

Nanotechnology- Based Hepatoprotective Drug Delivery Systems

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Abstract: Nanotechnology-based hepatoprotective drug delivery systems constitute a significant paradigm shift in contemporary pharmacology, providing innovative strategies to circumvent the limitations inherent in conventional therapeutic approaches for hepatic disorders. Liver diseases—including cirrhosis, hepatitis, and non-alcoholic fatty liver disease—remain substantial global health burdens owing to their multifactorial etiology and the paucity of effective treatment modalities. The clinical utility of traditional hepatoprotective agents, whether synthetic or phytochemical, is frequently restricted by poor aqueous solubility, inadequate bioavailability, rapid metabolic clearance, and the absence of site-specific targeting capabilities. Nanotechnology offers a promising platform to overcome these constraints through the design and implementation of nanoscale drug delivery systems that enhance the solubility, stability, and controlled release profiles of therapeutic compounds. A diverse array of nanocarriers—including liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, and nanoemulsions—has demonstrated marked improvements in pharmacokinetic and pharmacodynamic parameters. These systems enable targeted delivery to hepatic tissues, thereby increasing drug accumulation at the intended site of action while reducing systemic distribution and associated off-target toxicity. Moreover, nanotechnology significantly augments the delivery and therapeutic efficacy of bioactive phytoconstituents—such as curcumin, resveratrol, and silymarin—by enhancing their bioavailability and physicochemical stability. The capacity of nanocarriers to facilitate combination therapy through the co-encapsulation and co-delivery of multiple therapeutic agents provides a comprehensive strategy for managing multifactorial liver diseases. Notwithstanding these advantages, several challenges remain, including concerns regarding nanomaterial toxicity, physicochemical instability, elevated manufacturing costs, and regulatory hurdles. Consequently, rigorous preclinical investigations and well-designed clinical studies are imperative to ensure the safety, efficacy, and successful clinical translation of nano-technology based hepatoprotective drug delivery systems.

Keywords: Nanotechnology, Hepatoprotective Drug Delivery, Liver Disease, Nanocarriers, Liposome, Targeted Drug Delivery.

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I. INTRODUCTION

The emergence of nanotechnology has significantly transformed the domain of drug delivery by introducing advanced strategies to overcome the inherent limitations associated with conventional therapeutic systems. In recent years, its application in hepatoprotective drug delivery has attracted substantial scientific interest, largely due to the rising global incidence of liver diseases and the urgent need for more efficient and targeted therapeutic approaches. The liver plays a pivotal role in metabolic regulation, detoxification, and maintenance of biochemical homeostasis; however, it is highly vulnerable to damage induced by xenobiotics, drugs, alcohol, and infectious agents. Major hepatic disorders, including hepatitis, cirrhosis, non-alcoholic fatty liver disease, and drug-induced hepatotoxicity, continue to pose significant health challenges worldwide, often

requiring long-term and effective treatment strategies [1]. Traditional hepatoprotective agents, encompassing both synthetic drugs and phytoconstituents, are frequently limited by poor aqueous solubility, low bioavailability, rapid metabolic degradation, and lack of site-specific targeting. These limitations not only reduce therapeutic efficacy but may also lead to undesirable side effects. Notably, several bioactive phytochemicals such as curcumin, silymarin, and resveratrol, despite their well-documented hepatoprotective potential, suffer from poor absorption, rapid systemic clearance, and limited clinical applicability. Therefore, there is a critical need for advanced drug delivery systems capable of improving the pharmacokinetic and pharmacodynamic profiles of these compounds. Nanotechnology offers a promising platform to address these challenges through the development of nanoscale drug delivery systems. Nanoparticles, typically in the size range of 100–1000 nm, can be

engineered to enhance drug solubility, improve stability, protect active molecules from premature degradation, and provide controlled as well as sustained drug release [2]. Various nanocarrier systems, including liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, and nanoemulsions, have been extensively explored for liver-targeted drug delivery. These carriers are capable of encapsulating both hydrophilic and lipophilic drugs, thereby significantly enhancing their therapeutic performance. A key advantage of nanotechnology-based hepatoprotective systems is their ability to achieve targeted drug delivery. Due to the unique anatomical and physiological characteristics of the liver, such as fenestrated sinusoidal endothelium and the presence of Kupffer cells, nanoparticles can preferentially accumulate in hepatic tissue. Additionally, surface

modification of nanoparticles with specific ligands enables active targeting of hepatocytes or liver macrophages, thereby increasing therapeutic precision while reducing systemic toxicity [3]. Furthermore, nanotechnology facilitates combination therapy by enabling the co-encapsulation of multiple therapeutic agents, including synthetic drugs and herbal extracts, within a single nanocarrier system. This approach is particularly beneficial in the treatment of complex liver disorders that involve multiple pathological mechanisms such as oxidative stress, inflammation, and fibrosis. By improving drug stability, prolonging systemic circulation, and ensuring sitespecific delivery, nanotechnology-based systems ultimately enhance therapeutic efficacy and patient compliance [4].



Fig 1 Hepatoprotective Medication Delivery Using Nanotechnology.

II. TRADITIONAL HEPATOPROTECTIVE TREATMENTS

Conventional hepatoprotective agents have been extensively utilized for the prevention and management of a wide spectrum of liver disorders, including hepatitis, cirrhosis, fatty liver disease, and drug-induced hepatotoxicity. These agents, comprising both synthetic drugs and phytopharmaceuticals, are primarily aimed at preserving hepatocellular integrity, enhancing liver regeneration, attenuating inflammatory responses, and mitigating oxidative stress. Despite their broad clinical application, conventional

therapeutic strategies are associated with several inherent limitations, thereby necessitating the development of more advanced and targeted drug delivery approaches [5]. Synthetic hepatoprotective agents form a fundamental component of standard therapeutic regimens. Among these, silymarin—a flavonolignan complex isolated from *Silybum marianum*—is one of the most widely investigated and clinically employed compounds. It exhibits potent antioxidant, anti-inflammatory, and membrane-stabilizing properties, enabling it to scavenge reactive oxygen species, enhance ribosomal protein synthesis, and facilitate hepatocyte regeneration [6,7]. Ursodeoxycholic acid

(UDCA) is another clinically significant agent, particularly indicated in cholestatic liver diseases. It exerts its therapeutic action by improving bile flow, reducing the cytotoxicity of bile acids, and protecting hepatocytes from apoptosis. In addition, N-acetylcysteine plays a crucial role in the management of drug-induced liver injury, especially in cases of paracetamol toxicity, by replenishing intracellular glutathione reserves and thereby reducing oxidative damage [8,9]. Other pharmacological interventions include antiviral agents employed in the treatment of hepatitis B and C infections, which function by inhibiting viral replication and limiting disease progression. Corticosteroids are also used in autoimmune hepatitis to suppress immune-mediated hepatic injury. However, prolonged use of these synthetic agents is often associated with adverse effects such as immunosuppression, metabolic imbalances, and gastrointestinal disturbances, which may compromise patient compliance and safety [10]. In parallel, herbal medicines have played a significant role in hepatoprotection, particularly within traditional systems such as Ayurveda and Traditional Chinese Medicine. A variety of plant-derived bioactive compounds have demonstrated hepatoprotective potential, largely attributed to their antioxidant and anti-inflammatory properties [11]. Notable examples include curcumin from *Curcuma longa*, glycyrrhizin from *Glycyrrhiza glabra*, and extracts of *Phyllanthus niruri*. These phytoconstituents contribute to the reduction of lipid peroxidation, regulation of hepatic enzyme activity, and enhancement of detoxification mechanisms. Herbal formulations are often used as adjunct therapies in chronic liver conditions and are generally perceived to have a favorable safety profile. Despite their therapeutic advantages, conventional hepatoprotective agents are limited by several pharmacokinetic and pharmacodynamic constraints. Poor bioavailability remains a major concern, particularly for phytochemicals, many of which exhibit low aqueous solubility, rapid first-pass metabolism, and swift systemic elimination, ultimately reducing their clinical effectiveness [12,13]. Furthermore, non-specific biodistribution of these agents leads to inadequate drug concentrations at the hepatic site while increasing systemic exposure, thereby elevating the risk of off-target effects. Another significant limitation is the lack of site-specific drug targeting. Conventional dosage forms, whether administered orally or parenterally, generally lack mechanisms for selective hepatic delivery, resulting in the requirement for higher doses to achieve therapeutic efficacy. This, in turn, increases the likelihood of dose-dependent toxicity and variability in patient response [14]. Additionally, conventional therapies exhibit limited efficacy in reversing advanced pathological conditions such as hepatic fibrosis and cirrhosis, as they primarily focus on symptom management and slowing disease progression rather than promoting complete tissue regeneration. In cases of end-stage liver disease, liver transplantation remains the only definitive therapeutic option, highlighting the inadequacy of existing conventional treatments and underscoring the need for innovative approaches such as nanotechnology-based drug delivery systems to improve therapeutic outcomes [15].

