Application of Nanotechnology in Liver Fibrosis: An Overview

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ABSTRACT

Chronic liver disease constitutes a global health issue owning to their widespread prevalence and the scarcity of effective curative treatments. They are arising from various causes, both infectious and non-infectious diseases. A rapidly evolving field of interest is the use of nanoparticle (NP) systems for the safe administration of different medications and nucleic acid for the treatment of chronic liver disorder. The review examines the pathophysiology, diagnosis and new developments in nanoparticulate systems for the treatment of liver fibrosis related chronic liver disorder. Hepatic stellate cell (HSC) activation is thought to be the primary cause of liver fibrosis. Because of their unique abilities to transfer medications and other therapeutics moieties, liposomes, nanoparticulate systems have all been extensively researched. Currently, nanoparticle technology is used for liver fibrosis. Liver fibrosis can be caused by alcoholism, hepatitis viruses, genetic disorders, steatohepatitis, autoimmune, and other non-infectious conditions including fatty liver. Advanced liver fibrosis, or cirrhosis, is defined by the formation of nodules of regenerated hepatocytes after a fibrous scar caused by the accumulation of extracellular matrix (ECM) proteins disrupts the architecture of the liver.

Keywords: Liver fibrosis,Nanomedicine,Therapy,Theranostics,Application

INTRODUCTION

Liver fibrosis is the excessive accumulation of extracellular matrix proteins, particularly collagen that occurs in most of them of chronic liver disease.[1,2].Severe liver fibrosis induced cirrhosis, liver failure and portal hypertension, triggering liver transplantation. The knowledge of the cellular and molecular pathways behind liver fibrosis has drastically improved. Major collagen-producing cells in the seriously injured liver include activated hepatic stellate cells, portal fibroblasts and bone marrow-derived myofibroblasts. [3]

Fibrogenic cytokines,including TGF-β1,angiotensin II and leptin activate these cells.Reversibility of advanced liver fibrosis in patients has recently been revealed,prompting researchers to create antifibrotic medications[4].Emerging antifibrotic medicines make an effort to prevent the accumulation of fibrogenic cells /the development of extracellular matrix proteins[5].Although numerous therapeutic strategies work well in animal models of liver fibrosis,their efficacy and safety in humans kept uncertain.This review outlines recent advances in understanding the pathophysiology and diagnostics of liver fibrosis,as well as contemporary antifibrotic therapies[6].

Due to the focused delivery of therapeutic drugs into the liver, nanotechnology-based treatments have garnered increased attention recently. Many different nanoparticle(NP) system have been developed using a wide range of materials to effectively treat liver fibrosis[7]. The NP systems composition,architecture,shape,varied sizes,and surface characteristics all contribute to their special abilities for the effective delivery of medicinal precursors.This review addresses the potential future directions and provides an overview of NP systems for liver fibrosis treatment[8].

