ERURJ **2024**, *x*, x, Accepted

Review

Novel Trends in Revolutionizing Hepatic Diseases Treatment: Application of Nanotechnology

Reem A. Naimy [1], Omnya A. Elshafey [1], Mariem M. Ahmed [1], Ahmed T. Mohamed [1], Maha I. Rashwan [1], Hanan S. Mosaad [1], Eman S. Khater [1], Nada M. Abdallah [1], Yasmin H. Mohamed [1], Alaa H. Elsayed [1], Youstina L. Youssef [2], Ahmed Abdalla [2], Afaf A. Ramadan [2,3], Mohamed A. Megahed [2,*]

[1] *PharmD Students, Faculty of Pharmacy, Egyptian Russian University, Badr City, Cairo, Egypt.*

[2] *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Egyptian Russian University, Badr City, Cairo, Egypt.*

[3] *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy (Girls), Al-Azhar University, Cairo 11765, Egypt.*

*Corresponding author(s): Mohamed A. Megahed, E-mail: Mohamed_adel@eru.edu.eg.

ABSTRACT

Hepatic disorders such as hepatic fibrosis, microbial infections, and hepatocellular cancer remain the leading causes of death. Traditional therapy has limitations due to its side effects and inability to deliver appropriate concentration. Nanotechnology has the potential to produce and enable sooner and more accurate individual diagnosis, improve targeted therapies, reduce side effects, and enhance therapeutic monitoring. The field of nanomedicine has the potential to provide novel therapeutic techniques for liver illnesses. The four major cell types in the liver are crucially involved in the complex sequence of events that occur during the initiation and maintenance of liver inflammation and fibrosis. One major biological component believed to oversee the accumulation of nanoparticles in the liver is the kupffer cell. Recently, Nano therapies treat liver fibrosis and infections (Hepatitis B, murine hepatic schistosomiasis, and Sepsis-related liver injury). Nanotechnology also has several applications in treating liver cancer and liver failure. Nanotechnology has several applications in imaging liver disorders using nanomaterials and superparamagnetic iron oxide nanoparticles, and it has a role in addressing oxidative stress-related liver disorders.

Keywords: Nanomedicine – Liver cancer – Liver fibrosis – Liver infection – Oxidative stress- Targeted therapy.

1. Introduction

Globally, hepatic disorders such as hepatic fibrosis, microbial infections, and hepatocellular cancer remain leading causes of death despite the availability of conventional treatments and vaccines. One significant disadvantage of traditional therapy is the inability to deliver appropriate concentrations of medicines to the liver disease and/or contribute to adverse consequences (1) Nanotechnologies made of biocompatible materials have the potential to deliver drugs more precisely (2).

This can be done passively by optimizing the physicochemical properties of drug nanocarriers, such as size and surface properties, or actively by using organ/tissue-specific homing devices to target the disease site while minimizing side effects (3) Liver fibrosis is caused by persistent liver damage and the formation of extracellular cell matrix (ECM) proteins, which is common among chronic liver disorders. Liver fibrosis can be caused by alcohol consumption, hepatitis virus infections, genetic anomalies, steatohepatitis, autoimmune and noninfectious disorders such as fatty liver. Cirrhosis, also known as advanced liver fibrosis, occurs when ECM proteins accumulate and create a fibrous scar on the hepatic architecture. This leads to the formation of nodules of regenerated hepatocytes. Cirrhosis causes hepatocellular dysfunction, HCC, and liver failure. The overabundance of scar tissue that develops from liver cell inflammation leads to fibrosis. Nodules, or abnormally spherical regions of cells, form dying liver cells that regeneration cells will eventually replace. The liver becomes hard and eventually develops hepatic fibrosis because of a sequence of events that cause hepatocyte injury, the retention of inflammatory cells in the wounded liver, and the activation of collagen-producing cells. It is primarily caused by hepatic stellate cells (HSCs) and is defined by the excessive synthesis of extracellular matrix (ECM) proteins, particularly collagen type 1. Because conventional therapy cannot get therapeutic into the liver at a sufficient concentration, it is ineffective in treating liver illnesses (4).

2. Nanotechnology and its impact on the drug delivery system:

The potential for using nanoparticles as an efficient drug delivery mechanism is enormous. Current advancements in drug delivery nanotechnology were covered in this review. Recently,

there has been an increased interest in nanotechnology as a solution to the issues of gene and medicine delivery. Much research has been done on nanosystems with various biological characteristics and compositions for medication and gene delivery applications. Understanding how nanomaterials interact with the biological environment, target cell-surface receptors, release drugs, administer multiple drugs, maintain therapeutic agents, and comprehend the molecular mechanisms of cell signaling involved in the pathobiology of the disease under consideration is crucial for achieving effective drug delivery (5).

Several anti-cancer medications, such as doxorubicin, dexamethasone, 5-fluorouracil, and paclitaxel, have been effectively developed using nanomaterials. For in vitro RNAi administration, other materials such as quantum dots, chitosan, polylactic/glycolic acid (PLGA), and PLGA-based nanoparticles have been used. Because it is so difficult to get imaging and therapeutic agents past the blood-brain barrier and into the brain, brain cancer is among the most challenging cancers to diagnose and cure. It has been demonstrated that anti-cancer medications attached to nanomaterials, such as doxorubicin and loperamide, may pass through the blood-brain barrier and enter the brain at therapeutic quantities.

A novel strategy to regulate the course of illness is the use of nanomaterials, such as peptide-based nanotubes, to target the vascular endothelial growth factor (VEGF) receptor and cell adhesion molecules, including integrins, cadherins, and selectins (5).

The world is currently dealing with a serious issue with poorly soluble medications. While there are several approaches to improving solubility, nanotechnology is one of the most well-known and cutting-edge technologies. It deals with high surface area nanoparticles that can make poorly soluble medications more soluble. The primary aim is to enhance the solubility of poorly soluble pharmaceuticals in water using a range of nanotechnology-related approaches. Wet milling, high-pressure homogenization, emulsification, precipitation with a compressed fluid antisolvent (PCA), rapid expansion from a liquefied-gas solution (RESS), spray freezing into liquid (SFL), and evaporative precipitation into aqueous solution (EPAS) are some of the processes for producing nanoparticles that are included in the study methodology. Commercialized nanotechnology to improve the solubility of medications with low water solubility: Dissocubes, first Technology: 2) Nanocrystal; 3) Nanomorph; 4) Nanoedge; 5) Nanopure 6) Crititech technology 7) Nanochelate technology (6).

The "magic bullet" notion, proposed by Paul Ehrlich in 1891, was the first description of the drug-targeting paradigm. Drug targeting aims to deliver medications to the appropriate location, at the appropriate concentration, and for the appropriate amount of time. Drug effectiveness is challenging to determine due to differences in chemical composition, molecular size, hydrophilicity, and protein binding (7).

Despite extensive research, only a small percentage of compounds are developed for clinical usage. An in-depth discussion of the earlier advancements in drug delivery systems (DDS) based on nanoparticles will be covered in this review, along with novel research findings on the therapeutic improvement of antiretroviral treatment. Practitioners will be able to provide medications to target body parts by using nanoparticle DDS. The application of nanoparticles as a DDS has a discernible therapeutic impact on treating cancers. DDS will also be used in medical imaging to reveal brain function, cancer, or other biological processes. There is a huge potential benefit for using nanoparticle DDS to enhance human health (7)

Blindness is a serious global health issue that profoundly affects affected people and their families and has significant socioeconomic ramifications. Eye drops are commonly used for ocular drug delivery but have low bioavailability (less than 5%) due to poor pre-corneal retention and penetration. Pre-corneal retention can be affected by factors such as fast tear turnover, blinking, and solution drainage, leading to medication loss following topical administration. Frequent instillations of eye drops are necessary to maintain therapeutic medication levels on the pre-corneal surface. Excessive usage of concentrated eye drops can cause toxicity, corneal dryness, and serious systemic side effects (8).

The Middle East is one of the regions most affected by blindness, an issue made worse by the rising rate of diabetes among the populace. One essential component of ocular therapies is a suitable drug/gene delivery system that can maintain and deliver medications to the target tissues and cells. The use of nanotechnology in medicine is developing quickly, and new advances in therapeutic approaches based on nanomedicine may be very beneficial in treating the main causes of blindness, which include retinal degeneration, cataracts, glaucoma, and diabetic retinopathy. A few interesting nanomedicine-based therapeutic techniques were presented in this brief review that aims to transfer drugs and genes to the anterior and posterior regions (9)

The engineering and production of materials at the atomic and molecular scale is known as nanotechnology. According to the National Nanotechnology Initiative, structures with at least one

dimension approximately falling between 1 and 100 nm are called nanotechnology. Despite this size limit, structures as small as a few hundred nanometers are frequently called nanotechnology. These structures are created by top-down or bottom-up engineering of individual components. This article concentrates on the use of nanotechnology in medication distribution and identifies several promising areas where both established and developing nanotechnologies may open the door to new therapeutic classes (10).

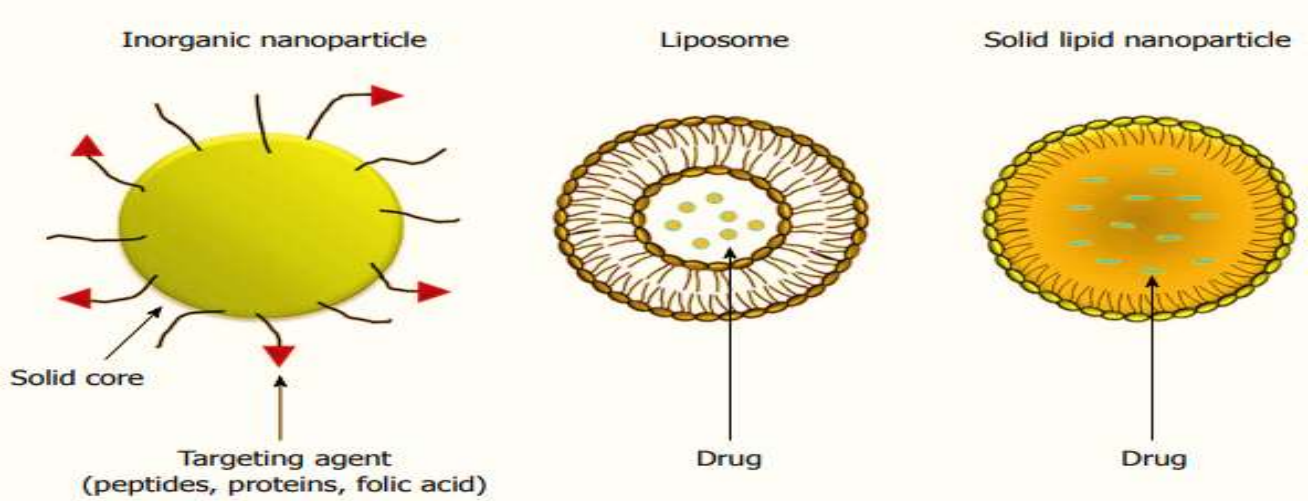

Figure 1. Basic types of nanoparticles include solid lipids, liposomes, and inorganic nanoparticles (11)

3. Common nanoparticle types to be employed for the treatment of liver diseases:

Chronic liver disorders pose a global health threat due to their prevalence and lack of effective treatments. Fibrogenesis, the development of fibrosis, leads to complications, costly treatments, and death. Despite advanced mechanisms, medications for liver fibrosis have limited therapeutic effects. Antifibrotic therapy targets hepatic stellate cells, which are essential for liver fibrogenesis. Nanoparticles are used to deliver therapeutic agents, including medicines and nucleic acids, for treating liver fibrosis (11).

There are several advantages to using NP Delivery systems: safeguarding the medicinal substance, particularly nucleic acid, from inactivation until it reaches the site of action; the viability of combining hydrophilic and hydrophobic agents (12–14).

Enhancement of pharmaceutical potency (higher bioavailability) of medications; decrease in the toxicity and adverse effects of the drug; lessening of variations in drug blood levels (lower danger of a hazardous or ineffective concentration) (15).

A wide range of delivery methods (parenteral, oral, ophthalmic, and external), Regulated medication release, And active targeting since there's a chance of getting an increased nanoparticle system affinity (16).

Liver illnesses are prevalent in clinical practice globally, with significant morbidity and mortality rates. These diseases include viral hepatitis, cirrhosis, and hepatocellular carcinoma. Due to their nonspecific absorption, many drugs used in liver disease diagnostic imaging and treatment may have serious side effects or be ineffective in vivo (17,18).

Conventional malaria treatment faces drug resistance, non-specific targeting, high dose requirements, and severe toxicity. Nanosized carriers aim to reduce these issues, improving bioavailability and drug selectivity (19).