III. NANOTECHNOLOGY FOR MEDICATION DELIVERY

Nanotechnology-based drug delivery systems represent a transformative advancement in modern pharmaceutical science, providing sophisticated approaches to enhance the therapeutic performance and safety profile of pharmacological agents. This technology involves the rational design, development, and application of nanoscale carriers—typically within the size range of 1–100 nm—for the controlled, site-specific, and efficient delivery of drugs [16–18]. Owing to their unique physicochemical properties, nanocarriers have demonstrated significant potential in overcoming the intrinsic limitations of conventional drug delivery systems, such as poor aqueous solubility, limited bioavailability, rapid systemic degradation, and non-specific tissue distribution. A major advantage of nanotechnology lies in its capacity to improve the solubility and dissolution behavior of poorly water-soluble drugs. Many therapeutic molecules, particularly lipophilic compounds and phytoconstituents, exhibit inadequate aqueous solubility, which adversely affects their absorption and systemic availability. Nanoscale formulations substantially increase the surface area-to-volume ratio of drug particles, thereby enhancing dissolution kinetics and facilitating improved absorption across biological membranes [19]. Additionally, nanocarriers provide a protective environment that shields encapsulated drugs from enzymatic and chemical degradation, ensuring improved stability and bioavailability at the target site. Another critical feature of nanotechnology-based systems is their ability to enable controlled and sustained drug release. By precisely engineering the composition and architecture of nanocarriers, it is possible to modulate drug release kinetics in a predictable manner. This ensures the maintenance of therapeutic drug concentrations over prolonged durations, thereby reducing dosing frequency and minimizing fluctuations in plasma drug levels [20]. Such controlled release systems are particularly beneficial in the management of chronic diseases, as they enhance patient adherence while reducing the incidence of dose-related toxicity and adverse effects. Targeted drug delivery is a defining characteristic of nanotechnology-driven systems, significantly improving therapeutic specificity and efficacy. Nanocarriers can be tailored to achieve both passive and active targeting. Passive targeting exploits physiological phenomena such as the enhanced permeability and retention (EPR) effect, which facilitates the preferential accumulation of nanoparticles in diseased tissues. In contrast, active targeting involves surface functionalization of nanoparticles with specific ligands, including antibodies, peptides, or carbohydrates, that selectively bind to receptors overexpressed on target cells. This targeted approach promotes selective drug localization at pathological sites while minimizing exposure to healthy tissues, thereby reducing systemic toxicity [21]. A diverse range of nanocarrier systems has been developed to address various drug delivery challenges. Liposomes, consisting of phospholipid bilayer vesicles, are capable of encapsulating both hydrophilic and lipophilic drugs and exhibit excellent biocompatibility. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) provide improved

stability and controlled release characteristics. Polymeric nanoparticles, commonly fabricated using biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), offer high versatility and tunable drug release profiles. Dendrimers, characterized by their highly branched threedimensional architecture and multiple functional groups, enable high drug loading efficiency and precise targeting capabilities. Additionally, nanoemulsions—colloidal dispersions of oil and water phases—are particularly effective in enhancing the delivery of hydrophobic drugs [22]. Nanotechnology has also significantly advanced the delivery of biotherapeutics, including proteins, peptides, and nucleic acids, which are inherently unstable in physiological environments. Nanocarriers protect these biomolecules from enzymatic degradation and facilitate their transport across biological barriers, thereby improving their therapeutic potential. This capability has important implications for emerging therapeutic modalities such as gene therapy, vaccine development, and personalized medicine [23]. Furthermore, nanotechnology plays an integral role in the field of

diagnostics and theranostics, where therapeutic and diagnostic functionalities are integrated within a single platform. Nanoparticles can be engineered to simultaneously deliver therapeutic agents and imaging probes, enabling real-time monitoring of drug distribution, disease progression, and treatment response. This convergence of therapy and diagnostics enhances the precision and effectiveness of clinical interventions. Despite these promising advantages, several challenges continue to hinder the widespread clinical translation of nanotechnology-based drug delivery systems. Key concerns include potential toxicity, long-term biocompatibility, large-scale manufacturing constraints, physicochemical stability during storage, and complex regulatory requirements [24,25]. Moreover, the long-term impact of nanoparticle exposure on human health and the environment remains an area of ongoing investigation. Therefore, rigorous preclinical and clinical evaluations are essential to establish the safety, efficacy, and regulatory acceptability of these advanced delivery systems.



Fig 2 Medication Delivery Systems Using Nanotechnology.

IV. KINDS OF HEPATOPROTECTIVE MEDICATION DELIVERY SYSTEMS BASED ON NANOTECHNOLOGY

Nanotechnology-based drug delivery systems have emerged as highly promising platforms in hepatoprotection, primarily due to their ability to enhance drug bioavailability, enable targeted delivery to hepatic tissues, and minimize

systemic toxicity. These nanoscale systems differ in their composition, structural organization, drug-loading efficiency, and release characteristics. Collectively, they provide advanced solutions to overcome the limitations of conventional hepatoprotective therapies. The major categories of nanocarriers employed in hepatoprotective drug delivery are discussed below.

➤ *Liposomes:*

Liposomes are spherical vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous core. Due to their excellent biocompatibility and structural versatility, they are among the most extensively explored nanocarriers for liver-targeted drug delivery [26]. Liposomes can encapsulate hydrophilic drugs within their aqueous core and lipophilic drugs within the lipid bilayer. In hepatoprotective applications, they are particularly effective in improving the delivery of poorly soluble phytoconstituents such as curcumin and silymarin. These systems enhance drug stability, prolong systemic circulation, and promote uptake by hepatic cells, especially Kupffer cells. Furthermore, surface functionalization with ligands such as galactose facilitates active targeting to hepatocytes via asialoglycoprotein receptors [27,28].

➤ *Solid Lipid Nanoparticles (SLNs):*

Solid lipid nanoparticles are submicron-sized carriers composed of solid lipids stabilized by surfactants. They offer several advantages, including improved physicochemical stability, protection of sensitive drugs from degradation, and controlled drug release profiles [29]. SLNs are particularly suitable for hepatoprotective agents, as they enhance oral bioavailability and reduce hepatic first-pass metabolism. For example, silymarin-loaded SLNs have demonstrated improved antioxidant activity and superior hepatoprotective effects compared to conventional formulations [30]. Additionally, their scalability and feasibility for large-scale production make them attractive for industrial applications.

➤ *Lipid Carriers with Nanostructures (NLCs):*

Nanostructured lipid carriers represent an advanced generation of lipid-based nanocarriers, consisting of a mixture of solid and liquid lipids. This composition creates structural imperfections within the lipid matrix, thereby enhancing drug loading capacity and preventing drug expulsion during storage [31]. NLCs are particularly effective in delivering lipophilic hepatoprotective compounds such as curcumin and resveratrol. They exhibit improved stability, sustained drug release, and enhanced therapeutic efficacy. Compared to SLNs, NLCs demonstrate superior performance due to higher drug-loading efficiency and reduced risk of drug leakage [32].

➤ *Nanoparticles Made of Polymers:*

Polymeric nanoparticles are formulated using biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and alginate. These systems can be engineered as nanospheres or nanocapsules depending on the drug incorporation method [33,34]. They provide controlled and sustained drug release and are widely used for targeted delivery of antioxidant and anti-inflammatory agents to the liver [35]. Surface modification with specific ligands enhances selective targeting to hepatocytes or Kupffer cells. Moreover, polymeric nanoparticles protect labile phytoconstituents from degradation, thereby improving their stability and bioavailability [36].

➤ *Dendrimers:*

Dendrimers are highly branched, nanoscale macromolecules with a well-defined architecture and multiple functional terminal groups [37]. These characteristics confer high drug-loading capacity and enable precise surface functionalization for targeted delivery [38]. In hepatoprotective therapy, dendrimers can be utilized for the delivery of drugs, genes, and diagnostic agents. Targeting ligands can be conjugated to their surface to achieve selective delivery to hepatic cells [39,40]. However, issues such as potential cytotoxicity and high production costs remain challenges for their clinical application.

➤ *Nanoemulsions:*

Nanoemulsions are thermodynamically stable, isotropic dispersions composed of oil, water, surfactants, and co-surfactants. They are particularly effective in enhancing the solubility and absorption of hydrophobic drugs [40]. In hepatoprotective applications, nanoemulsions facilitate the delivery of lipophilic compounds such as curcumin, essential oils, and herbal extracts, thereby improving their bioavailability and gastrointestinal absorption [41,42]. Additionally, they offer rapid onset of action and can be administered via multiple routes, including oral and parenteral pathways.

➤ *Metals and Nanoparticles:*

Metallic nanoparticles, including gold and silver nanoparticles, have attracted attention due to their unique physicochemical and biological properties [43]. Gold nanoparticles, in particular, exhibit intrinsic antioxidant and anti-inflammatory activities, making them promising candidates for hepatoprotective applications. They can also function as drug delivery carriers [44,45]. However, concerns related to long-term toxicity, bioaccumulation, and safety limit their widespread clinical use.

➤ *Nanoparticles Made of Carbon:*

Carbon-based nanomaterials, such as carbon nanotubes, graphene oxide, and fullerenes, possess high surface area and exceptional drug-loading capacity [46]. These materials can be functionalized to enhance biocompatibility and targeting efficiency. In hepatoprotective therapy, they are employed for efficient delivery of antioxidant and therapeutic agents [47,48]. Nevertheless, their potential toxicity and environmental impact remain significant concerns that must be addressed before clinical translation.

➤ *Nanoparticles Made of Proteins:*

Protein-based nanoparticles are derived from natural biomacromolecules such as albumin, gelatin, and casein. These systems are biodegradable, biocompatible, and exhibit minimal toxicity. Albumin nanoparticles are particularly advantageous due to their ability to bind a wide range of drugs and facilitate targeted delivery [49]. In hepatoprotection, these nanoparticles enhance drug stability and cellular uptake by liver cells, making them suitable for delivering poorly soluble drugs and phytoconstituents [50,51].

➤ **Micelles made of Polymers:**

Polymeric micelles are self-assembled nanostructures formed from amphiphilic block copolymers, consisting of a hydrophobic core and a hydrophilic shell. This architecture enables efficient solubilization of poorly water-soluble drugs [52,53]. These systems improve drug stability, prolong circulation time, and allow controlled drug release. In liver-targeted therapy, polymeric micelles facilitate preferential accumulation in hepatic tissues and are particularly useful for delivering hepatoprotective and anticancer agents [54].

➤ **Nanogels:**

Nanogels are nanoscale hydrogel systems characterized by a three-dimensional polymeric network capable of retaining large amounts of water while maintaining structural integrity [55]. They exhibit excellent biocompatibility and can respond to environmental stimuli such as pH,

temperature, and ionic strength. In hepatoprotective drug delivery, nanogels enable controlled and stimuli-responsive release of therapeutic agents, allowing site-specific drug delivery within the hepatic microenvironment [56,57].

➤ **Polymer-Lipid Hybrid Nanoparticles:**

Polymer-lipid hybrid nanoparticles represent an advanced class of nanocarriers that combine the beneficial properties of both polymeric and lipid-based systems [58]. Typically consisting of a polymeric core enveloped by a lipid shell, these hybrid systems offer enhanced stability, controlled drug release, and improved biocompatibility [59]. In hepatoprotective applications, they are employed for the efficient delivery of both synthetic drugs and herbal compounds, resulting in improved targeting efficiency and therapeutic outcomes [60].

