EGYPTIAN ACADEMIC JOURNAL OF
BIOLOGICAL SCIENCES
ZOOLOGY

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ISSN
2090-0759

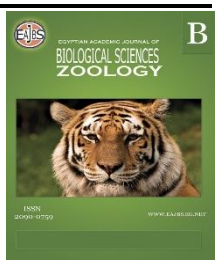
WWW.EAJBS.EG.NET

Vol. 17 No. 1 (2025)

Citation: *Egypt. Acad. J. Biolog. Sci. (B. Zoology) Vol. 17(1) pp:55-86 (2025)*
DOI: 10.21608/EAJBSZ.2025.410264

Egypt. Acad. J. Biolog. Sci., 17(1):55-86(2025)

Egyptian Academic Journal of Biological Sciences
B. Zoology
ISSN: 2090 – 0759
Res. Ethics No.: 03-2024-0009
http://eajbsz.journals.ek b.eg/



The Potential Therapeutic Advantages of Using Nanotechnology in the Treatment of Liver Fibrosis: A Review

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REVIEW INFO
Review History
Received:10/12/2024
Accepted:5/2/2025
Available:9/2/2025

Keywords:
Liver fibrosis, nanomedicine, inorganic nanoparticles, organic nanoparticles, drug delivery, combination therapy.

ABSTRACT

Liver fibrosis is a complex medical condition characterized by the abnormal and excessive buildup of extracellular matrix proteins, primarily collagen, in liver tissue, disrupting normal tissue architecture and functionality. This accumulation can lead to various complications and adversely affect the overall health of the involved organs. This pathological phenomenon typically arises from chronic liver injury, often caused by multiple factors. Early detection and intervention are crucial to minimize ongoing liver damage and enhance clinical outcomes for those affected. While significant progress has been made in understanding the molecular pathways involved in liver fibrosis, there remains a strong demand to expand the treatment options available for this condition. The use of nanoparticles (NPs) in combination therapies has gained popularity, leveraging advancements in drug delivery systems. This approach enables the simultaneous administration of several pharmacological agents, thus enhancing therapeutic effectiveness for liver fibrosis and other conditions. Researchers increasingly view NPs as innovative tools capable of optimizing combination therapies through targeted delivery of medications, thereby improving bioavailability and overall therapeutic impact. Recent research in nanotechnology highlights the potential of NP-mediated drug delivery systems to change the treatment landscape for liver fibrosis. Various NP systems, including both inorganic and organic NPs, present innovative avenues for achieving sustained drug release, targeted treatment, and enhanced stability, reducing the likelihood of rapid clearance in infected tissues. This review examines the evolving role of nanotechnology in managing liver fibrosis, summarizing recent findings and assessing various technologies for their effectiveness and potential. We will showcase innovative strategies and significant results while comparing nanoparticle methods to evaluate their efficacy. Furthermore, we will investigate the applications of nanomaterials in drug delivery, targeting, and diagnostics, unveiling the exciting advancements shaping the future of liver fibrosis treatment.

INTRODUCTION

The significance of prioritizing research in nanomedicine and drug delivery systems lies in the ability to create effective therapeutic strategies, especially for conditions like liver fibrosis. This review serves as an essential guide for discovering advanced medical treatments and improving healthcare outcomes, particularly in regions where research is limited, such as Saudi Arabia. The increasing prevalence of liver diseases in the area, including fibrosis and cirrhosis driven by obesity, diabetes, and hepatitis, necessitates

immediate attention. Emphasizing nanotechnology is in line with the Kingdom's Vision 2030, which seeks to promote healthcare research and expand treatment options. Moreover, utilizing nanotechnology could boost the effectiveness of treatments for liver fibrosis, resulting in improved patient outcomes and decreased healthcare.

A-Liver Fibrosis:

Definition and Causes of Liver Fibrosis:

Liver fibrosis represents a significant global health challenge, particularly within the context of chronic liver diseases. This condition frequently arises as a consequence of various long-standing liver disorders, including viral hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) (Ballestri *et al.,* 2021).

The liver has a distinctive structure featuring a complex vascular system. It is primarily supplied by the hepatic artery and is associated with two venous systems: the portal and hepatic veins. Additionally, the liver houses the intrahepatic biliary tract, which exits the organ as the common hepatic duct (Ugo *et al.,* 2021). The liver is segmented into polygonal units called lobules, divided by connective tissue. The functions of the liver, which include detoxification, the urea cycle, and the synthesis of plasma proteins, are essential roles fulfilled by hepatocytes. These hepatocytes are organized in linear formations that radiate from the central vein to the periphery of the lobule, creating sinusoids the spaces located between the radially aligned cell arrangements (Zhang *et al.,* 2020).

The hepatic sinusoids exhibit structural and functional characteristics that distinguish them from the capillaries found in other organs. A notable structural feature of the hepatic sinusoids is the absence of a basement membrane, which leads to the development of unique morphological attributes of the hepatic sinusoidal cells, namely liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), and hepatic stellate cells (HSCs). LSECs possess fenestrations and sieve plates that facilitate the efficient exchange of substances between the sinusoidal lumen and the space of Disse. HSCs adjacent to LSECs function as sinusoidal pericytes that adhere directly to hepatocytes. These cells remain in a quiescent state through these adhesions, with activation occurring upon their retraction. (Yuasa *et al.,* 2024).

Hepatic stellate cells (HSCs) are mesenchymal cells in the Disse space, located between liver sinusoidal endothelial cells and hepatocytes. These cells feature thorn-like micro-projections known as spines, which extend from their surface to traverse the Disse space, thereby establishing adherens junctions with adjacent hepatocytes. Research has investigated the disruption of adherens junctions between hepatic stellate cells (HSCs) and hepatocytes, identifying this disruption as a catalyst for HSC activation. Cell adhesion molecules are central to the progression of hepatic fibrosis and may serve as potential targets for antifibrotic therapies. Furthermore, integrins and cadherins emerge as critical components in liver fibrosis, suggesting they could represent promising therapeutic targets for treatment strategies (Hintermann and Christen 2019). Furthermore, epithelial cadherin (E-cadherin) has been identified as the adhesion molecule responsible for mediating the connection between hepatocytes and HSCs (Hintermann *et al.,* 2019; Urushima *et al.,* 2021).

Hepatic stellate cells (HSCs) are rich in lipids, a characteristic of a healthy liver. The liver plays a vital role in regulating lipid homeostasis by producing, storing, and releasing lipids, which serve two essential functions in the liver. However, excessive accumulation of lipids within hepatocytes can impair normal liver function. If not managed adequately, this lipid accumulation has the potential to result in hepatic fibrosis, primarily due to the activation of hepatic stellate cells, (Molenaar *et al.,* 2020).

Hepatocytes store limited quantities of neutral lipids within lipid droplets (LDs). Simultaneously, despite constituting less than 8% of the liver's cellular composition, HSCs retain substantial LDs primarily responsible for storing most vitamin A in the human body. When excessive lipid accumulation occurs within hepatocytes, HSCs deplete their significant vitamin A-enriched LDs and undergo a transactivation process into a phenotype characterized by extracellular matrix production, a defining feature of liver fibrosis. Approaches aimed at maintaining HSCs in an LD-rich state while concurrently reducing LD levels in hepatocytes are anticipated to be crucial in preventing or reversing liver fibrosis (Kusumoputro *et al.,* 2023; Molenaar *et al.,* 2020).

Additionally, HSCs are known to store substantial amounts of vitamin A in lipid droplets, which can also store retinoids in lipid vesicles. In specific pathological conditions, these cells may experience a reduction in retinoid content, leading to their transformation into fibroblast-like cells. This phenomenon significantly affects the fibrogenic response (Carmona *et al.,* 2019). In contrast, retinoic acid (RA) functions to activate the retinoic acid receptor (RAR), which is essential for the regulation of fibrogenesis (Delgado *et al.,* 2021; Khomich *et al.,* 2019).

Following this process, fibroblast-like hepatic stellate cells (HSCs) demonstrate an increase in the expression levels of fibroblast activation protein (FAP), which is a type II transmembrane glycoprotein found on the surfaces of activated hepatic stellate cells (aHSC). Consequently, there is an accumulation of extracellular matrix (ECM) components, predominantly collagen. The excessive accumulation of collagen disrupts the normal structural integrity of the liver, resulting in compromised liver function and the development of hepatic fibrosis (Hu *et al.,* 2019; Karsdal *et al.,* 2020).

Hepatic stellate cells (HSCs) are crucial in liver regeneration following injury. These cells synthesize and secrete hepatocyte growth factor (HGF), which interacts with the cMet receptor found on hepatocytes, biliary cells, and endothelial cells. The depletion or inhibition of HSCs negatively impacts the regeneration process. Additionally, genetically inhibiting HSC activation reduces hepatocyte proliferation and worsens liver injury (Acharya *et al.,* 2021).

