptors, such as mannose receptors, TfR, asialoglycoprotein (ASGP-R) receptors [14], and folate receptors (FR) [11,15-17], are expressed by the liver. ASGPR ligands are currently being evaluated in a number of Phase I clinical trials to target HCC. A review of the various targeting receptors in the liver, therapeutic approaches for liver cancer, targeting strategies, the role of passive and active targeting, and NPs used in HCC treatment are all intended to be included in this review [18-21].

PATHOPHYSIOLOGY OF LIVER DISEASE

The liver is essential for many physiological functions such as energy storage, detoxification, and biochemical synthesis. However, HCC can disrupt these processes. HCC has a multifactorial etiology (Fig. 1), which includes exposure to aflatoxin B1, alcoholism, obesity, viral hepatitis, and genetic mutations such as alterations in the PI3K-mTOR and HER-EGFR signaling pathways. Insulin resistance, liver cirrhosis, and ultimately HCC are caused by the NFκB signaling pathway and inflammatory cytokines such as Interleukin 6, Interleukin 12 (IL-12), and tumor necrosis factor-alpha (TNFα), which are triggered by hepatitis C virus infection. Severe inflammation, activation of TNFα and IL signaling pathways, and oxidative stress-induced liver cell death are features of alcohol-induced HCC. In patients with non-alcoholic fatty liver disease, lipid accumulation leads to insulin resistance, inflammatory macrophage activation, and alterations in signaling pathways such as PI3K-AKT-mTOR and β-catenin/WNT. Other factors such as obesity, lifestyle, and genetic mutations can also contribute to the development of HCC. Complex epigenetic changes and mutations associated with HCC trigger molecular signaling pathways that promote cell proliferation and avoidance of apoptosis. In addition, fibrosis-related sinusoidal fenestrations and decreased hepatic artery perfusion are two ways in which HCC alters hepatic perfusion. These changes result in endothelial, extracellular matrix, and tumor-stromal barriers that hinder drug delivery [2,22].

INTERVENTION USING NANOTECHNOLOGY IN THE MANAGEMENT OF HCC

Significant progress has been made in the treatment of cancer through the use of nanotechnology. With the increasing demand for nanomedicines for HCC, much research has been conducted to address the difficulties in targeted drug delivery. To overcome the disadvantages

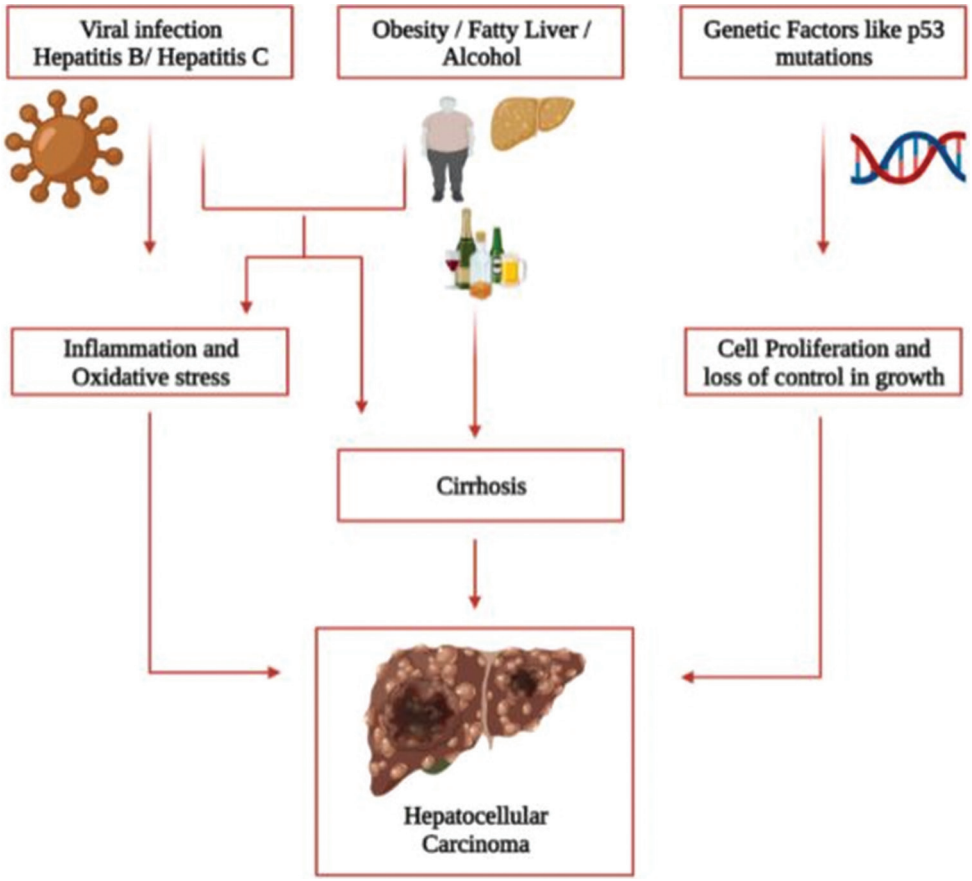

Fig. 1: Pictorial representation of etiology of Hepatocellular carcinoma [195]

of traditional nanocarriers, various types of nanocarriers have been developed over time by modifying their surface properties or structure, as explained below.

INORGANIC NPS

With a metal or metal oxide core and monodispersity, inorganic NPs exhibit special optical, electrical, and magnetic properties [23]. Compared to organic materials, these NPs are extremely stable, hydrophilic, non-toxic, and biocompatible [24,25]. They are also easy to functionalize. The ability of inorganic NPs to encapsulate a variety of drugs is a significant advantage [23]. As potential therapeutic and diagnostic agents in oncology, including tumor drug delivery, imaging, and radiotherapy, inorganic NPs have attracted great interest in pre-clinical development [24,26]. Noble metal NPs (gold, silver, platinum), metal oxide NPs (iron oxide, zinc oxide, arsenite trioxide, and hafnium oxide), and porous NPs (calcium-based, selenium-based, and silica NPs) are some types of inorganic nanocarriers [27,28]. Gold NPs (AuNPs), one of the noble metals, have attracted great interest in biomedical applications due to their remarkable properties, which include high surface area to volume ratio, tunable dimensions, excellent biocompatibility, controllable biodistribution, and distinct optoelectronic properties. Catalytic, antioxidant, and reactive properties [29-31]. Due to these properties, AuNPs can be used to diagnose and treat liver cancer. Furthermore, AuNPs exhibit high surface plasmon resonance (SPR), localized radioactivity, and X-ray absorption coefficients [32], which facilitates their conjugation with various functionalizing agents such as peptides, therapeutic agents, ligands, DNA, and proteins for active targeting [33-35]. Due to their antibacterial and anti-inflammatory properties, silver NPs (AgNPs) have shown promise in wound and burn dressings [36,37]. Interestingly, AgNPs are extremely toxic to microorganisms at very low concentrations but exhibit low toxicity to humans [38,39].

Due to their exceptional catalytic activity, electrical properties, corrosion resistance, ability to lower intracellular reactive oxygen species (ROS) levels, optical properties, localized SPR, and large surface area, despite being one of the most expensive noble metals, platinum NPs (PtNPs) have shown great promise in nanomedicine [40-43]. Medhat *et al*. proved the anticancer potential of PtNPs by comparing their antitumor effects with cisplatin and concluded that PtNPs exhibited stronger activity according to apoptosis and antioxidant parameters [44]. Metal oxide NPs, particularly iron oxide and zinc oxide NPs have been extensively studied for the treatment of HCC. In addition, hafnium oxide NPs and arsenite trioxide have shown promise in treating liver diseases. Iron oxide NPs are suitable for antibacterial, antifungal, and anticancer applications due to their unique properties, which include superparamagnetic behavior, biodegradability, stability, biocompatibility, low cytotoxicity, and abundant polymorphism [45,46]. Due to their high surface-to-volume ratio and high surface energies, surface coating is required to stop oxidation [47]. Due to their ability to inhibit agglomeration, regulate size, and promote certain interactions and tissue barrier penetration, iron oxide NPs are superior to other metallic NPs [48]. Due to their ease of synthesis, consistent and customizable pore sizes, easy surface modification, and high loading capacity, mesoporous silica NPs hold promise as therapeutic carriers [49,50].

Porous calcium carbonate NPs are also used due to their affordability, accessibility, biocompatibility, low cytotoxicity, pH sensitivity, and slow biodegradability [51,52]. These NPs are preferred due to their controlled behavior, chemical stability, and ability to encapsulate a wide range of molecules, such as proteins, oligonucleotides, dyes, and therapeutic agents. Their physical stability is enhanced by their surface modification ability and pH-sensitive behavior, making them suitable for targeted delivery [53]. Khan and associates. Created cisplatin-oleanolic acid-loaded calcium carbonate NPs, which showed a synergistic effect

on HCC cells, causing apoptosis and reducing hepatotoxicity. Compared to free therapeutics, results showed increased HepG2 cell apoptosis and pH-dependent therapeutic release [54].