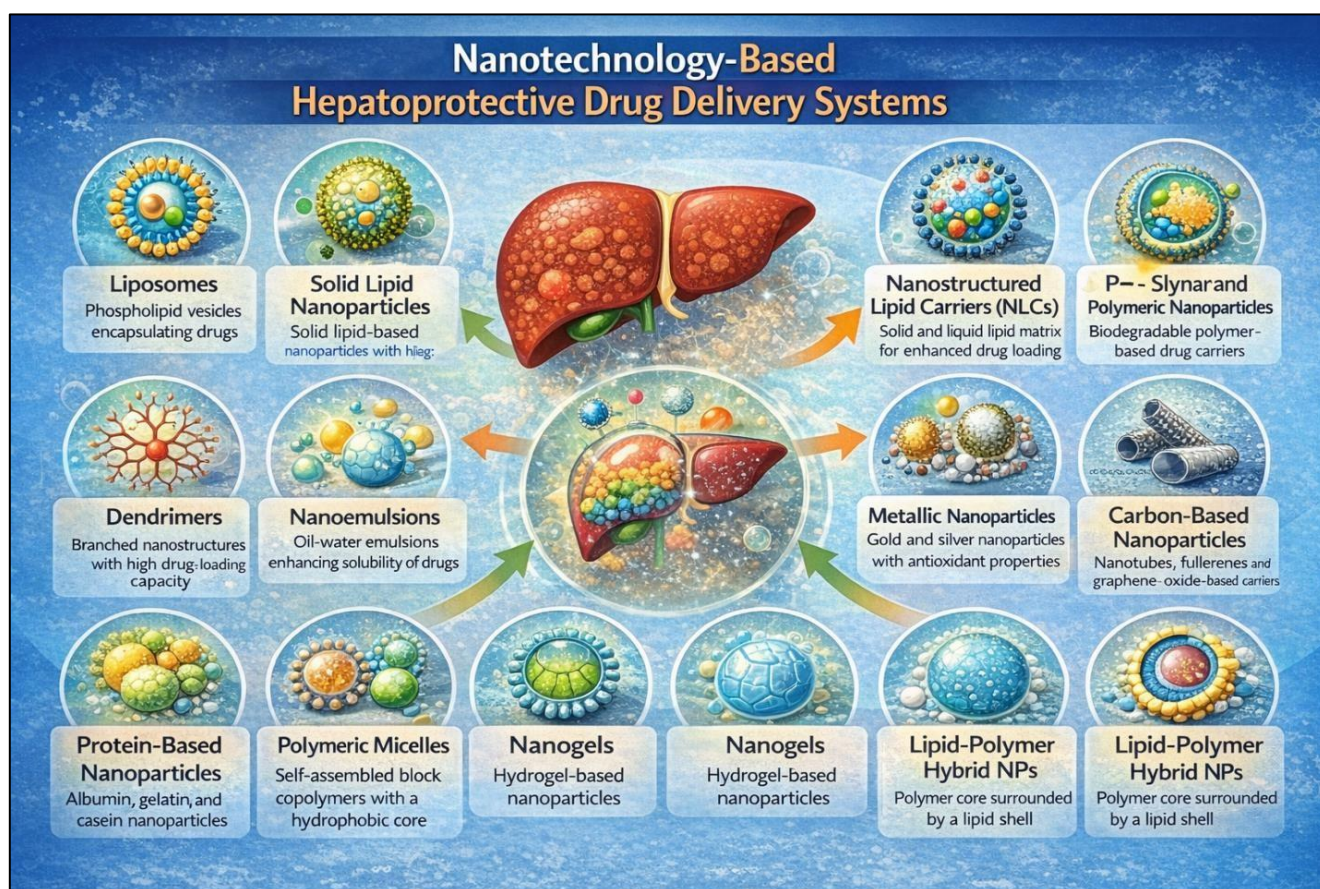


Fig 3 Kinds of Hepatoprotective Medication Delivery Systems Based on Nanotechnology.

V. DRUG DELIVERY OF HEPATOPROTECTIVE CHEMICALS BY NANOTECHNOLOGY

Nanotechnology-based delivery systems have emerged as highly promising strategies for enhancing the therapeutic efficacy of both synthetic drugs and natural phytoconstituents used in the management of liver disorders [61]. The liver, as a central organ responsible for metabolism, detoxification, and maintenance of physiological homeostasis, is particularly vulnerable to injury induced by xenobiotics, pharmacological agents, alcohol, and infectious pathogens. Hepatoprotective

compounds—such as silymarin, curcumin, resveratrol, and glycyrrhizin—exert their effects primarily through antioxidant, anti-inflammatory, and antifibrotic mechanisms [62,63]. However, their clinical application is often limited by poor aqueous solubility, rapid metabolic degradation, low bioavailability, and lack of site-specific delivery. Nanotechnology offers advanced solutions to overcome these limitations and significantly improve therapeutic outcomes [64].

One of the key advantages of nanotechnology-based drug delivery systems is the enhancement of solubility and

bioavailability of hepatoprotective agents. A large number of phytoconstituents, including curcumin and resveratrol, are lipophilic in nature and exhibit poor water solubility, which restricts their gastrointestinal absorption. Nanoformulations such as liposomes, nanoemulsions, and polymeric nanoparticles markedly increase the surface area of these compounds, thereby improving their dissolution rate and intestinal absorption [65,66]. For example, curcumin-loaded nanoparticles have demonstrated significantly improved bioavailability along with enhanced antioxidant activity compared to conventional formulations. Similarly, silymarin encapsulated within lipid-based nanoparticles exhibits improved pharmacokinetic behavior and enhanced accumulation in hepatic tissues [67].

In addition to improving solubility, nanocarriers provide protection to hepatoprotective agents against enzymatic and chemical degradation. Many natural compounds are inherently unstable in the gastrointestinal environment and are rapidly degraded before reaching their target site. Encapsulation within nanoscale carriers shields these bioactive molecules from adverse conditions such as pH variations and enzymatic activity, thereby preserving their structural integrity and therapeutic potential. This protective effect is particularly important for compounds such as resveratrol and glycyrrhizin, which are highly susceptible to metabolic degradation [68]. Targeted drug delivery is another critical advantage offered by nanotechnology in hepatoprotective therapy. Nanocarriers can be engineered to selectively deliver therapeutic agents to hepatic cells, thereby enhancing efficacy while minimizing systemic toxicity. Passive targeting is facilitated by the unique anatomical characteristics of the liver, including fenestrated sinusoidal endothelium that allows preferential accumulation of nanoparticles within hepatic tissues [69]. Active targeting strategies involve surface modification of nanocarriers with ligands such as galactose, mannose, or specific antibodies, which bind to receptors expressed on hepatocytes or Kupffer cells. This approach ensures selective drug localization at the site of action while reducing off-target exposure [70,71].

Controlled and sustained drug release represents another significant benefit of nanotechnology-based delivery systems. Conventional drug administration often results in rapid drug release and fluctuations in plasma drug concentrations, which may compromise therapeutic efficacy and increase the risk of adverse effects. Nanocarriers enable the controlled and prolonged release of drugs, maintaining plasma concentrations within the therapeutic window over extended durations [72,73]. This property is particularly advantageous in the long-term management of chronic liver diseases. Polymeric nanoparticles and nanogels are commonly employed to achieve sustained release profiles. Moreover, nanotechnology facilitates the co-delivery of multiple therapeutic agents within a single carrier system, enabling combination therapy. Liver diseases are typically multifactorial in nature, involving oxidative stress, inflammation, and fibrosis [74]. Co-encapsulation of multiple hepatoprotective agents allows for synergistic therapeutic effects and improved clinical outcomes. Nanocarriers are capable of incorporating both hydrophilic and lipophilic

compounds, thereby enabling simultaneous delivery of diverse therapeutic agents. For instance, co-delivery of curcumin and silymarin within a nanoparticulate system has demonstrated enhanced hepatoprotective efficacy compared to monotherapy [75]. In addition to phytoconstituents, nanotechnology is increasingly being utilized to improve the delivery of conventional hepatoprotective drugs. Agents such as N-acetylcysteine, widely used in the management of drug-induced liver injury, can be formulated into nanoparticulate systems to enhance their pharmacokinetic properties and reduce dosing frequency [76,77].

Similarly, targeted nanocarrier systems can improve the efficacy of antiviral drugs used in the treatment of viral hepatitis while minimizing systemic adverse effects. An emerging and highly promising area of research involves the application of nanotechnology in gene delivery and regenerative medicine for liver diseases. Nanocarriers can be employed to deliver nucleic acids, including DNA, RNA, and small interfering RNA (siRNA), to modulate gene expression and promote hepatic regeneration [78]. This approach holds significant potential for the treatment of genetic liver disorders and advanced hepatic conditions where conventional therapies are insufficient. Despite these advantages, several challenges continue to impede the clinical translation of nanotechnology-based hepatoprotective drug delivery systems. These include concerns related to nanomaterial toxicity, scalability of production, physicochemical stability during storage, and stringent regulatory requirements [79]. Furthermore, the long-term safety and biological interactions of nanoparticles remain incompletely understood. Therefore, comprehensive preclinical investigations and well-designed clinical trials are essential to ensure the safety, efficacy, and successful clinical implementation of these advanced therapeutic systems.