Furthermore, HSCs contribute to angiogenesis by releasing several growth factors, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGFβ), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and angiopoietin. In the later stages of regeneration, HSCs help reconstruct the basal extracellular matrix and sequester growth factors, as well as prevent their premature activation in hepatocytes. (Kamm *et al.,* 2022; Wiering *et al.,* 2023).

Gaining insight into the molecular mechanisms of fibrosis will help us better understand this biological process and identify possible targets for treatment. As per the findings of Vuppalanchi *et al.,* (2021), the complex nature of liver fibrosis makes it exceptionally challenging to address. However, considering these challenges, ongoing research, development, and focused efforts are underway to overcome these obstacles and achieve better patient outcomes. The discussion revolved around the implications of this knowledge for treating the specific illness. Despite tremendous progress in our comprehension of the subject, much remains to be discovered about the cellular and molecular processes involved in fibrogenesis (Salimi *et al.,* 2022).

Accordingly, Acharya *et al.* (2021) summarized the current understanding of crucial pathways and the cellular and molecular factors contributing to hepatic fibrosis. Given the intricate pathophysiological pathways involved, treating liver fibrosis must be more complex than expected. However, a substantial workforce and material resources have been dedicated to creating effective treatments (Agnihotri *et al.,* 2023).

B. Nanotechnology and its Potential in Medicine:

In recent years, nanotechnology has achieved significant advancements, resulting in the development of specialized nanodevices and nanomaterials that have identified intriguing applications within the medical field (Kim *et al.,* 2020; Li *et al.,* 2022). Health, the economy, the environment, and industry have all been directly impacted by the development of intelligent materials, biosensors, packaging materials, nutraceuticals, and nanodevices, all of which aim to address various medical-related issues (Park *et al.,* 2020; Durán-Lobato *et al.,* 2021).

Nanoparticles (NPs) are materials with dimensions ranging from 1 to 100 nanometres. In biomedicine, these nanoscale systems display unique physicochemical properties, such as their small size, large specific surface area, high reactivity, and quantum effects. These properties make nanoparticles highly suitable for biomedical applications, including drug delivery, imaging, and diagnostic purposes (NPs) (Lin *et al.,* 2023; Zhang *et al.,* 2023).

When particles exceed 100 μm in size, reticuloendothelial system (RES) cells, mainly found in the liver and spleen, efficiently recognize and engulf them for removal from the body. Similarly, particles smaller than 10 nm can be filtered by the kidneys and quickly eliminated through urine. This swift clearance process ensures that both large and

small particles are effectively disposed of, aiding in maintaining the body's homeostasis and overall health (Wang *et al.*, 2021).

In a pursuit characterized by both challenges and achievements, Wang and colleagues (2024) report that nanotechnology is crucial for progress in medicine, especially in nanomedicine, to overcome challenges in treating chronic diseases. The utilization of nanoparticle (NP) systems has become a rapidly advancing field of interest for the secure administration of diverse drugs and nucleic acids in the context of chronic liver diseases. (Surendran *et al.* 2017).

Several NPs have been documented in the last 25 years. However, only a small number have been converted into practical applications. (Ma *et al.*, 2017; Khan *et al.*, 2019; Wang et al., 2021). The promising approach of nanomedicines is demonstrated by the more than 90 approved for clinical use (Thapa and Kim, 2023). Moreover, nanotechnology is gaining increasing significance in liver disease treatment and diagnosis, mainly due to the emergence of novel treatment approaches (Singh *et al.*, 2023).

During the early stages of research, the authorized nanoparticles were primarily utilized for treating liver disorders or infectious diseases since they mainly gathered in the liver or were absorbed by the reticuloendothelial system (RES). Kaps *et al.* (2023) introduced innovative oral tablets that utilize nanoparticle technology, setting a new benchmark in the field of nanoformulation. This approach enhances the medication's effectiveness and revolutionizes how we deliver pharmaceutical compounds, leading to improved patient outcomes and advanced therapeutic possibilities.

Exceptional nanostructures transform liver fibrosis diagnostics, demonstrating capabilities surpassing traditional methods. These structures are active therapeutic agents, improve imaging contrast and function as advanced diagnostics nanoprobes. The benefits of nanoparticles include extended circulation times, better tissue penetration, controlled therapeutic release, enhanced imaging clarity, optimized drug pharmacokinetics, and reduced side effects (Zhang *et al.*, 2020).

This cutting-edge technology is instrumental in pinpointing crucial biomarkers and deepening our understanding of how liver fibrosis progresses. The choice of methodology hinges on the specific characteristics of the medicine being used and the disease it targets. Exploring drug combinations also involves various methodologies, highlighting the need for a comprehensive reference model tailored for all biomedical applications (Vakil and Trappe 2019).The modification and functionalization of nanoparticles (NPs) are essential for realizing their full potential, particularly in biocompatibility, colloidal stability, dispersion, and environmental interactions (Georgilis *et al.*, 2020). Surface functionalization, which entails adding a chemical functional group to the nanoparticle surface, significantly enhances self-organization and compatibility. Moreover, properties such as surface electrical charge, energy, topology, and bioreactivity can be tailored to meet the specific requirements of various applications (Li *et al.*, 2022).

Designing nanoparticles to target (HSCs) encompasses two primary strategies. The first involves the active targeting of HSCs by surface modification of organic nanoparticles to confer specificity to HSCs. The second strategy involves the passive targeting of HSCs through the systemic administration of organic and inorganic nanoparticles that do not rely on specific ligands (Hu *et al.* 2019).

The most common method is surface functionalization through in situ synthesis; ligands like inorganic compounds, polymers, biomolecules, and surfactants allow further surface modification. Surface modification can also be achieved using synthetic approaches involving a range of interactions, including electrostatic, covalent, non-covalent, and intrinsic bonding (Shukla, 2020). These strategies significantly enhance biocompatibility, dispersibility, reactivity, binding capacity, and catalytic activity, making them invaluable for advancing research and applications in the field (Natesan & Kim, 2023).

The anti-inflammatory properties of nanoparticles (NPs) are attributed to their capacity to inhibit the expression of pro-inflammatory cytokines such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (Zhou *et al.*, 2020). Furthermore, nanoparticles exhibit antioxidant functionality by obstructing the generation of reactive oxygen species (ROS) produced by substances inducing oxidative stress. Lastly, their pro-oxidant properties are recognized for elevating ROS levels, ultimately contributing to oxidative stress, which in turn triggers apoptosis in the cells of the liver and kidneys.

Consequently, NPs are like a double-edged sword; understanding their toxicity will help refine their inherent therapeutic benefits (Wal *et al.,* 2019; Hashim *et al.,* 2022).

Types of Nanoparticles for Disease Treatment:

Nanoparticles are conventionally categorized into three principal classifications: organic, inorganic, and carbon-based, although the latter may occasionally be amalgamated with the former categories. Organic nanoparticles are synthesized from naturally occurring substances, such as albumin. These nanoparticles present several advantageous characteristics, including enhanced biocompatibility and diminished antigenic effects, particularly pertinent in liposome applications (Ijaz *et al.,* 2020). One method of classifying nanoparticles is distinguishing them into protein, polymeric, metallic, liposomal, lipid-based, and various other structures. The specific application of a nanoparticle largely depends on its structural composition (Zahin *et al.,* 2020).

However, the most distinct types are based on the material they are made from: inorganic, polymeric, lipid-based, bioinspired, and hybrid. Encapsulating hydrophilic pharmaceuticals, such as proteins, has enhanced stability under biological conditions and improved transmission across cell membranes and the bloodstream (Yin and Zhong 2020).

Inorganic Nanoparticles (INPs):

Typical representatives of the inorganic category include metals and metal oxides. Nanomaterials possess unique physical and chemical properties that can be tailored to fulfil specific objectives in drug delivery systems (Namiot et al., 2023). Metal nanoparticles are tiny particles measuring 0 to 100 nm in size. Materials in this category consist of pure metals, including gold and silver, or metal oxides, such as cerium, iron, and zinc (Boey and Ho 2020). Metallic nanoparticles can take on various shapes, such as spheres, rods, and tubes. These features, such as surface area, charge, solubility, and stickiness, can change their physiochemical properties and biochemical fate (Khan *et al.,* 2019).

Metallic inorganic nanoparticles (INPs), specifically nanomaterials, can systematically release drugs and effectively infiltrate tissues at greater depths. This feature makes them a promising option for creating highly targeted and efficient drug delivery systems (Park *et al.,* 2020). Numerous nanoparticles have been utilized to treat liver fibrosis or chronic liver disease, including Fibroblast growth factor 2 conjugated superparamagnetic iron oxide nanoparticles (FGF2-SPIONs), silymarin-conjugated gold nanoparticles (SG-NPs), and cerium oxide nanoparticles (Ce-NPs) (Kurniawan *et al.,* 2020; Abdullah *et al.,* 2021; Flores-Rojas *et al.,* 2022; Lebda *et al.,* 2022).

