Scholars LITERATURE

Nanotechnology and Nanomaterials Research

Short Communication

DOI: https://doi.org/10.47275/2692-885X-131
Volume 7 Issue 1

Treating Fibrosis with Nanomedicine: A Clinical Review of Anti-fibrotic Strategies for Liver and Lung Disease

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Abstract

Fibrosis, a pathological scarring process in organs like the liver and lungs, remains a major cause of morbidity and mortality worldwide, with current therapies often limited by poor efficacy and significant side effects. The complex and multifactorial pathogenesis of fibrosis necessitates innovative therapeutic strategies that can precisely target underlying cellular and molecular mechanisms. This review critically examines the burgeoning role of nanomedicine in meeting this urgent clinical need by enabling targeted and efficient anti-fibrotic interventions. We explore the design and application of advanced nanocarrier platforms, including lipid nanoparticles, polymeric systems, and biomimetic vesicles, for enhanced drug delivery to fibrotic tissues. The review delves into how these nanoplatforms are engineered to target key pro-fibrotic pathways and cell types, such as hepatic stellate cells in liver fibrosis and M2 macrophages in pulmonary fibrosis. Further, we summarize promising preclinical applications of nanomedicine for both liver and lung diseases, highlighting significant reductions in collagen deposition and other fibrosis markers. The potential of natural compounds and herbal medicines, when formulated as nanomedicines, to provide synergistic anti-fibrotic effects is also discussed. Additionally, we present key case studies that demonstrate the superior therapeutic outcomes of targeted nanotherapies in animal models. Finally, the challenges and considerations in the clinical translation of these nanomedicine strategies are outlined. Looking forward, future progress in this field hinges on overcoming translational barriers such as scalable manufacturing and long-term biosafety profiles. The integration of diagnostic and therapeutic functions into single 'theranostic' nanoplatforms presents a promising direction for personalized medicine. Ultimately, the continued convergence of nanotechnology with a deepening understanding of fibrotic disease biology is poised to yield groundbreaking and effective anti-fibrotic therapies.

Keywords: Anti-fibrotic therapy, Drug delivery, Liver fibrosis, Lung fibrosis, Macrophage targeting, Nanocarriers, Nanomedicine, Targeted therapy

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Citation: Subashree S, Gill RK, Manjunath S, Shridhar (2026) Treating Fibrosis with Nanomedicine: A Clinical Review of Anti-fibrotic Strategies for Liver and Lung Disease. Nanotechnol Nanomater Res, Volume 7:1. 131. DOI: https://doi.org/10.47275/2692-885X-131

Received: February 14, 2026; **Accepted:** May 04, 2026; **Published:** May 08, 2026

Introduction

Treating fibrosis with nanomedicine has emerged as a promising frontier in the management of both liver and lung diseases, with recent research emphasizing targeted delivery systems, molecular pathway modulation, and innovative therapeutic agents [1-9]. This literature review presents current findings on anti-fibrotic strategies, focusing on nanomedicine applications, as derived from the literature. One of the central themes in anti-fibrotic therapy is the development of targeted delivery systems to enhance drug efficacy and reduce systemic side effects. Sun et al. [10] introduced a hybrid system combining clodronate-loaded liposomes with fibroblast-derived exosomal systems, designed specifically for pulmonary fibrosis. This approach exemplifies how nanocarriers can improve drug delivery to fibrotic lung tissue, potentially increasing therapeutic concentrations at the site of pathology. Similarly, the use of nanomedicine in liver fibrosis is implied through the exploration of molecular targets and delivery mechanisms [11-17].

Molecular signaling pathways are pivotal in the pathogenesis of fibrosis, and targeting these pathways with nanomedicine offers a strategic advantage [18-24]. Raguraman et al. [25] highlighted the significance of pathways common to diabetes, lung diseases, and cancer, such as Wnt/β-catenin and other signaling cascades. These pathways are attractive targets for nanomedicine-based interventions, which can deliver inhibitors or modulators directly to affected cells, thereby enhancing specificity and reducing off-target effects. For instance, Li et al. [26] discussed the Wnt/β-catenin pathway's role in renal fibrosis, suggesting that nanocarrier systems could be employed to deliver pathway-specific inhibitors, although direct nanomedicine applications are not explicitly described.