LIPID NPS

Lipid NPs are ionizable, spherical, lipophilic structures that accumulate in areas of increased vascular permeability [2] after undergoing cellular internalization and endolysosomal bypassing [55]. These nanocarriers not only feature minimal cytotoxicity, sustained therapeutic efficacy, and controlled pharmacokinetics, but are also versatile in their ability to deliver both hydrophilic and lipophilic molecules [56]. Furthermore, the surfaces of these lipid nanocarriers can be modified to improve the solubilization of therapeutic agents or to avoid immunological detection [56]. Liposomes, niosomes, solid lipophilic nanoparticles (SLN), lipophilic drug conjugates, lipophilic nanocapsules, nanostructured lipophilic carriers (NLC), and other nanoscopic lipid vesicles have been created [2,57,58].

Vesicular liposomal structures are small, spherical objects, usually between 30 and several micrometers in diameter. They consist of one or two lipid bilayers surrounding an aqueous compartment composed primarily of natural phospholipid and cholesteric molecules. With remarkable properties such as biocomplementarity, biodegradability, thermodynamic phase properties, and the ability to encapsulate both hydrophilic and lipophilic compounds, thereby preventing degradation and facilitating site-specific release, these entities have proven to be a promising modality for pharmaceutical delivery [59-61]. Van der Waals forces between hydrocarbon chains, hydrogen bonds, and hydrophilic interactions between polar headgroups can all alter the surface of these liposomal structures [62-64].

Due to their size range, which allows them to diffuse from the porous hepatic fenestrations into the extracellular space, these units are primarily used for hepatic targeting. Cannito and staff. PEGylated and hyaluronated liposomal structures were prepared and showed rapid internalization in Huh7 cells overexpressing CD44 [65]. Consisting of lipids, solid surfactants, and an appropriate solvent system, solidified lipid nanoparticles (SLNs) are spherical, solid, hydrophobic core matrices coated with phospholipids and range in size from 50 to 1000 nm [66,67]. By limiting drug diffusion into the emulsifier film, minimizing drug mobility within the lipid matrix, preventing particle aggregation, and protecting drugs from degradation, SLNs are a suitable drug delivery system. They also exhibit biocomplementarity, high surface area, high cellular uptake, and significant stability during storage [68-70]. Furthermore, they can encapsulate both hydrophilic and lipophilic drugs [70,71].

When administered orally, these NPs avoid first-pass metabolism and are absorbed by the reticuloendothelial system (RES), allowing surface modification of the carrier and potentially serving as a pharmaceutical delivery method [68,69]. Tunki and staff created sorafenib-loaded SLNs that use pegylated galactose to target ASGPR. By efficiently targeting ASGPR, the SLNs showed increased cell uptake, high cytotoxicity, and apoptosis in HepG2 cells [72]. Solidified lipid and liquid lipid (oil) binary mixtures as hybrid carriers and emulsifiers form nanostructured lipid carriers (NLCs), which have an average size of 200–500 nanometers [73]. By preventing drug leakage during storage, which occurs when a less ordered lipid matrix forms, NLCs overcome the major disadvantage of SLNs and liposomal structures [74,75].

A controlled drug release profile is achieved through better drug loading and accommodation enabled by the formation of an incomplete core during solidification [74,76-78]. Varshosaz and associates showed that surface-modified NLCs with lactobionic acid (LA) targeting ASGPR receptors exhibit increased cellular uptake and cytotoxicity [79].

POLYMERIC NPS

Both synthetic and organic polymeric materials can be used to produce polymeric NPs, which can then be formulated as a matrix system (nanospherical structures) or as repositories (nanocapsular structures) [80]. Covalent binding, adsorptive sequestration, or encapsulated retention on the surface of the nanoscale structure are three ways in which pharmacological agents can be entrapped therein [81]. While nanospherical structures consist of a continuous polymer network that holds the pharmacological agent inside or on the surface of the nanoscale units, nanocapsular structures consist of an oily core containing the pharmacological agent and surrounded by a polymer shell [82]. These nanoscale entities can improve the bioavailability and therapeutic efficacy of pharmaceutical agents while protecting them in the biological environment. They also show remarkable stability in biological fluids [80,83]. There are many different types of polymeric nanoscale units, such as polyethylene glycol (PEG)/poly (lactic-co-glycolic acid) (PLGA) NPs, chitin, chitosan-based NPs, PLGA NPs, polysaccharide NPs, and PEG NPs [27].

The most preferred macromolecular material is PEG, an inactive macromolecule with excellent biocompatibility, amphipathic properties, high structural flexibility, the ability to bypass the reticuloendothelial apparatus (RES), and high polarity, which enhances the hydrophilicity of nanoscale entities (NSEs) and facilitates dissolution and penetration [84]. PEGylation of NSE contributes to reducing immunogenic potential and toxicity, reducing enzymatic degradation, and prolonging metabolic half-life [85,86]. Devulapally and associates. Antisense microRNA and gemcitabine were co-encapsulated in PLGA-PEG-NSEs for HCC. These NSEs showed enhanced cellular internalization and cytotoxic potential [87]. PLGA, a copolymer of lactic acid and glycolic acid, is biodegradable because it is hydrolytically broken down in the body to produce lactic acid and glycolic acid monomers, which the body then metabolizes to reduce systemic toxicity [88,89].

Longer residence time in the bloodstream, ability to capture hydrophobic and hydrophilic therapeutic agents, superior biocompatibility, prolonged release of therapeutic agents, enhanced bioavailability, biodegradability, and site-specific action are some of the unique properties of PLGA [90]. Gao and staff. Modified PLGA-NSEs with a CXCR4 antagonist and grafted them using a lipid coating to deliver sorafenib to the liver to combat HCC. The results showed that sorafenib-loaded PLGA nanocarriers increased survival, delayed tumor progression, and improved antiangiogenic efficacy in orthotopic HCC model mice [91].

Due to its flexibility in linear chain configuration, chitosan possesses mucoadhesive properties that promote increased absorption efficiency [92]. Faris and staff designed simvastatin-chitosan nanocarriers (CH-NCs) for targeted delivery of HCC through ASGPR. Compared to pure simvastatin suspension, the nanocarriers showed improved bioavailability (2X), increased uptake through ASGPR-mediated endocytosis, and increased proliferative activity in HepG2 cells [93]. As a biodegradable proteomic entity, albumin has site-specific pharmaceutical delivery capabilities and is non-toxic, non-immunogenic, biocompatible, economical, and low in cytotoxicity [94]. Monodispersity, predictable placement of cross-linking groups, and programmable degradation kinetics are some of the advantages of albumin nanocarriers in drug delivery [95,96].

The natural ability of proteins to attack cancer cells can be enhanced by the facile functionalization of albumin nanocarriers with targeting moieties [96]. Human serum albumin, ovalbumin, rat serum albumin, and bovine serum albumin are among the different forms of albumin used to prepare nanocarriers [94,97]. Numerous methods can be used to prepare these nanocarriers, including desolvation, thermally induced aggregation, self-assembly techniques, and emulsification [94,96]. Dayani *et al*. Developed albumin-lipid nanocarriers loaded with LA to specifically deliver sorafenib to HCC patients. Cell uptake studies confirmed that these nanocarriers showed increased cytotoxicity and cellular uptake in HepG2 cells compared to non-targeted nanocarriers [98].

At a critical micellar concentration, amphipathic molecular building blocks spontaneously self-aggregate and form nanoscopic micellar constructs, which are colloidal aggregates with a central core and a peripheral shell structure. While the peripheral corona is hydrophilic (poly(N-vinyl-2-pyrrolidone), PEG, polyethyleneimine, and poly(vinyl alcohol)) and the central core is oleophilic (aspartic acid, L-lysine, propylene oxide, D, L-lactic acid, spermine, and PLGA), this arrangement is reversed in reversed nanoscopic micellar constructs [23,99,100]. While hydrophilic pharmacological agents are delivered to a specific anatomical site through inverted micellar constructs, oleophilic pharmacological agents are delivered into systemic circulation through conventional micellar constructs [99]. By encapsulating oleophilic pharmacological agents in the central core, nanoscopic micelle constructs eliminate the need for the use of hazardous organic solvents [99].

Direct dissolution and solvent casting, which include oil-in-water emulsion (O/W), cryodesiccation, dialysis, and solution casting, are the two methods that can be used to prepare the nanoscopic micellar constructs [100,101]. Zhang *et al*. Created nanoscopic micellar constructs loaded with triapine/Ce6 and decorated with lactose for the chemophotodynamic treatment of HCC. While the lactose moiety makes it easier to attack liver cancer cells, triapine and Ce6 act together as promoters of cytotoxic ROS through the Fenton reaction and near-infrared light (NIR) irradiation, respectively, and increase programmed cell death [102].

