Advances in Biology & Earth Sciences
Vol.9, Special Issue, 2024, pp.81-91
https://doi.org/10.62476/abes9s81

NOVEL NANOMATERIALS FOR HEPATOBILIARY DISEASES TREATMENT AND FUTURE PERSPECTIVES

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Abstract. Hepatobiliary diseases are serious universal health concerns that affects the liver and is responsible for around 2 million deaths annually. The limitations of standard drug-delivery systems, such as unequal and nonspecific drug distribution, which result in adverse effects on healthy tissues and a reduction in drug bioavailability, make successful therapy difficult even when choices for surgery and medicine are available. With the liver's distinct physiological and anatomical features, nanotechnology offers a potential approach to targeted medication delivery, making it a prime target for nanomedicine. In the context of liver illnesses, a number of nanomaterial categories, such as polymer, inorganic and multifunctional nanoparticles (NPs), have been investigated as possible agents for targeting this organ. Nanomaterials can be specifically targeted to liver tissue or hepatocytes by surface modification and functionalization, increasing the delivery of medications and reducing their adverse effects. Although there are many advantages to using nanomaterials, their toxicity and stability can cause problems for living things, including inflammation and protein adsorption. Notwithstanding the difficulties associated with the creation of nanoparticles, further study and development hold much promise for the use of nanotechnology to the targeted treatment of liver disorders. The nanomaterials used to address liver diseases nanozymes, Nano-based oligonucleotide, Lipid-based nanostructures and nanoemulsions and Extracellular Vesicles are first discussed in this study. Additionally, the ways in which nanomaterials target liver illness are examined. This study concludes with a discussion of the present issues and potential future avenues for this line of inquiry.

Keywords: *Liver, nanomedicine, drug delivery, nanomaterials.*

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Received: *22 January 2024;* ***Accepted:*** *18 March 2024;* ***Published:*** *8 April 2024.*

1. Introduction

Liver disorders, including cirrhosis, hepatitis and hepatocellular carcinoma (HCC), are major global health concerns. About 2 million fatalities globally are linked to liver disease each year, making it one of the top 10 causes of mortality (Ginès *et al*., 2021). One of the most vital organs in the human body, the liver is essential for synthesis, storage, detoxification and metabolism. However, liver disease is becoming more common and is a major public health concern due to poor lifestyles, environmental pollutants and hereditary factors (Tilg *et al*., 2016). Even though there

How to cite (APA):
Huseynov, E., Khalilov, R. & Mohamed, A.J. (2024). Novel nanomaterials for hepatobiliary diseases treatment and future perspectives. *Advances in Biology & Earth Sciences*, 9(Special Issue), 81-91 https://doi.org/10.62476/abes9s81

are a number of therapies for liver illnesses, including medicine and surgery, treating these problems effectively is still difficult. Liver disease treated surgically can result in postoperative complications that might negatively impact the patient's rehabilitation and survival, including bleeding, infection and liver failure (Nault *et al*., 2018). While medicine is a safer option than surgery for liver illness, there are still drawbacks to traditional drug delivery techniques and the prescription itself frequently has major adverse effects. The administration of medications using conventional means frequently results in an uneven and non-specific distribution of the drugs throughout the body, as they are not particularly administered to the location of liver disease (Sangro *et al*., 2021). Consequently, medications may be digested or eliminated by the liver, which lowers their bioavailability, and they may have detrimental effects on healthy tissues, resulting in additional side effects (Gillessen & Schmidt, 2020). One novel way to address these issues is the creation of tailored medicine delivery systems.