- **Gold Nanoparticles (Au-NPs):**

Gold nanoparticles (Au-NPs) are a commonly utilized nanocarrier for delivering therapeutic oligonucleotides (TOs) to specific targets (Debacker *et al.,* 2020; Wu *et al.,* 2022). They demonstrated that utilizing curcumin as a reducing agent and cetyltrimethylammonium bromide as a stabilizing agent enhances the production of Au-NPs at various pH levels. The creation of gold nanoparticles was confirmed by observing the color change in the solution. Regardless of the method used to create the nanoparticles, curcumin improves the effectiveness of the Au-NPs, which exhibit favorable characteristics for biomedical uses.

Commercial Blu-ray discs incorporate large nanostructured arrays used to create gold-coated nanoplasmonic surfaces. In a 2D fatty liver disease model, gold nanograting measured albumin and optimal fetal bovine serum (FBS) concentrations to enhance lipid levels in treated cells. Furthermore, fat exposure reduces hepatocyte viability and metabolism, increasing lipid accumulation (Lopez-Muñoz *et al.,* 2020).

Ribera's research (2021) has demonstrated that platelet-derived growth factor (PDGF) and its receptor β (PDGFRβ) play a critical role in the activation of hepatic stellate cells. These components may represent viable targets for the development of anti-fibrotic therapies. A new method employs plasmonic photothermal treatment using gold nanorods coated with polyethylene glycol and conjugated with PDGF and PDGFRβ antibodies. This therapy specifically targets activated hepatic stellate cells, reducing fibrosis, inflammation, and liver damage, therefore preventing accumulation in the liver.

A study investigated nanoparticles with natural compounds and fruit extracts. Gold nanoparticles capped with polyphenols from *Cornus sanguinea* (NPCS) were combined with blueberry extract (VL) to form NPCS-VL. This hybrid was tested on human hepatic stellate cells (LX-2) exposed to TGF-β. Results showed NPCS-VL reduced membrane

damage and inflammation but increased collagen III expression, indicating a fibrogenic effect. VL lowered LDH activity and pro-inflammatory cytokine release. NPCS alleviated TGF-β-induced inflammation and downregulated α-SMA. Thus, combining fruit extracts and gold nanoparticles may effectively lower collagen I synthesis and reduce fibrosis severity (Filip *et al.,* 2023).

Conversely, the findings by Alshammari et al. (2023) indicate that contamination with AuNPs during Doxorubicin therapy can lead to significant hepatic toxicity and steatosis in rats. The findings suggest that gold nanoparticles (AuNPs) and doxorubicin (DOX) may work synergistically to exacerbate liver damage and steatosis by upregulating various lipid-related lipogenic genes and inflammatory mediators while concurrently inhibiting their functional activity.

- **Silver Nanoparticles (Ag-NPs):**

H. Zhang *et al.* (2019) conducted a study regarding liver injury induced by carbon tetrachloride (CCl4) in mouse models. Investigators examined how *Rhizophora apiculata*-synthesized silver nanoparticles protected the livers of experimental mice from hepatotoxins. Assessment findings show silver nanoparticles effectively protected the liver from carbon tetrachloride-induced damage. Based on the existing literature, they concluded that this is the first method for assessing the hepatoprotective effects of nanoparticles from plant extracts found in mangrove ecosystems.

In another experiment, Teng *et al.* (2019) developed silver nanoparticles (Ag-NPs) using a non-toxic dose that does not induce overall toxicity in healthy mice. Later, it was reported that Ag+ ions were reduced to form Ag-NPs in fatty livers. The harmful effect of this nanoformulation was linked to the concentration of silver nanoparticles (Ag-NPs) in the liver rather than silver ions (Ag+). Ag-NPs increased hepatic inflammation by stimulating Kupffer cells in the liver and inhibiting fatty acid oxidation. Sameem *et al.* (2022) focused on silver nanoparticle biosynthesis. The nanoformulation has been developed to contain a high concentration of essential biomolecules found in *Ziziphus mauritiana* extract, successfully reducing oxidative stress and inhibiting liver cell damage.

Besides, concurrent administration of Ag-NPs coated with curcumin and chitosan inhibited the progression of liver fibrosis. In its nano form, Curcumin was discovered to be an effective medication against liver fibrosis. It maintains the structure and function of the liver intact as the condition progresses. This effectiveness is due to its inhibitory function, achieved by directly interacting with proteins mediating fibrosis, like PDGFRB, TIMP-1, TLR-9, and TGF-β. (Elzoheiry *et al.,* 2022).

Conversely, research conducted by Ziaolhagh *et al.* (2023) concentrated on evaluating the resistance of hepatocytes to chemicals compared to biological silver nanoparticles when subject to aerobic and anaerobic pre-conditioning during rodent treadmill training. Histopathological findings revealed that injecting nano-silver impacts the liver structure of male Wistar rats, leading to inflammation, hyperemia, and liver cell damage, particularly with chemical nano-silver. The study's findings suggest that chemical silver nanoparticles are more damaging to the liver than their biological counterparts. Furthermore, physical pre-conditioning enhances the resistance of hepatocytes to toxic nanoparticle doses, with aerobic preparation proving more beneficial than anaerobic.

Furthermore, Yousof *et al.* (2022) research explores how daily low-dose silver nanoparticles (Ag-NPs) influence liver structure and function in rats. The findings indicate that Ag-NPs induce hepatotoxicity in rats, resulting in elevated liver enzymes and hydrogen peroxide levels. Notably, the toxic effects continued even after ceasing exposure to Ag-NPs. Furthermore, the research indicates that prolonged exposure to Ag-NPs may result in permanent hepatotoxic injury, impairing the liver's natural capacity for rapid regeneration.

Al-Doaiss *et al.* (2020) study also examined the microscopic changes in the liver caused by small-sized silver nanoparticles (Ag NPs) measuring 10 nm, which are increasingly used in medical and industrial applications. The histological, histochemical, and ultrastructural alterations observed in the livers of mice exposed to 10 nm Ag NPs revealed significant damage, including hyperplasia of Kupffer cells, sinusoidal dilation, apoptosis, and glycogen depletion.

In addition, smaller Ag-NpS particles were examined, measured at 10 and 75 nanometers, and larger Ag-NPL particles ranged from 250 to 300 nanometres (Elfaky et al., 2022). The researchers determined that the larger particles could elicit a comparable

pharmacological response, thereby indicating a potentially safer alternative to the smaller silver nanoparticles, which are recognized for their elevated toxicity and propensity to precipitate within liver tissues. Salama *et al.* (2022) research explored the effects of AgNPs on oxidative stress in liver and kidney tissues. Thymoquinone (TQ) was given alongside AgNPs, alleviating this stress by lowering malondialdehyde (MDA) and nitric oxide (NO) levels while raising glutathione (GSH) levels. AgNPs were found to inhibit multiple antioxidant enzymes, such as superoxide dismutase and catalase, but treatment with TQ reinstated their functionality activity.

Additionally, zinc oxide nanoparticles (Zn-NPs) mitigated the histopathological and immunohistochemical changes caused by Ag-NPs. When administered together, Zn-NPs and Ag-NPs diminished oxidative stress, inflammation, and apoptosis while simultaneously enhancing the histological structure of liver and kidney tissues due to their antioxidative effects. Zn-NPs lowered the levels of inflammatory cytokines, oxidative stress, and lipid peroxidation in both hepatic and renal tissues (Shehata *et al.,* 2022).

- **Cerium Oxide Nanoparticles (CeO_2-NPs):**

Cerium oxide nanoparticles (CeO_2NPs) are gaining recognition as effective antioxidants with therapeutic benefits in experimental liver disease. Their varied biological activities and unique physicochemical characteristics render them suitable for biomedical applications. The properties of CeO_2NPs, such as their shape, size, and surface coatings, significantly influence their behavior inside the body. The size of the particles is particularly crucial in determining how cells uptake them and their activity. Smaller particles (<30 nm) have a higher percentage of Ce3+ valence status. CeO_2NPs serve as carriers for focused drug and gene delivery, and their distinct physical and chemical properties allow for easy detection with biomedical imaging methods (Attia *et al.,* 2022).

The antioxidant and enzyme-like properties of CeO_2NPs are well-documented. These nanoparticles have been shown to function as scavengers for reactive oxygen species (ROS) and reactive nitrogen species (RNS) and exhibit mimetic activities akin to superoxide dismutase (SOD), catalase, and peroxidase. These qualities include scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS), converting hydrogen peroxide into oxygen and water via catalase, and reducing hydroxyl radicals from hydrogen peroxide with peroxidase (Casals *et al.,* 2021).

CeO_2NPs feature numerous oxygen vacancy defects on their surface, rendering them effective for addressing disorders linked to reactive oxygen species (ROS). The formation of oxygen vacancies and electron transitions between Ce4+ and Ce3+ are the main factors determining CeO_2's catalytic properties, which have attracted interest in biomedical research. Oxygen vacancies and electron transitions between oxidation and reduction states are the main factors influencing CeO_2's catalytic properties (Beyene *et al.,* 2021; Han *et al.,* 2022).