TARGETING STRATEGIES

By overcoming the challenges presented by traditional NSEs, therapeutic nanoscale devices (NSEs) reduce the frequency of administration and toxicological effects on other organs. Fig. 2 shows the different targeting strategies used to utilize active and passive targeting mechanisms to deliver therapeutic agents to the tumor site [8,103]. Passive targeting strategies benefit from the pathophysiological features of the tumor microenvironment. On the other hand, active targeting uses molecular ligands to bind to target cells within the tumor site [8,25,104]. Since ligand-modified NSE therapies rely on passive hepatic uptake mechanisms before ligand-mediated cellular internalization, these two targeting approaches are usually used together [3]. The various NSEs used as active targeting strategies for drug delivery in HCC are summarized in Table 1.

TARGETING AGENTS

Hepatic stellate cells (HSCs), hepatocytes, endothelial cells, and Kupffer cells are among the various hepatic cell populations that the externally modified NPs can selectively target with pharmacological agents Fig. 3 [124-126]. The various targeting moieties for site-specific pharmacological delivery are discussed in detail below.

ANTIBODY (AB) DIRECTED ACTIVE TARGETING

The most widely used and well-known molecular adapters for precise targeting of NPs are immunoglobulins (Igs). However, the surface immobilization of Igs is limited due to their large molecular size, which leads to a significant increase in the diameter of the NPs. Igs can be used as targeting molecular adapters due to their known high specificity, strong affinity, and versatile target recognition capabilities. However, the limited compatibility of these biomolecules with organic solvents and their relative susceptibility to environmental stressors (ionic potency, thermal energy, and enzymatic catalysis) may present technological challenges for the production of repeatable NPs. This ultimately affects the stability and shelf life of the formulation as well as the cost/efficiency ratio of the preparation. The mercapto (cysteine), amino (lysine, asparagine, and glutamine), and carboxylate (glutamic and aspartic acid) groups of the Igs can all be bound by the NPs. Conversely, conjugated Ig on NPs exhibits uncontrollable spatial orientation due to the topological distribution of these amino acids and the Igs [127,128].

PROTEIN DIRECTED ACTIVE TARGETING

Polypeptides and other molecular conglomerates are large molecular aggregates composed of one or more long sequences of amino acid residues with reactive moieties at the carboxyl and amino terminal ends. Because polypeptides have a larger molecular mass, they remain in the vascular system longer. However, targeting polypeptide receptors is limited because too much polypeptide in blood plasma can coexist with polypeptides on NPs, potentially representing competition for the same receptor. Siderophilin (Sf) and other ferritin-binding glycoproteins are widely used for targeting due to their affinity for the Siderophilin receptor (SfR), which is overexpressed in many neoplastic cell types. Through receptor-mediated endocytosis in which SfR is overexpressed, Sf can be rapidly internalized into cells and contains two homologous domains for iron (III) binding [127-130].

APTAMER DIRECTED ACTIVE TARGETING

Single-stranded nucleic acid, ribonucleic acid, or oligonucleotide configurations that adopt precise three-dimensional conformations are called molecular adapters. Examples of this are oligonucleotide ligands [130]. Due to their high reactivity, small molecular size,

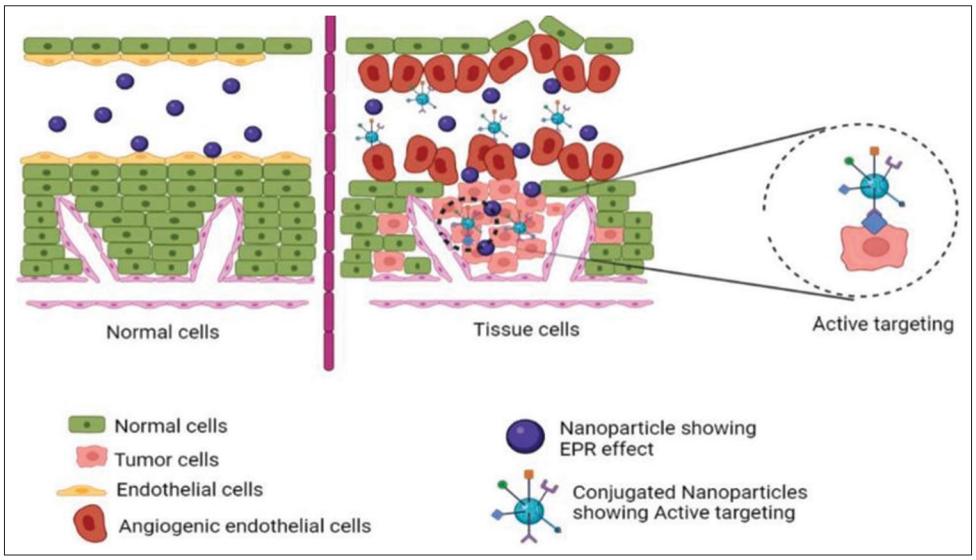

Fig. 2: Pictogram of passive and active targeting strategies in Hepatocellular carcinoma [195]

Table 1: An overview of several nanoparticles that offer an active targeting strategy for medication administration in HCC

S. No	Types of nanoarchitectures and nanoparticles	Focusing on the moiety or moieties	Identifying receptors	Methods of preparation	Size of the particle (nm)	Cellular lines	Animal models	Results	References
1.	Platform for Gold-PEG-Galactose NP	Galactose-PEG	ASGP-R.	-	-	HepG2	-	These nanoparticles demonstrated excellent stability, preserved the gold's optical characteristics, interacted with ASGPR, and increased uptake in HepG2 cells.	[107]
2.	119 DOX NPs of polyethylene sebacate-Gantrez	Pullulan	ASGP-R	Changes in nanoprecipitation	220	HepG2	Dawley Sprague rats	High liver absorption, particularly hepatocyte accumulation, subacute toxicity, and the absence of histological alterations indicating good tolerance in mice were all guaranteed by the ligand complex.	[105]
3.	Targeting RNA therapies with modified ionizable lipid nanoparticles	Mannose	Hepatocytes and liver sinusoidal endothelial cells	System that is microfluidic based	60 to 100	HepG2	C57BL/6 mice	Through the interaction of ApoE and LDLR *in vitro*, the NPs demonstrated cellular uptake. According to an *in vivo* investigation, ApoE association can enhance the delivery of LNPs to the liver through mannose receptors, primarily in the hepatocytes.	[109]
4.	NP loaded with oridion and covered in galactosylated chitosan	Galactose	ASGP-R	Graft-copolymerization, followed by the chemistry of carboimides	200	-	Kunming strain mice and Dawley-Sprague rats	*In vitro*, the NPs showed a biphasic drug release pattern, with the liver exhibiting a longer residence period and greater concentration.	[111]
5.	Lactose-modified mesoporous silica nanoparticles loaded with a platinum prodrug	Lactose	Lactobionic acid	Stober's Method	80–100	HepG2 and L292 fibroblasts	Kunming mice	By targeting HepG2 cells precisely, the NPs delivered the medication solely in the cancer cells' microenvironment. This demonstrated little toxicity to healthy tissues and improved therapeutic efficacy.	[113]
6.	Biodegradable PLGA-TPGS copolymer nanoparticles coated with N-acetylaminogalactosyl loaded with emodin	Acetyl amino galactose	ASGP-R	Emulsification	134	HepG2	PLC mouse	On HepG2 cells, the NPs demonstrated better liver targeting along with increased cytotoxicity and death rate. In the PLC mouse model, the *in vivo* treatment efficacy increased by multiple times.	[115]
7.	5-fluorouracil-loaded zein nanoparticles	Zein	-	Phase separation process	114	-	Mice	High drug entrapment and a sustained release profile were demonstrated by the negatively charged NPs. The targeting efficacy of the NPs was demonstrated by a biodistribution investigation that verified their accumulation in the mice's livers for 24 h following intravenous treatment.	[117]

(Contd...)