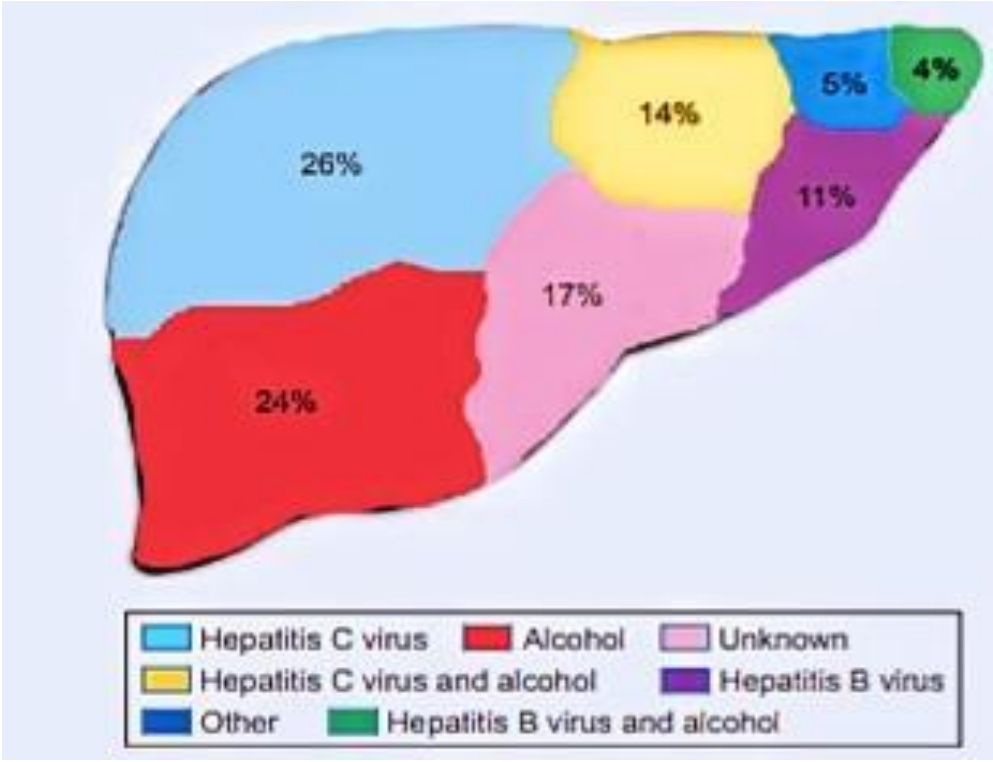

Figure-1 :Major cause of liver disease

Pathogenesis of Liver Fibrosis

The activation of hepatic fibrosis occurs in two stages: persistence and develop. Hepatic fibrogenesis is initiated by a number of growth factors and cytokines. Human fibrogenesis is primarily caused by transforming growth factor beta (TGF-β), which is expressed in different forms by the liver's kupffer cells, hepatocytes, and endothelial cells [18]. When charged with Smad protein, which is made up of structurally identical proteins, TGF-β1—which is an inactive protein—transmits through its receptors to activate important genes, such as procollagen 1 and 3 [9].

It stimulates the development of extracellular matrix (ECM) proteins, inhibits their breakdown, and helps transform hepatic stellate cells (HSC) into myofibroblasts that resemble cells. Hepatic fibrosis in test animals is decreased by platelet-derived growth factor, which is a powerful HSC and uptake stimulant in liver fibrosis [10]. Strong vasoconstrictor endothelin-1 stimulates type-A receptors to induce fibrogenesis [11]. Angiotensin II, a vasoactive cytokine, is another significant component in hepatic fibrogenesis. Hepatic inflammation incites and enhances fibrogenic processes in active HSCs, including pro-inflammatory cytokines, cell migration, and collagen formation [22]. Adipose tissue and stromal cells produce the adipokines ghrelin, leptin, and adiponectin, which are the primary adipokines that harm the liver [13, 14,15]. Leptin is required for fibrosis to develop and for the HSC to activate [15]. However, adiponectin dramatically lowers hepatic fibrosis in vivo and in vitro [14]. In laboratory animals, ghrelin lessens liver fibrosis [16]. The control of lipid and glucose metabolism peroxisome proliferator active receptors (PPARs), which exhibit decreased manifestation in reaction to HSC initiation [17]. Conversely, HSCs are suppressed by PPAR-γ,reduces hepatic fibrosis and fibrogenic activity [18, 19].Toll-like receptors (TLRs) are a class of highly conserved receptors that help host cells identify pathogen-associated chemical structures and recognize microbial infection.

It has been discovered that lipopolysaccharide-induced TLR-4 activation increases chemokine production and increases HSC susceptibility to TGF-β activity [20].Moreover, TLR-4 signaling promotes the production of fibrogenic cytokines, including IL-1, IL-2, and tumor necrosis factor (TNF-α). Several other evidence suggest the emergence of hepatic fibrosis, which includes the consistent hallmark of HSC alpha-smooth muscle actin (α-SMA).Activation that takes place prior to the development of fibrous tissue and is utilized to identify the beginning

of hepatic fibrosis [21, 22]. It is evident that hepatic fibrogenesis involves COX-2,due to the fact that quiescent HSCs do not express it in culture, while activated HSCs [23].

Dormant HSCs are activated at the cellular level by reactive oxygen species, transforming growth factor-1, platelet-derived growth factor, and chemokines produced by the liver's resident Kupffer cells and malfunctioning hepatocytes. To become MFB-like, these reactivated quiescent HSCs go through more trans differentiation,cells that are contractile, pro-inflammatory, and fibrogenic. MFBs, or myofibroblasts, are an essential part in the production and accumulation of collagen. a variety of cell types, including mesothelial cells, epithelial cells, endothelial cells, circulating fibrocytes, localized fibroblasts,Vascular smooth muscle cells and pro-fibrogenic pericytes typically exhibit become articulate ECM components, leading to an increase in the pool of MFBs[24].