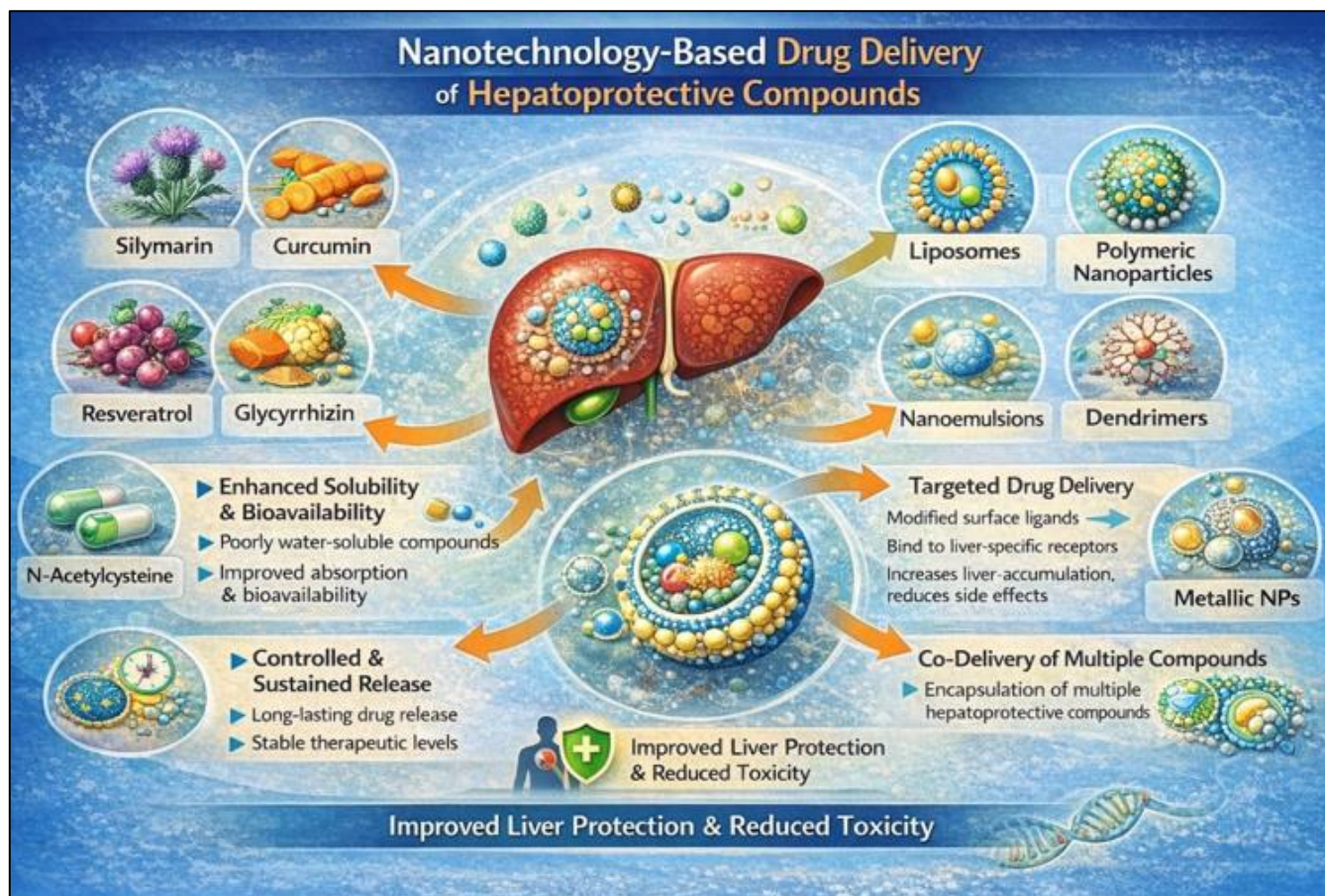


Fig 4 Hepatoprotective Medication Delivery Using Nanotechnology.

VI. EXPERIMENTAL MODELS FOR ASSESSMENT

Experimental models play a pivotal role in the evaluation of hepatoprotective drug delivery systems, particularly those based on nanotechnology, by enabling the systematic assessment of efficacy, safety, and underlying mechanisms of action. These models provide critical insights into the protective effects of therapeutic agents against hepatic injury and their potential to promote liver regeneration. Hepatoprotective activity is typically investigated using a combination of *in vitro* and *in vivo* experimental approaches, each offering distinct advantages in preclinical evaluation.

➤ *In Vitro* Models:

In vitro models serve as the primary screening platforms for hepatoprotective agents and nanoformulations. These studies commonly utilize cultured hepatic cells, including primary hepatocytes and established cell lines such as HepG2. Hepatotoxicity is experimentally induced using well-known toxicants, including carbon tetrachloride (CCl₄), paracetamol (acetaminophen), ethanol, and hydrogen peroxide. The hepatoprotective efficacy of test compounds is evaluated by assessing parameters such as cell viability, membrane integrity, and enzyme leakage—specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST)—along with oxidative stress markers and lipid peroxidation levels [80]. These models

offer several advantages, including rapid execution, cost-effectiveness, and the ability to elucidate cellular and molecular mechanisms such as antioxidant activity, anti-inflammatory responses, and cytoprotective effects. However, *in vitro* systems are inherently limited in their ability to replicate the complexity of whole-organism physiology, including systemic metabolism, immune responses, and tissue-level interactions.

➤ *Models in Vivo*:

In vivo experimental models provide a more comprehensive and physiologically relevant assessment of hepatoprotective activity. These models typically involve laboratory animals, particularly rodents such as mice and Wistar rats, in which liver injury is induced through the administration of specific hepatotoxins [81,82]. Among these, the carbon tetrachloride (CCl₄)-induced hepatotoxicity model is one of the most extensively employed. In this model, CCl₄ undergoes metabolic activation by hepatic cytochrome P450 enzymes, generating highly reactive free radicals that initiate lipid peroxidation, cellular membrane damage, and hepatocellular necrosis. The hepatoprotective potential of test formulations is evaluated by measuring serum biochemical markers, including ALT, AST, alkaline phosphatase (ALP), and bilirubin levels, in conjunction with histopathological analysis of liver tissue [83].

The paracetamol-induced hepatotoxicity model is another widely used system that closely mimics drug-induced

liver injury. At toxic doses, paracetamol is metabolized to a reactive intermediate that depletes intracellular glutathione and induces oxidative stress-mediated hepatocellular damage. This model is particularly valuable for assessing antioxidant-based therapeutic interventions [84]. In addition, alcohol-induced liver injury models are employed to study hepatic steatosis and chronic liver damage associated with prolonged ethanol exposure. Other experimental paradigms include bile duct ligation models for cholestatic liver injury, immune-mediated liver injury models, and thioacetamide-induced fibrosis models. These systems enable detailed investigation of diverse pathological processes, including inflammation, fibrosis, and cirrhosis [85].

In the context of nanotechnology-based drug delivery, additional parameters such as biodistribution, targeting efficiency, and pharmacokinetic behavior are evaluated using advanced imaging techniques and tissue distribution studies. Histopathological examination remains a critical component of hepatoprotective assessment. Microscopic evaluation of liver tissue sections is performed to identify structural alterations such as necrosis, inflammatory infiltration, fibrosis, and fatty degeneration. An effective hepatoprotective formulation is typically characterized by the preservation or restoration of normal hepatic architecture in comparison to toxic control groups [86].

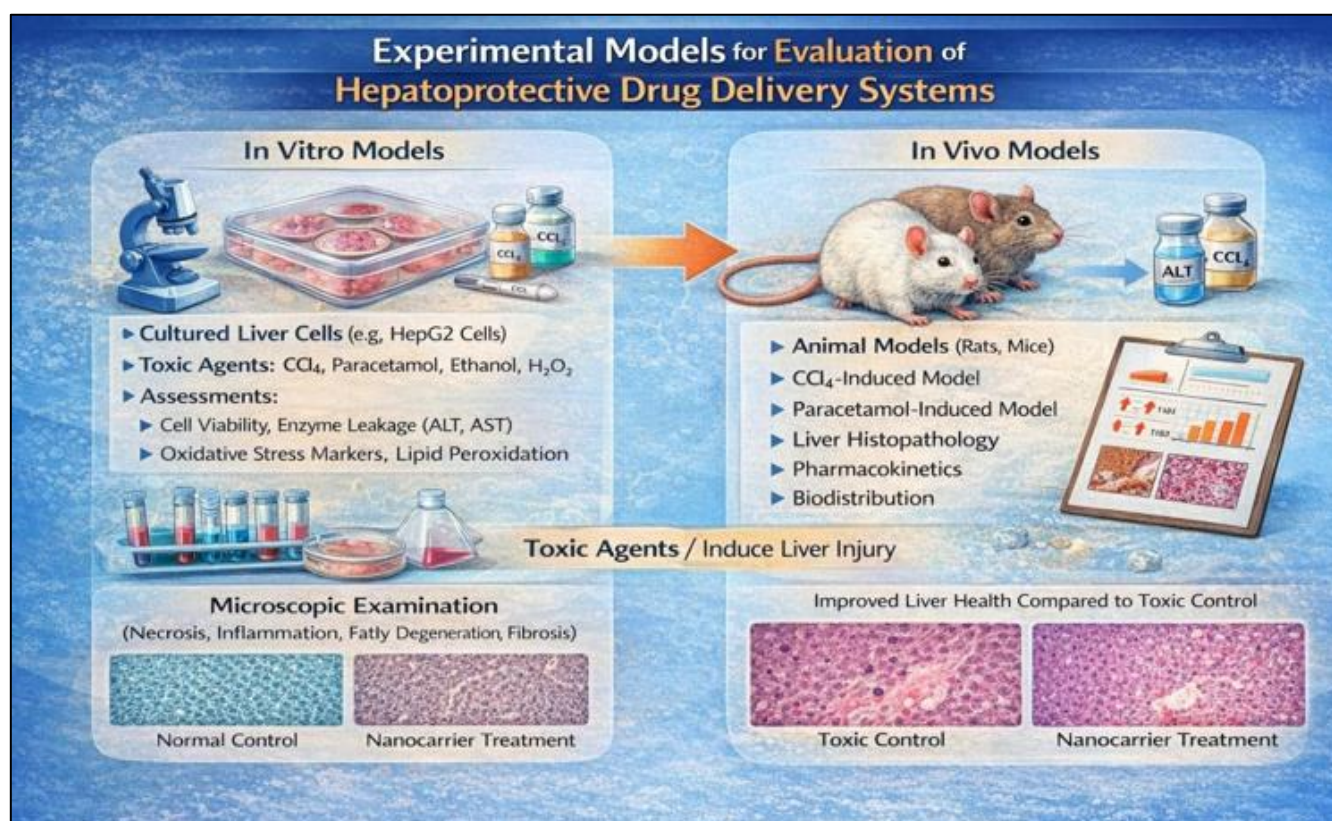


Fig 5 Hepatoprotective Medication Delivery Methods are Assessed Using Experimental Models.

VII. CLINICAL TRANSLATION AND RECENT STUDIES

The clinical translation of nanotechnology-based hepatoprotective drug delivery systems constitutes a critical phase in advancing experimental innovations toward safe and effective therapeutic applications in humans. Although a wide range of nanocarrier systems have demonstrated significant hepatoprotective efficacy in preclinical investigations, their successful transition to clinical use remains limited due to multiple scientific, regulatory, and safety-related challenges [87].