The liver is an excellent target for targeted drug delivery due to its unique anatomical and physiological structure, which permits efficient drug administration (Almazroo *et al*., 2017) and its role as the primary site of drug metabolism and clearance (Witzigmann *et al*., 2020). Nanotechnology has emerged as a potential technique in this regard. Furthermore, by customizing them for certain liver diseases, nanomaterials can deliver therapeutic compounds to specific liver cells, including hepatocytes in the case of hepatitis B virus (HBV) infection and HCC or hepatic stellate cells (HSCs) in the case of liver fibrosis. By boosting drug accumulation in the liver and reducing drug exposure in other organs, a drug delivery system based on nanotechnology can improve medication effectiveness and decrease toxicity (Witzigmann *et al*., 2020). The potential of nanomaterials as a target for liver illness is being investigated in great detail (Cheng *et al*., 2020). These materials might lead to better drug delivery systems (Salunkhe *et al*., 2020), visualization aids (Li *et al*., 2022) and liver disease treatment instruments (Bhia *et al*., 2021). Numerous nanomaterials, such as metallic nanoparticles (NPs), ceramic nanomaterials, micelles, polysaccharides, liposomes, dendrimers, carbon nanotubes (CNTs),and multifunctional NPs, have been investigated for their potential to treat liver disease. Targeted therapy and hyperthermia therapy approaches have been used to generate superparamagnetic iron oxide nanoparticles (SPIONs) as a possible therapeutic modality for the treatment of HCC (Böttger *et al*., 2020; Gharibkandi *et al*., 2023; You *et al*., 2023). Because of their synthetic flexibility, polymer-based nanoparticles (NPs) have a wide variety of applications. This is because it allows for the exact modification of their physicochemical features, such as size, charge and controlled release (Paramjot *et al*., 2015). Furthermore, they are especially well-suited for the insertion of surface alterations, including receptor ligands unique to liver cells. They have been extensively utilized for targeted intrahepatic administration (Rohilla *et al*., 2016). Multifunctional nanoparticles (NPs) have been investigated for the treatment of liver cancer due to their several capabilities, including drug administration, imaging and photothermal therapy (PTT) (Liu *et al*., 2021). Targeted delivery can be accomplished by changing the surface of these materials, which improves drug release and hepatocyte targeting while reducing harmful effects. For example, surface modification of antibodies targeting HCC cells can be used to target NPs specifically to hepatocytes (Zhang *et al*., 2016).

Therefore, exploring the potential of nanotechnology to create tailored medicine delivery systems to the liver seems encouraging. The use of nanomaterials for imaging and treatment of liver disease is set to transform medicine with further study and

development. We investigated the potential of a variety of nanomaterials to target liver disease in this study. Additionally, the ways in which nanomaterials target liver illness are examined. Lastly, the opportunities for future research areas in this field are discussed, along with the obstacles that now exist.

2. Hepatocytes targeting

A particular receptor known as ASGP-R is expressed on hepatocyte membranes close to sinusoids (Wang *et al*., 2015). Every hepatocyte surface has between 100,000 and 500,000 ASGP-R (Weigel & Yik, 2002). The intrinsic ability of ASGP-R to bind to galactose and N-acetyl-galactosamine residues is present. Common target ligands for it include lactobionic acid, asialofetuin, sterylglucoside, galactose, galactoside and galactosamine. These ligands are often used to alter nanomaterials for active targeting (Li *et al*., 2010; Mishra *et al*., 2013). ASGP-R can identify nanoparticles containing the aforementioned ligands and hepatocytes can then take them up by clathrin-mediated endocytosis. These receptors quickly reattach themselves to the cell membrane after releasing the ligand (Wang *et al*., 2015). Because ASGP-R can recognize hepatocytes, ligand-functionalized nanomedicines have been used extensively in liver-related illness research (Wang *et al*., 2015). In targeted treatment for ALF, galactose and lactobionic acid ligands are the most often utilized targeting methods. Galactosylated proteins or nanoparticles can be identified by ASGP-R of hepatocytes with a high affinity and a rapid internalization rate due to the unique interaction between ASGP-R and galactose (Baenziger & Fiete, 1980). The galactose-modified cationic liposome was created by Jiang et al. in order to successfully silence the Fas gene in ALF therapy by delivering Fas siRNA into hepatocytes (Jiang *et al*., 2012). Furthermore, it has been confirmed that lactobionic acid, an oligosaccharide aldonic acid, is the particular ligand of the hepatocyte (Selim *et al*., 2007). Lactobionic acid was coupled with IL-1Ra chitosan nanoparticles by Xiao et al. (2013) to create IL-1Ra-lactosylated chitosan nanoparticles, which were then used to transport IL-1Ra. As a result of the interaction between the ligand and receptor, the nanoparticles were successfully taken up by the hepatocytes.