Table 1: ***(Continued)***

S. No	Types of nanoarchitectures and nanoparticles	Focusing on the moiety or moieties	Identifying receptors	Methods of preparation	Size of the particle (nm)	Cellular lines	Animal models	Results	References
8.	Amphiphilic prodrug nanoparticles of camptothecin that respond to redox	A disulfide bond-conjugated lactose prodrug	ASGP-R	-	114.4	HepG2 and HUVEC	Female Balb/ c nude mice	*In vitro*, the NPs displayed regulated release. The NPs were taken up by cells by endocytosis. While the anti-tumor efficacy of NPs showed superior tumor inhibition over free drugs both *in vivo* and *in vitro*, the enhanced antitumor activity was validated by a cytotoxicity analysis.	[119]
9.	Silymarin-loaded galactosylated nanoparticles	Galactose	ASGP-R	Condensation method	123	-	Wistar rats	The modified NPs' 48-h sustained release behavior was validated by an *in vitro* release investigation. The liver cells exhibited a notable uptake of the NPs.	[121]
10.	Pullulan nanoparticles loaded with Paclitaxel that are redox sensitive	Folic acid	ASGP-R and FR	-	130–170	A549 or SMMC-7721 cells	SD rats	Core-crosslinking helped to improve the NPs' stability, according to an *in vitro* stability study, and endocytosis processes improved cellular absorption. An improved anti-tumor impact and decreased systemic toxicity were confirmed by an *in vivo* therapeutic efficacy investigation.	[123]
11.	Doxorubicin-loaded galactosamine-conjugated albumin nanoparticles (GAL-AN)	Galactosamine	ASGP-R	Desolvation	100	HepG2	-	While cytotoxicity experiments verified that GAL-AN is harmless, cellular uptake and kinetics investigations verified that GAL-AN was specifically integrated into HepG2 cells and bound to ASGP-R.	[122]
12.	Nanoliposomes specific to liver tumors modified with galactose and containing selective BRD4-targeted PROTAC	Galactose	ASGP-R	Modified hydration method	100	HepG2 and Hep3B	–	Because of the ligand-receptor-based interaction between the NPs and tumor cells, the modified NPs demonstrated an improvement in the drug's half-life and cellular uptake. Studies conducted *in vitro* verified that HCC cells exhibit increased cytotoxicity and apoptosis.	[106]
13.	Doxorubicin-loaded alginate nanoparticles modified with glycyrrhetinic acid	Glycyrrhetinic acid	Hepatocytes	Equilibrium dialysis method	274	HepG2	Kunming mice	Through GA-receptor-mediated endocytosis, these spherical NPs demonstrated increased cellular uptake and pH-dependent drug release. Through histological analysis, tumor cell death was verified, with no impact on healthy cells.	[108]

(contd...)

Table 1: ***(Continued)***

S. No	Types of nanoarchitectures and nanoparticles	Focusing on the moiety or moieties	Identifying receptors	Methods of preparation	Size of the particle (nm)	Cellular lines	Animal models	Results	References
14.	Galactosylated PLGA NPs loaded with tacrolimus	PLGA and galactose	ASGP-R	Modified ultrasonic emulsification	Less than 150	-	Wistar albino rats	It was discovered that the NPs were stable and had high drug entrapment. The liver absorbed more galactosylated NPs than it did in the unmodified medication solution. It was discovered that the uptake mechanism involved receptor-mediated endocytosis on liver cells through ASGP-R.	[110]
15.	Folate-decorated bovine serum albumin nanoparticles loaded with sorafenib	Folate	Folate receptor	Self-assembly method	158	LO2 and SMMC-7721	SD rats	When compared to normal drug liquid, the nanoparticles (NPs) demonstrated good stability and liver targeting. Consequently, it improved the bioavailability of the drug, enhanced therapeutic efficacy, and minimized systemic side effects, making it a promising strategy for liver cancer treatment.	[112]
16.	Doxorubicin-loaded dendrimers modified with lactobionic acid	PEG	ASGP-R	-	-	HepG2	-	The produced NPs' stability and surface potential analysis verified that the drug was loaded into the hydrophobic region of the dendrimers and displayed an 80% drug release rate.	[114]
17.	Anti-CD133 antibody-decorated nanoparticles loaded with Paclitaxel	poly(D,L-lactide-co-glycolide)	Liver cancer stem cells	Emulsification-solvent evaporation	429	HepG2 and Huh7	Athymic nude mice	Furthermore, it was discovered that PEG enhanced LA-mediated targeting. Both *in vitro* and *in vivo*, targeted NPs demonstrated cytotoxicity in tumor cells. In addition, there was a noticeable improvement in the therapeutic response.	[116]
18.	Galactosylated chitosan-graft-norcantharidin-loaded PEG nanoparticles	PEG and galactose	-	Ionic gelation	-	-	-	With site-specific targeting, the NPs showed a burst release followed by a sustained release.	[118]
19.	Ligand-Functionalized Polymer-Lipid Hybrid Nanoparticles Loaded with Sorafenib	Folic acid	FR	Thin-film hydration	146	-	-	Controlled release and impressive cellular absorption in the tumor cells were demonstrated by *in vitro* drug release. Both significant apoptosis of cancer cells and dose-dependent cytotoxicity were noted.	[120]
20.	Doxorubicin-loaded PEGylated mesoporous silica nanoparticles	PEG and galactose	ASGP-R	Stober's Method	100	HepG2	-	Endocytosis mediated by ASGPR enhanced NP absorption in cells. Galactose conjugation increased cell apoptosis and was successful in delivering the medications to the desired HepG2 cells.	[123]

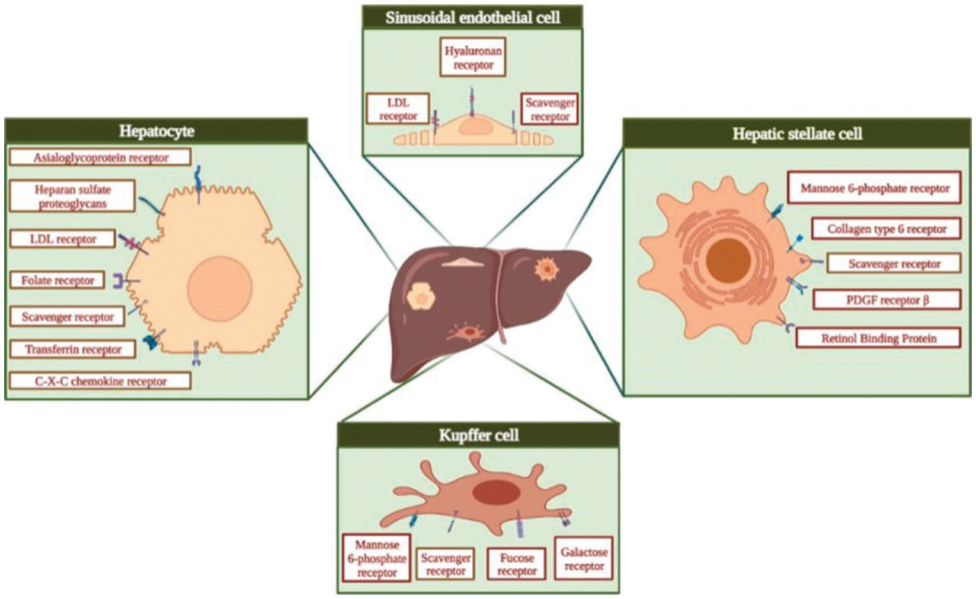

Fig. 3: List of various cells and receptors present in the liver [195]

biodegradability, and low immunoreactivity properties, oligonucleotide ligands are suitable molecular entities for precise targeting [129]. Nucleic acid sequences, inorganic molecular entities, polypeptides, peptide sequences, intact cellular structures, antibacterial agents, carbohydrate molecules, small organic molecular entities, and even microorganisms are among the many molecular targets with which they form high-affinity molecular complexes. Hydrophilic, electrostatic, and complementary spatial recognition enables the intermolecular interactions between oligonucleotide ligands and antigenic molecular entities. Furthermore, the binding affinity between oligonucleotide ligand-modified NPs and their molecular targets is increased by the multivalent molecular effect. However, oligonucleotide ligands have certain disadvantages, such as reduced binding affinity caused by hydrophobic and negatively charged antigenic molecules and degradation of modified NPs as a result of increased serum nuclease activity in the blood.

Since oligonucleotide ligands and antigenic molecular entities differ in their hydrophobicity-hydrophilicity properties, which can inhibit hydrogen bond formation and promote hydrophobic molecular interactions, the negatively charged phosphodiester backbone and hydrophilic molecular nature of oligonucleotide ligands can also hinder intermolecular binding [127,128].

PEPTIDE DIRECTED ACTIVE TARGETING

Sequences with fewer than 50 amino acid residues distinguish molecular fragments, such as oligopeptide sequences, from polymeric molecular chains. The small molecular size and straightforward three-dimensional topology of oligopeptide sequences improve their molecular stability and robustness to environmental influences, thereby facilitating chemical synthesis and bioconjugation. The binding affinity of oligopeptide sequences to antigenic molecular units can be increased through their multivalent molecular action. The arginine-glycine-aspartate (RGD) tripeptide sequence and its derivatives are widely used as molecular targeting agents because of their ability to form high-affinity molecular complexes with integrin receptors in solid neoplastic lesions. Due to their small size, oligopeptide sequences offer many advantages, such as improved molecular stability, lower production costs, and easy bioconjugation at high molecular densities. The advantages of RGD oligopeptide sequences include control over ligand presentation, low risk of immunoreactivity, and simple and inexpensive chemical synthesis [127-130].