The hepatoprotective approach of CeO_2-NPs was investigated in an experiment by Adebayo et al. (2020) in male mice given diethylnitrosamine (DEN). Diethylnitrosamine injection in mice induced hepatic oxidative stress due to imbalances in oxidants/antioxidants and pro-inflammatory enzymes and inhibited apoptosis. CeO2-NPs mitigated these effects by enhancing antioxidant enzyme activity and reducing inflammatory and anti-apoptotic proteins. In conclusion, CeO2-NPs protect the liver from oxidative damage at the tested dosages. In their study, Córdoba-Jover et al. (2019) were the first to report that CeO_2NPs promote in rat models of partial hepatectomy and drug-induced liver injury caused by acetaminophen (APAP) overdose. In their investigation of APAP metabolism in the rat liver, the researchers observed a significant increase in transaminase levels two days after APAP administration, with similar effects seen in both the vehicle and CeO_2NPs-treated groups.

The investigation of Carvajal *et al.* (2019) also revealed similar outcomes. Their research paves the way for future applications of CeO2-NPs in human liver illnesses by demonstrating that these nanoparticles directly shield hepatocytes obtained from humans from reducing oxidative stress by preventing the production of reactive oxygen species (ROS) and reducing inflammatory expression genes. It has also been found that cells subjected to oxidative stress can be treated with CeO_2-NPs, which downregulates specific cell kinase-mediated signaling pathways.

Moreover, the protective effect of cerium oxide nanoparticles (CeO_2NPs) on

thioacetamide (TAA)-induced hepatorenal injuries in rats was investigated. Bashandy et al.'s (2022) study found that CeO_2NPs improved antioxidant status, moderated the decrease in plasma catalase, total antioxidant capacity, and hepatorenal ATP content, and reduced the rise in plasma liver enzymes, kidney function markers, and inflammation levels markers. The study's key findings are that CeO_2NPs minimize oxidative stress, inflammation, and hepatorenal pathology induced by TAA and improve liver and kidney function.

From another viewpoint, Boey and colleagues conducted a study on the impact of CeO_2NPs on liver fibrosis using the human-cultured HSC cell line LX2. The study showed that the 25 nm cubic CeO_2-NP effectively prevented fibrosis in LX2 cells activated by TGF-β, primarily by decreasing oxidative stress and TGF-β signaling. This led to decreased HSC activation and, consequently, liver fibrosis. These results indicate a potential role for CeO2 NP in treating liver fibrosis (Boey et al. 2021).

- **Iron Oxide Nanoparticles** IONPs (Fe_2O_3):

In the field of regenerative medicine, iron oxide nanoparticles (IONPs) serve as cell-tracking tracers, among other techniques. Investigating and applying cells for therapeutic purposes constitutes a novel strategy for managing several illnesses (Rahman, 2023). Huang *et al.* (2021) discovered that IONPs of various sizes, shapes, magnetic characteristics, and surface coatings can significantly enhance mitochondrial transfer between cells. This allows for a broadly applicable strategy for human mesenchymal stem cell bioengineering.

Iron oxide nanoparticles are typically coated with a biocompatible substance either during or after their preparation synthesis. This ensures that the SPION remains stable in biological media, protects them from oxidation, makes them more biocompatible, and allows them to attach functional molecules like medicines or targeting ligands (Dadfar *et al.*, 2019).

The dimensions of iron oxide nanoparticles (IONPs) differ depending on their production method and coating. These particles can range from under 50 nanometers to over 100 nanometers. Saraswathy *et al.* (2021) undertook research aimed at creating and assessing a novel iron oxide-based MR contrast agent tailored for the early identification of liver fibrosis and exploring its therapeutic potential. They developed a dual-function, biocompatible nanoprobe, pullulan-stabilized iron oxide nanoparticles (P-SPIONs), suitable for liver-specific diagnostics and treatments, which allows for high specificity in liver imaging, effective hyperthermia, and targeted dual imaging in models of liver fibrosis.

Small heterogeneous iron oxide/dysprosium oxide nanoparticles (IO-DyO-NPs) were developed as a contrast agent for MRI to precisely assess liver fibrosis in living organisms (Fernández-Barahona *et al.*, 2020). Moreover, Balachandran et al.'s (2022) findings show robust magnetic resonance imaging (MRI) signals, accurately categorize the liver tissues affected by fibrosis and distinguish between mild and severe cases of clinically relevant conditions. The biocompatible IO-DyO-NPs CAs promote initial fibrosis recognition, which is advantageous due to MRI's noninvasiveness and lack of radiation.

Zhu *et al.* (2021) investigated the effects of COOH-IONPs and NH2-IONPs on NAFLD in vitro and in vivo. The research indicated that IONP exposure notably exacerbated hepatic steatosis and led to liver damage in NAFLD models. Mice administered IONPs displayed considerable liver injury, as evidenced by increased plasma levels of ALT, AST, and TG, alongside a higher hepatic TG content and more severe hepatic steatosis in H&E staining. These results suggest that iron overload from IONPs in the liver is linked to hepatic inflammation and accelerates the progression from steatosis to steatohepatitis. This aligns with another study conducted by (Kanamori et al. 2021).

- **Zinc Oxide Nanoparticles (**ZnO-NPs):

Zinc is a fundamental mineral that is mineralized in several tissues, including the muscles, brain, skin, and bones. It is essential in various processes, including hematopoiesis, neurogenesis, protein and macromolecule synthesis, and most enzyme systems. ZnO has several potential uses. Nonmaterial ZnO has several desirable qualities, including biodegradability and low toxicity.

Thanks to its OH groups, numerous surface-decorating compounds can functionalize ZnO. The odorless, white, and insoluble zinc oxide nanoparticles, or ZnO-NPs, are not soluble in water or alcohol. The unique semiconducting, piezoelectric, and optical characteristics of nano-ZnO, combined with its small particle size, enable quick

absorption by the body (Deka *et al.*, 2022). Furthermore, ZnO-NPs can induce apoptosis and generate reactive oxygen species (ROS) in cells (Afzal *et al.*, 2020).

Since ZnO is safe to use, it is Generally Recognized as Safe "GRAS" material by the US Food and Drug Administration (FDA) since ZnO nanoparticles >100 nm are considered biocompatible (Bilensoy and Varan 2023). Therefore, ZnO-NPs have already been helpful in some fields, including healthcare, commerce, food production, agriculture, and electronics, with most of these applications being deemed safe (Krauss *et al.*, 2019). Production methods can cause ZnO-NPs to exhibit various physicochemical properties. These unique physicochemical features influence the biological activity of ZnO-NPs both in vitro and in vivo applications. The performance of synthetic ZnO-NPs improves by forming hierarchically porous network structures or one-, two-, or three-dimensional structures (Jin and Jin 2019).

Researchers conducted a study to determine the preventive impact of zinc oxide nanoparticles on liver damage, fibrosis, and oxidative stress, attributing it to their diverse pharmacological features, such as anti-diabetic, anti-inflammatory, and antioxidant activities. (Moatamed *et al.*, 2019; Keerthana & Kumar, 2020; Mandal *et al.*, 2022).

Comprehensive histopathological and immunohistochemical research has shown that ZnO nanoparticles provide considerable protection for liver biochemistry. The findings indicate that ZnO nanoparticles effectively protect against detrimental biochemical alterations in the liver (Bashandy *et al.*, 2018).

Rajeshkumar and Sandhiya (2020) Summarized biosynthetic processes for zinc oxide nanoparticles, including methods using plants, bacteria, and algae. These biomolecule-enriched materials effectively reduce metals, highlighting a key mechanism in producing zinc oxide nanoparticles under various conditions. Biological techniques assess the efficacy of newly developed zinc oxide nanoparticles. Experimental methods like X-ray diffraction (XRD), scanning electron microscopy (SEM), and Fourier transform infrared (FT-IR) are used to analyze the size and functionality of the nanoparticle groups.

The biological and environmental remediation potential of biogenic ZnO nanoparticles has prompted substantial research into these materials (Sportelli *et al.*, 2022). Because of this, ZnO-NPs have recently been evaluated by Prasad *et al.* (2021). They have focused on biogenic ZnO-NPs for their possible biological applications; synthesizing NPs with controlled particle size, shape, crystallinity, and other features has been a significant objective in materials science. Singh et al. (2020) produced zinc oxide nanoparticles (ZnONPCS) with casein as a reducing and capping agent by a biogenic approach. They created a bio-nanoconjugate (ZnONPCS–Cur) by surface loading curcumin through surface activation. Green synthesis of ZnO-NPs, called Cur-ZnO-NPs, was accomplished with an ethanolic extract of Curcuma longa (Agarwal, Nakara, and Shanmugam 2019; El-Kattan et al. 2022). The mean particle sizes, with a spherical shape, were around 20 ñ 5 nm for Cur-ZnO-NPs. Casein was used as both a reduction and coating agent in a biogenic approach developed by Somu and Paul (2019) to create zinc oxide nanoparticles (ZnO-NPCS). The researchers then used surface activation to establish a bio-nanoconjugates of these nanoparticles with curcumin (ZnO-NPCS-Cur). The green-synthesized Cur-ZnO-NPs demonstrated superior biocompatibility (Perera *et al.*, 2020).