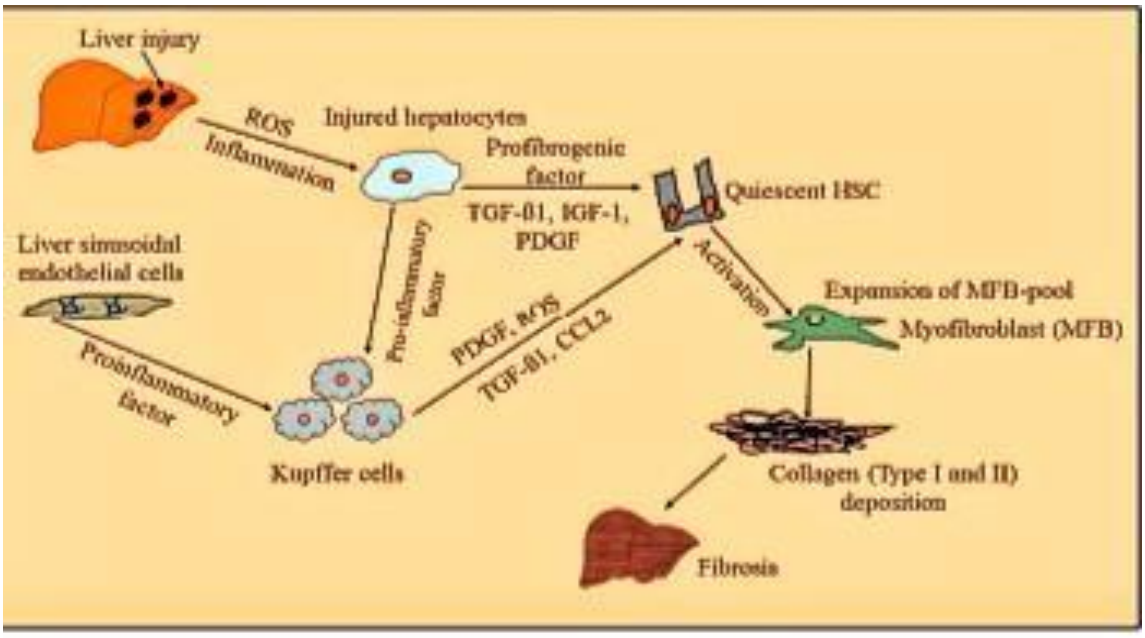

Figure -2. Schematic depiction of pathogenesis and pathophysiology during liver fibrosis progression. Chronic hepatic inflammation causes activation of quiescent hepatic stellate cells, which trans- differentiate into MFB-like cells, which have contractile, proinflammatory, and fibrogenic properties. *MFB: myofibroblast, HSC: hepatic stellate cell, ROS: reactive oxygen species, TGF-β1: transforming growth factor-ß1, PDGF: platelet-derived growth factor, and CCL2: chemokine.*

Role of Nanotechnology in Liver Fibrosis Therapy Using Synthetic Drugs

Nanotechnology-based therapies have emerged as an intriguing and superior option to traditional therapeutic methods in recent times. The study of molecules with sizes ranging from 10 to 500 nanometers is the focus of the quickly developing discipline of nanoscience in pharmaceutical science [25,26]. At the moment, nanomedicines are constructed from sustainable, biocompatible materials and hold a lot of promise for precise administration of medication. This can be done passively by improving the physicochemical characteristics of nano-drug carriers, such as size, shape, and surface qualities, or actively by implementing tissue-or cell-specific devices that allow precise disease site targeting while limiting side effects [27].

Liposomes are artificial vesicles that resemble spheres and are surrounded by two or three lipid bilayers encircling an aqueous compartment. Liposomes have the ability to entrap a broad range of molecules that are both hydrophilic and lipophilic because of their dual structural arrangement. Medication that are hydrophobic can be introduced into the lipid bilayer, while lipophilic ones can be found inside the core of the lipid membrane that is water soluble. NPs of the most basic kind are those composed of liposomes, which have a number of benefits including ease of production,superior absorption, little systemic toxicity, and outstanding biocompatibility [28,29]. Valsartan was often given using liposomes combined with vitamin A. The drugs that are nanoscale improved the hepatic Mas-

receptor's function, and PPAR potently adjusted the level of fibrogenic cytokines by boosting valsartan's permeability and efficacy.