SMALL MOLECULES DIRECTED ACTIVE TARGETING

Pteroylglutamic acid, sometimes called folinic acid or vitamin B9, is the most commonly used of these small molecules. Pteroylglutamic acid is a stable, non-immunoreactive, and commercially viable molecule and promotes rapid internalization into cancerous cell structures. Numerous advantages, such as easy bioconjugation and high specificity and affinity for FR overexpressed in neoplastic cell aggregates, are responsible for its widespread use. However, the main disadvantage of pteroylglutamic acid is that FR is also present in healthy tissue and normal epithelial cell structures of various organs, which complicates the selectivity of the ligand for diseased cell structures. Triphenylphosphine oxide and its derivatives are another small molecules commonly used to target mitochondrial structures. This comparatively large, cationic, and lipophilic molecule can quickly cross cell membranes and accumulate significantly in mitochondrial structures. Since lectin proteins recognize glycan moieties such as glucopyranose, manopyranose, galactopyranose, and their derivatives, they are mainly used as targeting ligands [127-130].

METHODS FOR ATTACHING TARGETING LIGANDS

Both molecular binding and intermolecular association techniques can be used to immobilize molecular adapters on the surface of NPs. The molecular binding method involves exposing organic molecular solvents to covalently immobilize NPs containing polypeptide sequences, small molecules, or oligonucleotide aptamers in a single step. The intermolecular association approach, on the other hand, is a relatively simple technique for attaching molecular adapters during NPs preparation; nevertheless, this often leads to low immobilization efficiency of the molecular adapter, frequent NPs aggregation, and difficulties in measuring and managing the immobilized molecular adapter. Furthermore, the correct spatial orientation of the immobilized molecular adapter is not guaranteed, which increases the risk of detachment of the molecular adapter [128].

COVALENT BONDING STRATEGIES

Numerous bioconjugation techniques can be used to immobilize molecular adapters on the surface of nanoscale particles (NSPs). These include thiol-mediated conjugation, which involves the covalent coupling of polymers with thiol groups on the ligand or maleimide groups on NSP surfaces, leading to the formation of a stable thioether bond; formation of a Schiff base, which is a nucleophilic addition reaction of aldehyde groups with primary amine units, leading to the formation

of an imine bond; and carbodiimide-facilitated conjugation, which involves the synergistic interaction of carboxylic acid moieties with primary amine groups, resulting in the formation of a stable peptide bond. Furthermore, bioorthogonal conjugation techniques such as click chemistry provide a flexible way to immobilize molecular adapters on NSPs by forming heteroatom bonds in a single step. There are different types of click chemistry reactions, such as cycloaddition, nucleophilic substitution, and carbonyl chemistry, and they often require a catalyst such as copper(I) ions to accelerate the reaction between the azide and alkyne functional groups [127,128,131,132].

NON-COVALENT BONDING STRATEGIES

The tetrameric glycoprotein moiety avidin has four binding domains for biotin molecular moieties, facilitating pairing with biotinylated molecular adapters. This makes the avidin-biotin complex unique due to its remarkably strong non-covalent molecular interaction. A common bioconjugation method for connecting molecular adapters to nanoscale particle surfaces (NSPs) is physical adsorption. By simply adding the molecular adapter to the NSP solution, Igs-bound phospholipid-based NSPs can be generated. The adsorption of Igs to NSPs is regulated by hydrophobic molecular interactions and ionic charges; 4–40% of immunoglobulin G (IgG) binds to liposomal NSPs, and this percentage increases to approximately 50% for anionic phospholipid molecular entities. Compared to free Igs, Igs -bound NSPs show 30–50% higher antigen binding affinity. However, the therapeutic efficacy of Igs-NSP conjugates may be compromised if opsonins with a higher binding affinity displace adsorbed Igs in the bloodstream. Furthermore, this bioconjugation approach is unsuitable for therapeutic applications in humans because exogenous protein-containing molecular entities on the surface of NSPs can trigger immunogenic reactions [127,128].

***IN VITRO* AND *IN VIVO* LIVER CANCER MODELS FOR EVALUATION OF NANOMEDICINES**

Significant progress has been made in understanding the underlying molecular, biological, genetic, and epigenetic mechanisms, pathogenic processes, and novel therapeutic approaches of HCC. To illustrate the complexity of this complicated process, pre-clinical experimental models are used, which are briefly explained below.

***IN VITRO* HCC MODELS**

Studies conducted in controlled laboratory environments, in which isolated cell populations are cultured in carefully prepared, nutrient-rich media, have provided invaluable insights. Proliferative capabilities, invasive capabilities, biochemical processes, intracellular communication pathways, therapeutic recalcitrance, responsiveness to pharmacological or radiological interventions, as well as the molecular basis of oncogenesis and metastatic dissemination are all crucially revealed by neoplastic cell lines that are widely used in routine scientific research. Most genetic and epigenetic changes typical of malignant lesions are accurately reproduced by these cell lines. Therefore, they are essential research tools for the screening of pharmacological agents, the identification of molecular targets, and the development of *in vivo* xenograft models that enable rapid and economical evaluation of potential treatment approaches. Approximately thirty cell lines have been examined as part of research into HCC. In particular, the cell lines HepG2, HepaRG, Hep3B, C3A, and HuH-7 are often used. With an estimated IC50 value of 3.31 μM, the Hep3B cell line showed the most striking sensitivity to sorafenib among them. Due to its wide availability and well-characterized properties that facilitate toxicological and pharmacological studies, the HepG2 cell line is widely used in HCC research [133,134].

***IN VIVO* HCC MODELS**

Important information about human neoplastic biology, disease pathophysiology and causative factors, and genetic abnormalities that lead to the development and spread of malignant tumors can be obtained from organismal models. Due to the complexity of causative factors and tumor heterogeneity, establishing a high-precision animal experimental paradigm for HCC is a difficult task. To facilitate the evaluation of potential pharmacological interventions in pre-clinical studies and support the development of targeted therapeutic modalities, an ideal model must closely mimic the pathophysiological and biochemical features of actual HCC, including its chronological progression.

MOUSE MODELS

Fig. 4 delineates the diverse methodologies employed to induce HCC in murine models.

The chemically induced HCC mouse model (CIM) mimics the immunological, genetic, and environmental factors that lead to the development of cancer in humans. This causes serious damage due to the detoxification of xenobiotic substances, which leads to certain carcinogenic substances causing liver damage. Classification is based

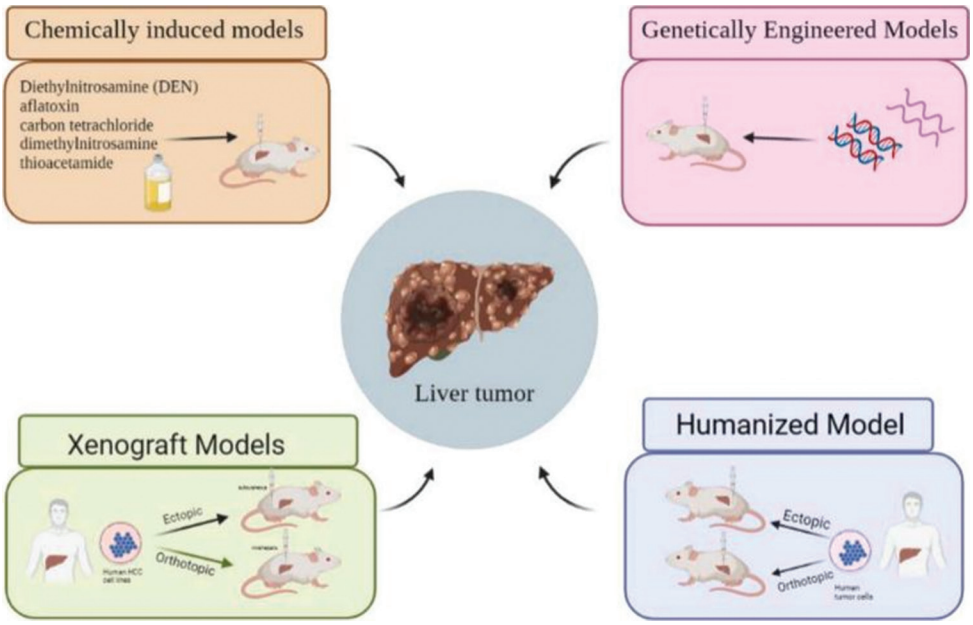

Fig. 4: Schematic representation of Hepatocellular carcinoma induction methods in mouse models [195]

on the type of carcinogen used. Because the genetic, histological, and molecular variations typical of human cancers are preserved, the xenograft HCC model involves the transplantation of human cancer cell lines or biopsy materials into the liver tissue or subcutaneous area of immunocompromised mice. By simulating tumors in a natural, non-immunocompromised environment and reproducing human histological, pathological, and molecular heterogeneity, genetically engineered HCC mouse models facilitate the interpretation of tumorigenesis mechanisms, progression, therapeutic response, and innate drug resistance. Using a variety of techniques, such as intravenous transplantation of human peripheral blood mononuclear cells and inoculation of CD34+ hematopoietic stem cells (HSCs), the humanized HCCMouse model (HMs) involves the transplantation of patient-derived xenografts or human tumor cells in immunocompromised patient mice that have components of the human immune system, recreate interactions between tumor and immune system and the development of cancer, and restoration of the human immune system *in vivo* [133,135-138].