Furthermore, the enhanced therapeutic and protective effects of zinc-curcumin complexes were reviewed. Conjugates of zinc and curcumin have shown improved antioxidant and anti-inflammatory capabilities. Additionally, zinc-curcumin complexes have shown hepatoprotective activity. Decreased inflammatory cytokines, enhanced antioxidant enzymes, reduced free radicals, and triggered apoptotic markers were among several molecular pathways linked to zinc-curcumin conjugates' preventive and therapeutic efficacies (Prasad and Lall, 2022).

Organic Nanoparticles:

Recently, there has been an increasing interest in nanoparticle (NP)-mediated drug delivery systems as potential treatments for various diseases. These systems have several advantages over conventional drug delivery techniques, including liposomal-NPs, polymeric-NPs, and nanocrystals (Li *et al.*, 2024).

Polymer-Based Nanoparticles:

Polymeric nanoparticles (P-NPs) are small polymeric particles with a core that can be filled with active chemicals either by entrapping them within or by adsorption onto their

surface. The umbrella term "nanoparticle " describes nanocapsules and nanospheres based on their morphology (Zielinska *et al.,* 2020). In addition, polymer materials undergo functionalization with biocompatible molecules, including proteins, to significantly enhance their biointegration properties. This process aims to promote better interactions between the polymer surface and biological systems, thereby improving the overall compatibility of the material within a biological environment. (Kittel *et al.,* 2022).

Despite its good toxicity profile, the FDA approved only 19 medication formulations based on Polylactic-Co-Glycolic Acid (PLGA) until 2019. Park et al. (2019) state that these formulations comprise solid implants, in situ gels, and PLGA microparticles; none are PLGA NP formulations. This observation suggests difficulties, such as low drug release kinetics and drug entrapment efficiency from PLGA nanoformulations (Chiu *et al.,* 2021). According to recent research, vitamin A (VA) can be used with polymer-based nanoparticles (NPs) to target hepatic stellate cells (HSCs) in the treatment of liver fibrosis. The methodology for conjugating retinol to poly (lactic-co-glycolic acid)-poly (ethylene glycol)-maleimide (PLGA-PEG-Mal) nano-drug delivery systems is elaborated to treat liver fibrosis through the targeted delivery to hepatic stellate cells (HSCs) (Fan *et al.,* 2020).

Lipid-Based Nanoparticles (LNPs):

Researchers in both the preclinical and clinical stages are very interested in lipid-based nanoparticles (LNPs) due to their impressive pharmacological performance and potential therapeutic benefits. The primary physicochemical characteristics and therapeutic potential of the various forms of lipid nanoparticles (LNPs) utilized in drug formulations are introduced by (Kumar *et al.,* 2022; Mehta *et al.,* 2023). The types of LNPs comprise liposomes, nano-emulsions, solid lipid nanoparticles, nanostructured lipid carriers, and lipid-polymer hybrid nanoparticles (Lu *et al.,* 2021).

Lipid-based nanocarriers provide several benefits for delivering peptides and proteins orally. They protect therapeutic peptides and proteins from enzymatic degradation and unwanted thiol/disulfide exchange reactions. Furthermore, these nanocarriers increase the lipophilicity of therapeutic agents and enhance drug permeability through the absorption membrane. Due to their lipophilic characteristics, gastrointestinal peptidases and sulfhydryl compounds, such as glutathione and dietary proteins, cannot penetrate these carriers. This effectively protects therapeutic peptides and proteins from enzymatic degradation and prevents unintentional thiol/disulfide exchange reactions. A comprehensive understanding of the behavior of lipid nanoparticles (LNPs) at the absorption membrane will facilitate the advancement of more effective delivery methods. In summary, LNPs are poised to significantly impact oral peptide and protein therapeutics' administration (Plaza-Oliver *et al.,* 2021; Haddadzadegan *et al.,* 2022;). Jampilek and Kralova (2020) review the latest research on nanoformulation-processed nutraceuticals and their potential benefits for community health. Tulbah and Lee (2021) also discuss various types of LNPs, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and nano-emulsions. Agame-Lagunes *et al.* (2021) have examined the therapeutic effects of curcumin (Curcuma longa) in nano-emulsions stabilized by medium-chain fatty acids. This nanosystem enhanced curcumin's bioactivity and the need for large drug concentrations, preventing possible adverse effects.

The properties of nanoparticles (NPs) can be customized to enhance their accumulation in tissues such as the liver and spleen, which are primary sites for generating immunological antigens. Implementing immune-recruiting systems, such as polymeric hydrogels and scaffolds, can enhance interactions with antigen-presenting cells (APCs), thereby contributing to the modulation of immune responses (Mitchell *et al.,* 2021).

- **Liposomes:**

Lipid nanoparticles have become a favored option for simultaneously delivering drugs because of their outstanding capacity to enclose various therapeutic agents. Liposomes can vary in size and form unilamellar or multilamellar structures (Kumar, 2019). Their membranes are made of two layers of phospholipids, and they can be loaded with drugs. These carriers are highly efficient and biocompatible, making them ideal for drug delivery applications (Patel 2020).

Liposome-mediated drug delivery systems (LDDS) are the most widely employed multifunctional carriers in treating liver fibrosis (Xiao *et al.,* 2018; He *et al.,* 2019; Antimisiaris *et al.,* 2021; Lee *et al.,* 2023). These systems are designed to address

hyperproliferation and anti-apoptosis issues, thereby improving the efficacy of liver disease therapeutic drugs (Cheng *et al.*, 2023). It has been reported that these LDDS have demonstrated their effectiveness in delivering drugs for disease treatment since they exhibit the advantage of being nano-sized carriers, which involves targeting liver cells while minimizing harm to healthy cells (Li *et al.*, 2024). For example, scientists propose various methods to improve curcumin's bioavailability. Among these methods is the utilization of enhancers, which involve combining curcumin with phospholipids or incorporating it into nanoparticles or liposomes (Smirnova *et al.*, 2023).

- **Micelles:**

Nanomicelles are nano-sized colloidal dispersions that self-assemble and have a hydrophobic core and hydrophilic shell. Due to their size, solubility, customized surface, and environmental exposure, nanomicelles exhibit unique and novel characteristics, making them multifunctional and essential for use in biomedical applications and other fields. They are guided to a particular spot on the body through ligand-receptor interactions and the attachment of targeting ligands. They may overcome many difficulties traditional pharmacotherapy could not conquer (Nel, 2020; Bose *et al.*, 2021; Huang *et al.*, 2024).

According to Zhao *et al.* (2023), liver sinusoidal endothelial cells (LSECs) play a crucial role in absorbing and metabolizing more than 90% of hyaluronic acid (HA), a natural ligand and encapsulated micelle known for its prolonged drug release and low cytotoxicity when directed at LSECs. A study led by Mar Gil and colleagues (2023) focused on improving the delivery of statins to liver cells. The researchers optimized a delivery system using polymeric micelles and peptide ligands to release simvastatin gradually. This could aid in preserving the specialized phenotype of liver cells and maintaining liver function.

Due to specific targeting, for example, the concentration of the drug is increased within the target cell or tissue while reducing adverse effects on other cell types (Gu et al., 2022). Accordingly, Radwan et al. (2020) designed and optimized reverse micelle-loaded lipid nanocapsules (RMLNC), aiming to suppress hepatic fibrosis progression by targeting activated hepatic stellate cells (aHSCs) via increased cellular uptake and anti-fibrotic activities.

Micelles that target hepatic macrophages have been suggested for treating liver disorders (Colino et al., 2020). The liver macrophages' preference for liposome absorption makes them ideal for delivering anti-inflammatory, anti-infective, or other medications to treat liver disorders. Combined with anti-inflammatory drugs, they can improve the regulatory status of macrophages and lower the dosage needed to treat acute and chronic liver injury (Dong *et al.*, 2019; Cheng *et al.*, 2021; Martínez-Sánchez *et al.*, 2023).

C-Applications of Nanotechnology in Disease Treatment:

a) Drug Delivery Systems:

Medication combinations may be the most effective course of treatment without more advanced biopharmaceutical delivery methods (Bondarenko *et al.*, 2021). Combining medications can lead to additive, synergistic, or antagonistic effects, resulting in reactions that are the same, increased, or decreased compared to taking them separately. Using multiple drugs that function together within complex biological networks is crucial to achieving a synergistic effect rather than targeting a specific area alone. This collaborative approach ensures the medicines work harmoniously, maximizing their strengths for a more effective treatment outcome (Yuan and Chen 2019).

Multiple medications enable the biological network to be targeted at various points, thus mitigating the possibility of resistance to the treatment by the network. Therefore, employing a synergistic approach is instrumental in achieving optimal treatment outcomes (Wang & Huang, 2020). Each compound presents unique pharmacokinetic characteristics for free drugs and is metabolized at varying rates. Consequently, when administering synergistic combinations of free drugs to target cells, it is essential to account for and mitigate the effects of these pharmacokinetic processes (Anselmo and Mitragotri 2019).