Therefore, medication efficiency may be significantly increased by directing drug administration into the liver or certain liver cells. Particularly covered are targeting tactics, improved effects mechanisms, and nanoparticles' clinical uses (17).

New targeting nanotechnology, such as multifunctional nanoparticles and nanoprobes for multi-modality imaging, could, in our opinion, soon enable major improvements in this field of active study. Organ imaging is one of the main uses of nanoparticles in medicine (18).

Magnetic resonance imaging (MRI) and computed tomography (CT) are the two techniques used to image the liver. The contrast agents that are used in imaging are Iron oxide (IONPs) and superparamagnetic iron oxide nanoparticles (SPIONs), several forms of liver-specific enhanced magnetic resonance imaging, and gold nanoparticles (AuNPs),, which is employed to create innovative agents for CT imaging. Particles ranging in size from 1 to 100 nm are used in nanotechnology (20–22).

This contemporary technology is a helpful approach that has opened up new possibilities in cancer imaging and medication. To quickly diagnose cancers. Certain nanoparticles are useful for improving the quality of MRI or CT imaging and identifyingtifying cancers of the liver. The prompt identification of HCC is necessary for therapy to be effective. The burgeoning field of medical applications for nanotechnology, including medication delivery systems based on

nanomaterials, is known as nanomedicine. With this technology, new therapeutic approaches to liver illnesses may be possible in a very big way (22).

Targeting macrophages both specifically and randomly, hepatic Using nanomedicine to treat stellate cells (HSC), hepatocytes, and liver sinusoidal endothelial cells (LSEC) has been created and put to the test in preclinical environments. The liver's four primary cell types play a critical role in the intricate chain of events that starts and continues with hepatic inflammation and fibrosis. The ability of various cell types to absorb surrounding substances can be used to target them. Endocytosis can target certain structures, resulting in specificity for a particular cell type, such as peptide sequences, sugar moieties, or receptors (23).

Nanomedicine focuses on macrophages, particularly the liver-resident Kupffer cells, because of their crucial pathogenic roles during inflammation and fibrogenesis, as well as their very efficient and non-specific uptake of most nanomaterials. Targeting macrophages in liver illness is made possible by the mannose receptor; however, macrophages can also develop Activated by certain nanomaterials, including gold nanorods (AuNRs) modified with peptides, which make them Inflammatory (23,24).

Targeting HSC, the primary collagen-producing cells during fibrosis, involves the use of nano-constructs that identify integrins peroxisome proliferator-activated receptor 1, platelet-derived growth factor (PDGF) receptor β, and mannose 6-phosphate and insulin-like growth factor II. Focusing on targeting the primary hepatocyte, the predominant liver parenchymal cell, has only been accomplished with excellent specificity by imitating the body’s naturally produced apolipoprotein nanoparticles. This review discusses the effectiveness of carboxy-modified micelles and integrin receptors in targeting LSEC in livers, highlighting the role of various cell types in both healthy and sick livers (22,24).

4. The liver’s four main cell types in both healthy and pathological circumstances:

Hepatocytes are the main parenchymal cell type in the liver, with macrophages, hepatic stellate cells (HSC), and LSEC being the main non-parenchymal cell type. These cells are crucial for disease progression and may be targets for nanomedicine. Hepatocytes, or parenchymal cells, comprise most of the liver and can account for 80% of its volume. Non-parenchymal cells make up 40% of the liver. Liver cells overall, although just 6.5% of the organ’s total loudness.

Hepatocytes have been demonstrated to have a 200-day lifetime. In rats and 400 days in mice, which illustrates the ongoing process in which the liver renews itself (24,25).

Hepatocytes perform numerous essential liver processes in a healthy state, including protein production and storage. Turnover of carbohydrates, phospholipid synthesis, bile salt synthesis, And cholesterol, cleansing, adjustments, and removal of both endogenous and external materials. When liver disease is present, which can be brought on by a variety of injuries such as metabolic syndrome, viral infections, or heavy alcohol consumption, apoptosis occurs in hepatocytes. It is substituted with ECM, a procedure engaged in the crucial process of hepatic fibrogenesis. HSCs comprise 5-8% of the liver cells in the perisinusoidal region. They secrete ECM proteins and store vitamin A in healthy persons (26).

They differentiate into myofibroblasts in liver illness, which results in excess connective tissue and liver fibrosis. Activated HSCs bring on increased liver stiffness, a defining feature of liver fibrosis and cirrhosis. Innate hepatic immune cells, especially macrophages, can activate HSCs. In addition to being vital for preserving tissue homeostasis, macrophages play a crucial role in the liver's response to injury and the advancement of liver disease (22,26).

TNF are two proinflammatory cytokines that are necessary for almost all inflammatory diseases. Anti-inflammatory cytokines directly suppress proinflammatory mediators; IL10, the primary anti-inflammatory cytokine, inhibits IL6 and TNF synthesis (27).

Hepatocyte transplantation is the most common liver cell therapy for treating liver failure and metabolic illnesses. However, no conclusive proof exists for treatment benefits. Cell types effective in preclinical models include macrophages, mesenchymal stem cells, liver sinusoidal endothelial cells, and hepatocytes. Research is needed to determine optimal immunosuppressive regimens, cell transplantation methods, and tissue engineering for transplanting cells in extrahepatic sites. The potential for hepatocytes from pluripotent cells and creating pluripotent cells with equivalent functional capacity are also discussed (28).

5. Applications of Nanotechnology in liver fibrosis treatment:

Liver fibrosis is a treatable condition caused by different causes of liver damage. If left untreated, it can result in serious consequences such as liver cirrhosis, liver failure, and even liver cancer. Liver fibrosis is an asymptomatic disease that progresses slowly and is accompanied by persistent damage and deposition in the extracellular matrix (ECM) (29)

Traditional pharmacotherapies, such as chemical drugs, Chinese herbal medicines, and monoclonal antibodies, possess undesirable side effects and insufficient therapeutic efficiency. For instance, sorafenib and interferon-γ (IFNγ) have demonstrated strong antifibrotic properties in vitro, although their effects in vivo are not as strong (30)

There isn't a licensed medication for liver fibrosis available right now, so the development and application of nanomedicine for the detection and treatment of chronic liver disease (CLD) has benefited immensely from advancements in nanotechnology. The nanoparticles' size, shape, composition, and surface properties result in enhanced benefits, such as increased internalization and penetration, regulated medication release, sustained circulation, enhanced drug pharmacokinetics, and fewer adverse responses (29).

For the treatment of liver fibrosis, numerous organic and inorganic nanoparticles (NPs) have been produced, including lipid nanoparticles, metal nanoparticles, nanoparticles made of polymers and proteins (31).

5.1. Cell target in liver fibrosis

Since HSCs activation is thought to be the primary cause of liver fibrosis, it is a key target for anti-fibrotic drugs. Various mechanisms result in liver fibrosis, such as chronic hepatocyte injury, inflammatory cytokines release, endothelial barrier damage, excessive accumulation of ECM, and HSC activation. When removing the above factors, the fibrosis will regress, pro-inflammatory or profibrogenic cytokines will decrease, a HSCs will disappear, increased collagenolytic activity, and ECM production will suppressed (32)

5.1.1. Nanoparticles-based drug delivery strategies for liver fibrosis:

5.1.1.1. Targeting Platelet-Derived Growth Factor Receptor (PDGFR)

PDGF receptor (PDGFR) consists of a dimer containing two related chains connected by disulfide bonds. PDGFR is specifically overexpressed on aHSCs, so scientists developed a receptor recognizing cyclic peptide-modified albumin (pPB) peptide “Cp SRNLIDCp ” for targeting HSCs (33).

Scientists used the pPB peptide-modified sterically stable liposomes encapsulating IFNγ (pPB-SSL-IFN-γ) to target HSCs specifically. In vitro, the NPs inhibited HSC growth, and in mice given thioacetamide, they reduced fibrosis. This method of drug delivery extended the circulation half-life of IFNγ, and adverse effects in hepatic fibrosis were reduced. A gold Nano rod with anti-

PDGFRβ to target aHSC specifically was created. The gold nanorods reduce inflammation and regress fibrosis (29).

5.1.1.2. Targeting Sigma-1 Receptor

Relaxin (RLN) is an antifibrotic peptide hormone that can reverse HSC activation directly for fibrosis regression. Its primary receptor, relaxin receptor family peptide-1 (RXFP1) is upregulated on aHSCs. The binding of RLN and RXFP1 can initiate the NO signaling against profibrogenic pathways (34). RLN-plasmid (pRLN)-loaded lipid-calcium-phosphate NPs (LCPs), surface modified with AEAA (aminoethyl anisamide adenosine monophosphate; PKA, protein kinase A CREB cAMP-responsive element binding protein) pathway by activating Nur77 in macrophages was engineered. Lipid–protamine–hyaluronic acid (LPH) nanoparticles encapsulating the relaxin gene and miR-30a-5p with surface modified AEAA were created in response. This exhibits synergistic antifractal effects in rodent models. MiR-30a-5p is derived from exosomes and secreted by relaxin-educated macrophages that can deactivate HSCs (35).

5.1.1.3. Targeting Integrin αvβ3

Integrins are receptors for most adhesion proteins like collagen type VI and fibronectin, responsible for the interaction between ECM and cells. They all contain the arginine-glycine-aspartic sequence (RGD) peptide. For HSC targeting, the RGD peptide -modified nano delivery systems have been applied (29).

Liposomes containing the cyclic peptides [cRGDyK, Cyclo (Arg-Gly-Asp-DTyr-Lys)] were prepared. It has a high affinity to αvβ3 to target aHSCs, with no effect on quiescent HSCs specifically. This overcomes the lack of specificity in the previous RGD-modified systems targeting activated and quiescent HSCs. Vismodegib (VIS), a Hh inhibitor, attenuates hepatic fibrosis by inhibiting HSC activation. The therapeutic efficacy of Vismodegib was enhanced by the cRGDyK modified SSLs, which minimized undesirable characteristics such as off-target effects, short half-life, and water insolubility. This cyclic peptide is used to modify germacrone (GMO)-and-miR-29b-loaded nanoparticles, which have a great cytotoxic effect on aHSCs and inhibit the production of collagen CRGDyK used as an imaging modality for liver fibrosis. It is a useful MRI tracer and can assess the extent of liver fibrosis quantitatively and non-invasively (29).

5.1.1.4. Targeting liver sinusoidal endothelial cells

CLD undergoes the loss of endothelial permeability. TiO2 nanoparticles could restore sinusoidal permeability by inducing transient leakiness in primary human hepatic sinusoidal

endothelial cells (HHSECs), which could upregulate drug uptake and improve hepatic recovery (36).

5.1.2. Nanoparticles used in liver fibrosis:

5.1.2.1.Liposome nanoparticles

Valsartan was administered utilizing vitamin A-coupled liposomes. The platelet-derived growth factor receptor beta (PDGFR-beta) on the surface of HSCs may recognize vitamin A. This nanomedicine enhanced hepatic Mas-receptor function, and the level of fibrogenic cytokines was normalized by increasing valsartan permeability and efficiency (37).

5.1.2.2. Inorganic nanoparticles (NPs)

The inorganic nanoparticles (NPs) may be used as therapeutic agents for liver fibrosis treatment. Titanium dioxide and silicon dioxide nanoparticles can suppress the activity of Type 1 collagen and alpha-smooth muscle actin. Titanium dioxide and silicon dioxide nanoparticles also accelerate the degradation of type 1 collagen (38).

Mn3O4 (manganese oxide) nanoparticles show high antioxidant activity, so citrate functionalized manganese oxide NPs can protect the liver from cirrhosis fibrosis and free oxygen radicals (39). Zinc oxide NPs frequently reduce free pro-inflammatory cytokines and free oxygen radicals, which prevent liver fibrosis in liver damage induced by dimethyl nitrosamine (40).

5.2. Nanotechnology in Hepatic Infections:

Parasites and viruses can infect the liver, causing swelling and irritation (known as inflammation). Inflammation prevents the liver from performing as it should. The viruses that cause liver damage can spread via blood, contaminated food or water, or close contact with an infected person. Bacterial infection is a serious and often fatal complication of liver disease that can cause gastrointestinal bleeding, renal failure, or hepatic encephalopathy (41).

Nanoparticles' special chemical and physical characteristics have resulted in many studies over the decades. Nanomaterials' properties primarily depend on their morphology and particle size. Commercialized nanoparticles like AgNPs and SeNPs are commonly used in medical research for gene, antimicrobial, and drug delivery. Traditional chemotherapy and anti-fibrotic treatments are no longer effective for treating chronic liver diseases due to drug resistance. AgNPs may be a safer

treatment option for targeting hepatic stellate cells (HSCs), which are the main cause of liver cirrhosis and fibrosis (41).