NON-MOUSE MODEL

The Buffalo rodent, which has been most commonly used in rat HCC models, develops neoplasia after exposure to N-2-fluorenylphthalamic acid. This leads to the creation of the MCA-RH 7777 cell line by intrahepatic injection of syngeneic neoplastic cells, also known as the Morris hepatoma paradigm. This paradigm provides a high vaccination rate, α-fetoprotein secretion, and therapeutic monitoring. However, disadvantages include the absence of buffalo rodents, aggressive metastatic behavior, and differences in imaging and histopathological analysis. Another paradigm is the Novikoff hepatoma model developed in Sprague-Dawley rodents exposed to 4-dimethylaminoazobenzene. Intrahepatic injection of syngeneic neoplastic cells generated the N1-S1 cell line. By ligation of the common bile duct, these paradigms can simultaneously cause liver cirrhosis. However, there are disadvantages, such as the possibility of spontaneous regression and non-ideal neoplasm induction rates. Wistar rodents have also been used to simulate liver cirrhosis, hepatocyte damage, and the evolutionary cycle of malignancies occurring in human HCC, liver disease, and neoplasm hypervascularity. However, the 3-month induction period required for full development of the neoplasm is a major drawback of this paradigm [133,139]. The Woodchuck HCC model is widely used to study diseases such as HCC that are associated with HBV. Upon exposure to WHV, this paradigm naturally develops chronic hepatitis, eventually leading to HCC. This model is suitable for exploring intra-arterial treatments because HCC develops within 24–32 months. However, there are disadvantages, such as B. Handling and breeding problems. With advantages such as small size, rapid development, convenient pharmacological administration, high genetic and molecular homology with humans, high reproduction rate, cheap testing cost, and optical transparency, the zebrafish HCC model is becoming increasingly popular. Numerous zebrafish paradigms have been created, such as those driven by β-catenin, KRAS, Xmrk (EGFR), and Myc [133]. Rapid neoplasm growth, easy proliferation, and reliability of neoplasm induction are some of the advantages of the rabbit HCC model using VX2 neoplasm induction. Thanks to this paradigm, transarterial and ablative therapies can be performed. However, variations in neoplasm kinetics, peripheral vascularization, unclear neoplasm biology, and unclear genome organization are some of the limitations [139].

THERAPEUTIC APPLICATIONS

Chemotherapy

A rapidly developing area for the treatment of HCC is modified pharmacotherapy. Fig. 5 gives a detailed overview of the mechanisms of action of the pharmacologically active ingredients. Tian and associates. Created HKUST-1 metal-organic frameworks (MOFs) based on Cu2+ loaded with sorafenib and meloxicam for the treatment of HCC. According to the results, MEL/SFB-HKUST-1 MOFs outperformed other groups in terms of cell toxicity, dose-dependent cell viability, and chemodynamic profile. Ferroptosis and pharmacotherapy are both effective nanoplatforms for the treatment of HCC [140]. Janus NPs have proven to be promising therapeutics for HCC. LA has a high affinity for the ASGP-R found on HCC cells. Zhang *et al*. Developed LA-decorated gold nanorods (AuNRs)®zeolitic imidazolate framework (ZIF)-based amphiphilic Janus NPs simultaneously loaded with DOX and SFB. The results showed significant tumor reduction in HCC cells, increased targeting efficiency, and pH-sensitive release of DOX and SFB [141].

Wang *et al*. CH-NCs integrated with engineered naringin (NA) to reduce HCC caused by aflatoxin B1. CH-NCs incorporated NA due to its limited pharmacological availability. The electrokinetic potential and dimensions of NA-CH NCs varied from +31.6±2.3 mV to 54.5±3.6 mV and 92.4±4 nm to 188.54±3 nm, respectively. Administration of NA-CH-NCs and FNRG demonstrated their therapeutic potential against HCC by significantly reducing the levels of serum biochemical markers AST and ALT in aflatoxin B1-induced HCC [142].

Photothermal therapy (PTT)

The ability of PTT to destroy cancerous tissue while leaving healthy tissue intact has attracted attention. To induce localized hyperthermia and eradicate tumors, PTT uses a photoreactive agent that absorbs radiant energy and converts it into thermal energy, as shown in Fig. 6 [143]. Jin and staff. Designed multifunctional NPs to study their photothermal activity and demonstrated remarkable cellular internalization and targeting ability in Hep3B cells [144]. The disadvantages of PTT have been overcome by hybrid therapies. Grześkowiak and colleagues. Developed polydopamine NPs for targeted chemo-photothermal treatment, which resulted in the reduction of tumor growth and reversal of malignancy [145]. Gong and staff. Demonstrated pH/NIR dual stimulus sensitivity and remarkable cytotoxic effect against liver cancer cells when they grafted triformylcholic acid and folic acid onto Fe_3O_4-modified graphene oxide for synergistic chemo-PTT [146].

Photodynamic therapy (PDT)

As shown in Fig. 7, photodynamic treatment (PDT) is a minimally invasive therapeutic strategy in which a cytotoxic photosensitizer is administered and the tumor is then irradiated with a laser [147]. PDT has attracted great interest in the treatment of various neoplasms because it is non-intrusive [148]. PDT has been effectively used in the treatment of cholangiocarcinoma, hepatoblastoma, HCC, and liver metastasis. It is considered a viable palliative treatment for advanced liver carcinoma [149]. However, a number of problems, such as low sensitivity and specificity toward malignant liver tissue and problems with laser penetration due to liver density, hinder the clinical use of PDT

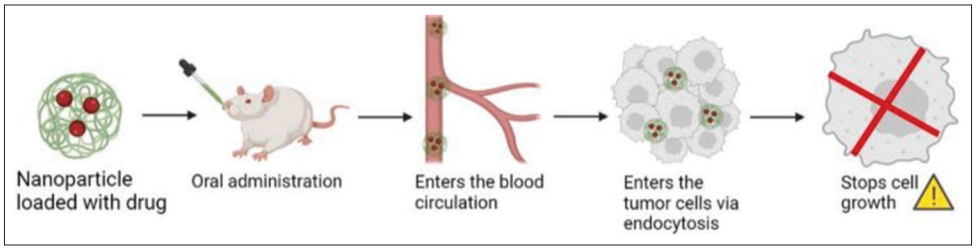

Fig. 5: Illustration of Chemotherapy on the tumor cell [195]

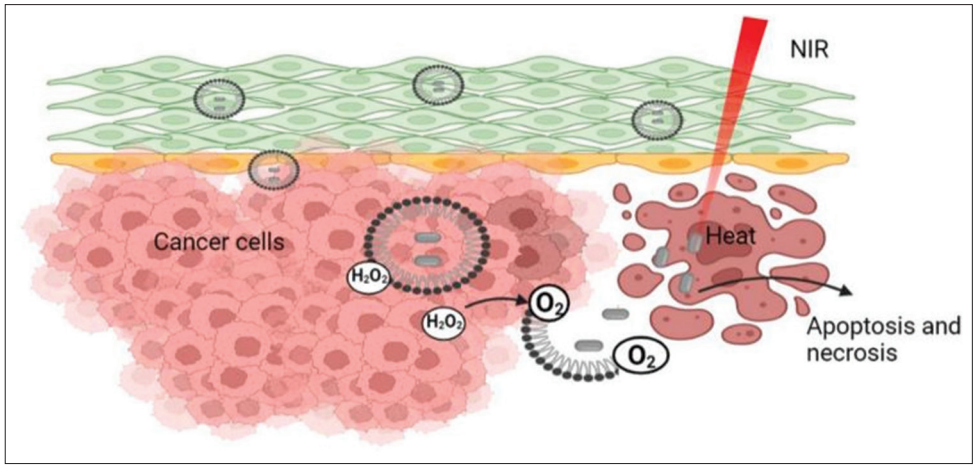

Fig. 6: Schematic representation of the effect of photothermal therapy on tumor cells [195]