The translational pathway involves optimization of formulation parameters, scale-up manufacturing, rigorous toxicological evaluation, and the execution of well-structured clinical trials to establish safety, efficacy, and reproducibility in human populations. A major focus of contemporary

research is the application of nanotechnology to enhance the therapeutic performance of well-established hepatoprotective agents, including silymarin, curcumin, and resveratrol. Despite their proven pharmacological activity in experimental models, these compounds exhibit suboptimal pharmacokinetic profiles when administered in conventional dosage forms, primarily due to poor solubility, limited absorption, and rapid metabolic clearance [88]. To address these limitations, various nanoformulations—such as liposomes, solid lipid nanoparticles, and polymeric nanoparticles—are being extensively investigated for their ability to improve drug stability, prolong systemic circulation, and enhance hepatic accumulation. For example, silymarin-loaded nanoparticulate systems have demonstrated improved liver targeting efficiency, extended plasma half-life, and enhanced antioxidant potential relative to conventional formulations [89].

The development of targeted nanocarrier systems represents a key advancement in clinical research. Surface-functionalized nanoparticles incorporating specific ligands, such as galactose or mannose, enable selective targeting of hepatocytes and Kupffer cells through receptor-mediated interactions. This targeted delivery approach significantly enhances drug localization at the site of action while minimizing systemic exposure and associated adverse effects, thereby addressing a major limitation of conventional therapies. In addition, nanocarrier platforms are being explored for the co-delivery of multiple therapeutic agents, facilitating combination therapy strategies for complex liver disorders characterized by multifactorial pathogenesis, including oxidative stress, inflammation, and fibrosis [90]. Nanotechnology is also increasingly integrated with advanced therapeutic strategies such as gene therapy and regenerative medicine. Nanocarriers are being engineered for the delivery of nucleic acids, including small interfering RNA (siRNA) and messenger RNA (mRNA), to regulate gene expression and stimulate hepatic regeneration [91]. This approach offers significant potential for the treatment of genetic liver disorders and advanced-stage hepatic diseases where conventional pharmacotherapy is often inadequate. Despite these promising developments, several challenges continue to hinder the clinical translation of nanotechnology-based hepatoprotective systems. Key concerns include potential nanoparticle-induced toxicity, immunogenic responses, and long-term accumulation within biological tissues. Furthermore, issues related to large-scale production, batch-to-batch consistency, and physicochemical stability during storage must be addressed to ensure successful commercialization. Regulatory approval remains particularly complex, as standardized guidelines for the evaluation and approval of nanomedicines are still evolving [92]. To date, only a limited number of nanotechnology-based drug delivery systems have progressed to clinical trials or achieved regulatory approval for liver-related indications. Nevertheless, ongoing advancements in nanotechnology, coupled with interdisciplinary collaboration among researchers, clinicians, and regulatory authorities, are expected to facilitate the translation of these innovative systems from experimental settings to clinical practice in the near future [93].

VIII. DIFFICULTY AND CONSTRAINTS

Despite the significant therapeutic potential of nanotechnology-based hepatoprotective drug delivery systems, several critical challenges must be addressed before their widespread clinical and commercial implementation. These limitations encompass safety concerns, pharmacokinetic uncertainties, formulation and manufacturing complexities, regulatory barriers, and translational gaps. Toxicity and safety concerns remain a major limitation in the application of nanotechnology. Although many nanocarriers are engineered to be biocompatible and biodegradable, their nanoscale dimensions and high surface reactivity can result in unanticipated interactions with biological systems [94].

Nanoparticles may accumulate in vital organs such as the liver, spleen, and kidneys, potentially leading to long-term toxicity. Reported adverse effects include oxidative stress, inflammatory responses, and activation of the immune system. Therefore, comprehensive toxicological profiling, including chronic exposure and long-term safety assessments, is essential prior to clinical application. Limited understanding of pharmacokinetics and bio-distribution represents another significant constraint. Although nanocarriers are designed to enhance targeted delivery, their *in vivo* behavior is influenced by multiple physicochemical parameters, including particle size, morphology, surface charge, and composition. These factors can lead to variability in distribution and clearance. In particular, rapid uptake by the reticulo-endothelial system (RES), especially Kupffer cells in the liver, may result in premature clearance of nanoparticles, thereby reducing drug availability at the intended target site or causing unintended accumulation. Stability-related challenges also hinder the practical application of nanoformulations.

Nanoparticles are susceptible to aggregation, degradation, and premature drug leakage during storage and transportation. External environmental factors such as temperature, pH, and light exposure can significantly affect their physicochemical stability [95]. Ensuring long-term stability and maintaining consistent product quality are critical requirements for pharmaceutical development and commercialization. High production costs and formulation complexity further restrict the widespread adoption of nanotechnology-based systems. The fabrication of nanocarriers often involves advanced methodologies, specialized instrumentation, and stringent process control. Scaling up production from laboratory to industrial levels while maintaining batch-to-batch consistency and reproducibility remains a significant challenge [96]. These factors contribute to increased manufacturing costs, limiting accessibility, particularly in resource-constrained settings. Regulatory challenges constitute another major barrier to clinical translation. Regulatory authorities require extensive and rigorous data regarding the safety, efficacy, quality, and environmental impact of nanomedicines. However, the absence of universally accepted and standardized regulatory guidelines specific to nanotechnology-based drug delivery systems creates uncertainty in the approval process [97].

Additionally, variations in regulatory frameworks across different countries further complicate global development and commercialization. Insufficient clinical data and translational limitations also impede progress in this field. While numerous nanoformulations have demonstrated promising outcomes in *in vitro* and preclinical animal studies, only a limited number have advanced to clinical trials. The extrapolation of preclinical findings to human systems remains challenging due to physiological and metabolic differences, often resulting in discrepancies in therapeutic outcomes [98]. Immunogenicity and hypersensitivity reactions present additional concerns. Certain nanocarrier systems, particularly those incorporating synthetic materials or surface modifications, may elicit immune responses, leading to adverse reactions. This is particularly relevant in

chronic liver diseases, where long-term or repeated administration is required, thereby increasing the risk of immunological complications [99]. Finally, ethical and environmental considerations must be carefully evaluated. The long-term environmental impact of nanoparticle disposal and their potential ecological consequences remain inadequately understood. Furthermore, ethical considerations—including patient safety, informed consent, and risk–benefit assessment—are critical in the clinical development and application of nanomedicine-based therapies [100].

IX. FUTURE PROSPECTS

Nanotechnology-based hepatoprotective drug delivery systems are poised to play a transformative role in the future management of liver diseases. Continuous advancements in pharmaceutical sciences, biotechnology, and materials engineering are driving the evolution of nanotechnology toward more precise, efficient, and patient-centric therapeutic strategies. The integration of emerging technologies, coupled with an improved understanding of liver pathophysiology, is expected to further enhance the clinical potential of nanocarrier-based hepatoprotective interventions [101].

A major future direction lies in the development of personalized and targeted drug delivery systems. Progress in molecular biology and genomics has enabled the identification of diseasespecific biomarkers associated with various hepatic disorders. This knowledge facilitates the design of nanocarriers capable of selectively targeting specific liver cell populations or pathological sites based on individual patient profiles [102]. Such personalized nanomedicine approaches are anticipated to optimize dosing regimens, reduce adverse effects, and improve therapeutic outcomes, particularly in chronic liver conditions such as fibrosis and cirrhosis. Gene therapy and regenerative medicine represent another promising frontier. Nanocarriers are increasingly being engineered for the delivery of genetic materials, including small interfering RNA (siRNA), messenger RNA (mRNA), and CRISPR-Cas systems, to modulate gene expression and correct underlying genetic abnormalities. This strategy holds considerable potential for the treatment of inherited liver disorders and for promoting hepatic regeneration. By enabling targeted genetic modulation and tissue repair, nanotechnology may significantly reduce the future reliance on liver transplantation as a definitive treatment modality [103].

The development of stimuli-responsive or “smart” nanocarriers is expected to further advance hepatoprotective therapy. These systems can be designed to respond to specific physiological or pathological triggers, such as variations in pH, temperature, enzymatic activity, or oxidative stress levels within the hepatic microenvironment. Such responsive nanocarriers allow for sitespecific and controlled drug release, thereby maximizing therapeutic efficacy while minimizing systemic toxicity. This approach is particularly advantageous in conditions requiring localized and regulated drug delivery [104]. Multifunctional nanocarriers for combination therapy are also gaining significant attention.

Given that liver diseases are often multifactorial—characterized by oxidative stress, inflammation, apoptosis, and fibrosis—nanocarriers capable of co-delivering multiple therapeutic agents can provide synergistic effects and improved clinical outcomes. These systems enable the simultaneous delivery of synthetic drugs and phytoconstituents, making them especially relevant for complex conditions such as non-alcoholic fatty liver disease and hepatocellular carcinoma [105].

Another emerging area is the development of theranostic nanoplatforms, which integrate diagnostic and therapeutic functionalities within a single system. These platforms can simultaneously deliver therapeutic agents and facilitate real-time monitoring of drug distribution and treatment response advanced imaging modalities. This dual capability allows for dynamic assessment and optimization of therapeutic regimens, thereby enhancing the precision of disease management [106]. Significant efforts are also being directed toward improving the biocompatibility, safety, and scalability of nanocarriers. The utilization of natural and biodegradable materials, such as lipids, proteins, and polysaccharides, is being emphasized to minimize toxicity and enhance clinical acceptability. Concurrently, advancements in manufacturing technologies are expected to enable efficient large-scale production, improve reproducibility, and reduce overall costs, thereby increasing the accessibility of nanotechnology-based therapies [107]. The integration of artificial intelligence (AI) and machine learning (ML) into nanomedicine design is another rapidly advancing domain. These computational tools can analyze complex datasets to predict nanoparticle behavior, optimize formulation parameters, and enhance targeting efficiency. The application of AI-driven approaches is expected to accelerate drug development processes and improve the precision and effectiveness of hepatoprotective therapies. Despite these promising advancements, several challenges must still be addressed to ensure successful clinical translation. These include long-term safety concerns, inter-individual variability in therapeutic response, and regulatory complexities. The establishment of standardized regulatory frameworks and the execution of robust clinical trials will be essential for the effective integration of nanotechnology-based hepatoprotective systems into routine clinical practice [108].