AgNPs have been proven to treat chronic liver diseases (42) effectively. AgNPs can target specific injured tissues in blood circulation by combining antibody-based ligand targeting with material composition. In vitro, high concentrations of Ag ions are effective at killing bacteria. Studies indicate that AgNPs can effectively treat liver diseases such as bacterial infection and hepatic fibrosis. SeNPs, a new type of nanoparticle, have gained acceptance for their anti-inflammatory, antiviral, and antitumor properties, as well as their lower toxicity to normal cells compared to other nanoparticles (43).

AgNPs and SeNPs both affect liver tissue injury caused by viruses and bacteria. AgNPs can affect liver tissue at low concentrations through particle size or by inhibiting cytokine secretion by hepatic cells, potentially leading to HSC activation. Another evidence was found in dose-dependent histological changes such as necrosis and hepatocellular degeneration (44)

Several studies confirmed that the liver is the primary target organ for the effect of AgNPs, and that Treatment with AgNPs may be associated with a reduction in oxidative stress. Silver nanoparticles are known to treat injured liver tissues through oxidative stress. Oxidative stress and inflammatory markers were assessed in liver tissues. In hepatocytes, GSH levels decreased while TNF- and IL-6 levels increased significantly. AgNPs can reduce apoptosis by lowering inflammation and oxidative stress (45).

AgNPs significantly reduced AST and ALT levels in groups treated with NAC and small and large particles compared to LPS and NAC alone, indicating their protective role. Endocytosis has been identified as a key cellular uptake mechanism for nanoparticles. Previous studies have shown that selenium nanoparticles break down into smaller particles in the acidic environment of lysosomes, facilitating drug release. Another study found that treating HBV cell lines with SeNPs reduced DNA damage significantly compared to untreated HBV cell lines. Previous studies have shown that SeNPs have significant therapeutic action for diseases like inflammation, cancer, and viral infection (41).

This nanosystem is gaining popularity in therapy due to its high stability, antiviral activity, anti-inflammatory activity, and low toxicity compared to other nanoparticles. Various biochemical approaches were used to investigate the efficacy of AgNPs, which were found to be dose and particle-dependent. Biochemical changes in inflammatory and oxidative stress markers may

indicate antioxidant activity and inhibition of cell proliferation caused by AgNPs in liver tissue. SeNPs were more effective than AgNPs in reducing DNA damage and cytokines in HBV-cell lines, indicating a potential for antiviral and anti-inflammatory properties (41).

5.2.1. Sepsis:

Sepsis, a systemic inflammatory response syndrome caused by infection, is associated with a high morbidity and mortality rate. One of the signs and symptoms of sepsis-induced multiple organ syndrome is liver damage. Due to their unique physical and chemical properties, drug-delivery nanosystems can effectively treat sepsis-related liver injury (19).

Nanoparticles smaller than 100 nm typically target hepatocytes and hepatic stellate cells (HSCs), but those bigger than 100 nm can passively target Kupffer cells (KC) and hepatic sinusoidal endothelial cells. Kupffer cells are specialized macrophages found in hepatic tissue. Sepsis activates Kupffer cells, causing them to release inflammatory mediators like TGF, IL-6, and oxygen-free radicals (19).

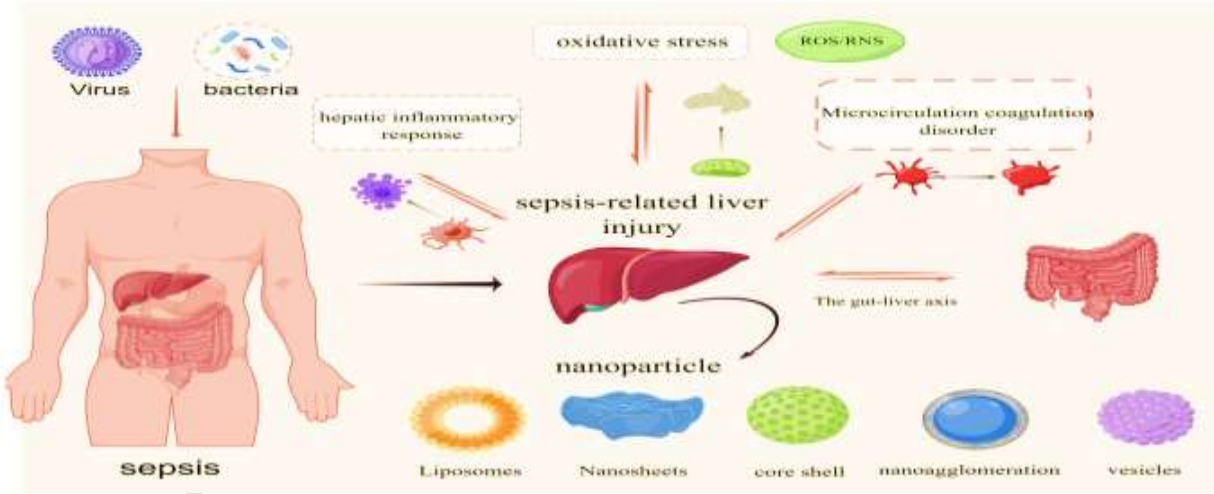

Figure 2 : Drug delivery nanosystems in sepsis-related liver injury (46)

This accelerates liver injury. Furthermore, spherical mesoporous silica NPs (Nanoparticles) accumulate in the liver faster than rod-shaped mesoporous silica particles. Positively charged nanoparticles disrupt the endosomal system, specifically targeting hepatocytes.26 Other nanoparticles, like antimicrobial peptides (AMPs) with anti-intercellular adhesion molecule-1 (ICAM-1) and polymers, can potentially improve pharmacokinetics, drug delivery stability, and

bioavailability. These agents work together to promote the use of drug-delivery nanosystems for the treatment of sepsis-related liver injury (47).

5.2.2. Hepatoprotective role of gold nanoparticles against murine hepatic schistosomiasis:

Bilharziasis is a common parasitic disease that primarily affects the liver, resulting in granuloma and fibrosis. The disease is considered a significant helminthic infection due to its severe morbidity. Gold complexes may be effective against leishmaniasis and malaria. AuNPs were examined for structural morphology and crystalline character using a transmission electron microscope with HR-TEM abilities (48).

All nanoparticles are spherical with a rough surface and exhibit no agglomeration behavior. Using different doses of AuNPs reduced inflammation and granuloma diameter. Furthermore, AuNPs reduced hepatic worm burden compared to infected individuals. Dkhil et al.32 found that treating infected schistosome mice with AuNPs reduced histological disturbances in their brains (48).

5.2.3. Applicability of Metal Nanoparticles in the Detection and Monitoring of Hepatitis B Virus Infection:

Hepatitis B virus (HBV) infections are frequently chronic, particularly in children. Chronic HBV infection has a strong link to the development of liver diseases like cirrhosis and hepatocellular carcinoma (49).

Gold nanoparticles (AuNPs) are widely used in biomedical applications due to their biocompatibility, optical and electronic properties, and ease of manufacture. AuNPs can be functionalized with various biological macromolecules, such as antibodies, oligonucleotides, and aptamers, to detect a wide range of (bio) molecules. Antibody-coated AuNPs can stain substrates for electron microscopy, showing the subcellular location of viral proteins (46).

Over the last few decades, various methods have been developed to detect and quantify biological molecules in samples by taking advantage of AuNPs' unique physical properties. These methods can potentially increase the sensitivity, ease of use, and applicability of HBV detection. Wu et al., for example, used AuNPs labeled with anti-HBsAg antibodies and human alpha-thrombin (HAT, an enzyme that converts a bisamide substrate into a fluorescent reaction product). AuNPs were used to detect HBsAg on anti-HBsAg-coated ELISA plates using enhanced fluorescence enzyme-linked immunosorbent assay (FELISA) (50).

Under optimal conditions (HBsAg was dissolved in PBS). This method detects HBsAg concentrations as low as $5 \times 10{-}4$ IU/mL, which is approximately 104 times lower than other

fluorescence-based methods and 106 times lower than conventional ELISA. Using NP-based detection techniques can improve safety and reduce testing costs for blood transfusion products. The signal enhancement of LFA-based detection strips by NPs may increase their applicability, particularly in point-of-care HBV testing. Combining these techniques can result in cost-effective, reagent-free HBsAg tests. Improving the sensitivity of these tests could make them a better option for determining POC HBV status in resource-limited settings (50).

5.3. Applications of Nanotechnology in Hepatocellular carcinoma:

Hepatocellular carcinoma (HCC): patients' quality of life may be significantly impacted and constitutes a serious hazard. It is the fourth most common cause of mortality worldwide and the sixth most common type of cancer. Therefore, more attention should be paid to treating HCC because of its high rates of morbidity and mortality (51).

A novel method of treating cancer has been made possible by the science of nanomedicine. There were 841,000 new cases of HCC detected in 2018, which resulted in 782,000 deaths. The two main forms of liver cancer are HCC and intrahepatic cholangiocarcinoma, with HCC making up 75–85% of cases (52,53).

HCC can be predisposed by infections with hepatitis B and hepatitis C viruses, as well as by obesity, diabetes, alcoholism, and aflatoxin. Currently, available treatments for HCC include radiation, targeted medicines, organ transplantation, and surgical resection. Nevertheless, HCC has a poor prognosis and a high recurrence rate, and sadly, the disease is frequently diagnosed at an advanced or intermediate metastatic stage (53,54)

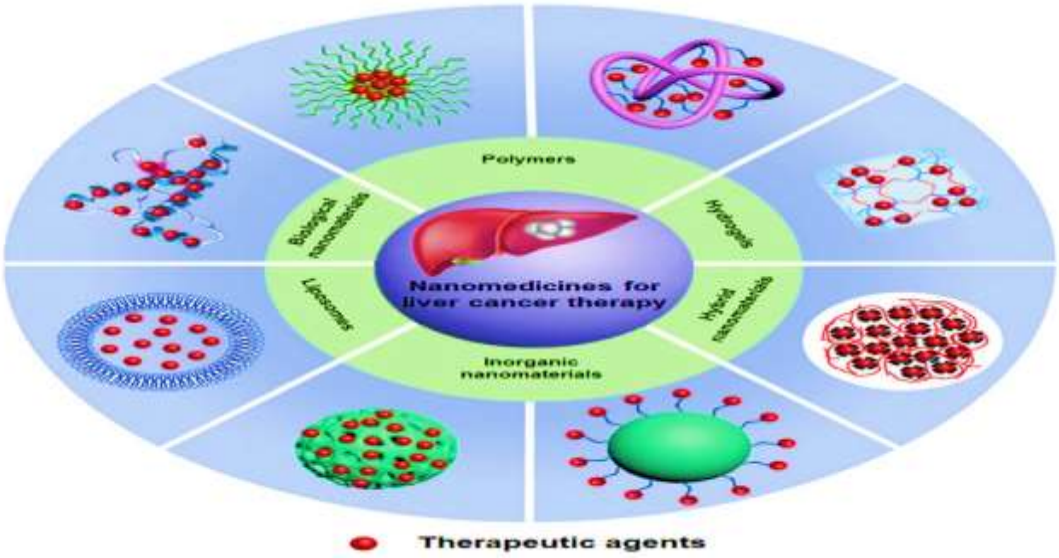

Figure 3: Nanocarrier in liver cancer therapy (55).

Several factors limit the efficacy of the existing HCC therapy approaches. When HCC is detected in its early stages, surgical resection is a highly effective treatment. However, this approach is less feasible because cancer has already spread by the time the diagnosis is made. Its potential is further limited by high rates of recurrence following surgery. Although radiotherapy and chemotherapy have demonstrated benefits in treating hepatocellular carcinoma (HCC) and increasing survival rates, their frequent and widespread use can set off alternate pathways and mechanisms that lead to the development of therapy resistance in cancer cells. Since there aren't many extremely effective treatments for HCC, researchers should focus on creating novel medications to stop the disease's progression and avoid therapy resistance (56,57).

Nano-platforms have recently surfaced as novel HCC treatment options. Owing to the difficulties in getting medications and genes to HCC and the insufficient removal of tumor cells with earlier therapeutic approaches, nanoparticles have become the go-to approach for treating HCC. Magnetic nanostructures may deliver chemotherapeutic drugs and help phototherapy-induced HCC cell ablation. Furthermore, liposomal nanostructures can be created for HCC cell targeting imaging. Functionalization of the surface of nanostructures through peptide modification can be carried out in HCC cells to promote their internalization (58).