In the context of lung fibrosis, mesenchymal stromal cells have garnered attention due to their regenerative and anti-fibrotic properties [27-34]. Pelizzo et al. [35] reviewed the potential of mesenchymal stromal cells in pediatric interstitial lung disease, emphasizing their tissue-regenerative capabilities. While the review does not specify

nanomedicine techniques, the combination of mesenchymal stromal cells with nanocarriers could potentiate their therapeutic effects, a concept supported by the broader trend of integrating cell therapy with nanotechnology to improve delivery and efficacy. Natural compounds and herbal formulations also feature as potential anti-fibrotic agents. Lao et al. [36] discussed Maimendong Decoction, which has shown anti-fibrotic effects. Although the review does not specify nanomedicine delivery systems, encapsulating such herbal extracts within nanoparticles could enhance bioavailability and targeted delivery, aligning with the overall trend of nanomedicine in fibrosis treatment.

Preclinical studies have provided compelling evidence for the efficacy of nanomedicine-based approaches. Thannickal et al. [37] examined the role of NOX1/4 inhibitors, such as setanaxib, in liver, kidney, and lung fibrosis. While the review focuses on the preclinical evidence of setanaxib, it underscores the potential of nanocarrier systems to improve the delivery and potency of such inhibitors across multiple fibrotic diseases. Similarly, Zhang et al. [38] highlighted various molecular targets, including small molecules and natural compounds, which could be delivered via nanocarriers to enhance therapeutic outcomes. In lung fibrosis, innovative nanomedicine strategies are also evident in the development of exosomal systems. Sun et al. [10] demonstrated how fibroblast-derived exosomal hybrids could serve as delivery vehicles, potentially applicable to other fibrotic conditions. Exosomes, as natural nanocarriers, offer advantages such as biocompatibility and intrinsic targeting capabilities, making them attractive for clinical translation.

Furthermore, the potential of nanomedicine extends to gene therapy approaches. Harrison [39] reviewed RNA- and DNA-based therapies for cystic fibrosis lung disease, emphasizing the importance of delivery systems. Although not explicitly focused on fibrosis, these methodologies could be adapted for delivering anti-fibrotic nucleic acids, such as small interfering RNAs (siRNAs) or antisense oligonucleotides, to fibrotic tissues, thereby modulating pathogenic gene expression. Emerging molecular targets like CCL24 and bone morphogenetic proteins are also being explored for their anti-fibrotic potential. Levy et al. [40] discussed CCL24-blocking antibodies, which could be delivered via nanocarriers to modulate immune and fibrotic pathways. Similarly, Ye et al. [41] reviewed bone morphogenetic proteins and their receptors in pulmonary fibrosis, suggesting that nanomedicine could facilitate targeted delivery of bone morphogenetic proteins mimetics or modulators to promote fibrosis resolution.

In summary, the integration of nanomedicine into anti-fibrotic strategies offers a multifaceted approach to tackling fibrosis in liver and lung diseases. The ability to enhance targeted delivery, improve bioavailability, and modulate specific molecular pathways positions nanomedicine as a transformative tool in this field. While many of these strategies are still in preclinical or early clinical stages, the evidence underscores their potential to revolutionize fibrosis treatment by enabling precise, effective, and safe therapeutic interventions.

Nanocarrier Platforms for Targeted Drug Delivery in Fibrosis

Nanocarrier platforms significantly enhance targeted drug delivery in fibrotic diseases by improving the precision, efficacy, and safety of therapeutic interventions (Table 1). These platforms are engineered to deliver drugs directly to the fibrotic tissues, thereby minimizing systemic side effects and maximizing therapeutic outcomes. The use of nanocarriers in fibrotic diseases such as liver fibrosis, idiopathic pulmonary fibrosis, and renal fibrosis has shown promising results in preclinical studies [42-48]. These nanocarriers are designed to target specific cells or proteins involved in the fibrotic process, ensuring that the therapeutic agents are delivered precisely where they are needed.

Supramolecular peptide-based nanomaterials have shown promise in treating fibrosis due to their high biocompatibility and ease of modification. These nanocarriers can be engineered to deliver a range of therapeutic agents, including peptides, proteins, and genes, directly to fibrotic tissues, thereby enhancing their antifibrotic properties [49]. Self-assembling peptides can form nanostructures that facilitate the delivery of therapeutic agents to specific sites, such as hepatic stellate cells in liver fibrosis, improving the therapeutic outcomes by targeting the cells responsible for fibrosis progression [50]. Metal-organic frameworks, such as Mn-curcumin frameworks, have been utilized to target fibrosis-promoting macrophages (FPM) in idiopathic pulmonary fibrosis. These nanocarriers can deliver immune inhibitors directly to fibrotic lung tissues, depleting macrophages and reducing inflammation and oxidative stress, which are key contributors to fibrosis [51].