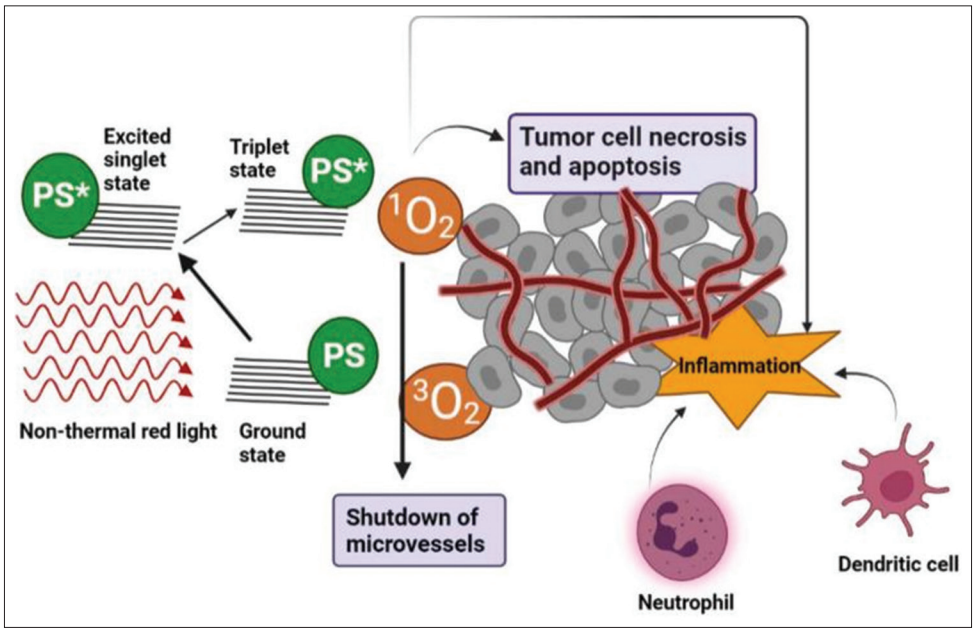

Fig. 7: Illustration of the mechanism of action of Photodynamic therapy on tumor cells. PS: Photosensitizer material [195]

in the treatment of liver carcinoma [150]. Some of the disadvantages of PDT have been addressed by recent developments in photosensitizer technology, such as the creation of metal phthalocyanine complexes, gold NPs, polymeric micelles, radachlorin, pH-responsive photosensitizers, and MOFs [150]. Shao and staff. Prepared amphipathic photocyanin analogs and examined their effects on HepG2 cells both *in vitro* and *in vivo*, both with and without radiation [150]. Zinc(II) phthalocyanine (ZnPC) is also used in PDT therapy and Abdel Fadeel *et al*. To increase PDT activity, ZnPc modified with thiophenyl groups was loaded into liposomes and transferosomes [151]. Tsuda and staff. Investigated how lactosomes loaded with indocyanine green influenced the response of the human cell line HuH7 to PDT and NIR treatment of HCC [152]. Ke and employees. Developed a photosensitizer and pH-responsive fluorescent probe based on the self-quenching mechanism of phthalocyanine moieties [153]. To overcome the disadvantages of pH-dependent photosensitizers, layered double hydroxides with anion exchange capabilities and the ability to transport drugs or genetic material have been developed [153,154]. Compared to first-generation photosensitizers, second-generation photosensitizers such as radachlorin have better light penetration into target tissues and remarkable physical and chemical properties such as low toxicity and rapid *in vivo* metabolism [155].

Sonodynamic therapy

ROS generated by photonic energy have a transient existence that limits their diffusion to a depth of 10–55 nm [156], so close proximity between the photosensitizer and target cell structures is required to induce programmed cell death. Unaffected cell structures, on the other hand, suffer no damage. Sonodynamic treatment (SDT) has emerged as a promising alternative therapy method to overcome the disadvantages of photodynamic treatment (PDT). To enable deep tissue penetration, SDT uses ultrasound energy in combination with a sonosensitizing agent, as shown in Fig. 8 [157]. Similar to PDT, the mechanism of action involves the generation of ROS; other proposed mechanisms include thermal decomposition, sonoluminescence, and acoustic cavitation. Studies have shown that SDT is effective in causing cellular structures of HepG2 liver cancer to undergo programmed cell death. When 2-deoxyglucose (2-DG), 5-aminolevulinic acid (ALA), and microbubbles are combined, enhanced apoptotic properties are observed [157]. Xu *et al*. Excellent cytotoxic effects on the mouse hepatoma H22 cell line were found when the efficacy of SDT with pyropheophorbide-a-methyl ester (MPPa) on malignant hepatic mitochondrial cell structures was investigated for the treatment of liver cancer [157]. Wu and associates. Discovered that SDT caused oxidative phosphorylation of mitochondrial membranes, decreased mitochondrial membrane potential, and

significantly reduced the expression of P-glycoprotein and multidrug resistance protein (MDR) in HepG2/ADM tumor cell structures [158].

Chemodynamic therapy (CDT)

Cancer cells are more susceptible to ROS-induced cancer treatments [159], including photodynamic therapy (PDT), sonodynamic therapy (SDT), radiotherapy, and chemotherapy. By converting hydrogen peroxide (H_2O_2) into toxic hydroxyl radicals, chemodynamic agents – also called Fenton agents – catalyze Fenton or Fenton-like reactions to produce ROS, damaging cellular genetic material and ultimately triggering cellular apoptosis. Fig. 9 illustrates this mechanism. Because CDT specifically responds to H_2O_2, has tumor cell specificity, has no drug resistance, and does not require external stimulation, it provides a more reliable therapeutic approach that can be clinically implemented. Inorganic nanocrystals based on transition metals [160], nanoenzymes [161], electron-rich hybrid nanomaterials [162], MOFs [163], covalent organic frameworks [164], and macromolecular nanomaterials [165] are often used to prepare CDT agents. Zeng *et al*. Have developed tumor microenvironment (TME)-responsive Fenton nanoreactors consisting of molybdenum disulfide (MoS_2) modified with gallic acid (GA) and loaded with iron (III) (MoS_2@GA-Fe) [166]. Through a glutathione reaction, the GA-iron(III) complex converts iron(III) into iron(II), thereby generating harmful hydroxyl radicals. In addition, the complex exhibits dual imaging ability due to the magnetic resonance property of iron(III) and the photoacoustic property of MoS_2. The increased permeability and retention effect (EPR) causes the complex to accumulate in HepG2 cellular units. The Fenton reaction, driven by the reduction of ferric iron to ferrous iron, produces a snowball-like effect that is enhanced by the addition of GA, which increases oxidative stress. Iron (III) can be reduced to iron (II) by molybdenum (IV), creating another Fenton reaction cycle. Over time, the reaction is accelerated by the exposure of molybdenum (IV) on the MoS_2 surface due to repeated decomposition. After degradation, free GA iron(III) is reabsorbed onto the MoS_2 surface, producing further harmful hydrogen sulfide and hydroxyl radicals. The improved therapeutic efficacy of this nanoreactor is confirmed by *in vivo* photoacoustic/magnetic resonance imaging (MRI) [166]. Combination therapy is recommended because although CDT eliminates tumor cell units, the tumor itself is still difficult to eliminate. Therefore, treatment of liver cancer with a combination of CDT and chemotherapy is the preferred choice [167,168]. Cai *et al*. Developed a novel multifunctional NPs for liver cancer chemotherapy/CDT therapy guided by MRI [169].

Immunotherapy in liver cancer

The immune system has proven to be a key player in the fight against liver cancer. Adoptive immune cell transfer therapy and checkpoint inhibitors are two immunotherapeutic approaches that have shown promise in the treatment of liver cancer (Fig. 10) [170]. NPs have been investigated by researchers as a potential new therapeutic approach. Xu Ligeng *et al*. studied selenium NPs that reprogrammed tumor-associated macrophages and activated natural killer cells to combat liver cancer [171]. Cheng *et al*. Demonstrated antitumor effects against free IFN-alpha in liver cancer models by encapsulating interferon-alpha 2a in an organometallic NPs [172]. In another study, small interfering RNA was delivered through extracellular vesicles, slowing the growth of tumors and improving treatment outcomes [173]. Liu *et al*. Created LA-PegPI, a novel copolymer that exhibited reduced toxicity and increased stability in liver cells [175]. Guo and staff. Developed Nano-FdUMP, a nanoformulation that combines Nano-Folox and FdUMP and showed synergistic efficacy in orthotopic HCC mouse models [176]. In addition, a study by Zhang *et al*. Involved the formation of chitosan nanocomplexes with doxorubicin and recombinant human IL-2, which decreased cell viability and increased cellular uptake of doxorubicin [174].

Radiotherapy

Radiation therapy uses high-energy photon radiation to destroy cancer cells and is an effective treatment option for liver cancer [179]. This method works through two different mechanisms: Direct ionization, which fragments DNA immediately, and indirect ionization, which generates ROS that cause DNA damage and cellular stress (Fig. 11) [177,178]. Radiosensitizers are designed to improve radiation sensitivity and specificity, thereby reducing the damage that radiation causes to surrounding tissue [180,181]. These substances, which include noble metal NPs such as silver and gold, have the ability to interact with cancer cells, absorb X-ray energy, and increase the production of ROS, making tumor cells more susceptible to radiation [182]. Zeng *et al*. Investigated the potential for radioactivity of nanogold and nanosilver in HepG2 cells and showed increased cell death and radiosensitivity [183]. In another study, a pH-responsive gold radiosensitizer was developed that showed selective accumulation and improved therapeutic efficacy in hepatoma cells [184].