For the synergistic administration of sorafenib and curcumin against the HCC, lactosylated pH-responsive nanostructures are one type of stimuli-responsive nanoparticles that can be employed. The upcoming steps will cover the application of CS-based biomaterials in the management of HCC. Research indicates that CS-based nanostructures exhibit strong cytotoxicity against HCC cells and are effective and prospective drug delivery platforms. The efficacy of current HCC therapy approaches is limited for several reasons. Although early surgical resection is very successful, this technique is less practical when cancer has already progressed and the diagnosis of HCC occurs at an intermediate or later stage. Furthermore, its promise is limited by high rates of post-operative recurrence. While radiation and chemotherapy have demonstrated advantages in their frequent and widespread usage, they can result in alternate pathways and mechanisms that cause cancer cells to acquire resistance to treatment, even if they are intended to treat HCC and increase survival rates (58,59).

5.3.1. Chitosan nanoparticles and targeted drug delivery:

The advent of several anti-tumor medicines that target different processes within cancer cells has brought about significant changes to the landscape of cancer treatment. Different types of anti-cancer drugs target different pathways within cancer cells. Some stop DNA replications to hinder replication, while others produce more reactive oxygen species (ROS) to cause cell death. Furthermore, some substances disrupt the process of cell division. Cancer treatment has come a long way thanks to the discovery of novel chemicals and medications through drug discovery. However, people with HCC are usually discovered at an advanced stage, and the disease frequently exhibits no distinctive symptoms in its early stages (60–66)

5.3.2. Polymeric nanoparticles (doxorubicin trans-drug (DT)):

Is a doxorubicin-loaded poly (isohexyl cyanoacrylate) nanoparticle formulation: In an in vivo model of multidrug-resistant protein-overexpressing hepatocellular carcinoma, doxorubicin trans drug (DT), a formulation of poly (isohexyl cyanoacrylate) nanoparticles loaded with doxorubicin, had significant anticancer efficacy. A clinical trial is being conducted on this nanomedicine to treat liver cancers. The maximum tolerated dose (MTD) of intra-arterial hepatic injection (40 mg/m2) in patients with HCC was found to be associated with significant toxicities, including grade-4 neutropenia, severe hypotension, pseudo-allergic reactions, and acute respiratory distress syndrome. The acceptable safety threshold was determined to be 35 mg/m2 (63).

An 88.9% survival rate was noted following 18 months of DT treatment in a recent phase II trial that assessed the effectiveness of DT (30 mg/m2 repeated doses) to the current standard of care (transarterial chemoembolization with a cytotoxic agent), The primary adverse effects, however, were identical toxic events to those seen during the phase I research. Another nanoparticle that has undergone clinical testing (phase II) is the formulation of mitoxantrone-loaded polybutylcyanacrylate (PBCA) nanoparticles administered intravenously. With a 2.2 month longer median survival time, a 10.5% objective response rate (ORR) compared to no ORR in the free mitoxantrone-treated group, and better safety compared to free mitoxantrone, this treatment demonstrated a minor improvement in efficacy. It would be intriguing to observe if this tiny increase in efficacy justifies more clinical research on this formulation (63).

5.4. Nanozyme Therapy in Acute Liver Failure:

One type of nanomaterial with enzyme-like properties is Nanozyme .It has many advantages over natural enzymes as Nanozymes are more stable, mass-produced, and low-cost . The unique physicochemical properties of nanomaterials provide multiple functionalities for nanozymes (67).

Various reactive oxygen species (ROS) like superoxide anion ($O2^-$) and $H2O2$, which cause different diseases, can be detoxified by Superoxide dismutase (SOD) and catalase drug activities due to its effective protection. Natural antioxidant enzymes, SOD, and catalase can be imitated by Metalloporphyrin (68,69).

Zhang's work synthesized the water-soluble metalloporphyrin-based catalase mimic as pegylated manganese protoporphyrin. It was found that pegylated manganese protoporphyrin could be a potent therapeutic agent for Acute Liver failure (ALF) that is effective in removing $H2O2$ and decreasing the liver-to-body weight ratio and serum ALT levels in vivo also in acetaminophen (APAP)-related ALF model its therapeutic efficacy was evaluated (70).

The presence of the nitroxide radicals in the antioxidative nanoparticle enabled them to gain the capacity to scavenge ROS on the hydrophobic segment side chain. The levels of ALT, AST, alkaline phosphatase (ALP) , and O^{2-} are inhibited by antioxidative nanomaterial ,and the amount of serum albumin in APAP-associated ALF increases by it (71,72).

6. Mechanism for Nanomedicine Targeting in Acute Liver Failure Therapy:

Passive accumulation and active targeting (receptor-mediated targeting) are the approaches for nanoparticle delivery .The physiological and anatomical features of the liver provide the accumulation of therapeutic nanoparticles with specific surfaces and sizes inside it for enhanced diffusion to the diseased cells, which passive targeting indicates (73).

On a certain type of liver cell, specific ligands bind to receptors to obtain a selective drug delivery to specific cells, which is done by active targeting. Factually, the two targeting strategies mentioned are complement to each other. Cellular internalization of ligand-modified nanoparticles depends on passive liver uptake mechanisms (72,73).

6.1. Passive Targeting

To determine whether nanoparticles have superior cell or tissue targeting capacity, there are fundamental factors such as size, surface charge, and hydrophilic properties. The adjustments of

physicochemical features in nano medicine enable it to reach and enter liver cells in a passive-targeted manner, which leads to an increase in the accumulation of the liver, reducing renal clearance and unwanted distribution in other organs (74)**.**

The low plaque accumulation is due to rapidly cleared nanoparticles by renal filtration, which is smaller than 5 nm. The forced extrusion is used in diffusing nanoparticles with diameters > 400 nm through the sinusoid endothelial fenestrations ,supposing due to transient interaction with the sinusoidal endothelial cells (74,75).

So, by Kupffer cells, the particles with larger sizes ,especially 200–1000 nm, are more likely to be phagocytized. The mononuclear phagocyte system readily identifies Nanoparticles with hydrophobic surfaces and is captured by the spleen and liver. So, in systemic circulation ,they are removed from it quickly (75,76).

In contrast, nanoscaled particles with hydrophilic surfaces taken by the mononuclear phagocyte system are hard. The hydrophilic properties in nanoparticles improve their permeation and retention effects, leading to increased accumulation in the liver (72).

The cellular uptake of nanoparticles can be affected by the surface charge. Hepatocytes prefer the particles with positive charge internalizing. While the nanoparticles have negative charges , Kupffer cells tend to ingest it more. For the greatest membrane affinity and nucleic acid binding affinity, the particles with proper density of cationic charge are necessary (77).

On the surface of the nanoparticles, serum protein with negative charges may be adsorbed on it in blood circulation. Furthermore, poor serum stability can occur due to antibodies or complement proteins deposition on the nanoparticle's surface (76). The balance between cell internalization and serum stability is important, so PEG decoration on the surface of nanoparticles is a method to improve blood stability (78).

After administration of nanoparticles in blood, The protein corona is formed due to non-specific interactions between serum proteins and nanoparticles, which mediates the uptake of non-targeted nanoparticles into hepatic cells (74).

The non-parenchymal cells in the liver, such as Kupffer cells, liver sinusoidal endothelial cells (LSECs), and hepatic stellate cells, absorbed non-targeted or unmodified nanomaterials (79).

6.2. Active targeting

Specific receptors of a disease or a specific cell identify the functionalization of nanoparticles by ligands .The delivery nanosystem of active targeting decreases the side effects of non-specific

cellular uptake and reaches the maximum therapeutic effects of drugs. In diagnosing or treating liver diseases, ligand-mediated active targeting has been applied. The most common therapeutic strategies target hepatocytes and macrophages (Kupffer cells) in ALF treatment (72,73)**.**

6.3. Targeting Hepatocytes

Asialoglycoprotein ASGP-R is the receptor on the membrane of hepatocytes near sinusoids, and the number of them on each hepatocyte surface is between 100,000 and 500,000 .It is the most popular technique to improve clathrin-mediated endocytotic absorption of therapeutic nanoparticles by hepatocytes (80,81)

ASGP−R has the affinity binding to galactose and residues of N-acetyl-galactosamine. Galactose, galactoside, galactosamine, lactobionic acid, asialofetuin, and sterylglucoside are common target ligands that modify nanomaterials for active targeting (73).

These receptors return to the cell membrane rapidly when releasing of ligands occur. Functional nanomedicines have been widely used in studies of liver-related diseases due to taking advantage of the recognition ability of ASGP-R on hepatocytes (80).

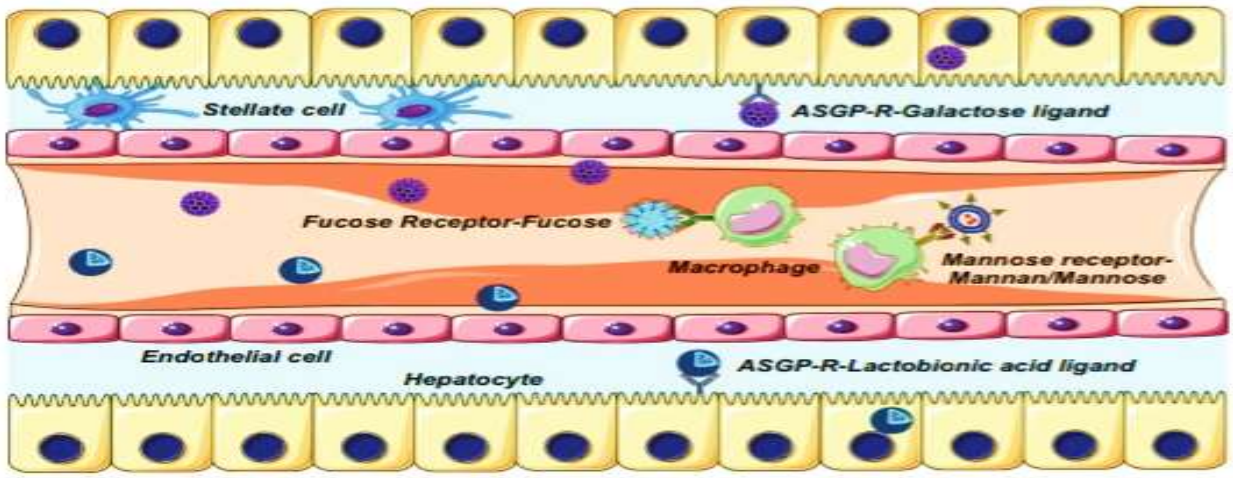

Figure 4: scheme represents active targeting of hepatocytes and macrophages in ALF therapy (72)

The most frequently used targeting modalities are galactose and lactobionic acid ligands in targeted therapy of ALF. It is verified that the specific ligand of the hepatocyte is lactobionic acid, an oligosaccharide aldonic acid (82).

The galactose-modified cationic liposome that silenced the Fas gene in delivering Fas siRNA into hepatocytes to treat ALF, is the construction of Jiang et al. In transporting IL-1Ra ,IL-1Ra nanoparticles of chitosan coupled with lactobionic acid to form the IL-1Ra-lactosylated chitosan nanoparticles synthesized by Xiao et al. Through interaction between ligand and receptor, the nanoparticles taken in hepatocytes successfully (83,84).

The combination of nanoparticles with galactoside or galactosamine used in targeting drug delivery systems for hepatocellular carcinoma and ASGP-R ligand-modified nanomaterials have been studied in targeting the treatment of liver cancer or hepatitis. the potential target ligands of ALF therapy are galactosamine, asialofetuin, galactoside, and sterylglucoside (72).

6.4. Targeting Macrophages

Kupffer cells are positioned in liver sinusoids, residence, self-renewing, and non-migrating macrophages. On the surface of macrophages or Kupffer cells, transmembrane protein Mannose receptor is overexpressed. By its receptor, D-mannose can be recognized .The feature has been used to create macrophage-target nanoparticles (85).

Binding mannose receptors on macrophages with carboxyl mannan-modified Se-PEI/TNF-α siRNA nanopolyplexes were applied to improve the cellular internalization rate of TNF-α siRNA. Higuchi and co-workers, similar, for targeted delivery of NF-κB decoy to Kupffer cells used mannosylated cationic liposomes (86,87).

On Kupffer cells, there are unique receptors such as fucose receptors so the potential way to target Kupffer cells is fucose receptor-mediated delivery. By macrophage, the fucosylated protein is easily phagocytized (88).

Nanomedicine can be enriched in the liver due to size and surface properties. Modifying Nanomaterials by ligands for targeting gives the ability to selectively target certain cells, significantly increasing drug distribution and gene transfection .This improves the advantages of nanomedicine in terms of therapeutic effect and decreases side effects (72).