Poly(lactic-co-glycolic acid) nanoparticles have been developed for liver fibrosis treatment, demonstrating improved drug stability, bioavailability, and therapeutic efficacy compared to free drugs. These nanoparticles can reduce collagen deposition and inflammatory responses in fibrotic tissues [52]. Dual-targeted nanocarriers functionalized with ligands for α-smooth muscle actin (α-SMA) and vascular cell adhesion molecule-1 (VCAM-1) have been developed to simultaneously inhibit activated hepatic stellate cells and endothelial

Table 1: Overview of key nanocarrier platforms for fibrosis treatment.

Nanocarrier platform	Key characteristics	Application in fibrosis	Key advantage
Lipid nanoparticles	Biocompatible; can encapsulate hydrophobic/hydrophilic drugs and nucleic acids	siRNA delivery for cardiac fibrosis; inhalable formulations for idiopathic pulmonary fibrosis	High encapsulation efficiency and clinical validation for RNA delivery
Poly(lactic-co-glycolic acid)	Biodegradable, FDA-approved polymer; sustained release profile	Liver fibrosis (e.g., hepatic stellate cells targeted PLGA-BAY); general drug delivery	Tunable degradation kinetics and excellent safety profile
Metal-organic frameworks	High porosity and loading capacity; can be intrinsically therapeutic	Macrophage targeting idiopathic pulmonary fibrosis (Mn-curcumin frameworks)	Combines drug delivery with intrinsic anti-inflammatory/antioxidant effects
Supramolecular peptides	High biocompatibility; self-assembling; easily functionalized	Target-specific delivery to hepatic stellate cells in liver fibrosis	Programmable structures for precise targeting and low immunogenicity
Biomimetic nanocarriers	Coated with cell membranes (e.g., hepatic stellate cells, red blood cells) for immune evasion	Hepatic stellate cell membrane-camouflaged nanoparticles for homologous targeting in liver	Enhanced biocompatibility and superior active targeting
Extracellular vesicles	Natural nanocarriers with inherent targeting capabilities	Engineered extracellular vesicles delivering anti-fibrotic miRNAs to hepatic stellate cells	Innate biological functions and low immunogenicity
Inhalable hybrid systems	Engineered for mucus penetration and lung barrier crossing	Idiopathic pulmonary fibrosis (e.g., pirfenidone (PFD)@functionalized polymeric nanoparticles (FPNs)-catalase for hypoxia relief)	Direct pulmonary administration, maximizing lung bioavailability

cells in liver fibrosis. This approach disrupts the inflammation-fibrogenesis feedback loop, offering enhanced therapeutic efficacy [53]. Cysteine-based redox-responsive nanoparticles have been designed for fibroblast-targeted drug delivery in myocardial infarction. These nanoparticles can selectively deliver therapeutic agents to activated cardiac fibroblasts, reducing systemic toxicity and improving therapeutic outcomes [54]. Inhalable nanocarriers have been explored for pulmonary fibrosis treatment, offering advantages such as improved drug solubility, penetration of lung barriers, and targeted delivery to fibrotic tissues. This approach enhances drug bioavailability and reduces systemic toxicity [55].

Targeted delivery mechanisms

- Ligand modification: Nanocarriers can be modified with ligands that target specific cell types or proteins. For instance, vitamin A-modified micelles and biomimetic nanoclusters have been used to target hepatic stellate cells in liver fibrosis, achieving significant fibrosis reduction in animal models [56]. Similarly, α-SMA/VCAM-1 dual-targeted nanocarriers have been developed to target activated hepatic stellate cells and endothelial cells, disrupting the inflammation-fibrogenesis feedback loop in liver fibrosis [53].

- Peptide functionalization: In idiopathic pulmonary fibrosis, nanocarriers functionalized with M2-like FPM binding peptides have been used to target FPM, leading to their depletion and improved therapeutic outcomes [51].

Enhanced drug release and retention

- Sustained release: Nanocarriers are designed to provide sustained release of therapeutic agents, which is crucial for maintaining effective drug concentrations at the target site. For example, dual-targeted nanocarriers in liver fibrosis achieved a sustained release rate exceeding 80% over 72 h [53].

- Environment-responsive release: Some nanocarriers are engineered to release their payload in response to specific environmental triggers, such as pH changes. This ensures that the drug is released only in the fibrotic tissue, enhancing the specificity and efficacy of the treatment [57].

Improved therapeutic efficacy

- Synergistic effects: Nanocarriers can be loaded with multiple therapeutic agents to achieve synergistic effects. For instance, Mn-curcumin metal-organic frameworks used in pulmonary fibrosis not only target macrophages but also release manganese (Mn^{2+}) and curcumin, which have additional anti-inflammatory and antioxidative effects [51].