3. Nanozymes

One class of nanomaterials having properties similar to those of an enzyme is nanozyme (Wu *et al*., 2019). Superoxide anion (O2−) and H2O2, which have been employed in oxidative stress-related disorders, may be detoxified by SOD and catalase mimics (Kubota *et al*., 2014). Catalase, SOD and other naturally occurring antioxidant enzymes can be mimicked by metalloporphyrin. Manganese porphyrin, for example, has been studied in many research as a catalase and SOD mimic (Batinic-Haberle *et al*., 2012). Zhang's study recently created pegylated manganese protoporphyrin, a water-soluble metalloporphyrin-based catalase mimic. Additionally, the APAP-related ALF model was used to assess its therapeutic effectiveness. In vivo, chelated manganese protoporphyrin efficiently eliminated H_2O_2, decreased the liver-to-body weight ratio and decreased blood ALT levels. Pegylated manganese protoporphyrin was thought to be a promising treatment for ALF (Zhang *et al*., 2019). Antioxidative nanobiomaterials might lessen oxidative stress and hepatotoxicity brought on by APAP, much as nanozyme. Boonruamkaew et al. (2016) conducted research on a new antioxidative nanoparticle that was created by crosslinking methoxy-poly(ethylene glycol)-b-poly[4-

(2,2,6,6-tetramethylpiperidine-1-oxyl) aminomethylstyrene], an amphiphilic block copolymer. The antioxidative nanoparticle had nitroxide radicals on the side chain of the hydrophobic segment, which gave it the ability to scavenge reactive oxygen species (ROS). In APAP-associated ALF, the antioxidative nanomaterial enhanced serum albumin levels while inhibiting ALT, AST, alkaline phosphatase (ALP) and O_2.

4. Nanomedine and RNA

As previously shown, DAMPs and PAMPs are the primary initiators of liver inflammation in ALF. They activate monocytes or macrophages and encourage the release of pro-inflammatory cytokines, reactive oxygen species and chemotactic factors. Following that, there is an increase in the recruitment of inflammatory cells such monocytes and neutrophils. SIRS is the end outcome of these mechanisms, which in turn intensify the inflammatory process (Kubes & Mehal, 2012). Anti-inflammation is therefore essential to the treatment of ALF (Rolando *et al*., 2000). Gene silencing using RNA interference (RNAi) is a significant therapeutic approach for disorders associated with inflammation (Oh & Lee, 2014). Short hairpin RNA (shRNA), microRNA (miRNA) and siRNA are typically used to downregulate certain biological signaling molecules, such as chemokines and cytokines (Nam *et al*., 2019). Through the process of RNA-induced silencing complex (RISC), double-stranded RNA molecules known as siRNA attach to complementary mRNA and degrade it, therefore precisely suppressing the expression of that gene (Whitehead *et al*., 2009). Silencing the genes of inflammatory cytokines with siRNA is an essential technique (Whitehead *et al*., 2009). However, because to its easy digestion by nucleases, bare siRNA is not stable in serum. Furthermore, because of its negative charge on the surface, bare siRNA finds it challenging to pass through cell membranes and form RISC in the cytoplasm (Dong *et al*., 2018). These obstacles can be overcome by non-viral gene delivery based on nanotechnology. Targeted gene silencing has been achieved and the effectiveness of gene therapy in the treatment of ALF has been enhanced by the use of nanobiomaterials-based siRNA delivery methods.

5. Nano-delivery for liver fibrosis

Even though many antifibrotic medications are highly effective in vitro, in vivo side effects are typically only mildly noticeable. As of right now, this fibrotic illness can not be treated with medication. Despite the fact that combination therapy is now much more effective, there are still a number of problems that need to be resolved and several obstacles, chief among which is the medication itself. The primary issue with these medications in vivo is their short half-life and lack of selectivity for the liver, which can lead to an accumulation of drug concentrations in the target organ and cells (Trautwein *et al*., 2015; Yoon *et al*., 2016). Furthermore, when a medicine is used over an extended period of time, it may induce major adverse effects due to drug absorption in non-target cells. Altered pharmacodynamics improve the possibility of a particular action in the target HSC while decrease the likelihood of side effects, leading to a greater therapeutic impact in the treatment of liver fibrosis (Kummar *et al*., 2010). Therapeutic outcomes require nano delivery systems to be achieved. One of the most successful therapies has been shown to be medication combination therapy, which employs many medicines at the same time, using nano delivery devices for this purpose. In this part, we mainly

covered the utilization of drug delivery technologies, such as the polymer micelle system (Qiao *et al*., 2018), liposome system (Luo *et al*., 2019), etc. in medication combination treatment. With the use of these preparation technologies, drugs can be more effectively targeted, have a slower release, need less dose, have fewer harmful side effects and be more effective overall.