6.5. Liver imaging using superparamagnetic iron oxide nanoparticles (SPION):

Superparamagnetic iron oxide nanoparticles (SPION) are a powerful, non-invasive method for biomedical imaging, treatments, and clinical diagnostics in magnetic resonance imaging (MRI). Superparamagnetic iron oxide nanoparticles (SPION) are excellent magnetic resonance contrast agents because to their distinct magnetic properties and strong shortening effects during both transverse and longitudinal relaxation (T1) (89).

The following reasons have led to the recognition SPIONs as extremely promising materials for biomedical applications. Because of their large surface area, SPIONs may form stronger bonds with various receptors, peptides, antibodies, or ligands. This allows them to connect to certain targets and release their medicine at the right dosage, a process known as “controlled drug release”. By specifically targeting an organ, tissue, or cell type, SPIONs can reduce the amount of medication exposed to the surrounding area (90).

Since the human body has a large iron pool of 3-5 g per person and a daily requirement of 20–25 mg, comparable to the amount of contrast agent injection per person (≈0.5 mg/kg), SPION has good biocompatibility and is a better alternative. Also, biodegradable iron can enter the body's iron pool and contribute to physiological iron homeostasis (91). Another application of this biosafety is in SPION-based therapy (92).

Clinical applications and fundamental research both frequently use SPION contrasted imaging. It has been primarily utilized for gene and drug delivery, cell therapy, inflammatory diseases, cancer imaging, cardiovascular illness, and cell therapy. In general, aqueous precipitation of ferric and ferrous ions in a basic environment with the addition of dextran or carboxydextran is used to generate SPION-based MRI contrast agents. The hydrophilic polymer covering materials significantly impact the body’s biodistribution and circulation time. In the absence of a surface coating, SPION are unstable colloidal elements in solutions and tend to precipitate and agglomerate in physiological environments and water (93)

SPION-based MR imaging has also been used for diagnosis in neuroinflammation, renal inflammation, inflammatory bowel disease, disease, obesity, diabetes, infectious osteomyelitis and aseptic vertebral inflammation, liver fibrosis, chronic obstructive pulmonary disease (COPD), and breakdown of the BBB. It could obtain morphological and pathophysiological details of these diseases noninvasively by phagocytosis of macrophages recruited to inflammatory areas chemotactically (94).

Crucial tracer compounds for magnetic particle imaging (MPI) are SPION. Magnetic particle imaging (MPI) is a new and widely used hot-spot imaging method that provides high temporal and spatial resolution when visualizing magnetic nanoparticles. MPI can be used for various medical imaging applications and can offer real-time 3D imaging information on the concentration and location of magnetic nanoparticles. The capacity of MPI to produce high-quality images is heavily reliant on the availability of size-optimized SPION. The generation of MPI contrast is actually

very dependent on the size distribution and SPION size since these two parameters have a significant impact on the magnetization response (95)

While colorectal cancer (HCC) can be diagnosed using a variety of imaging modalities, such as dynamic computed tomography and dynamic/non-enhanced/enhanced magnetic resonance imaging (MRI), SPION-enhanced MRI is still a major tool for diagnosing and imaging different types of HCC both before and after treatment. SPIONs with a mean diameter of 150 nm are rapidly entrapped by the liver's Kupffer cells after intravenous delivery, increasing the tumor-to-liver ratio. However, this methodology has certain drawbacks, such as the inability to assess lesion vascularity and a limited decrease in signal intensity of the cirrhotic liver relative to the normal liver (91).

The two SPIONS that are clinically approved for liver cancer imaging are ferumoxide (dextran-coated SPION, End-orem, Ferridex) and ferucarbotran (carboxydextran-coated SPI-ON, Resovist). Interestingly, UltraSPION has since been included in squalene-drug conjugate nanoparticles to create a “nanotheragnostic” system that combines anticancer and imaging capabilities. Contrast because the tumor lacks Kupffer cells. For example, hypovascular HCC has been identified on SPION imaging, while not being noticed after a dynamic Gd-contrast study (3,96)

Furthermore, SPIONs accumulate in benign hepatocellular lesions/dysplastic nodules but not in HCC, so SPION helps distinguish the two conditions. Nevertheless, this methodology has several limitations, including the incapacity to evaluate lesion vascularity and a restricted reduction in signal intensity of the cirrhotic liver compared to the normal liver. The two SPIONS that are clinically approved for liver cancer imaging are Ferumoxide (dextran-coated SPION, End-orem, Ferridex) and Ferucarbotran (carboxy dextran-coated SPI-ON, Resovist) (97).

6.5. Nanobiomaterials as Theragnostic Imaging Agents for Acute Liver Failure:

In ultrasonography, X-ray, computed tomography (CT), or magnetic resonance imaging (MRI), nanomaterials possessing optical or magnetic characteristics can be employed as contrast agents for tissues or cells; usually, they are used to indicate the site of liver damage for the diagnosis of ALF or the assessment of the therapeutic effect or to label transplanted stem cells to evaluate cell distribution or viability (72).

6.5.1. Fluorescence Imaging

For ALF patients, stem cell transplantation is being explored as a potential substitute for liver transplantation. In clinical settings, it exhibits encouraging therapeutic effects for patients

(98,99). The development of stem cell-based ALF therapy is limited by the absence of technology for long-term tracking of transplanted cells' biological distribution and behavior, even though stem cell transplantation has great potential in encouraging liver regeneration (100–102).

6.5.2. Magnetic Resonance Imaging

In cellular magnetic resonance imaging, magnetic nanoparticles are also employed as contrasting agents for cell labeling. Superparamagnetic iron oxide particles, or SPIOs, are a popular contrast-enhancing agent in cellular magnetic resonance imaging (MRI) because of their big magnetic moment, which exhibits the highest signal intensity change per metal unit (103).

An FDA-approved iron oxide compound called SPIO coated with dextran has been widely used in biomedical research. Hepatocytes were tagged with SPIOs and protamine sulfate in vitro in Puppi's work, which enhanced cellular iron uptake without compromising hepatocyte viability or metabolic function (104).

The nanowire's surface was treated with chitosan and sodium alginate to improve their biocompatibility. According to the study, the nanowires have exceptional MRI diagnostic capacity for recent liver damage. Using the nanocomposites improved the damaged liver tissues contrast-to- noise ratio from 3.71 to 5.39 (105).

6.5.3. Computed Tomography Imaging

Other than being used for transplant cell tracking and ALF diagnosis, stimuli-responsive nanomaterials with exceptional optical or magnetic characteristics can be used as multipurpose nanomedicines having a wide range of uses, including imaging, targeted therapy, diagnosis, and treatment process monitoring (106,107). Using the microfluidics-assisted nanoprecipitation approach, a new nanocomposite consisting of porous silicon, gold nanoparticles, and surface-coated acetylated dextran was created (108). This device was a multipurpose platform that could boost the CT signal in ALF theragnostic and encapsulate and transport drugs (109).

6.5.4. Ultrasound Imaging

Because ultrasound imaging is radiation-free, inexpensive, and simple to detect, it is a popular diagnostic technique for liver disease. Conventional ultrasonography contrast agents consist of gas-filled microbubbles with a lipid and protein coating (110,111).

Unwanted imaging abnormalities do, however, exist. These include short echo persistence, poor blood vessel stability, and difficulty penetrating surrounding tissues(112). On the other hand,

pathological stimulus-triggered echogenic nanoparticles can produce bubbles at the sites of injury. These bubbles can enter via blood arteries and build up in specific tissues, improving ultrasound imaging findings (113).

An example of a pathological stimulus-activatable nano platform that might concurrently transport therapeutic and imaging drugs to the acidic inflammatory location is the acid-triggered echogenic ketalized maltodextrin nanoparticle described by go et al. (114).

In APAP-induced ALF, it functioned as an ultrasonography contrast agent and a targeted therapeutic agent. Due to acid-triggered carbonate decarboxylation, ketalized maltodextrin nanoparticles produced CO2 bubbles in the acidic inflammatory zones, enhancing the ultrasound signal in the harmed liver (115).

Silymarin was delivered to the targeted drug delivery system of ketolized maltodextrin in combination with ultrasound imaging agents. Strong antioxidants were present in silymarin. and hepatoprotective properties, as well as anti-inflammatory actions. Thus, in a dose-dependent manner, the nanocomposite significantly decreased the ALT level and TNF-α expression in APAP-intoxicated animals (111).

Due to its ability to provide hydrogen atoms, curcumin has strong pharmacological effects that are both antioxidant and ROS scavenging (116).

However, inadequate solubility and stability restrict its use in inflammatory conditions (117). In animal models, nanotechnology makes the precise tracking and labeling of transplanted stem cells possible. Additionally, the multifunctional nanoparticles are crucial in therapeutic decision-making and offer the possibility of more precisely focused therapy and detection. Currently, Au NPs (108,118).

According to earlier studies, iron oxide-based nanomaterials coupled with hemosiderin or ferritin were gradually broken down in the mononuclear phagocyte system(119). However, some studies found that inorganic nanoparticles, like gold, were comparatively stable and might remain in the liver for up to six to fifteen months after being administered (120,121) and gold nanoparticles coated with iron oxide(122).

Notably, the long-term toxicity of gold nanostructures was avoided. It was discovered that the animals were not negatively affected by the gold nanoparticles during that period (a few weeks to a year), despite significant variations in biodistribution(123)**.** Thus, more research on

nanomaterials' fate and removal mechanisms in vivo is required to manage ALF, which are key obstacles to these nanoparticles' continued clinical use (72).

7. Nanotechnology in Addressing Oxidative Stress-Related Liver Disorders:

Reactive oxygen species (ROS) naturally occur as products of normal cell activity that play a function in cellular signaling. A rise in ROS levels has a negative impact on the structures, functions, and homeostasis of cells (124). This results in oxidative stress. Consequently, changing cellular redox balance raises the risk of getting several diseases (125).

Oxidative stress contributes significantly to the development and progression of hepatic steatosis. This occurs when there is an imbalance between ROS generation and the body's antioxidant defense mechanisms. Hepatic steatosis causes increased oxidative stress due to fat buildup in liver cells (126).

In fact, nanoparticles can be viewed as having two sides to oxidative stress. There are various methods for engineering nanoparticles to function as antioxidant molecules. Modifying the surface: Antioxidant molecules or chemicals can be added to the nanoparticles' surface to functionalize them. As an illustration, natural antioxidants like polyphenols, flavonoids, or vitamin E can be conjugated or coated onto nanoparticles. Catalytic activity: Some nanoparticles, such as nanoceria made of cerium oxide, have an inherent catalytic activity that allows them to function as antioxidants (124).

Fullerene nanoparticles, such as C6O, may directly scavenge free radicals. Fullerenes can receive and fix unpaired electrons, neutralizing ROS and avoiding its negative consequences. Nanoparticle Composites: Nanoparticles can be integrated into composite materials, serving as antioxidants. Nanoparticles placed in polymers or other matrices can increase the material's antioxidant capability. Nanoparticles have pro- and anti-oxidant characteristics, making them a promising treatment for oxidative stress illnesses. However, care is advised due to their probable prooxidant action (127).

Nanoparticles enter cells, and the subsequent release can cause the cells to produce ROS. This can lead to increased ROS levels in the mitochondria and decreased ATP levels. A disturbance of the tricarboxylic acid (TCA) cycle (128).

Nanoparticles' antioxidant capabilities vary depending on their synthesis technique. Metal nanoparticles, including silver, gold, and transition metal oxides like copper and nickel oxide, have

been extensively studied for their antioxidant properties. Combining various chemicals into NPs, whether single or bimetallic, increases antioxidant activity. Because of their innate physicochemical characteristics, certain oxide nanoparticles can mimic enzymes or antioxidant molecules and scavenge reactive oxygen and nitrogen species (124).

7. Miscellaneous nanotherapeutic systems for the treatment of liver disorders:

a. *Prussian blue nanoparticles:*

They are added to MSCs as ROS scavengers to aid in MSC survival in environments with high levels of oxidative stress. b) CeO2-Nanoparticles: Hepatoprotective action by lowering ROS levels and lowering inflammatory reaction In. c) MnO2 Mn4+ nanoparticles: these particles take up electrons from bacteria and accelerate the breakdown of H2O2 to stop lactic acid buildup. d) MoS2 nanoparticles: Attenuating electron transport in cytochrome c/H2O2 to improve antioxidant defense system. H2O2 scavengers include 1- DATS nanoparticles, which generate H2S to boost intracellular GSH and decrease oxidative stress in mitochondria. 2-NAC nanoparticles: GSH precursors used to counteract cell damage caused by Fe3O4 NPs (129).