BIOSENSORS USED IN THE DIAGNOSIS AND TREATMENT OF HCC

By converting biological signals into electrical impulses, diagnostic tools called biosensors have revolutionized the diagnosis of cancer. These state-of-the-art tools provide accurate visualization of cancer cells, tracking of metastases, and detection of angiogenesis [185]. Due to their remarkable sensitivity and accuracy, nanoscale materials have become attractive biosensing platforms [186]. Abnormal changes in nucleic acid levels that trigger cancer-causing pathways indicate HCC. Biosensor technologies can identify biomarkers such as des-γ-carboxyprothrombin (DCP), glypican-3 (GPC3), and alpha-fetoprotein (AFP) [187]. Affordability, compactness, sensitivity, and integrability are some advantages of electrochemical techniques. Terahertz metamaterial biosensors [188], biosensors based on MOFs [189], Au

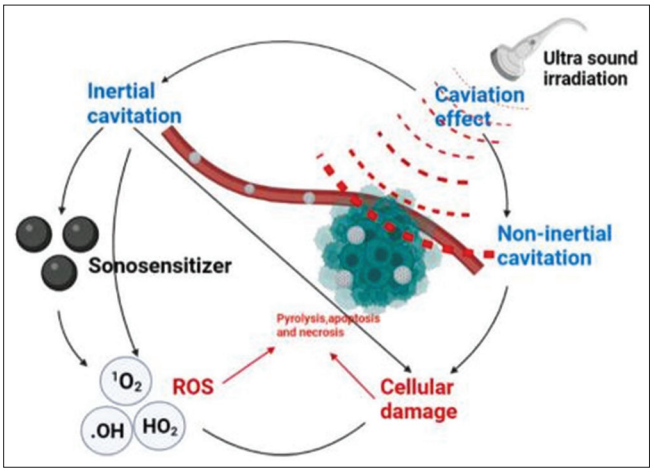

Fig. 8: Pictorial representation of the effect of ultrasound irradiation on tumor cells explaining the Sonodynamic therapy [195]

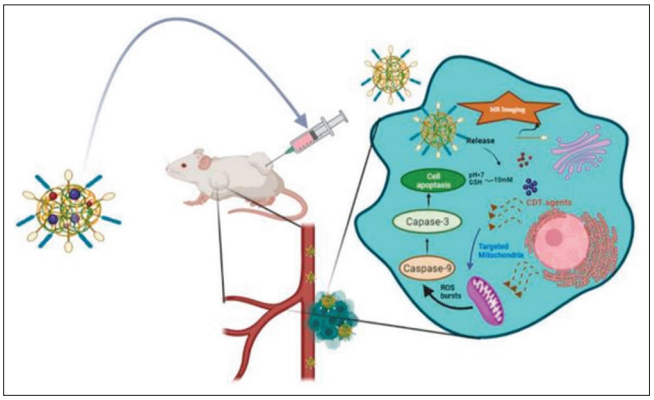

Fig. 9: Schematic representation of the effect of chemodynamic therapeutic agents on the cell components [195]

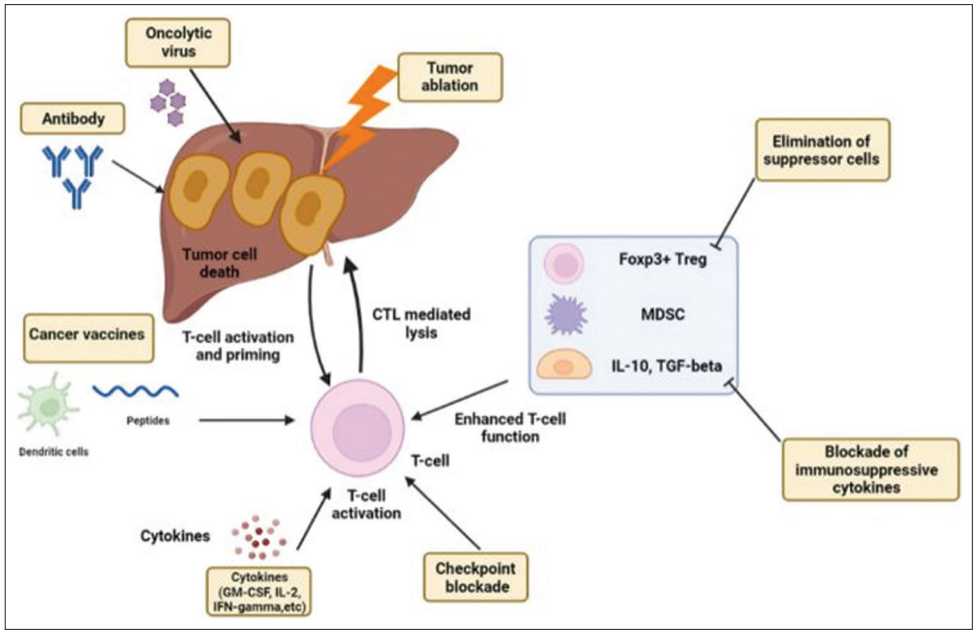

Fig. 10: Pictogram of Hepatocellular carcinoma Immunotherapy [195]

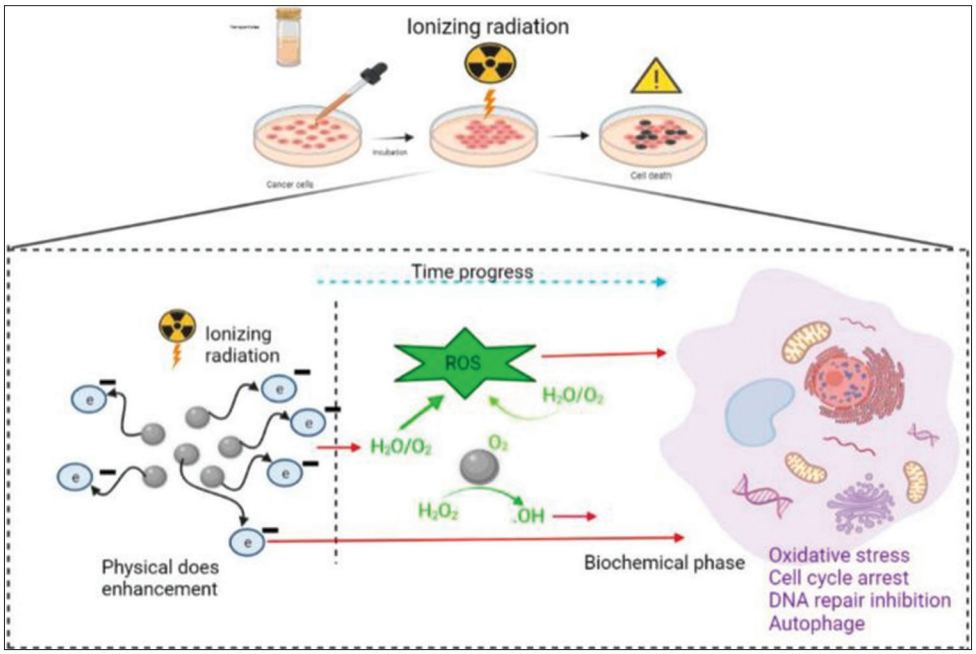

Fig. 11: Schematic representation of the effect of indirect ionizing radiations on cell death [195]

biosensors with SPR [190], biosensors based on organic field effect transistors [191], microcantilever biosensors based on aptamers [192], and ultrasensitive electrochemiluminescence biosensors for alkaline phosphatase detection (ALP). [193] are just some of the biosensors that researchers have developed.

When it comes to identifying HCC biomarkers, these biosensors have shown remarkable sensitivity, specificity, and accuracy. Future developments will concentrate on detecting complicated biological samples, creating novel sensing modes for improved repeatability, and amplifying signals utilizing novel nanoscale materials [194].

CONCLUSION AND FUTURE PROSPECTIVE

The latest developments in nanoscale pharmaceutical platforms for HCC treatment and diagnostic methods are highlighted in this thorough study. Extensive research efforts have focused on developing nanoscale drug formulations that specifically target cancerous cells for both diagnostic and therapeutic purposes to successfully battle HCC. However, because the tumor microenvironment might hinder clinical translatability, effectively addressing HCC requires a thorough understanding of the physiological mechanisms underlying the diseased liver. A synergistic combination of particular ligands for matching receptors is necessary for the creation of NPs for active targeting of HCC. Because of their accessibility and complex characterization, HepG2 cells are often used as an *in vitro* cellular model, which makes toxicological and pharmacological studies easier. On the other hand, *in vivo,* murine models have proven to be widely used in clinical research for HCC. For the effective treatment of HCC, a variety of therapeutic modalities, including immunotherapy, radiation therapy, PTT, photodynamic therapy (PDT), cytotoxic chemotherapy, and CDT, can be used either alone or in combination.

Due to insufficient testing in animal models, scalability problems, and a lack of thorough evaluation standards, few NPs have shown comparable results in clinical trials, despite notable advancements in NPs demonstrating efficacy in pre-clinical investigations. As a result, significant challenges remain in the field of nanomedicine. As a result, current efforts should focus on resolving issues at the clinical stage and optimizing the manufacturing and scaling-up process.

ETHICAL APPROVAL

Not applicable.

CONFLICTS OF INTEREST

Nil.

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