X. CONCLUSION

In conclusion, nanotechnology-based hepatoprotective drug delivery systems represent a substantial advancement in contemporary pharmacology, providing innovative and efficient strategies to overcome the intrinsic limitations associated with conventional therapies for liver diseases. Hepatic disorders continue to impose a significant global health burden due to their multifactorial etiology and the limited efficacy of existing treatment options. Although conventional hepatoprotective agents—including synthetic drugs and phytoconstituents such as silymarin—have demonstrated therapeutic benefits, their clinical utility is often restricted by poor bioavailability, rapid metabolic degradation, low aqueous solubility, and lack of sitespecific

targeting. Nanotechnology offers a robust platform to address these limitations through the development of advanced drug delivery systems that enhance the pharmacokinetic and pharmacodynamic profiles of hepatoprotective agents. A wide spectrum of nanocarriers—including liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, and nanoemulsions—has been shown to improve drug solubility, stability, and controlled release characteristics.

More importantly, these nanosystems facilitate targeted delivery to hepatic tissues, resulting in increased drug accumulation at the site of action while minimizing systemic exposure and associated adverse effects. This targeted approach significantly enhances therapeutic efficacy and safety. Moreover, nanotechnology has demonstrated considerable potential in improving the delivery of bioactive phytoconstituents such as curcumin and resveratrol, which possess strong antioxidant and anti-inflammatory properties but suffer from poor pharmacokinetic behavior in conventional formulations. Encapsulation of these compounds within nanocarriers enhances their stability, bioavailability, and overall therapeutic effectiveness. Additionally, the ability of nanocarriers to enable combination therapy through co-delivery of multiple agents provides a comprehensive strategy for managing complex liver diseases involving multiple pathological mechanisms. Despite these promising advantages, several challenges persist, including concerns related to nanoparticle toxicity, physicochemical stability, scalability of production, and regulatory approval processes. Furthermore, the limited availability of clinical data and discrepancies between preclinical findings and clinical outcomes highlight the necessity for extensive research and well-designed clinical trials. Addressing these challenges is essential for the safe and effective translation of nanotechnology-based systems into routine clinical practice. Looking forward, the integration of nanotechnology with emerging fields such as gene therapy, personalized medicine, and artificial intelligence is expected to further revolutionize hepatoprotective therapy. These advancements will facilitate the development of intelligent, targeted, and patient-specific drug delivery systems, ultimately improving therapeutic outcomes and reducing the global burden of liver diseases. Overall, nanotechnology-based hepatoprotective drug delivery systems hold immense potential to redefine the current therapeutic paradigm. Continued interdisciplinary research, technological innovation, and collaborative efforts will be instrumental in realizing their full clinical potential and establishing their role in the effective prevention and treatment of liver disorders.

REFERENCES

- [1]. Asrani, S. K., Devarbhavi, H., Eaton, J., & Kamath, P. S. (2019). Burden of liver diseases in the world. *Journal of Hepatology*, 70(1), 151–171. <https://doi.org/10.1016/j.jhep.2018.09.014>
- [2]. Marcellin, P., & Kutala, B. K. (2020). Liver diseases: A major, neglected global public health problem requiring urgent actions. *Clinical Liver Disease*, 15(3), 105–109. <https://doi.org/10.1002/cld.896>
- [3]. Moon, A. M., Singal, A. G., & Tapper, E. B. (2020). Contemporary epidemiology of chronic liver disease and cirrhosis. *Clinical Gastroenterology and Hepatology*, 18(12), 2650–2666. <https://doi.org/10.1016/j.cgh.2019.07.060>
- [4]. Younossi, Z. M., & Henry, L. (2021). The impact of obesity and type 2 diabetes on chronic liver disease. *Journal of Hepatology*, 74(4), 970–980. <https://doi.org/10.1016/j.jhep.2021.01.010>
- [5]. Abenavoli, L., Capasso, R., Milic, N., & Capasso, F. (2019). Milk thistle in liver diseases: Past, present, future. *Phytotherapy Research*, 24(10), 1423–1432. <https://doi.org/10.1002/ptr.3207>
- [6]. Bansal, S., & Goel, M. (2019). Silymarin-loaded solid lipid nanoparticles: A promising approach for hepatoprotection. *Journal of Drug Delivery Science and Technology*, 52, 781–788. <https://doi.org/10.1016/j.jddst.2019.05.045>
- [7]. Bilia, A. R., Piazzini, V., Guccione, C., Risaliti, L., & Bergonzi, M. C. (2019). Nanomedicine for the delivery of natural compounds with hepatoprotective activity. *Expert Opinion on Drug Delivery*, 16(5), 489–503. <https://doi.org/10.1080/17425247.2019.1604672>
- [8]. Loguercio, C., & Festi, D. (2020). Silybin and the liver: From basic research to clinical practice. *World Journal of Gastroenterology*, 26(27), 3859–3872. <https://doi.org/10.3748/wjg.v26.i27.3859>
- [9]. Paumgartner, G., & Beuers, U. (2020). Ursodeoxycholic acid in cholestatic liver disease: Mechanisms of action and therapeutic use revisited. *Hepatology*, 36(3), 525–531. <https://doi.org/10.1053/jhep.2002.36088>
- [10]. Sadowska-Woda, I., & Bieszczad-Bedrejcuk, E. (2020). N-acetylcysteine in the treatment of drug-induced liver injury. *Current Drug Metabolism*, 21(5), 357–366. <https://doi.org/10.2174/1389200221666200523152543>
- [11]. Polyzos, S. A., & Kountouras, J. (2020). Corticosteroids in autoimmune hepatitis: Current concepts and future directions. *Annals of Gastroenterology*, 33(2), 123–134. <https://doi.org/10.20524/aog.2020.0453>
- [12]. Chung, R. T., & Baumert, T. F. (2021). Advances in antiviral therapy for hepatitis B and C. *Nature Reviews Gastroenterology & Hepatology*, 18(5), 305–317. <https://doi.org/10.1038/s41575-021-00423-z>
- [13]. Kaur, I. P., & Bhandari, R. (2020). Silymarin-loaded nanocarriers: A promising approach for hepatoprotection. *Drug Delivery and Translational Research*, 10(3), 641–658. <https://doi.org/10.1007/s13346-020-00733-6>
- [14]. Gupta, S., & Kesarla, R. (2021). Nanotechnology in hepatoprotective drug delivery: Current trends and future perspectives. *Journal of Pharmaceutical Innovation*, 16(3), 657–672. <https://doi.org/10.1007/s12247-020-09512-5>
- [15]. Akhter, S., Ahmad, I., & Ahmad, M. Z. (Eds.). (2022). *Nanocarriers for drug delivery: Concepts and applications*. Springer.

- [16]. Farokhzad, O. C., & Langer, R. (2019). Impact of nanotechnology on drug delivery. *ACS Nano*, 13(3), 2678–2689. <https://doi.org/10.1021/acsnano.9b01770>
- [17]. Mitchell, M. J., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., & Langer, R. (2021). Engineering precision nanoparticles for drug delivery. *Nature Reviews Drug Discovery*, 20(2), 101–124. <https://doi.org/10.1038/s41573-020-0090-8>
- [18]. Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M. P., Acosta-Torres, L. S., & Shin, H. S. (2020). Nano based drug delivery systems: Recent developments and future prospects. *Journal of Nanobiotechnology*, 16(1), 71. <https://doi.org/10.1186/s12951-018-0392-8>
- [19]. Rizvi, S. A., & Saleh, A. M. (2020). Applications of nanoparticle systems in drug delivery technology. *Saudi Pharmaceutical Journal*, 28(12), 1693–1705. <https://doi.org/10.1016/j.jsps.2020.10.012>
- [20]. Shi, J., Kantoff, P. W., Wooster, R., & Farokhzad, O. C. (2019). Cancer nanomedicine: Progress, challenges and opportunities. *Nature Reviews Cancer*, 17(1), 20–37. <https://doi.org/10.1038/nrc.2016.108>
- [21]. Torchilin, V. P. (2020). Multifunctional nanocarriers for drug delivery. *Advanced Drug Delivery Reviews*, 158, 2–15. <https://doi.org/10.1016/j.addr.2020.06.008>
- [22]. Zhang, L., & Wang, H. (2020). Clinical translation of nanomedicines for liver diseases: Challenges and opportunities. *Advanced Therapeutics*, 3(5), 1900198. <https://doi.org/10.1002/adtp.201900198>
- [23]. Petros, R. A., & DeSimone, J. M. (2020). Strategies in the design of nanoparticles for therapeutic applications. *Nature Reviews Drug Discovery*, 9(8), 615–627. <https://doi.org/10.1038/nrd2591>
- [24]. Singh, R., & Lillard, J. W., Jr. (2020). Nanoparticle-based targeted drug delivery. *Experimental and Molecular Pathology*, 86(3), 215–223. <https://doi.org/10.1016/j.yexmp.2008.12.004>
- [25]. Bamrungsap, S., Zhao, Z., Chen, T., Wang, L., Li, C., Fu, T., & Tan, W. (2020). Nanotechnology in therapeutics: A focus on nanoparticles as drug delivery systems. *Nanomedicine*, 7(8), 1253–1271. <https://doi.org/10.2217/nmm.12.87>
- [26]. Raj, S., & Jose, S. (2020). Liposomes for liver-targeted drug delivery: A review. *Journal of Liposome Research*, 30(4), 325–339. <https://doi.org/10.1080/08982104.2019.1674321>
- [27]. Akbarzadeh, A., Rezaei-Sadabady, R., Davaran, S., Joo, S. W., Zarghami, N., Hanifehpour, Y., ... & Nejati-Koshki, K. (2019). Liposome: Classification, preparation, and applications. *Nanoscale Research Letters*, 8(1), 102. <https://doi.org/10.1186/1556-276X-8-102>
- [28]. Sercombe, L., Veerati, T., Moheimani, F., Wu, S. Y., Sood, A. K., & Hua, S. (2020). Advances and challenges of liposome assisted drug delivery. *Frontiers in Pharmacology*, 6, 286. <https://doi.org/10.3389/fphar.2015.00286>
- [29]. Duan, Y., Dhar, A., Patel, C., Khimani, M., Neogi, S., & Sharma, P. (2020). A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. *RSC Advances*, 10(45), 26777–26791. <https://doi.org/10.1039/D0RA03491F>
- [30]. Ghasemiyeh, P., & Mohammadi-Samani, S. (2020). Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: Applications, advantages, and disadvantages. *Research in Pharmaceutical Sciences*, 15(5), 419–433. <https://doi.org/10.4103/1735-5362.297847>
- [31]. Garg, N. K., Singh, B., Jain, A., & Tyagi, R. K. (2020). Nanostructured lipid carriers: A promising drug delivery system for liver targeting. *Current Nanomedicine*, 10(2), 88–102. <https://doi.org/10.2174/2468187310666200210122628>
- [32]. Müller, R. H., Mäder, K., & Gohla, S. (2020). Solid lipid nanoparticles (SLN) for controlled drug delivery: A review of the state of the art. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1), 161–177. [https://doi.org/10.1016/S0939-6411\(00\)00087-4](https://doi.org/10.1016/S0939-6411(00)00087-4)
- [33]. El-Say, K. M., & El-Sawy, H. S. (2019). Polymeric nanoparticles: Promising platform for drug delivery. *International Journal of Pharmaceutics*, 528(1–2), 675–691. <https://doi.org/10.1016/j.ijpharm.2017.06.052>
- [34]. Chen, Y., Li, J., & Li, Q. (2022). Advances in polymeric nanoparticles for liver-targeted drug delivery. *Frontiers in Bioengineering and Biotechnology*, 10, 857210. <https://doi.org/10.3389/fbioe.2022.857210>
- [35]. Kumari, A., Yadav, S. K., & Yadav, S. C. (2020). Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids and Surfaces B: Biointerfaces*, 75(1), 1–18. <https://doi.org/10.1016/j.colsurfb.2009.09.001>
- [36]. Crucho, C. I. C., & Barros, M. T. (2021). Polymeric nanoparticles: A study on the preparation variables and characterization methods. **Materials Science and Engineering: C*, 80, 771–784. <https://doi.org/10.1016/j.msec.2017.06.004>
- [37]. Hu, X., & Zhang, J. (2020). Dendrimers in drug delivery: Recent advances and future perspectives. *Biomaterials Science*, 8(10), 2755–2771. <https://doi.org/10.1039/D0BM00224K>
- [38]. Abbasi, E., Aval, S. F., Akbarzadeh, A., Milani, M., Nasrabadi, H. T., Joo, S. W., ... & Pashaei-Asl, R. (2020). Dendrimers: Synthesis, applications, and properties. *Nanoscale Research Letters*, 9(1), 247. <https://doi.org/10.1186/1556-276X-9-247>
- [39]. Mignani, S., Rodrigues, J., Tomas, H., Roy, R., Shi, X., & Majoral, J. P. (2021). Dendrimers in nanomedicine: Concepts, challenges and prospects. *Drug Discovery Today*, 26(3), 714–724. <https://doi.org/10.1016/j.drudis.2020.12.010>
- [40]. Mishra, V., & Bansal, K. K. (2021). Nanoemulsions: A promising vehicle for hepatoprotective drug delivery. *Current Pharmaceutical Design*, 27(13), 1558–1570. <https://doi.org/10.2174/1381612826666201118095809>
- [41]. Singh, Y., Meher, J. G., Raval, K., Khan, F. A., Chaurasia, M., Jain, N. K., & Chourasia, M. K. (2020).