B. GSH nanoparticles:

GSH, in its thiol-reduced form, may efficiently react with ROS to produce GSSH. The class of H2O2-sensitive nanosystems includes- PBEM-co-DPA nanoparticles, A dual-sensitive block polymer for polydatin release in response to ROS and pH. 2-Diselenide nanoparticles: release TNF-α siRNA in response to ROS breakdown. 3-NPs of POC: H2O2 oxidizes peroxalate esters in POC. RABA nanoparticles conjugated with atRA and boronic acid for H2O2 and other ROS species scavenging (129,130)

C. Nanotherapeutics for treating HCC

The class of nanozymes includes a) Nanosystem of Porous PB loaded with sorafenib: PB catalyzed H2O2 into O2 to relieve tumor hypoxia and had a strong photothermal impact. b) Nanosystem of Hollow PB nanocage loaded with MCT4 siRNAs and LAP: LAP caused H2O2 generation and was paired with PB to limit tumor growth via the Fenton reaction. c) CeO2 nanoparticles preferentially targeted hepatic tumors and generated increased ROS destruction (129,131). d) Nanosystem of PEGylated Mn2O3 NPs: T1-contrast enhancement in tumor and T2-shortening in the background allowed for effective imaging of liver metastasis (132). 5-

Nanosystem of Verteporfin-loaded MnO2 nanocomposites: Mn2+ reduced the energy gap between Verteporfin and triplet O2, resulting in O2 for PDT (133).

6-Nanosystem Fe-HMON-Tf loaded with DOX: DOX self-generated H2O2 and improved Fe2+/Fe3+ Fenton reaction. 7-Nanosystem of Fe-TCPP MOFs with hypoxic prodrug TPZ: TCPP PDT depleted O2 produced by Fe3+ and activated TPZ. One example of an H2O2 scavenger class is the a) Nanosystem of Rutin-loaded PLGA NPs. In DEN-induced HCC, Rutin upregulated antioxidant enzyme levels and downregulated proinflammatory cytokines (129) b) Nanosystem of fluorinated chitosan constructed with TCPP-conjugated CAT:CAT catalyzed O2 production assisted in improving TCPP's SDT therapeutic effectiveness (134)

Nanosystem of Sorafenib-CAT-PLGA Microspheres: CAT can increase tumor hypoxic microenvironment and sorafenib function. The class of H2O2-sensitive nanosystems includes a) Nanosystem of ROS-responsive GalSLP for sorafenib and shUSP22: Sorafenib acted as a ROS inducer, causing shUSP22 release to decrease HCC glycolysis. b) Nanosystem of Solid Lipid Microparticle for GSH Oral Administration: GSH-loaded NPs demonstrated ROS scavenging activity in the presence of H2O. c) Nanosystem of PEG-b-PBEMA integrated PA micelle: PA upregulates H2O2 and increases oxidative damage to tumor cells (129).

8. Challenges in nanomedicines for treating liver diseases:

The difficulty in using nanomedicines to treat liver problems Given the liver's specific anatomical position and KC content, targeting the liver with NPs is difficult. Macrophage and other immune cells that are not residents have exceptional immune clearance capabilities (135).

When the liver's macrophage population is chemically decreased, the uptake of nanoparticles into hepatocytes increases. Surface charge is critical to the internalization of NPs. Hepatocyte internalization of the NPs is charge-specific. Hepatocytes only take up positively charged nanoparticles. PEG coating can prevent the biological characteristics of NPs from being altered by the protein corona formation, which varies according to the kind of NPs. One important component in corona development is the hydrophobic property of NPs' surface(135). Delivery techniques for nanobiomaterials have numerous advantages over biological agents. Generally speaking, drugs enclosed in nanocarriers have better bioavailability and are more stable in blood circulation than unbound drugs (72,114).

Nanokinetic challenges

Rally-administered NPs need to maintain high systemic bioavailability of pharmaceuticals after overcoming many barriers, absorb from the stomach, and have good stability in the gastrointestinal tract (136).

As a result, when it comes to NPs taken orally, the physicochemical characteristics need to be monitored. The distribution, metabolism, excretion, and absorption of NPs, among other nanokinetic characteristics, should be extensively examined for several NPs. The NP taken orally ought to pass through the liver before entering the bloodstream. Luckily or unfortunately, 90% of systemically administered NPs concentrate in the liver, which restricts NPs' ability to be delivered to specific sites (137).

Physicochemical challenges

The physicochemical properties of nanoparticles (NPs), including their size, stability, surface charge, and storage, directly impact their medicinal efficacy. The chemical composition, size, shape, and surface charge of NPs determine how they are delivered to hepatocytes, SECs, KC, and other immune cells. The more compact NPs are ready. may impede quick clearance since the liver reticuloendothelial system can remove bigger NPs (138).

Positively charged NPs are typically taken up by hepatocytes, while negatively charged NPs are typically taken up by KC and SECs.(139)

The pH of the cationic-charged NPs has disrupted the endosomal system, enhanced cellular interference, and improved hepatocyte delivery. Buffering ability: It has been determined that NPs with an ideal size range of 50–200 nm will more effectively permeate various hepatic cell types, For example, after intravenous Treatment, NPs <200 nm in size may pass through sinusoidal fissures, while NPs <3 nm in size extravasate into hepatocytes from the perisinusoidal area (139). Given this situation, NPs are far less available to hepatocytes than to other liver cells, and their release rate is also much lower. To maximize hepatocyte delivery and enhance extravasation into the perisinusoidal area, nanoparticles (NPs) should be manufactured to be as small as possible (<10 nm). Reduce the number of KCs that accumulate and that they consume in this way. Results also imply that NPs smaller than 3 nm may extravasate into tissues in an unspecific manner. Enhance the accumulation of HSCs and hepatocytes, NPs should be coated with molecules specific to hepatocytes and HSCs, such as retinol or other agents (135).

Kupffer cells and other immune cells-related challenges

Because the hepatocytes in the liver live in a small space, several biological barriers prevent NPs from traveling as far as they should. Moreover, the liver has KC, the resident immune. Anatomically speaking, these cells are found in the liver's sinusoidal region, which absorbs foreign substances like bacteria, viruses, and NPs and injured cells (140). Because they are involved in both the uptake and trafficking of NPs in vivo, Ketter cells play a major role in the cellular uptake of NPs in the liver and determine the fate of NPs in the body (141).

Anatomical and disease environment-related challenges.

The buildup of extracellular matrix (ECM) in the perisinusoidal region impacts the solute transport from sinusoidal endothelium to hepatocytes. The lack of SEC fenestration limits the distribution of blood-borne NPs to activated HSCs and damaged hepatocytes. Because of the buildup of ECM in the perisinusoidal region, hepatocytes cannot receive the blood containing NPs. To solve this issue, TiO2 NPs have allegedly improved the drug permeability and leakiness in primary human hepatic SECs during in vitro testing (36).

Green synthesis of NPs and its related challenge

Medicinal plants are extensively employed in the environmentally friendly manufacturing of nanoparticles and have been tested in trials to treat a range of CLD symptoms(142). In most investigations, plant extracts were employed as a reducing medium to create metallic nanoparticles, or NPs (142–144).

9. Conclusion

The review has highlighted the progress made in nanomaterials for liver disease therapy. One efficient method of delivering nano-based medications to the specific cell type in the injured liver is through nanotechnology. To enhance logical carrier design, NPs' cellular uptake and intracellular accumulation, trafficking, and endosomal sorting should be thoroughly investigated. In recent years, research on the Treatment of ALF has increasingly focused on multifunctional nanobiomaterials with imaging, diagnostic, and therapeutic capabilities. These materials offer a fresh approach to theranostics of ALF. Future research efforts must focus on developing multifunctional nanomedicine with both therapeutic and diagnostic capabilities. These nanomedicines are anticipated to alleviate the present clinical shortcomings in treating liver diseases.

References

1. Alving CR. Delivery of liposome-encapsulated drugs to macrophages. Pharmacol Ther. 1983;22(3):407–24.

2. Couvreur P, Vauthier C. Nanotechnology: Intelligent design to treat complex disease. Vol. 23, Pharmaceutical Research. 2006. 1417–1450 p.

3. Reddy LH, Couvreur P. Nanotechnology for therapy and imaging of liver diseases. J Hepatol. 2011;55(6):1461–6.

4. Surendran SP, Thomas RG, Moon MJ, Jeong YY. Nanoparticles for the treatment of liver fibrosis. Int J Nanomedicine. 2017;12:6997–7006.

5. Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. J Occup Med Toxicol. 2007;2(1):1–6.

6. Bhatt DA, Pethe AM. Available online through Nanotechnology : A promising Drug Delivery for Poorly Water Soluble Drugs. 2010;3(8):1748–51.

7. Kingsley JD, Dou H, Morehead J, Rabinow B, Gendelman HE, Destache CJ. Nanotechnology: A focus on nanoparticles as a drug delivery system. J Neuroimmune Pharmacol. 2006;1(3):340–50.

8. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Deliv Rev. 2005;57(11):1595–639.

9. Xu Q, Kambhampati SP, Kannan RM. Nanotechnology approaches for ocular drug delivery. Middle East Afr J Ophthalmol. 2013;20(1):26–37.

10. Farokhzad OC, Langer R. Impact of Nanotechnology on Hair Attributes. ACS Nano. 2009;3(1):1–7.

11. Giannitrapani L, Soresi M, Bondì ML, Montalto G, Cervello M. Nanotechnology applications for the therapy of liver fibrosis. World J Gastroenterol. 2014;20(23):7242–51.

12. Rockey DC. Current and Future Anti-Fibrotic Therapies for Chronic Liver Disease. Clin Liver Dis. 2008;12(4):939–62.

13. Moghimi SM, Hunter AC, Murray JC. Long-circulating and target-specific nanoparticles:

Theory to practice. Pharmacol Rev. 2001;53(2):283–318.

14. Demoy M, Gibaud S, Andreux JP, Weingarten C, Gouritin B, Couvreur P. Splenic trapping of nanoparticles: Complementary approaches for in situ studies. Vol. 14, Pharmaceutical Research. 1997. p. 463–8.

15. Zhou et al. 基因的改变NIH Public Access. Bone. 2012;23(1):1–7.

16. Sandhiya S, Dkhar SA, Surendiran A. Emerging trends of nanomedicine - an overview. Fundam Clin Pharmacol. 2009;23(3):263–9.

17. Santos-Magalhães NS, Mosqueira VCF. Nanotechnology applied to the treatment of malaria. Adv Drug Deliv Rev. 2010;62(4–5):560–75.

18. Moghadam FF. Using nanoparticles in medicine for liver cancer imaging. Oman Med J. 2017;32(4):269–74.

19. Bottaro, Larsen B, Madhur. 基因的改变NIH Public Access. Bone. 2008;23(1):1–7.

20. Oh J, Feldman MD, Kim J, Condit C, Emelianov S, Milner TE. Detection of magnetic nanoparticles in tissue using magneto-motive ultrasound. Nanotechnology. 2006;17(16):4183–90.

21. Feynman RP. There's Plenty of Room at the Bottom: An Invitation to Enter a New Field of Physics*. Handbook of Nanoscience, Engineering, and Technology: Third Edition. 2012. p. 3–12.

22. Bartneck M, Warzecha KT, Tacke F. Therapeutic targeting of liver inflammation and fibrosis by nanomedicine. 2014;3(6):364–76.

23. Yin J, Liu C, Guo J, Li M, Chen B, Zhang X, et al. A copper-loaded self-assembled nanoparticle for disturbing the tumor redox balance and triple anti-tumor therapy. 2024;

24. Magami Y, Azuma T, Inokuchi H, Kokuno S, Moriyasu F, Kawai K, et al. Cell proliferation and renewal of normal hepatocytes and bile duct cells in adult mouse liver. Liver. 2002;22(5):419–25.

25. Department of Pediatric Gastroenterology and Department of 1 Cell Biology, Cleveland

Clinic Foundation, Cleveland, OH and Department of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN. Gastroenterology. 2005;3093–9.

26. Pradere JP, Kluwe J, De Minicis S, Jiao JJ, Gwak GY, Dapito DH, et al. Hepatic macrophages but not dendritic cells contribute to liver fibrosis by promoting the survival of activated hepatic stellate cells in mice. Hepatology. 2013;58(4):1461–73.

27. Trindade MCD, Lind M, Nakashima Y, Sun D, Goodman SB, Schurman DJ, et al. Interleukin-10 inhibits polymethylmethacrylate particle induced interleukin-6 and tumor necrosis factor-α release by human monocyte/macrophages in vitro. Biomaterials. 2001;22(15):2067–73.

28. Forbes SJ, Gupta S, Dhawan A. Cell therapy for liver disease: From liver transplantation to cell factory. J Hepatol. 2015;62(S1):S157–69.