Combination therapy is becoming increasingly integral to advancing medical treatments and improving patient outcomes, as it enhances treatment outcomes and substantially increases patient survival rates. This robust approach amalgamates various treatment modalities, resulting in improved results and greater optimism for individuals

confronting health challenges (Keservani *et al.*, 2020; Peng *et al.*, 2021).

One of the main advantages of NP-mediated drug delivery is its ability to provide targeted drug delivery, which means that drugs can be delivered directly to the site of infection or disease without affecting healthy tissues (Sharma *et al.*, 2019). In addition, these systems can also provide extended drug release, which ensures that drugs are released gradually over a more extended period, thus improving their efficacy and reducing the need for frequent dosing (Zhang *et al.* 2019). The drug-delivering-drug (DDD) platform is an innovative procedure that enables the concurrent administration of a secondary drug alongside insoluble drugs, utilizing drug crystals as a carrier (Du *et al.* 2021).

The delivery of drugs through nanoparticles is a promising technique that has the potential to enhance the stability and effectiveness of medication. By preventing drugs from being rapidly cleared at the site of infection or disease, they remain active for longer, improving therapeutic outcomes for various diseases (Pathak *et al.*, 2019). Nanoparticle-mediated drug delivery systems possess distinctive characteristics, including elevated biocompatibility, adaptability, and target selectivity, rendering them up-and-coming contenders for drug development (Park *et al.*, 2022). By precisely delivering therapeutics to specific cells, tissues, and organs, nanoparticle-mediated drug delivery systems can reduce off-target effects and minimize the required drug doses, making treatments more effective and safer (Nag and Delehanty, 2023).

Many new ways of preparing herbal drugs as particles, such as liposomes, nanoparticles (NPs), micelles, nano-suspensions, nano-capsulation, nano-emulsions, and more, can be used to make drug delivery systems (DDSs) more effective at targeting receptors on HSCs, hepatocytes, macrophages, and other cells (Xiao et al., 2018; Devaraj & Rajeshkumar, 2020; Castro-Pastrana *et al.*, 2021; Saadh, 2021; Haddadzadegan *et al.*, 2022; Ibrahimiyah *et al.*, 2023). Fan *et al.* (2019) created a polymeric micelle (CRM) featuring a co-decorated surface of collagenase I and retinol to demonstrate this mechanism. This design allows it to break down pericellular collagen I and target HSCs. Human HSCs effectively took up the CRM and showed remarkable accumulation in the fibrotic liver, indicating its promise as a delivery system for drugs aimed at liver fibrosis. Additionally, they developed a CRM loaded with nilotinib (CRM/NIL), which displayed optimal antifibrotic activity and a favorable toxicity profile, highlighting its potential in liver fibrosis treatment. This method enhances co-delivery and is particularly useful for delivering biopharmaceuticals and small molecular-weight compounds (Du *et al.*, 2021; Teng *et al.*, 2022).

To effectively target the liver following systemic administration, utilizing particles smaller than 100 nm is essential. This size is critical as only such nanoparticles can successfully navigate through the liver fenestrae to access hepatocytes and hepatic stellate cells (Younis et al. 2021). The fenestrae function as selective filters, regulating the movement of solutions, solutes, and particles between the sinusoidal lumen and the space of Disse. They exclusively facilitate the transit of particles that are smaller than the fenestrae, thereby enabling the delivery of these particles to the parenchymal cells or their removal from the space of Disse. These dynamic structures are aggregated into sieve plates that function as regulatory gatekeepers, controlling the passage of fluids, solutes, and macromolecules between the sinusoid and the space of Disse (Zapotoczny *et al.*, 2019; Gracia-Sancho *et al.*, 2021)

When NPs are utilized as drug delivery systems, they have the potential to stimulate several immune pathways simultaneously (Liu et al., 2019; Thorp et al., 2020). By doing so, NPs can enhance the effectiveness of the drug treatment, as they can target multiple aspects of the immune system at once (López-Saucedo *et al.*, 2018). This is particularly beneficial in medical contexts as eliciting a broad immune response to combat disease or infection or improving the delivery efficiency and reducing side effects is desirable (Q. Hu *et al.*, 2019; Jacob *et al.*, 2023; Kusumoputro *et al.*, 2023; Li *et al.*, 2023).

Furthermore, nanoparticle-mediated delivery systems offer vital benefits, primarily improved targeting for precise therapeutics delivery. This method minimizes harm to healthy tissues while enhancing efficacy. Additionally, these systems support therapy via various routes, including intravenous, oral, or localized methods. Meeting individual patient needs, they address clinical demands and enhance treatment outcomes (Li *et al.*, 2024).

Unlike the other methods, drug delivery through nanoparticles allows precise drug delivery to fibrotic areas and controlled release, which may lessen the adverse effects on the whole body. In any case, targeted therapy with dual-ligand nanoparticles improves the healing effects of anti-fibrotic drugs (Kumar *et al.,* 2021). Diagnostic nanoprobes, like MRI-based probes, provide helpful information about how diseases progress and how gene therapy uses nanocarriers to go after the genes that cause fibrosis (Sehl *et al.,* 2020; Murar *et al.,* 2022).

Developing targeted nanocarriers incorporating multiple pharmacological agents presents a promising strategy for addressing liver fibrosis. This research focuses on integrating various therapeutic agents into a single nanocarrier system to enhance treatment efficacy. Recent advancements in active targeting strategies for hepatic fibrosis have predominantly concentrated on exploiting hepatic stellate cells (HSCs) as specific targets. However, there is a need for more comprehensive research that incorporates a broader array of ligands to effectively target other liver cell populations (Setyawati *et al.,* 2024).

Chen *et al.* (2019) highlighted HSC-specific markers that may be leveraged for the targeted delivery of antifibrotic agents to the fibrotic liver. Activated hepatic stellate cells (aHSCs) demonstrate significant overexpression of various protein markers, including the type VI collagen receptor, retinol-binding protein receptor (RBP-R), platelet-derived growth factor receptors (PDGF-R), synaptophysin (p38), insulin-like growth factor II receptor (IGFII-R), low-density lipoprotein receptor (LDL-R), and cluster of differentiation 44 (CD44). These markers provide potential targets for the selective delivery of antifibrotic therapies to activated HSCs, enabling more precise treatment strategies in fibrosis management (Chen *et al.,* 2019).

Zhang *et al.* (2024) stated that the interplay among capillaries, liver sinusoidal endothelial cells (LSECs), activated hepatic stellate cells (HSCs), and defective hepatocytes creates a vicious cycle in developing liver fibrosis. This vicious cycle exaggerates the disease and reduces the effectiveness of any therapy. To inhibit the malicious progression of liver fibrosis, they offer a potential new direction for developing anti-fibrotic treatments, emphasize the need to regulate cellular interaction, and propose a vicious cycle-breaking approach that independently targets and repairs diseased cells.

Additionally, nanosystems for vaccine delivery are advancing rapidly in their development. 2023, a quantitative analysis was performed on clinical trials involving nanoparticles between 2016 and 2021. The study aimed to elucidate emerging trends in nanoparticle research, focusing on their applications in treating COVID-19. Additionally, the findings were compared against existing literature reviews to identify advancements and gaps in the current knowledge base. Both polymeric and liposomal nanoparticles serve as effective carriers and adjuvants. Furthermore, lipid-based nanoparticles were utilized in two of the most widely administered COVID-19 vaccines Moderna and Pfizer-BioNTech (Namiot *et al.,* 2023).

b) Gene Therapy and Editing:

Research has demonstrated various strategies for inducing anti-fibrotic effects, particularly in treating liver fibrosis. One notable approach involves using Relaxin, which explicitly targets hepatic macrophages. Research conducted by Hu *et al.* (2021) demonstrated that gene therapy utilizing Relaxin effectively eradicated fibrosis, highlighting this approach's therapeutic potential in managing liver fibrosis.

To better understand the reasons behind the variations in gene expression of transmitted genes, a study by Kimura and Harashima (2023) analyzes two distinct types of lipid nanoparticles (LNPs): those that target the liver selectively and those that are more spleen-selective. The findings suggest that variations in gene expression effectiveness are influenced more by endogenous factors than by the extent of biodistribution across tissues.

Research on zinc oxide nanoparticles (ZnONPs) has increasingly focused on their medicinal properties, especially regarding gene expression. Studies indicate that ZnONPs can enhance the expression of critical genes, such as glutathione peroxidase and superoxide dismutase, which are crucial for protecting cells from oxidative damage. Additionally, they have been shown to upregulate interleukin-8 (IL-8), a cytokine involved in the inflammatory response. This evidence suggests that ZnONPs have potential therapeutic applications in modulating oxidative stress and inflammation (Poon *et al.* 2020; Abdel-Latif *et al.* 2021).