A cyclic peptide called the pPB recognizes the platelet-derived growth factor receptor beta (PDGFR-beta) on the surface of HSCs and has potential to identify vitamin A.Recombinant human tumor necrosis factor-related cell apoptosis-inspired ligands were converted to the HSC surface membrane in a study using pPB-altered liposomes, preserving circulation of ligands inspired by apoptosis in live organisms via recombinant human TNF and lowering fibrosis in vivo as well as in vitro [30]. Similarly, AMD3100, a CXCR4 antagonist possesses the capacity to assault HSCs. In fibrotic livers, Liu and his team aimed to halt angiogenesis.Using CXCR4-targeted nanoparticles, colleagues delivered siRNAs to combat vascular VEGF, or endothelial growth factor.

They discovered that a reduction in VEGF expression suppresses angiogenesis, which restores normalcy to the deformed vasculature in fibrotic individuals. AMD3100-associated liposomes successfully activated chemokine receptor type 4-overexpressed HSCs by delivering analeptic vascular endothelial growth factor siRNAs. Reduced HSC activation and replication was the reason behind AMD3100 liposomal encapsulated anti-fibrotic actions [31]. Biodegradable natural polymers such rosin, albumin, sodium alginate, gelatin, and chitosan as well as synthetic polymers like polylactic acid, polylactide-co-glycolide, and polyamino acid conjugates make up the polymeric nanoparticles [32–35]. Current study suggests that the structure of collagenase may make it easier for nanocarriers to enter the cirrhotic liver.The two drugs, silibinin and siCol11, loaded into self-assembled polymeric micelles based polylactide-co-glycolide-poly spermine-polyethylene glycol-vitamin. A polymers, act in fibrotic livers and selectively target over the activated HSCs, suppressing collagen I production and improving liver fibrosis in a synergistic manner [36]. Given their significant influence on the pathogenesis of liver fibrosis, liver macrophages may be investigated a potential pharmaceutical target for liver fibrosis treatment. Liver endothelial surface cells, in addition to kupffer cells, have scavenger receptors that can be targeted by nanoformulations.

Nanomedicine for Liver Fibrosis Therapy

Inorganic NPs alone can be utilized as therapeutic agents for liver fibrosis therapy because of their unique bioactive qualities [37–39]. The expression of collagen I and α-SMA can be inhibited by both silicon dioxide NPs (SiO2 NPs) and titanium dioxide NPs (TiO2 NPs). Additionally, they promote collagen degradation by tissue inhibitor downregulation and matrix metalloproteinases (MMPs) upregulation of metalloproteinases (TIMPs), suggesting that SiO2 and TiO2 NPs may have antifibrotic properties.NPs in a lab setting [40]. By controlling these NPs, they also demonstrate anti-adhesive and anti-migratory properties.

Gene expression associated with the epithelial-mesenchymal transition (EMT) and restore TGF-β-activated HSCs to a inactive condition (Figure 3). Because cerium oxide NPs have anti-inflammatory qualities, they decrease liver rats with hepatic fibrosis, portal hypertension, and steatosis [41].Due to the enhanced antioxidant qualities of Mn3O4 NPs following acid treatment in the stomach, oral exposure to citrate-functionalized Mn3O4 NPs can shield the liver against oxidative stress, cirrhosis, and fibrosis caused by carbon tetrachloride (CCl4) [42]. ZnO NPs also lessen inflammation, oxidative stress, and lipid peroxidation in liver damage caused by dimethylnitrosamine, which helps to improve liver fibrosis [43].