29. Gu L, Zhang F, Wu J, Zhuge Y. Nanotechnology in Drug Delivery for Liver Fibrosis. Front Mol Biosci. 2022;8(January):1–14.

30. Li Y, Shang W, Liang X, Zeng C, Liu M, Wang S, et al. The diagnosis of hepatic fibrosis by magnetic resonance and near-infrared imaging using dual-modality nanoparticles. RSC Adv. 2018;8(12):6699–708.

31. Petros RA, Desimone JM. Strategies in the design of nanoparticles for therapeutic applications. Nat Rev Drug Discov. 2010;9(8):615–27.

32. Aydin MM, Akcali KC. Liver fibrosis. Turkish J Gastroenterol. 2018;29(1):14–21.

33. Beljaars L, Weert B, Geerts A, Meijer DKF, Poelstra K. The preferential homing of a platelet derived growth factor receptor-recognizing macromolecule to fibroblast-like cells in fibrotic tissue. Biochem Pharmacol. 2003;66(7):1307–17.

34. Fallowfield JA, Hayden AL, Snowdon VK, Aucott RL, Stutchfield BM, Mole DJ, et al. Relaxin modulates human and rat hepatic myofibroblast function and ameliorates portal hypertension in vivo. Hepatology. 2014;59(4):1492–504.

35. Hu M, Wang Y, Xu L, An S, Tang Y, Zhou X, et al. Relaxin gene delivery mitigates liver metastasis and synergizes with check point therapy. Nat Commun. 2019;10(1):1–14.

36. Tee JK, Ng LY, Koh HY, Leong DT, Ho HK. Titanium dioxide nanoparticles enhance leakiness and drug permeability in primary human hepatic sinusoidal endothelial cells. Int J Mol Sci. 2019;20(1).

37. Li Q, Ding Y, Guo X, Luo S, Zhuang H, Zhou JE, et al. Chemically modified liposomes carrying TRAIL target activated hepatic stellate cells and ameliorate hepatic fibrosis in vitro and in vivo. J Cell Mol Med. 2019;23(3):1951–62.

38. Singh S, Sharma N, Shukla S, Behl T, Gupta S, Anwer MK, et al. Understanding the Potential Role of Nanotechnology in Liver Fibrosis: A Paradigm in Therapeutics. Molecules. 2023;28(6):1–25.

39. Adhikari A, Polley N, Darbar S, Bagchi D, Pal SK. Citrate functionalized Mn3O4 in nanotherapy of hepatic fibrosis by oral administration. Futur Sci OA. 2016;2(4).

40. Rani V, Verma Y, Rana SVS. Zinc Oxide Nanoparticles Ameliorate Dimethylnitrosamine-Induced Renal Toxicity in Rat. Appl Biochem Biotechnol. 2022;194(4):1699–715.

41. Gad SS, Abdelrahim DS, Ismail SH, Ibrahim SM. Nanotechnology applications for treatment of hepatic infections via modulating Hepatic histopathological and DNA alterations. Bioorg Chem. 2022;127(June):105927.

42. Xu X, Yang Q, Bai J, Lu T, Li Y, Jing X. Fabrication of biodegradable electrospun poly(L-lactide-co-glycolide) fibers with antimicrobial nanosilver particles. J Nanosci Nanotechnol. 2008;8(10):5066–70.

43. Li Y, Schluesener HJ, Xu S. Gold nanoparticle-based biosensors. 2010;43(1):29–41.

44. Zhou T, Guo H, Guo J tao, Cuconati A, Mehta A, Block TM. Hepatitis B virus e antigen production is dependent upon covalently closed circular (ccc) DNA in HepAD38 cell cultures and may serve as a cccDNA surrogate in antiviral screening assays. 2006;72:116–24.

45. Wu Y, Zhou Q. Silver nanoparticles cause oxidative damage and histological changes in medaka (Oryzias latipes) after 14 days of exposure. Environ Toxicol Chem. 2013;32(1):165–73.

46. Lu Y, Shi Y, Wu Q, Sun X, Zhang WZ, Xu XL, et al. An Overview of Drug Delivery Nanosystems for Sepsis-Related Liver Injury Treatment. Int J Nanomedicine. 2023;18(February):765–79.

47. Shevtsov M, Zhao L, Protzer U, van de Klundert MAA. Applicability of metal nanoparticles in the detection and monitoring of hepatitis B virus infection. Viruses. 2017;9(7):1–11.

48. Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. Science (80-). 2006;311(5761):622–7.

49. Jin F, Liu D, Yu H, Qi J, You Y, Xu X, et al. Sialic Acid-Functionalized PEG-PLGA Microspheres Loading Mitochondrial-Targeting-Modified Curcumin for Acute Lung Injury Therapy. Mol Pharm. 2019;16(1):71–85.

50. Dkhil MA, Bauomy AA, Diab MSM, Al-Quraishy S. Antioxidant and hepatoprotective role of gold nanoparticles against murine hepatic schistosomiasis. Int J Nanomedicine. 2015;10:7467–75.

51. Yu L, Wang Z, Mo Z, Zou B, Yang Y, Sun R, et al. Synergetic delivery of triptolide and Ce6 with light-activatable liposomes for efficient hepatocellular carcinoma therapy. Acta Pharm Sin B. 2021;11(7):2004–15.

52. Taheriazam A, Abad GGY, Hajimazdarany S, Imani MH, Ziaolhagh S, Zandieh MA, et al. Graphene oxide nanoarchitectures in cancer biology: Nano-modulators of autophagy and apoptosis. J Control Release. 2023;354:503–22.

53. Yang Y, Liu X, Ma W, Xu Q, Chen G, Wang Y, et al. Light-activatable liposomes for repetitive on-demand drug release and immunopotentiation in hypoxic tumor therapy. Biomaterials. 2021;265:120456.

54. Li SL, Gao M, Li ZM, Song LJ, Gao XZ, Han J, et al. p53 and P-glycoprotein influence chemoresistance in hepatocellular carcinoma. Front Biosci - Elit. 2018;10(3):461–8.

55. Chi X, Liu K, Luo X, Yin Z, Lin H, Gao J. Recent advances of nanomedicines for liver cancer therapy. J Mater Chem B. 2020;8(17):3747–71.

56. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of Hepatocellular

Cancer after Resection: Patterns, Treatments, and Prognosis. Ann Surg. 2015;261(5):947–55.

57. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.

58. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019;16(10):589–604.

59. Zheng X, Jin W, Wang S, Ding H. Progression on the Roles and Mechanisms of Tumor-Infiltrating T Lymphocytes in Patients With Hepatocellular Carcinoma. Front Immunol. 2021;12(September):1–11.

60. Deldar Abad Paskeh M, Mirzaei S, Ashrafizadeh M, Zarrabi A, Sethi G. Wnt/β-Catenin Signaling as a Driver of Hepatocellular Carcinoma Progression: An Emphasis on Molecular Pathways. J Hepatocell Carcinoma. 2021;Volume 8(August):1415–44.

61. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

62. Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, et al. Hepatocellular carcinoma. Nat Rev Dis Prim. 2016;2(April).

63. Barraud L, Merle P, Soma E, Lefrançois L, Guerret S, Chevallier M, et al. Increase of doxorubicin sensitivity by doxorubicin-loading into nanoparticles for hepatocellular carcinoma cells in vitro and in vivo. J Hepatol. 2005;42(5):736–43.

64. Zaky MF, Hammady TM, Gad S, Alattar A, Alshaman R, Hegazy A, et al. Influence of Surface-Modification via PEGylation or Chitosanization of Lipidic Nanocarriers on In Vivo Pharmacokinetic/Pharmacodynamic Profiles of Apixaban. Pharm 2023, Vol 15, Page 1668. 2023 Jun;15(6):1668.

65. Zaky M, Youssef Y, Megahed M. Impact of Surface Design and Coating on The Efficacy of Nano-Carriers as Drug Delivery Systems: A Review. Vol. 2, ERU Research Journal.

2023. p. 415–46.

66. Zaky MF, Megahed MA, Hammady TM, Gad S, Ghorab MM. Tailoring Apixaban in Nanostructured Lipid Carrier Enhancing Its Oral Bioavailability and Anticoagulant Activity. 2023;

67. Wei H. Nanomaterials with enzyme-like characteristics (nanozymes): next-generation artificial enzymes (II). 2019;48(4).

68. Kubota R, Imamura S, Shimizu T, Asayama S, Kawakami H. Synthesis of Water-Soluble Dinuclear Mn-Porphyrin with Multiple Antioxidative Activities. 2014;

69. Batinic-haberle I, Tovmasyan A, Spasojevic I. Redox Biology An educational overview of the chemistry , biochemistry and ther- apeutic aspects of Mn porphyrins – From superoxide dismutation to H 2 O 2 -driven pathways. Redox Biol. 2015;5:43–65.

70. Zhang T, Fang J, Tsutsuki H, Ono K, Islam W, Sawa T. Synthesis of Pegylated Manganese Protoporphyrin as a Catalase Mimic and Its Therapeutic Application to Acetaminophen-Induced Acute Liver Failure. 2019;42(7):1199–206.

71. Boonruamkaew P, Chonpathompikunlert P, Nagasaki Y. Redox Nanoparticle Therapeutics for Acetaminophen-Induced Hepatotoxicity in Mice. 2016;2016.

72. Jin Y, Wang H, Yi K, Lv S, Hu H, Li M. Applications of Nanobiomaterials in the Therapy and Imaging of Acute Liver Failure. 2021.

73. Li L, Wang H, Yuin Z, Xu K, Lai P, Ee R, et al. Polymer- and lipid-based nanoparticle therapeutics for the treatment of liver diseases. Nano Today. 2010;5(4):296–312.

74. Hu M, Huang L. Nanomaterial Manipulation of Immune Microenvironment in the Diseased Liver. 2018;1805760:1–20.

75. Morilla I, Regts J, P GAK, I ELR, Scherphof GL. On the mechanism of hepatic transendothelial passage of large liposomes. 1999;448:193–6.

76. Fluorescence IM, Lee H shu, Chen C tu, Dong C yuan, Lo L wei. Visualizing Dynamics of Sub-Hepatic Distribution of Nanoparticles Using Microscopy. 2012;

77. Brannon-peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy ☆. Adv Drug Deliv Rev. 2012;64:206–12.

78. Kong L, Qiu J, Sun W, Yang J, Shen M, Wang L, et al. Biomaterials Science. 2016;

79. Zhang Y nan, Poon W, Tavares AJ, Mcgilvray ID, Chan WCW. Nanoparticle – liver interactions : Cellular uptake and hepatobiliary elimination. J Control Release. 2016;240:332–48.

80. Manuscript A. Materials Chemistry B.

81. Smedsrød B. Clearance function of scavenger endothelial cells. 2004;10:1–10.

82. Selim KMK, Ha Y soo, Kim S jung, Chang Y, Kim T jeong, Ho G, et al. Surface modification of magnetite nanoparticles using lactobionic acid and their interaction with hepatocytes. 2007;28:710–6.

83. Jiang N, Zhang X, Zheng X, Chen D, Siu K, Wang H, et al. A Novel In Vivo siRNA Delivery System Specifically Targeting Liver Cells for Protection of ConA-Induced Fulminant Hepatitis. 2012;7(9):1–10.

84. Xiao J qiang, Shi X lei, Ma H cheng, Tan J jun, Xu Q. Administration of IL-1Ra Chitosan Nanoparticles Enhances the Therapeutic Efficacy of Mesenchymal Stem Cell Transplantation in Acute Liver Failure. Arch Med Res. 2013;44(5):370–9.

85. Weis WI, Taylor ME. The C-type lectin superfamily in the immune system. 1998;163:19–34.

86. Manuscript A. Biomaterials Science. 2018;

87. Higuchi Y, Kawakami S, Oka M, Yabe Y, Yamashita F, Hashida M. Intravenous administration of mannosylated cationic liposome / NF j B decoy complexes effectively prevent LPS-induced cytokine production in a murine liver failure model. 2006;580:3706–14.

88. Opanasopit P, Nishikawa M, Yamashita F, Takakura Y. Pharmacokinetic Analysis of Lectin-dependent Biodistribution of Fucosylated Bovine Serum Albumin : A Possible Carrier for Kupffer Cells. 2001;9:341–51.

89. Aziz OAA, Arafa K, Dena ASA, El-sherbiny IM. Superparamagnetic Iron Oxide Nanoparticles (SPIONs): Preparation and Recent Applications. 2020;29(1):21–9.

90. Budime P, Poklar N. Multifunctional superparamagnetic iron oxide nanoparticles : Promising tools in cancer theranostics. Cancer Lett. 2013;336(1):8–17.