Pourmohammad *et al.* (2021) have studied the influence of ZnO nanoparticles on

hepatic hepcidin gene expression to explore a potential treatment for iron overload and anemia. ZnO and ZnO nanoparticles were administered via injection to rats. Subsequent analyses measured serum concentrations of iron, ferritin, and interleukin-6 (IL-6). The expression levels of the hepcidin gene were assessed using real-time PCR, revealing significantly elevated expression in both the ZnO and ZnO nanoparticle groups compared to the control group. Associated with pure ZnO, ZnONPs significantly increased hepcidin gene expression. This demonstrated that hepcidin gene expression was dramatically upregulated after exposure to ZnO nanoparticles.

Jacob *et al.* (2023) found that the rate at which cells were taken up and kept by cells was strongly linked to several factors, including the nanoparticles' surface charge, size, and ligand properties. They concluded that LNPs with ligands are still used to target the liver and deliver medicines like siRNA, mRNA, and pDNA. Moreover, innovative functionalization strategies are currently being developed to enhance the stability of drugs, mitigate opsonization, facilitate the escape of endosomes, and enable the specific targeting of cells utilizing lipid nanoparticles (Park *et al.*, 2022).

The Limitations of Conventional Disease Treatment:

Conventional treatments typically aim to address the root causes of liver disease or damage while also working to reduce inflammation in the liver. These approaches may involve a combination of lifestyle changes, medications, and other therapies designed to restore liver health and prevent further complications (Tan *et al.,* 2021). Among various kinds of research, the activation of HSCs has emerged as a pivotal phenomenon that plays a crucial role in the process of fibrogenesis. This activation marks a significant turning point, initiating a cascade of events that ultimately contribute to the development of fibrosis within the liver (Bruno et al., 2020; Wang *et al.,* 2023).

Therapies that rely exclusively on antifibrotic effects are insufficient to address the underlying factors contributing to disease processes, including cellular stress, inflammation, and apoptosis. Much of the research concentrates on the activation processes of hepatic stellate cells (HSCs) and inflammatory pathways; however, more attention should be given to the interactions between diverse cell types and organs. It is essential to address the etiology of liver disease and its associated complications (Gu *et al.,* 2022).

Mao *et al*. (2024), focus on established methodologies utilizing rodent models that mimic both the pathogenesis and severity of liver injuries observed in clinical environments, aiming to elucidate mechanisms underlying hepatotoxicity and to devise more effective therapeutic strategies. The primary objective is to develop robust rodent models that facilitate research into hepatoprotective agents and interventions against liver injury. The review encompasses various standard models employed for chemically induced liver injury, immune-mediated liver damage, alcoholic liver disease, and drug-induced hepatotoxicity. It provides an in-depth analysis of modeling techniques, cascades of pathogenic mechanisms, and action pathways while systematically assessing the advantages and limitations of each model. The insights from this review are intended to inform the development of more targeted theoretical frameworks for clinical liver injury treatment approaches (Mao *et al.* 2024).

Although biological drugs are effective, they have significant drawbacks regarding their stability and half-life, resulting in the need for frequent administration or even the implantation of a pump in patients (Peng *et al.*, 2021). This can lead to lower compliance and a greater risk of infection. According to Spagnolo et al., there is still much-unresolved research and a significant need to devise a way to target the pathophysiological mechanism that specifically causes extracellular matrix (ECM) accumulation and makes it disappear. Effectively translating information into clinical therapies that can halt, or reverse fibrosis progression presents a considerable challenge (Ramos-Tovar and Muriel, 2020).

D. Treatment of Liver Fibrosis using Nanoparticles

a) Advantages of Using Nanoparticles for Liver Fibrosis Treatment:

Natural killer cells and macrophages are immune cells linked to liver fibrosis. Molecular processes like the failure of hepatocytes to regenerate, the release of inflammatory cytokines, and the buildup of too much extracellular matrix all play a part in developing liver fibrosis. Liver sinusoidal endothelial cells (LSECs) and hepatocytes also play essential roles in liver fibrosis (Bai *et al.,* 2020; Bhandari *et al.,* 2021). Nanoparticle drug delivery systems possess the capability to selectively target specific cell types, such as

hematopoietic stem cells (HSCs) and liver sinusoidal endothelial cells (LSECs), and modulate their therapeutic efficacy (Gil *et al.*, 2023).

Recent studies have illuminated the potential of nanotechnology-based interventions in treating liver fibrosis, offering hope for precision medicine approaches. Nanomedicine amplifies imaging contrast, promotes tissue penetration, and improves cellular internalization. It also accomplishes focused medication administration and combination therapy and serves diagnostic and therapeutic purposes, known as the nanostics (Mazari *et al.*, 2021; Sun *et al.*, 2021; Park *et al.*, 2022). Within the exciting field of nanomedicine, the concept of "nanostics" represents a pioneering approach that integrates imaging agents and therapeutic molecules within a singular nanoparticle. This avant-garde technique augments diagnostic accuracy and enhances the efficacy of treatments, thereby facilitating the development of more intelligent and targeted therapeutic strategies. Envision the potential of employing a diminutive carrier capable of visualization and treatment, thus transforming our approach to medicine (Ferreira *et al.*, 2020).

Since activated hepatic stellate cells (aHSC) are acknowledged as the principal contributors to liver fibrosis, contemporary nanoparticle (NP) therapies are directed at explicitly targeting HSC through various nanoparticulate systems. In the context of liver injury, macrophages are known to release profibrogenic factors that lead to the activation of HSC. Therefore, focusing on macrophages is a promising therapeutic approach for treating liver fibrosis, particularly given hepatocytes' significant role in promoting fibroblast accumulation within damaged hepatic tissue (Trivella et al., 2020). Hue et al. conducted a study that shows synergistic antifibrotic effects in rodent models. A synergistic strategy that targets both macrophages and hepatocytes could enhance treatment efficacy. Several pharmacological agents are designed to address the various pathways associated with the progression of liver fibrosis related to macrophages and hepatocytes; however, only a limited number are currently being investigated in nanoparticle formulations (Hu, Lee, and Luo 2019). For liver fibrosis, different nanotechnology-based drug delivery methods have been studied. These include liposomes, protein-based delivery systems, and inorganic delivery systems. New research suggests that a helpful way to treat liver fibrosis could be to use delivery methods changed with hyaluronic acid (HA) and target liver sinusoidal endothelial cells (LSEC). Improved liver function has resulted from these approaches, which have decreased inflammation, accelerated scar tissue breakdown, and markedly reduced fibrosis markers—all of which play critical roles in developing hepatic fibrosis. Targeting LSEC specifically through these delivery methods can minimize off-target effects and improve treatment safety and efficacy. Overall, HA-modified delivery methods and LSEC targeting represent a promising new avenue for treating liver fibrosis (Bhandari *et al.*, 2021; Peng *et al.*, 2021; Essa *et al.*, 2022).

Lee *et al.* (2022) investigated the possibility that a specific anti-fibrotic impact could be achieved in the liver by Fibroblast Activation Protein (FAP) selectively liberating the anti-fibrotic peptide, melittin on the surfaces of aHSC overexpressing FAP. So, scientists devised a delivery mechanism that releases melittin into the fibrotic hepatic microenvironment by cleaving promelittin exclusively in FAP-expressing areas of the liver. Promellitin-modified liposomes (PRL) treatment shows that (PRL) has anti-fibrotic and survival-prolonging effects. They confirmed that (PRL) can be cleaved by FAP in fibrotic liver tissues, then FAP-liberated melittin kills aHSC and relieves fibrosis in mouse models.

Xia *et al.* (2023) have developed biomimetic nanoparticles that can effectively target and induce apoptosis in activated hepatic stellate cells (aHSCs), which are involved in liver fibrosis. These nanoparticles are coated with membranes expressing the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and contain all-trans retinoic acid (ATRA) in the core. The biomimetic TRAIL coating targets HSCs and induces apoptosis in aHSCs, while ATRA can induce quiescence in activated fibroblasts. The combination of TRAIL-coated ATRA nanoparticles enhanced fibrosis improvement in mouse models of liver fibrosis. This novel approach may offer an effective antifibrosis therapy.

Other approaches have attempted to suppress HSC activation through metabolic regulation to promote anti-fibrotic effects (Khomich *et al.*, 2019; Mehal 2023). For instance, an adiponectin-based agonist inhibited HSC activation by regulating glucose and lipid metabolism via binding to appropriate receptors (Xu *et al.*, 2020). Likewise, Lipid

nanoparticles engineered with HSC surface-targeting ligands represent a promising advancement in hepatic fibrosis treatment. Their advantages over inorganic nanoparticles include reduced toxicity, enhanced biodegradability, and lower immunogenicity (Swarupananda, Ayon, and Dipanjana, 2021).