6. Nano-based oligonucleotide in hepato neoplasms

A portion of the protein is necessary for tumor cells to develop and spread. In order to prevent the progression and metastasis of liver cancer cells, exogenous genes (oligonucleotides, siRNA, pDNA) are injected into the affected area based on the association between these essential proteins and the corresponding genes. The goal is to suppress the expression of some genes and reduce the abnormal protein. The use of nuclear acids to replace, repair, control, add or delete a portion of the gene sequence that causes human illness has advanced significantly.

This is the fundamental idea of the new oligonucleotide therapy for liver cancer; nonetheless, the primary barrier is the poor transport efficiency to the cancer cells. For instance, RNA interference (RNAi) is one of the most promising therapeutic approaches for hepatocellular carcinoma. The primary obstacle to siRNA therapeutics, however, is their poor delivery efficiency to target cells and the inability to effectively target tumors through systemic administration.

Consequently, there has been a lot of focus lately on the use of nanomaterials as oligonucleotide targeting carriers for liver cancer cells. In order to address oligonucleotides' poor efficacy in targeting liver cancer cells, researchers are hoping to use the unique characteristics of nanomaterials. At the nanoscale, amphiphilic alkylated poly(α)glutamate amine (APA) may function as a cationic carrier for oligonucleotides with a negative charge. When APA polymers combined with siRNA, they created spherical, uniform and repeatable nano-sized polyplexes that were about 50 nm in size and had a small negative charge. These polyplexes have been identified as possible liver tumor gene regulators (Krivitsky *et al*., 2018).

In a similar manner, Yuling and colleagues (He *et al*., 2019) created upconversion nano-onions (UCNOs) using stacked polymer to deliver siRNA that could react to the extracellular milieu and near-infrared stimulation, breaking down layer by layer. It caused a quick and effective release of siRNA, which effectively increases the efficacy of gene silencing in vitro and inhibits the development of liver tumors in vivo. Nano-graphene oxide (NGO) conjugate (GA-PEG-NGO-Dendrimer, GPND (Qu *et al*., 2019) was used for the delivery of siRNA in order to address the deficiencies of siRNA's easy degradation, short half-life, low transfection efficiency and poor stability. The excellent absorption of GPND/siRNA nano-complex by HepG2 cells was demonstrated by cell imaging and flow and gene silencing was successfully accomplished due to the decreased expression of VEGFa in mRNA and protein (VEGFa gene is overexpressed in liver cancer cells which was chose to evaluate the effect of this study).

7. Nanostructures for NAFLD treatment

The liver is a vital organ that carries out a variety of tasks necessary to preserve proper homeostasis and support healthy cellular activities (Robinson *et al*., 2016). Furthermore, the turnover rate of liver hepatocytes in a healthy adult is quite low and

they can quickly replace the liver cells when they lose bulk. Furthermore, insulin—the hormone that raises free fatty acids and lipogenesis—is innately resistant to a damaged liver (Malhi & Gores, 2008). Hepatocytes or parenchymal cells, are identified as the main structural element of the liver, when treating NAFLD, a number of techniques that researchers have developed—such as the use of hydrogen-rich water (HRW), electrolyzed-alkaline water (EAW) (Jackson *et al*., 2018) and active vitamin D (VD) (Ma *et al*., 2020)—have resulted in negative side effects. Bioactive molecule-coated nanostructures may offer a more effective and widely accepted method of treating NAFLD.

Nanotechnology-based methods have been demonstrated to be successful in lowering blood triglyceride lipid levels and hepatic lipid deposition, hence suppressing nonalcoholic fatty liver disease (NAFLD), which is a silent killer. Here, it is necessary to assess the hepatoprotective effects of nanomaterials on lipotoxicity and triglyceride buildup using cellular and animal models, which are likely to show impacts on the GI25 value and cell survival in HepG2 steatotic liver cancer cells.

Furthermore, because of their relationship and connection to a disease, 77 proteins linked to non-alcoholic fatty liver disease (NAFLD) are extremely significant and have use in NAFLD clinical practice (Amanatidou & Dedoussis, 2021). In this regard, nanoformulations have garnered a lot of attention due to their recent benefits for treating nonalcoholic fatty liver disease (NAFLD) with manageable features, leading to the development of novel nanomedicine systems for enhancing liver functions by lowering blood levels of AST and ALT (Zhou *et al*., 2021).