- Nanoemulsion: Concepts, development and applications in drug delivery. *Journal of Controlled Release*, 252, 28–49. <https://doi.org/10.1016/j.jconrel.2017.03.008>
- [42]. Azeem, A., Rizwan, M., Ahmad, F. J., Iqbal, Z., Khar, R. K., Aqil, M., & Talegaonkar, S. (2020). Nanoemulsion components screening and selection: A technical note. *AAPS PharmSciTech*, 10(1), 69–76. <https://doi.org/10.1208/s12249-008-9178-x>
- [43]. Li, Y., & Zhang, X. (2022). Metallic nanoparticles in liver disease therapy: Opportunities and challenges. *Biomaterials*, 280, 121301. <https://doi.org/10.1016/j.biomaterials.2021.121301>
- [44]. El-Sayed, I. H., & El-Sayed, M. A. (2020). Gold nanoparticles for biomedical applications: Past, present, and future. *Accounts of Chemical Research*, 53(2), 452–463. <https://doi.org/10.1021/acs.accounts.9b00552>
- [45]. Zhang, X. F., Liu, Z. G., Shen, W., & Gurnathan, S. (2021). Silver nanoparticles: Synthesis, characterization, properties, applications, and therapeutic approaches. *International Journal of Molecular Sciences*, 17(9), 1534. <https://doi.org/10.3390/ijms17091534>
- [46]. Lai, L., & Chen, X. (2021). Carbon-based nanomaterials for drug delivery in liver diseases. *Carbon*, 172, 544–558. <https://doi.org/10.1016/j.carbon.2020.10.047>
- [47]. Liu, Z., Robinson, J. T., Tabakman, S. M., Yang, K., & Dai, H. (2020). Carbon nanotubes for drug delivery. *Materials Today*, 14(7–8), 316–323. [https://doi.org/10.1016/S1369-7021\(11\)70161-4](https://doi.org/10.1016/S1369-7021(11)70161-4)
- [48]. Goenka, S., Sant, V., & Sant, S. (2020). Graphene-based nanomaterials for drug delivery and tissue engineering. *Journal of Controlled Release*, 173, 75–88. <https://doi.org/10.1016/j.jconrel.2013.10.017>
- [49]. Liu, D., & Yang, F. (2021). Protein-based nanoparticles for drug delivery applications. *Journal of Controlled Release*, 330, 1092–1108. <https://doi.org/10.1016/j.jconrel.2020.12.010>
- [50]. Elzoghby, A. O., Samy, W. M., & Elgindy, N. A. (2020). Albumin-based nanoparticles as potential controlled release drug delivery systems. *Journal of Controlled Release*, 157(2), 168–182. <https://doi.org/10.1016/j.jconrel.2011.07.031>
- [51]. Lohcharoenkal, W., Wang, L., Chen, Y. C., & Rojanasakul, Y. (2020). Protein nanoparticles as drug delivery carriers for cancer therapy. *BioMed Research International*, 2014, 180549. <https://doi.org/10.1155/2014/180549>
- [52]. Kumar, A., & Sharma, P. K. (2022). Polymeric micelles in liver-targeted drug delivery: A review. *Current Drug Delivery*, 19(4), 442–456. <https://doi.org/10.2174/1567201818666210910114215>
- [53]. Torchilin, V. P. (2020). Micellar nanocarriers: Pharmaceutical perspectives. *Pharmaceutical Research*, 24(1), 1–16. <https://doi.org/10.1007/s11095-006-9132-0>
- [54]. Ghezzi, M., Pescina, S., Padula, C., Santi, P., & Nicoli, S. (2021). Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. *Journal of Controlled Release*, 332, 312–336. <https://doi.org/10.1016/j.jconrel.2021.02.031>
- [55]. Liu, Y., & Wang, S. (2020). Stimuli-responsive nanogels for controlled drug delivery. *Biomacromolecules*, 21(7), 2531–2547. <https://doi.org/10.1021/acs.biomac.0c00678>
- [56]. Soni, K. S., Desale, S. S., & Bronich, T. K. (2021). Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation. *Journal of Controlled Release*, 240, 109–126. <https://doi.org/10.1016/j.jconrel.2015.10.041>
- [57]. Mauri, E., Perale, G., & Rossi, F. (2020). Nanogels for biomedical applications: A review. *Gels*, 4(2), 46. <https://doi.org/10.3390/gels4020046>
- [58]. Saleh, T., & Shojaosadati, S. A. (2020). Lipid-polymer hybrid nanoparticles as a next-generation drug delivery platform: State of the art, emerging technologies, and future perspectives. *Journal of Controlled Release*, 327, 217–239. <https://doi.org/10.1016/j.jconrel.2020.08.016>
- [59]. Mukherjee, A., Waters, A. K., Kalyan, P., Achrol, A. S., & Kesari, S. (2021). Lipid-polymer hybrid nanoparticles as a next-generation drug delivery platform: A review. *Nanomaterials*, 11(3), 621. <https://doi.org/10.3390/nano11030621>
- [60]. Zhang, L., & Zhang, N. (2020). How nanotechnology can enhance docetaxel therapy: A review of recent developments. *International Journal of Nanomedicine*, 15, 5209–5226. <https://doi.org/10.2147/IJN.S258319>
- [61]. Ahmad, J., Akhter, S., Rizwanullah, M., Amin, S., & Ahmad, M. Z. (2020). Nanotechnology-based hepatoprotective drug delivery systems: A promising therapeutic approach for liver diseases. *Current Drug Metabolism*, 21(4), 256–269. <https://doi.org/10.2174/1389200221666200420102411>
- [62]. Alsaab, H. O., Alharbi, F. D., Alhibis, A. S., Alanazi, A. F., & Alshehri, S. (2022). Nanotechnology-based strategies for the management of liver diseases. *Pharmaceuticals*, 15(7), 821. <https://doi.org/10.3390/ph15070821>
- [63]. Cai, X., Luo, Y., Zhang, W., Du, D., & Lin, Y. (2021). Nanotechnology for the treatment of liver diseases. *Nano Today*, 37, 101085. <https://doi.org/10.1016/j.nantod.2021.101085>
- [64]. Feng, L., & Liu, Z. (2021). Nanomedicine for the treatment of liver diseases: Progress and challenges. *Biomaterials Science*, 9(8), 2825–2842. <https://doi.org/10.1039/D1BM00018A>
- [65]. Ganesan, P., & Choi, D. K. (2019). Current application of phytocompound-based nanocosmeceuticals for beauty and skin therapy. *International Journal of Nanomedicine*, 14, 2543–2556. <https://doi.org/10.2147/IJN.S198833>
- [66]. Prabhakar, P. K., & Kaur, S. (2021). Curcumin-loaded nanocarriers for hepatoprotection: A review. *Journal of Drug Delivery Science and Technology*, 61, 102192. <https://doi.org/10.1016/j.jddst.2020.102192>