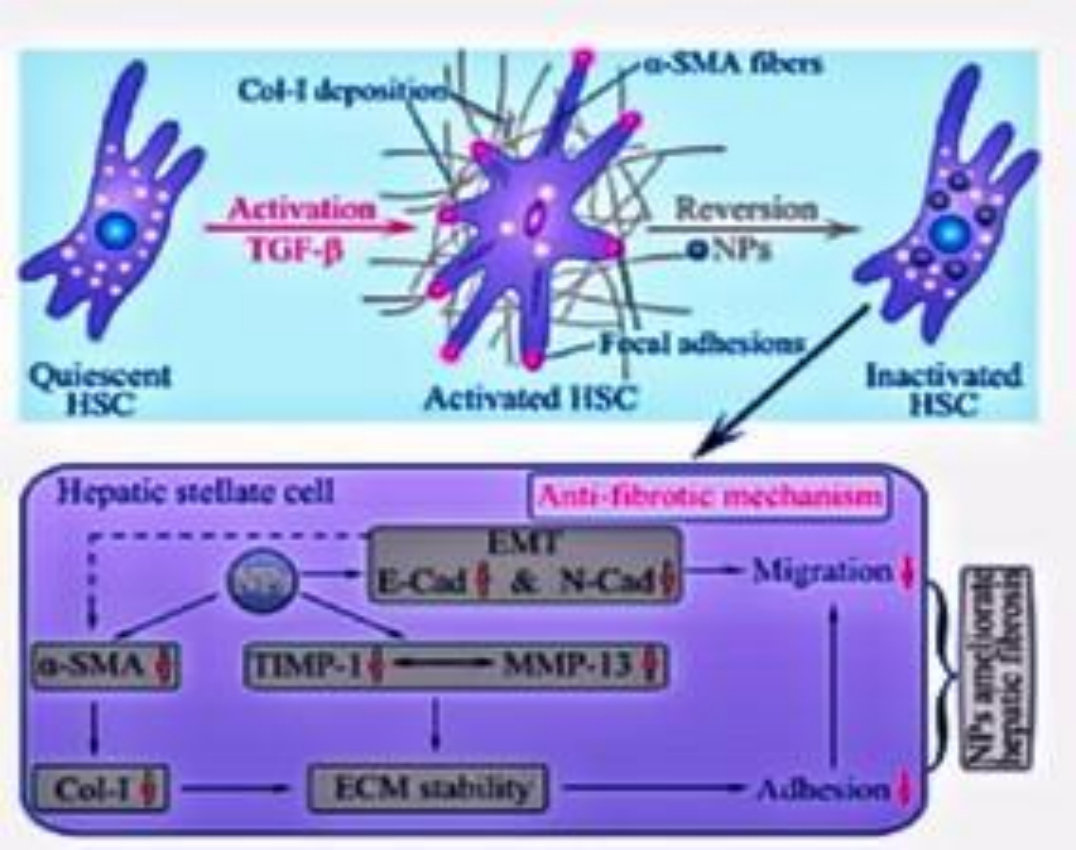

Figure 3. Model for TiO2 NPs and SiO2 NPs ameliorated fibrosis, adhesion and migration of HSCs. TiO2 NPs and SiO2 NPs can suppress the expression of α-SMA and deposition of Col-I induced by TGF-β.ECM was degraded by upregulating MMP-13 and downregulating TIMP-1. Therefore, adhesion of LX-2cells was reduced. Furthermore, NPs stimulated the expression of E-Cad and reduced the expression of N-Cad, and, therefore, aggravated the migratory phenotype.

Using Nanoparticles as Drug Carriers to Treat Liver Fibrosis by Targeting Ligands

The efficient clinical use of conventional antifibrotic medications is restricted by non-specific drug disposition. Up until now, medication delivery targeting the fibrotic area has been possible with nanoformulations. By conjugating NPs with VA, HSCs—the only hepatic VA storage cells—have been actively targeted, given their critical involvement in liver fibrosis. To treat liver fibrosis, liposomes containing medications and components that target HSCs have been produced.

In one investigation, imatinib was to be administered via VA-coupled liposomes. Comparing imatinib treatment alone to the hepatic buildup of imatinib, there was an approximate 13.5-fold increase [48]. With fewer side effects, the nanoformulations decreased the expression of profibrotic mediators like hydroxyproline, TGF-β, and MMP2 in addition to inhibiting the expression of phosphorylated PDGFR-β. Another study used VA-coupled liposomes to deliver the angiotensin II receptor antagonist valsartan [49]. By enhancing valsartan's permeability and effectiveness, the nanoformulations strengthened the expression of PPAR-γ and the hepatic Mas-receptor while potentially restoring the amount of fibrogenic mediators.