8. Lipid-based nanostructures and nanoemulsions

This section covers steroid-based lipid NPs, liposomes, solid lipid NPs, nanostructured lipid carriers, self-nanoemulsifying drug delivery systems and stable nucleic acid-lipid NPs. Targeting hepatic stellate cells is one strategy that may be investigated in order to clarify the intricate molecular processes that link the pathophysiology of liver fibrosis, elevated free fatty acid levels, insulin resistance and diabetes.

The growing need for efficient active chemical delivery has led to the development of colloid chemistry and nanotechnology. Recent developments in the production of a broad range of soft nanostructures, including single or multiple nano-sized emulsions, have prompted the study of several novel formulations with promising therapeutic applications. In general, nanoemulsions are thought of as transparent/translucent heterogeneous systems made up of a continuous phase and a dispersed phase that resembles droplets. On the other hand, changes in composition and temperature adversely affect them because of their tiny size and thermodynamic stability (Gupta *et al*., 2016). For instance, Agame-Lagunes et al. (2021) used medium-chain fatty acids (as mono and di-acylglycerides) as stabilizers in order to study the therapeutic effects of curcumin (Curcuma longa)-loaded nanoemulsions. Consequently, our nanosystem avoided possible adverse effects and increased curcumin bioactivity without the need for large drug doses.

9. Extracellular Vesicles

Mammalian cells secrete lipid bilayer-encapsulated biological nanoparticles known as extracellular vesicles or EVs. They facilitate intercellular communication because they may be absorbed by surrounding cells and carry their payload with them. Additionally, found in blood and bodily fluids, EVs can travel to far-off tissues to affect biological processes. Clarifying the biological functions of extracellular vegetables (EVs) and their participation in physiological or disease-relevant processes is of increasing attention. EVs come in a variety of forms, including exosomes and microvesicles (MVs). Their sizes, morphologies, membrane compositions, cargo profiles and biogenesis processes vary. The development of electric vehicles (EVs) as a treatment platform for human ailments is supported by their biophysical and biological features. Despite reports of the therapeutic use of many vesicle subtypes, it is difficult to discriminate between them because of their simultaneous existence in the biological milieu, the overlap of their size, composition and cargo and the absence of subtype-specific markers. The majority of cell types, if not all of them, express EVs widely and they may be found in bodily fluids including plasma, cerebrospinal fluid, milk and urine as well as in the tissue milieu and circulation (Merchant *et al*., 2017; Zonneveld *et al*., 2014). The safety and efficacy of therapeutic applications must be proven using EVs that can be manufactured uniformly and at a large enough scale for human usage. EVs for medicinal uses can come from a variety of sources. These include fully developed or pluripotent stem cells, which may be genetically altered to express desired medicinal compounds and kept in cell banks for larger-scale manufacturing. Furthermore, EVs may be separated from plasma, tissue sources, milk or plants; these sources all have the benefits of scalable production, lower batch-to-batch fluctuations in production and economical production when compared to cellular sources. Hepatocytes, mesenchymal stem cells (MSCs), liver stem cells (LSCs), hepatocytes (Bruno *et al*., 2020) and hepatocyte stem cells (HSCs) are some of the different sources of therapeutic EVs employed in preclinical investigations of liver illnesses (Chen *et al*., 2015). Additionally, recent research has demonstrated the potential utility of EVs derived from edible plants or cow's milk as medicinal drug delivery systems (Ishiguro *et al*., 2020).

10. Conclusion

Liver disease is a widespread health issue that impacts millions of individuals globally. Even though there are many different treatment options accessible today, many liver illnesses are still incurable due to their low efficiency. The creation of tailored nanomaterials has shown a lot of promise as a novel liver disease treatment strategy in recent years.

Targeted nanoparticles (NPs) are NPs made specifically to deliver medications or therapeutic substances to the liver's afflicted cells. The trained models generated from this research might be used in the future to direct the creation of similar formulations. This approach's primary benefit is that it speeds up drug design and development, leading to the quicker production of medications with improved efficacy and less toxicity to humans.

As a result, this model may also be used to create nanomaterials that are intended to treat liver disorders. To sum up, targeted nanomaterials provide a promising new avenue for the treatment of liver disorders. Despite the fact that there are still a number

of issues to be resolved, these NPs have enormous potential advantages. Targeted nanomaterials are expected to play a bigger part in the treatment of liver illnesses as research and development in nanotechnology and biomedicine continue to progress, offering patients more individualized and efficient options.

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