However, there are still challenges to overcome before clinical implementation. According to Tan *et al.* (2021) and Xing et al. (2021), activating hepatic stellate cells (HSCs) is an essential aspect of liver fibrosis and a significant target for therapies that attempt to reduce fibrosis. Numerous research studies have delved into the promising potential of therapies centered on hematopoietic stem cells (HSCs). These therapies are emerging as an exciting alternative treatment option for a wide range of medical conditions, showcasing the ability of HSCs to regenerate and repair damaged tissues and to modulate immune responses. Exploring HSC-based treatments holds the key to innovative approaches in medicine, offering hope for those affected by various diseases. (Fan *et al.,* 2020; Ruman *et al.,* 2020; Lee *et al.,* 2023; Zhao *et al.,* 2023)

Researchers have extensively studied targeting vectors and modified ligands to enhance the effectiveness of targeted therapy for liver fibrosis. Many nanocarriers and strategies have been created for liver fibrosis, providing a fresh way to target cell therapy and a theoretical basis for achieving the highly effective therapy goal (Bayda *et al.,* 2020).

According to Wei Peng and colleagues (2021), significant research has been done on the advancement of nanocarriers and targeted therapy techniques for liver fibrosis to enhance the effectiveness of treatment. Their research has concentrated on nano-delivery vectors and modified ligands, presenting a novel approach for precise cell treatment targeting. Liver fibrosis is a substantial health hazard.

Nanoparticles have emerged as effective carriers for anti-fibrotic agents. The field of nanotechnology holds promise for developing drug-delivery systems to combat liver fibrosis. However, advances in nanotechnology have led to the development of nanoprobes that have the potential to work as both drug-delivery agents and diagnostic tools (Eftekhari *et al.,* 2021; Rahman, 2023). Advanced nanotechnology strategies take advantage of the distinct characteristics of nanoscale materials, allowing for the development of novel solutions that address the challenges posed by current therapeutic methods. By harnessing these innovative techniques, researchers can create treatments that enhance the efficacy of interventions for liver fibrosis, potentially revolutionizing patient care and outcomes in this complex condition (Pop *et al.,* 2020; Gu *et al.,* 2022).

Bai *et al.* (2020) conducted a study that thoroughly examined potential targets and the application of novel nanomedicine systems for identifying and managing liver fibrosis. The systems include liposomes, polymers, proteins, inorganics, and hybrid nanoparticles. Compared to conventional methods, nanomedicine systems generally improve the treatment of liver fibrosis. The authors also examined the perspectives and challenges of successfully transitioning these nanomedicine systems from the confines of the laboratory to practical clinical applications (Zhai *et al.,* 2020). Pote *et al.* (2022) demonstrated the utility of mesoporous silica nanoparticles loaded with curcumin, a natural anti-fibrotic compound. The objective of the study was to make and describe silica adorned with curcumin-loaded zinc oxide nanoparticles to develop a tissue adhesive in the form of liquid stitches. The mesoporous silica nanoparticles serve to facilitate tissue adhesion through the mechanism of nano-bridging. The progression of fibrosis in rats was slowed down, and the sustained release and improved bioavailability of these nanoparticles suggested a possible way to deliver drugs to fibrotic areas. The extended duration and reduced adverse effects of drug administration via nanoparticles are attributed to their controlled-release features.

Zinc is highly appropriate as a prominent micronutrient and a necessary component for over 300 enzymes in the human body. Moreover, zinc plays a crucial role in various fundamental cellular functions, including regulating cellular redox equilibrium, DNA replication, DNA repair, cell cycle advancement, and programmed cell death (Kim *et al.,* 2020; Negrescu *et al.,* 2022). The work conducted by Ghosh *et al.* (2022) investigated different methods of synthesizing ZnO nanoparticles to explore their potential as carriers in nanomedicine for disease treatment. Elevated zinc levels have been demonstrated to induce protein imbalance, increasing oxidative stress within targeted cells.

Nevertheless, a decrease in zinc levels has been observed to expedite the advancement of Liver fibrosis. Zinc oxide (ZnO) nanoparticles have demonstrated

encouraging results in liver disease treatment owing to their aptitude for surface chemistry modification and enhanced permeability and retention effect (EPR). The potential of these nanoparticles in oncology warrants further investigation and could lead to the development of improved liver disease therapies (Perera *et al.,* 2020; He *et al.,* 2021).

b) Diagnostic Nanoprobes:

A liver biopsy is the standard diagnostic method for liver fibrosis. Liver fibrosis can be identified by staining the cells or extracellular matrix proteins using histological or histochemical techniques. Histological staining techniques frequently employed to assess liver fibrosis include hematoxylin-eosin with Masson's trichrome or Sirius Red staining (Heyens *et al.*, 2021).

It is possible to give "personalized treatment" to patients who show significant drug absorption by affected liver cells with the help of these versatile nanoparticles. Zhang & Zhang (2022) laid the foundation for creating a structured External Quality Assessment (EQA) to identify liver fibrosis biomarkers accurately. EQA is a crucial instrument for detecting issues in a clinical laboratory. The study emphasizes the constraints of accurately measuring liver fibrosis biomarkers using quantitative methods and proposes enhanced detection kits and quality control protocols. Additionally, it lays the groundwork for creating a structured External Quality Assessment (EQA) to identify biomarkers for liver fibrosis. Furthermore, it guides the choice of the appropriate apparatus, procedures, and reagents for laboratory detection of liver fibrosis indicators.

The most extensively researched biomarkers associated with liver fibrosis encompass the products resulting from extracellular matrix synthesis and degradation alongside the enzymes responsible for their generation or modification. These biomarkers include hyaluronic acid, matrix metalloproteinases, tissue inhibitors of metalloproteinases (TIMPs), and cytokines such as transforming growth factor beta (TGF-β). An essential characteristic of a prognostic marker lies in its capacity to anticipate the future onset of a disease (Mercedes *et al.,* 2020; Zhang & Zhang, 2022).

According to Loomba and Adams (2020), non-invasive techniques are needed to diagnose and determine the stage of liver fibrosis. They proposed using isotope techniques to measure the pace at which hepatic collagen is replaced in liver biopsies. *Plasma lumican* is a peptide that encourages collagen synthesis and is found in higher amounts in liver fibrosis. It dramatically affects this measurement because it shows how constant liver collagen is being replaced.

Sargazi *et al.* (2023) created nanosensors for diagnosing non-alcoholic fatty liver disease by modifying inorganic nanoparticles with polymers, bimetallic nanoparticles, superparamagnetic nanoparticles, and ultra-small superparamagnetic nanoparticles (Flores-Rojas *et al.,* 2022). Modifying several nanostructures with specific ligands or chemicals influencing liver tissues can enhance their effectiveness.

Conclusion

The versatility of nanotechnology can enhance its benefits, positioning it as a valuable asset across diverse medical fields and improving outcomes for a broader range of patients. This cutting-edge technology has the potential to be tailored and utilized in various medical contexts, thereby creating new opportunities for advancing patient care. Nanotechnology has advanced significantly in using nanoparticles to optimize the efficacy of combination therapy for different pathologies, particularly liver fibrosis. This discipline shows considerable promise for targeted drug delivery systems, facilitating prolonged release profiles and enhancing drug stability.

Recent advancements in nanoparticle-based drug delivery systems have demonstrated significant potential for transforming the management of liver fibrosis through targeted therapies and improved diagnostic methods. Studies consistently highlight the effectiveness of nanomaterials in ensuring precise drug delivery to hepatic tissues, which reduces the reliance on systemic administration and alleviates associated adverse effects. A key advantage of this approach is the direct delivery of drugs to the liver, which markedly increases their therapeutic potency.

Moreover, advancements in nanotechnology enable precise targeting of specific cells and tissues within the liver, allowing for personalized and more effective treatment strategies for liver fibrosis. This improved targeting enhances treatment outcomes and strengthens diagnostic capabilities, enabling earlier disease detection. Furthermore, these

innovations provide avenues for a deeper understanding of the underlying pathophysiological mechanisms associated with various conditions. Ultimately, these developments expand the repertoire of therapeutic options available, thereby increasing choices for patients and clinicians in managing liver fibrosis.

Recommendation:

Nanotechnology offers significant advantages in managing liver fibrosis, impacting millions globally. It enables the development of accurate diagnostic tools for early identification of the condition, allowing timely intervention. In therapy, it facilitates targeted drug delivery systems aimed at specific fibrotic tissue, reducing side effects and improving treatment efficacy. This precision could lead to personalized treatment plans and better patient outcomes. As research advances, we may see breakthroughs that enhance our understanding and revolutionize care for liver fibrosis.

Availability of Data and Materials:

It is important to note that data sharing does not apply to this review article, as no datasets were generated or analyzed. All the data referenced come from existing literature sources, which are comprehensively documented within the text.

Declarations:

Ethical Approval: Not applicable.

Competing interests: The authors declare that there is no conflict of interest.

Data Availability Statement: It is important to note that data sharing does not apply to this review article, as no datasets were generated or analyzed. All the data referenced come from existing literature sources, which are comprehensively documented within the text.

Authors Contributions: All authors contributed equally, and have read and agreed to the published version of the manuscript.

Funding: This study didn't receive any funding support.

Acknowledgments: Not applicable.

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