The synthesis of retinol and collagenase I co-decorated with polymeric micelles (CRM) based on PLGA-b-poly(ethylene glycol)-maleimide (PLGA-PEG-Mal) was described in an article [50]. These nano drug delivery systems target HSCs and are intended for application in liver fibrosis therapy. Collagenase I ornamentation in the current study may make it easier for nanocarriers to enter the fibrotic liver. In a mouse model of hepatic fibrosis, CRMs were reported to accurately target activated HSCs and to efficiently destroy pericellular collagen I. They also showed great accumulation in the fibrotic liver.[50-52]

In addition, PLGA-polyspermine-PEG-VA polymeric micelles (PVMs) were employed to specifically target HSCs and transport the chemical medication silibinin and the genetic drug siCol1α1 to the location of liver fibrosis [53]. When compared to PVMS loaded with either the chemical medicine or the genetic drug alone, the double-laden polymer micelle reduced collagen I and improved liver fibrosis more effectively. Activated HSCs and hepatoma cells selectively absorbed chondroitin sulfate micelles in combination with retinoic acid and doxorubicin (DOX) (DOX + RA–CS micelles); normal hepatocytes (LO2) did not absorb them [54]. In vitro, the Golgi apparatus was preferentially accumulated in by DOX + RA–CS micelles, which also caused the Golgi structure to collapse, downregulated the production of collagen I, and had synergistic antifibrotic effects on CCl4-induced fibrotic rat models.

Other polymer nanoformulations have been developed in addition to polymeric micelles for the administration of medications, nucleic acids, and other therapeutic components for the treatment of liver fibrosis (Table 2). Retinol-conjugated polyetherimine NPs were found to form a protein-coated complex in one investigation where they adsorbed plasma proteins, specifically retinol-binding protein 4 (RBP) [55]. The NPs may be guided into HSCs by the adsorbed RBP. NPs substantially inhibited the expression of collagen I after being loaded with antisense oligonucleotides, which improved hepatic fibrosis.