- [67]. Poonia, N., Lather, V., & Pandita, D. (2019). Nanotechnology-based drug delivery systems for hepatoprotective agents: A review. *Artificial Cells, Nanomedicine, and Biotechnology*, 47(1), 2729–2740. <https://doi.org/10.1080/21691401.2019.1634573>
- [68]. Das, S., & Chaudhury, A. (2021). Recent advances in lipid-based nanocarriers for liver-targeted drug delivery. *Journal of Liposome Research*, 31(3), 235–248. <https://doi.org/10.1080/08982104.2020.1820522>
- [69]. Khurana, B., Goyal, A. K., & Garg, T. (2021). Nanocarriers for the treatment of liver diseases: A review. *Journal of Drug Targeting*, 29(5), 489–504. <https://doi.org/10.1080/1061186X.2020.1864746>
- [70]. Rahman, H. S., Othman, H. H., & Abdullah, R. (2021). The role of nanotechnology in the treatment of liver diseases. *Nanomedicine: Nanotechnology, Biology and Medicine*, 32, 102326. <https://doi.org/10.1016/j.nano.2020.102326>
- [71]. Sharma, A., & Madhunapantula, S. V. (2021). Nanotechnology-based drug delivery systems for the management of liver diseases: A comprehensive review. *Journal of Nanomaterials*, 2021, 8822345. <https://doi.org/10.1155/2021/8822345>
- [72]. Thapa, R. K., & Kim, J. O. (2021). Nanomedicine-based strategies for the treatment of liver diseases. *Journal of Pharmaceutical Investigation*, 51(3), 265–282. <https://doi.org/10.1007/s40005-021-00519-z>
- [73]. Tan, M. L., & Choong, P. F. (2021). Nanotechnology in liver diseases: A systematic review. *Nanomedicine*, 16(14), 1219–1237. <https://doi.org/10.2217/nnm-2021-0012>
- [74]. Jampilek, J., & Kralova, K. (2020). Nanotechnology-based formulations for drug delivery to the liver. *Nanomaterials*, 10(8), 1518. <https://doi.org/10.3390/nano10081518>
- [75]. Chaudhary, S., Garg, T., & Goyal, A. K. (2020). Nanotechnology-based approaches for the management of liver diseases. *Current Pharmaceutical Design*, 26(26), 3105–3116. <https://doi.org/10.2174/1381612826666200518111304>
- [76]. Yin, H., Kanasty, R. L., Eltoukhy, A. A., Vegas, A. J., Dorkin, J. R., & Anderson, D. G. (2020). Non-viral vectors for gene-based therapy. *Nature Reviews Genetics*, 15(8), 541–555. <https://doi.org/10.1038/nrg3763>
- [77]. Zatsepin, T. S., Kotelevtsev, Y. V., & Koteliensky, V. (2021). Lipid nanoparticles for targeted siRNA delivery: From bench to bedside. *Nanomedicine*, 11(14), 1823–1840. <https://doi.org/10.2217/nnm-2016-0164>
- [78]. Witzigmann, D., Kulkarni, J. A., Leung, J., Chen, S., Cullis, P. R., & van der Meel, R. (2020). Lipid nanoparticle technology for therapeutic gene regulation in the liver. *Advanced Drug Delivery Reviews*, 159, 344–363. <https://doi.org/10.1016/j.addr.2020.06.019>
- [79]. Wang, H. X., Li, M., Lee, C. M., Chakraborty, S., Kim, H. W., Bao, G., & Leong, K. W. (2021). CRISPR/Cas9-based genome editing for disease modeling and therapy: Challenges and opportunities for non-viral delivery. *Chemical Reviews*, 117(15), 9874–9906. <https://doi.org/10.1021/acs.chemrev.6b00799>
- [80]. Amawi, H., Ashby, C. R., Jr., & Tiwari, A. K. (2021). Nanomedicine and liver diseases: From bench to bedside. *World Journal of Hepatology*, 13(1), 1–18. <https://doi.org/10.4254/wjh.v13.i1.1>
- [81]. Delgado, D., & Gaspar, M. M. (2020). Nanomedicine for the treatment of hepatic diseases. **International Journal of Molecular Sciences**, 21(17), 6076. <https://doi.org/10.3390/ijms21176076>
- [82]. Nair, A. B., & Jacob, S. (2020). A simple practice guide for dose conversion between animals and human. *Journal of Basic and Clinical Pharmacy*, 7(2), 27–31. <https://doi.org/10.4103/0976-0105.177703>
- [83]. McGill, M. R., & Jaeschke, H. (2020). Animal models of drug-induced liver injury. *Methods in Molecular Biology*, 2108, 157–173. https://doi.org/10.1007/978-1-0716-0239-3_9
- [84]. Liedtke, C., Luedde, T., Sauerbruch, T., Scholten, D., Streetz, K., Tacke, F., ... & Trautwein, C. (2020). Experimental liver fibrosis research: Update on animal models, legal issues and translational aspects. *Fibrogenesis & Tissue Repair*, 6(1), 19. <https://doi.org/10.1186/1755-1536-6-19>
- [85]. Donato, M. T., & Tolosa, L. (2021). High-content screening for the detection of drug-induced oxidative stress in hepatocytes. *Methods in Molecular Biology*, 2240, 189–203. https://doi.org/10.1007/978-1-0716-1091-6_13
- [86]. Godoy, P., Hewitt, N. J., Albrecht, U., Andersen, M. E., Ansari, N., Bhattacharya, S., ... & Hengstler, J. G. (2020). Recent advances in 2D and 3D in vitro systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME. *Archives of Toxicology*, 87(8), 1315–1530. <https://doi.org/10.1007/s00204-013-1078-5>
- [87]. Goyal, R., Macri, L. K., Kaplan, H. M., & Kohn, J. (2019). Nanoparticles for the treatment of liver diseases. *Nanomedicine*, 14(8), 957–972. <https://doi.org/10.2217/nnm-2018-0450>
- [88]. Zhang, L., & Wang, H. (2020). Clinical translation of nanomedicines for liver diseases: Challenges and opportunities. *Advanced Therapeutics*, 3(5), 1900198. <https://doi.org/10.1002/adtp.201900198>
- [89]. Sabitha, M., & Sanoj Rejinold, N. (2021). Nanotheranostics for the management of liver diseases. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 13(4), e1696. <https://doi.org/10.1002/wnan.1696>
- [90]. Hare, J. I., Lammers, T., Ashford, M. B., Puri, S., Storm, G., & Barry, S. T. (2020). Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. *Advanced Drug Delivery Reviews*, 108, 25–38. <https://doi.org/10.1016/j.addr.2016.04.025>
- [91]. Metselaar, J. M., & Lammers, T. (2020). Challenges in nanomedicine clinical translation. *Drug Delivery and*

- Translational Research, 10(3), 721–725. <https://doi.org/10.1007/s13346-020-00740-7>
- [92]. Hua, S., & de Matos, M. B. C. (2021). The current landscape of nanomedicine clinical translation. *Frontiers in Pharmacology*, 12, 742049. <https://doi.org/10.3389/fphar.2021.742049>
- [93]. Anselmo, A. C., & Mitragotri, S. (2021). Nanoparticles in the clinic: An update post COVID-19 vaccines. *Bioengineering & Translational Medicine*, 6(3), e10246. <https://doi.org/10.1002/btm2.10246>
- [94]. Hossen, S., Hossain, M. K., Basher, M. K., Mia, M. N. H., Rahman, M. T., & Uddin, M. J. (2019). Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: A review. *Journal of Advanced Research*, 15, 1–18. <https://doi.org/10.1016/j.jare.2018.06.005>
- [95]. Jain, A., & Jain, S. K. (2021). Nanotechnology-based approaches for hepatoprotective drug delivery. *Current Nanoscience*, 17(3), 386–399. <https://doi.org/10.2174/1573413716999200820123233>
- [96]. Kumari, P., Ghosh, B., & Biswas, S. (2020). Nanocarriers for the treatment of liver diseases: Recent advances and challenges. *Journal of Materials Chemistry B*, 8(31), 6837–6855. <https://doi.org/10.1039/D0TB00916D>
- [97]. Li, J., & Mooney, D. J. (2020). Designing hydrogels for controlled drug delivery. *Nature Reviews Materials*, 1(12), 16071. <https://doi.org/10.1038/natrevmats.2016.71>
- [98]. Wolfram, J., & Ferrari, M. (2019). Clinical cancer nanomedicine. *Nano Today*, 25, 85–98. <https://doi.org/10.1016/j.nantod.2019.02.005>
- [99]. Nel, A. E., Mädler, L., Velegol, D., Xia, T., Hoek, E. M., Somasundaran, P., ... & Thompson, M. (2020). Understanding biophysicochemical interactions at the nano-bio interface. *Nature Materials*, 8(7), 543–557. <https://doi.org/10.1038/nmat2442>
- [100]. Dobrovolskaia, M. A., & McNeil, S. E. (2020). Immunological properties of engineered nanomaterials. *Nature Nanotechnology*, 2(8), 469–478. <https://doi.org/10.1038/nnano.2007.223>
- [101]. Wang, Y., & Li, Z. (2022). Artificial intelligence in nanomedicine: From design to clinical translation. *Advanced Drug Delivery Reviews*, 180, 114073. <https://doi.org/10.1016/j.addr.2021.114073>
- [102]. Vargason, A. M., Anselmo, A. C., & Mitragotri, S. (2021). The evolution of commercial drug delivery technologies. *Nature Biomedical Engineering*, 5(9), 951–967. <https://doi.org/10.1038/s41551-021-00698-w>
- [103]. Manzari, M. T., Shamay, Y., Kiguchi, H., Rosen, N., Scaltriti, M., & Heller, D. A. (2021). Targeted drug delivery strategies for precision medicines. *Nature Reviews Materials*, 6(4), 351–370. <https://doi.org/10.1038/s41578-020-00269-6>
- [104]. Kim, J., & Decker, E. A. (2020). Nanotechnology in food and agriculture: A review of the state of the art. *Journal of Agricultural and Food Chemistry*, 68(46), 12891–12902. <https://doi.org/10.1021/acs.jafc.0c04717>
- [105]. Blanco, E., Shen, H., & Ferrari, M. (2020). Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology*, 33(9), 941–951. <https://doi.org/10.1038/nbt.3330>
- [106]. Chen, G., Roy, I., Yang, C., & Prasad, P. N. (2021). Nanochemistry and nanomedicine for nanoparticle-based diagnostics and therapy. *Chemical Reviews*, 116(5), 2826–2885. <https://doi.org/10.1021/acs.chemrev.5b00148>
- [107]. Mura, S., & Couvreur, P. (2020). Stimuli-responsive nanocarriers for drug delivery. *Nature Materials*, 12(11), 991–1003. <https://doi.org/10.1038/nmat3776>
- [108]. Sun, T., Zhang, Y. S., Pang, B., Hyun, D. C., Yang, M., & Xia, Y. (2020). Engineered nanoparticles for drug delivery in cancer therapy.