91. Wahajuddin, Arora S. Superparamagnetic iron oxide nanoparticles: Magnetic nanoplatforms as drug carriers. Int J Nanomedicine. 2012;7:3445–71.

92. Palanisamy S, Wang Y ming. Superparamagnetic iron oxide nanoparticulate system: synthesis, targeting, drug delivery and therapy in cancer. 2019;48(26).

93. Asgari S, Nikkam N, Saniee P. Metallic Nanoparticles as promising tools to eradicate H. pylori: A comprehensive review on recent advancements. Talanta Open. 2022;6(June):100129.

94. Jin R, Lin B, Li D, Ai H. Superparamagnetic iron oxide nanoparticles for MR imaging and therapy: Design considerations and clinical applications. Curr Opin Pharmacol. 2014;18:18–27.

95. Dadfar SM, Camozzi D, Darguzyte M, Roemhild K, Varvarà P, Metselaar J, et al. Size-isolation of superparamagnetic iron oxide nanoparticles improves MRI, MPI and hyperthermia performance. J Nanobiotechnology. 2020;18(1):1–13.

96. Lu A hui, Salabas EL, Schüth F. Magnetic Nanoparticles : Synthesis , Protection , Functionalization , and Application Angewandte. 2007;1222–44.

97. Dulińska-Litewka J, Łazarczyk A, Hałubiec P, Szafrański O, Karnas K, Karewicz A. Superparamagnetic iron oxide nanoparticles-current and prospective medical applications. Materials (Basel). 2019;12(4).

98. Lee CW, Chen YF, Wu HH, Lee OK. Historical Perspectives and Advances in Mesenchymal Stem Cell Research for the Treatment of Liver Diseases. Gastroenterology. 2018;154(1):46–56.

99. Li L, Shi D, Zhang J, Zhou Q, Xin J, Jiang J, et al. Quantitative evaluation of human bone mesenchymal stem cells rescuing fulminant hepatic failure in pigs. Gut. 2017

May;66(5):955–64.

100. Yi DK, Nanda SS, Kim K, Tamil Selvan S. Recent progress in nanotechnology for stem cell differentiation, labeling, tracking and therapy. J Mater Chem B. 2017;5(48):9429–51.

101. Yukawa H, Watanabe M, Kaji N, Okamoto Y, Tokeshi M, Miyamoto Y, et al. Monitoring transplanted adipose tissue-derived stem cells combined with heparin in the liver by fluorescence imaging using quantum dots. Biomaterials. 2012;33(7):2177–86.

102. Chen G, Lin S, Huang D, Zhang Y, Li C, Wang M, et al. Revealing the Fate of Transplanted Stem Cells In Vivo with a Novel Optical Imaging Strategy. Small. 2018;14(3):1–10.

103. Bulte JWM, Kraitchman DL. Iron oxide MR contrast agents for molecular and cellular imaging. NMR Biomed. 2004;17(7):484–99.

104. Puppi J, Modo M, Dhawan A, Lehec SC, Mitry RR, Hughes RD. Ex vivo magnetic resonance imaging of transplanted hepatocytes in a rat model of acute liver failure. Cell Transplant. 2014;23(3):329–43.

105. Xu YJ, Dong L, Lu Y, Zhang LC, An D, Gao HL, et al. Magnetic hydroxyapatite nanoworms for magnetic resonance diagnosis of acute hepatic injury. Nanoscale. 2016;8(3):1684–90.

106. He H, Zheng N, Song Z, Kim KH, Yao C, Zhang R, et al. Suppression of Hepatic Inflammation via Systemic siRNA Delivery by Membrane-Disruptive and Endosomolytic Helical Polypeptide Hybrid Nanoparticles. ACS Nano. 2016;10(2):1859–70.

107. Wang H, Thorling CA, Liang X, Bridle KR, Grice JE, Zhu Y, et al. Diagnostic imaging and therapeutic application of nanoparticles targeting the liver. J Mater Chem B. 2015 Jan;3(6):939–58.

108. Liu Z, Li Y, Li W, Xiao C, Liu D, Dong C, et al. Multifunctional Nanohybrid Based on Porous Silicon Nanoparticles, Gold Nanoparticles, and Acetalated Dextran for Liver Regeneration and Acute Liver Failure Theranostics. Adv Mater. 2018;30(24):1–10.

109. Bernal W, Lee WM, Wendon J, Larsen FS, Williams R. Acute liver failure: A curable disease by 2024? J Hepatol. 2015;62(S1):S112–20.

110. Min KH, Min HS, Lee HJ, Park DJ, Yhee JY, Kim K, et al. PH-controlled gas-generating mineralized nanoparticles: A theranostic agent for ultrasound imaging and therapy of cancers. ACS Nano. 2015;9(1):134–45.

111. Kim GW, Kang C, Oh Y Bin, Ko MH, Seo JH, Lee D. Ultrasonographic imaging and anti-inflammatory therapy of muscle and tendon injuries using polymer nanoparticles. Theranostics. 2017;7(9):2463–76.

112. Son S, Min HS, You DG, Kim BS, Kwon IC. Echogenic nanoparticles for ultrasound technologies: Evolution from diagnostic imaging modality to multimodal theranostic agent. Nano Today. 2014;9(4):525–40.

113. Wei S, Fu N, Sun Y, Yang Z, Lei L, Huang P, et al. Targeted contrast-enhanced ultrasound imaging of angiogenesis in an orthotopic mouse tumor model of renal carcinoma. Ultrasound Med Biol. 2014;40(6):1250–9.

114. Go Y, Lee H, Jeong L, Sun S, Hong E, Jung E, et al. Acid-triggered echogenic nanoparticles for contrast-enhanced ultrasound imaging and therapy of acute liver failure. Biomaterials. 2018 Dec;186:22–30.

115. Kang C, Cho W, Park M, Kim J, Park S, Shin D, et al. H2O2-triggered bubble generating antioxidant polymeric nanoparticles as ischemia/reperfusion targeted nanotheranostics. Biomaterials. 2016;85:195–203.

116. Fujisawa S, Atsumi T, Ishihara M, Kadoma Y. Cytotoxicity, ROS-generation Activity and Radical-scavenging Activity of Curcumin and Related Compounds. Anticancer Res. 2004;24(2 B):563–9.

117. Baker M. Deceptive curcumin offers cautionary tale for chemists. Nature. 2017;541(7636):144–5.

118. Libutti SK, Paciotti GF, Byrnes AA, Alexander HR, Gannon WE, Walker M, et al. Cancer Therapy : Clinical Phase I and Pharmacokinetic Studies of CYT-6091 , a Novel PEGylated Colloidal Gold-rhTNF Nanomedicine. :6139–49.

119. Jain TK, Reddy MK, Morales MA, Leslie-Pelecky DL, Labhasetwar V. Biodistribution, clearance, and biocompatibility of iron oxide magnetic nanoparticles in rats. Mol Pharm.

2008 Mar;5(2):316–27.

120. Ali MRK, Rahman MA, Wu Y, Han T, Peng X, Mackey MA, et al. Efficacy, long-term toxicity, and mechanistic studies of gold nanorods photothermal therapy of cancer in xenograft mice. Proc Natl Acad Sci U S A. 2017;114(15):E3110–8.

121. Balasubramanian SK, Jittiwat J, Manikandan J, Ong CN, Yu LE, Ong WY. Biodistribution of gold nanoparticles and gene expression changes in the liver and spleen after intravenous administration in rats. Biomaterials. 2010;31(8):2034–42.

122. Kolosnjaj-Tabi J, Javed Y, Lartigue L, Volatron J, Elgrabli D, Marangon I, et al. The One Year Fate of Iron Oxide Coated Gold Nanoparticles in Mice. ACS Nano. 2015;9(8):7925–39.

123. Yang X, Yang M, Pang B, Vara M, Xia Y. Gold Nanomaterials at Work in Biomedicine. Chem Rev. 2015;115(19):10410–88.

124. Padmanaban S, Pully D, Samrot A V., Gosu V, Sadasivam N, Park IK, et al. Rising Influence of Nanotechnology in Addressing Oxidative Stress-Related Liver Disorders. Antioxidants. 2023;12(7):1–25.

125. Snezhkina A V, Kudryavtseva A V, Kardymon OL, Savvateeva M V, Melnikova N V, Krasnov GS, et al. Review Article ROS Generation and Antioxidant Defense Systems in Normal and Malignant Cells. 2019;2019.

126. Cotter TG, Rinella M. Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. Gastroenterology. 2020;158(7):1851–64.

127. Khanna P, Ong C, Bay BH, Baeg GH. Nanotoxicity: An interplay of oxidative stress, inflammation and cell death. Nanomaterials. 2015;5(3):1163–80.

128. Manke A, Wang L, Rojanasakul Y. Mechanisms of nanoparticle-induced oxidative stress and toxicity. Biomed Res Int. 2013;2013.

129. Shao M, Wang Y, Dong H, Wang L, Zhang X, Han X, et al. From liver fibrosis to hepatocarcinogenesis: Role of excessive liver H2O2 and targeting nanotherapeutics. Bioact Mater. 2023;23(November 2022):187–205.

130. Bertoni S, Albertini B, Facchini C, Prata C, Passerini N. Glutathione-Loaded Solid Lipid Microparticles as Innovative Delivery System for Oral Antioxidant Therapy. 2019;(Figure 1).

131. Fernández-Varo G, Perramón M, Carvajal S, Oró D, Casals E, Boix L, et al. Bespoken Nanoceria: An Effective Treatment in Experimental Hepatocellular Carcinoma. Hepatology. 2020;72(4):1267–82.

132. Mi P, Kokuryo D, Cabral H, Wu H, Terada Y, Saga T, et al. A pH-activatable nanoparticle with signal-amplification capabilities for non-invasive imaging of tumour malignancy. Nat Nanotechnol. 2016;11(8):724–30.

133. Wang Y, Shang W, Zhong H, Luo T, Niu M, Xu K, et al. Tumor vessel targeted self-assemble nanoparticles for amplification and prediction of the embolization effect in hepatocellular carcinoma. ACS Nano. 2020;14(11):14907–18.

134. Li G, Wang S, Deng D, Xiao Z, Dong Z, Wang Z, et al. Fluorinated Chitosan to Enhance Transmucosal Delivery of Sonosensitizer-Conjugated Catalase for Sonodynamic Bladder Cancer Treatment Post-intravesical Instillation. ACS Nano. 2020;14(2):1586–99.

135. Ezhilarasan D. Advantages and challenges in nanomedicines for chronic liver diseases: A hepatologist's perspectives. Eur J Pharmacol. 2021;893(October 2020):173832.

136. Wu LP, Wang D, Li Z. Grand challenges in nanomedicine. Mater Sci Eng C. 2020 Jan;106:110302.

137. Samuelsson E, Shen H, Blanco E, Ferrari M, Wolfram J. Contribution of Kupffer cells to liposome accumulation in the liver. Colloids Surfaces B Biointerfaces. 2017 Oct;158:356–62.

138. Lorenzer C, Dirin M, Winkler AM, Baumann V, Winkler J. Going beyond the liver: Progress and challenges of targeted delivery of siRNA therapeutics. J Control Release. 2015 Apr;203:1–15.

139. Park JK, Utsumi T, Seo YE, Deng Y, Satoh A, Saltzman WM, et al. Cellular distribution of injected PLGA-nanoparticles in the liver. Nanomedicine Nanotechnology, Biol Med. 2016;12(5):1365–74.

140. Dixon LJ, Barnes M, Tang H, Pritchard MT, Nagy LE. Kupffer Cells in the Liver. Compr Physiol. 2013;3(2):785–97.

141. Gustafson HH, Holt-Casper D, Grainger DW, Ghandehari H. Nanoparticle uptake: The phagocyte problem. Nano Today. 2015 Aug;10(4):487–510.

142. Ji Y, Cao Y, Song Y. Green synthesis of gold nanoparticles using a Cordyceps militaris extract and their antiproliferative effect in liver cancer cells (HepG2). Artif Cells, Nanomedicine, Biotechnol. 2019 Dec;47(1):2737–45.

143. Cui D, Liang T, Sun L, Meng L, Yang C, Wang L, et al. Green synthesis of selenium nanoparticles with extract of hawthorn fruit induced HepG2 cells apoptosis. Pharm Biol. 2018 Jan;56(1):528–34.

144. Safer AMA, Hanafy NA, Bharali DJ, Cui H, Mousa SA. Effect of green tea extract encapsulated into chitosan nanoparticles on hepatic fibrosis collagen fibers assessed by atomic force microscopy in rat hepatic fibrosis model. J Nanosci Nanotechnol. 2015 Sep;15(9):6452–9.