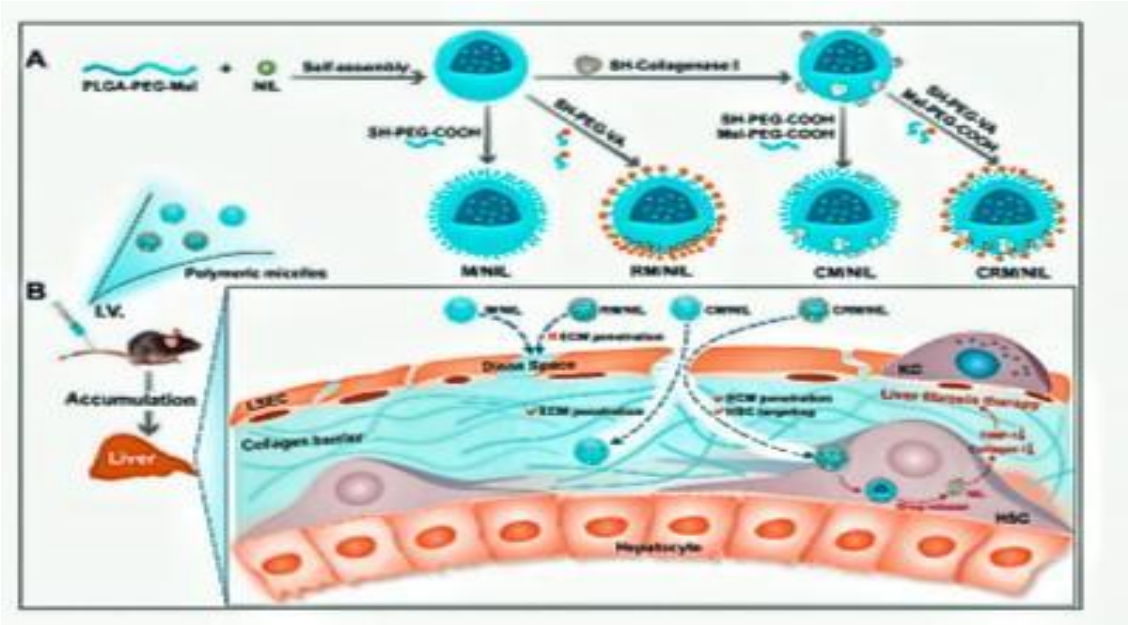

Figure 4. Extracellular matrix-penetrating polymeric micelles for liver fibrosis therapy. (A) Schematic illustration of the preparation of four different polymeric micelles. (B) Schematic illustration of the proposed destiny of the four different polymeric micelles in vivo. The CRM/NIL is able to penetrate the collagen barrier and target activated HSCs. Internalization of CRM/NIL allows the release of NIL,which reduces expression of the metallopeptidase inhibitor, TIMP-1, which in turn enhances collagen I degradation, thereby exerting therapeutic action against liver fibrosis.

Theranostics of Nanomedicine in Liver Fibrosis

By combining diagnostic and therapeutic capabilities into one nanoplatform, "theranostics," a combination of "therapeutics" and "diagnostics," is achieved. A novel and ground-breaking therapeutic idea called theranostics has been put out for a number of disease types, including liver fibrosis [57]. This approach uses very accurate and specialized tailored medicine to enable simultaneous diagnosis and therapy response. In one work, RGD-HBc/QR-coated Hepatitis B core protein nanocages showed selectivity to active HSCs by targeting integrin αvβ3, and they effectively suppressed HSC activation and proliferation in vitro and in vivo [58].

The resulting nanoformulations (RGD–HBc/QGd) showed tremendous potential as MRI contrast agents and NIR fluorescent agents for liver fibrosis diagnosis in vivo (by encapsulating a quercetin–gadolinium complex and/or tagging it with NIR fluorescent probes, specifically Cy5.5). According to a different study, relaxin-conjugated PEGylated superparamagnetic iron oxide NPs (RLX-SPIONs) significantly reduced cirrhosis and improved contrast in MRI, as well as exhibiting selective binding and uptake in TGFβ-activated HSCs [60]. Additionally, micellar conjugates with inorganic elements were created for liver fibrosis theranostics. When combined with a superparamagnetic iron oxide nanoparticle, a pH-sensitive, VA-conjugated copolymer cationic micelle was able to MRI-visible transfer miRNA-29b and miRNA-112 to HSCs.Additionally, micellar conjugates with inorganic elements were created for liver fibrosis theranostics. When combined with a superparamagnetic iron oxide nanoparticle, a pH-sensitive, VA-conjugated copolymer cationic micelle could MRI-visible deliver miRNA-29b and miRNA-112 to HSCs. Downregulating the expression of fibrosis-related genes, such as collagen Iα1, α-SMA, and a tissue inhibitor of MMP1, led to synergistic antifibrotic treatment effectiveness.[61]

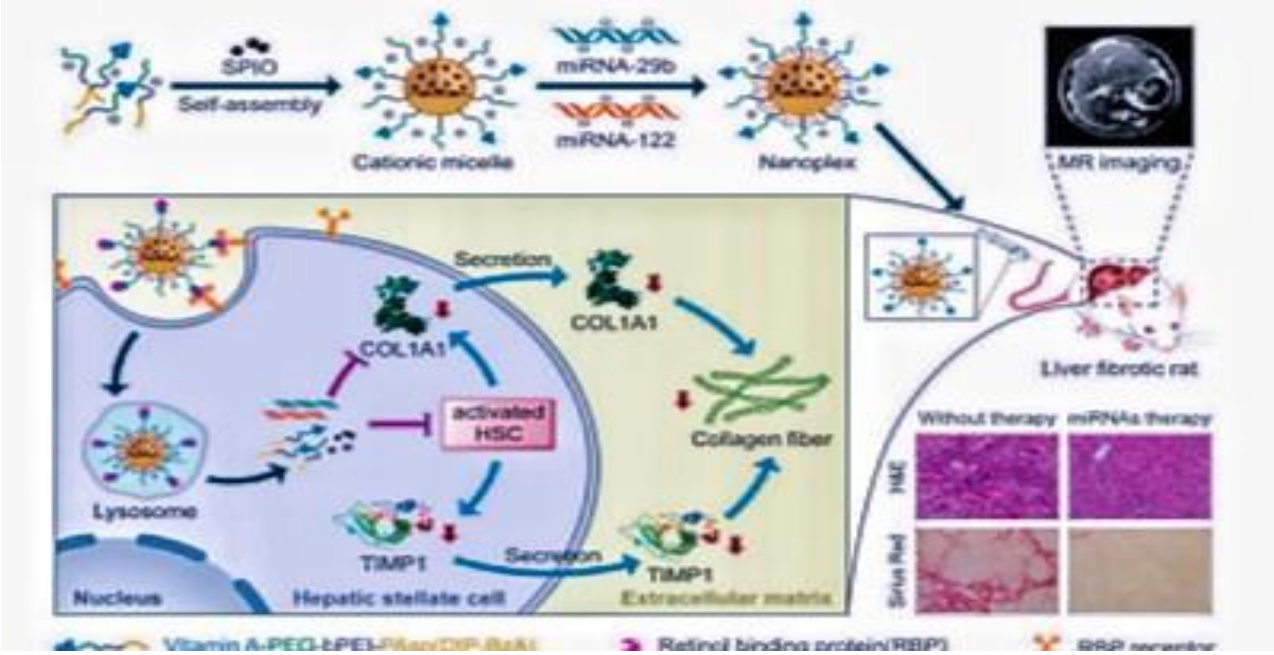

Figure 5. Vitamin A–decorated pH-sensitive and SPIO-loaded nanocomplex T-PBP@miRNA/SPIO (T-miRNA/S) for miRNA targeting delivery in the therapy of liver fibrosis. Expression of liver fibrosis-related genes for alleviating liver fibrosis were synergistically downregulated. The red arrows indicate the reduction of COL1A1, TIMP1, and collagen fiber. Abbreviations: COL1A1, collagen type I Alpha 1 protein; TIMP1, tissue inhibitor of metalloproteinase 1; SPIO, superparamagnetic iron oxide.

CONCLUSION

This review provides an overview of the approaches being taken to create innovative liver fibrosis treatment plans based on multifunctional NPs. The use of nanomedicine systems in the detection and management of liver fibrosis has been extensively documented in the literature and is still an area of research that is expanding quickly, with a focus on theranostics and active targeted drug delivery. Extensive research has been conducted on a wide range of inorganic and organic NPs, such as metal oxide NPs, metal NPs, liposomes, polymer NPs, dendrimers, protein NPs, and organic–inorganic hybrid NPs. Every variety has benefits and drawbacks. Although inorganic nanoparticles have comparatively low manufacturing costs and are inherently durable, their utility and design flexibility are restricted.

Both organic–inorganic hybrid NPs and protein NPs. Every kind has pros and cons of its own. Though their design flexibility and utility are limited, inorganic nanoparticles have a low manufacturing cost and are innately durable. Though they exhibit structural instability and have high production costs and fabrication complexity, organic nanoparticles (NPs) offer considerable design freedom for merging many activities into one platform. Because they combine the benefits of inorganic and organic NPs, organic–inorganic hybrid NPs are favored in the creation of theranostic platforms.NPs have demonstrated significant promise for treating liver fibrosis; however, they can cause hepatotoxicity. It is important to thoroughly

and comprehensively assess the long-term hepatotoxicity of NPs, especially when administering them to patients who have liver disease. Due to weakened immune systems, impaired self-defense mechanisms, and impaired capacity for self-healing, patients are more vulnerable to NPs. According to studies, pathological damage is increased when NPs are exposed. Therefore, careful consideration needs to be given to the health hazards associated with using NPs for liver fibrosis therapy.To target HSCs and cure advanced liver fibrosis brought on by NASH or hepatitis C virus infection, lipid nanoparticles (NPs) carrying siRNA against heat shock protein 47 were created. According to study findings, this nanomedicine system was safe and effective when it was in clinical phase 1b/2.In order to enhance the clinical suitability of nanomedicine systems in the future, the following approaches ought to be taken into account: (1) Creating highly sensitive, stimulus-responsive nanomedicine devices that can react intelligently to internal or external stimuli and release payload at specific locations.

(2) Using a "all-in-one" approach to create intelligent nanomedicine systems with a variety of features, including as targeted delivery, extended blood retention, improved cellular internalization and tissue penetration, stimuli response, and disease progression tracking.

(3) Methodical assessment of medication systems' immunogenicity, pharmacokinetics, and long-term toxicity.

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