- Reduction in fibrosis markers: In various models of fibrosis, nanocarrier-based treatments have shown significant reductions in fibrosis markers such as collagen deposition and transforming growth factor-beta 1 (TGF-β1) expression, alongside improvements in biochemical markers like alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels [53].

In summary, nanocarrier platforms represent a promising strategy for enhancing targeted drug delivery in fibrotic diseases. By improving the precision and efficacy of drug delivery, these platforms have the potential to transform the treatment landscape for these challenging conditions. However, further research and development are needed to overcome existing challenges and fully realize their clinical potential.

Targeting Pro-fibrotic Signaling Pathways with Nanomedicine

Nanomedicine offers a promising approach to targeting pro-fibrotic signaling pathways (Table 2), providing innovative solutions for treating fibrosis across various organs. By leveraging the unique properties of nanoparticles and other nanomaterials, researchers can deliver therapeutic agents directly to fibrotic tissues, enhancing efficacy and minimizing side effects [58-60]. This approach is particularly beneficial in addressing the complex pathophysiology of fibrosis, which involves multiple signaling pathways and cell types. This section explores different strategies and applications of nanomedicine in targeting pro-fibrotic signaling pathways.

Peptide-based nanomaterials

- Supramolecular peptide-based nanomaterials have shown potential in treating fibrosis by utilizing self-assembling peptides that offer high biocompatibility and programmability. These materials can be tailored for various therapeutic applications, including peptide, protein, gene, and cell therapies, as well as extracellular vesicle therapy [49].

- Peptide-based nanomaterials can be engineered to target specific signaling pathways involved in fibrosis, such as the TGF-β/Smad pathway, which is crucial in the progression of liver fibrosis [61].

Targeted nanoparticle delivery

- Myofibroblast-specific nanoparticles have been developed to inhibit the Rho kinase-myocardin-related transcription factor

Table 2: Promising molecular targets for anti-fibrotic nanomedicine.

Target/pathway	Role in fibrosis	Nanomedicine approach
TGF-β/Smad	Master regulator of extra cellular matrix production and myofibroblast activation	Delivery of siRNA, miRNAs, or small-molecule inhibitors
Wnt/β-catenin	Promotes fibroblast proliferation and epithelial-mesenchymal transition	Nanoparticles carrying pathway inhibitors (e.g., small molecules)
CCL24	Chemokine driving immune cell recruitment and fibrotic pathways	Nanocarriers for delivering CCL24-blocking antibodies
Rho kinase-MRTF-SRF	Central to actin cytoskeleton signaling and myofibroblast differentiation	Myofibroblast-specific nanoparticles with Rho-kinase inhibitors
Nicotinamide adenine dinucleotide phosphate oxidase 4(NOX4)/reactive oxygen species	Key source of reactive oxygen species, driving hepatic stellate cell activation and epithelial-mesenchymal transition	Nanoparticles co-loaded with NOX inhibitors (e.g., setanaxib) and antioxidants
Bone morphogenetic proteins	Dysregulated in idiopathic pulmonary fibrosis; can have both pro-and anti-fibrotic roles	Delivery of bone morphogenetic proteins mimetics or modulators to restore balance
NLRP3 inflammasome	Drives macrophage pyroptosis, inflammation, and lung injury	Albumin nanoparticles delivering pyroptosis inhibitors (e.g., formononetin)

(MRTF)-serum response factor (SRF) pathway, a key player in pulmonary fibrosis. These nanoparticles target myofibroblasts via the angiotensin 2 receptor, reducing fibrosis in murine models [62].

- In liver fibrosis, nanoparticles targeting hepatic stellate cells have been designed to deliver miRNA and other therapeutic agents, effectively inhibiting fibrotic signaling pathways and reducing extracellular matrix deposition [63].

RNA and gene therapy

- Lipid nanoparticles loaded with siRNAs have been used to silence genes like silencing bromodomain-containing protein 4, which are involved in cardiac fibrosis. These nanoparticles are conjugated with antibodies to target activated fibroblasts, reducing fibrosis and improving cardiac function [64].

- Extracellular vesicles engineered to deliver therapeutic miRNAs have shown promise in liver fibrosis, targeting hepatic stellate cells and inhibiting the TGF-β/Smad pathway, thereby reducing fibrosis and improving liver function [64].

Multifunctional nanoparticles

- Multifunctional nanoparticles co-loaded with inhibitors and antioxidants have been developed to target multiple pathways in liver fibrosis. For instance, nanoparticles containing a hedgehog inhibitor and a reactive oxygen species scavenger can effectively target and deactivate hepatic stellate cells, reducing oxidative stress and fibrosis [63].

- Similarly, nanocomplexes combining PI3K/Akt inhibitors with anti-inflammatory agents have been shown to suppress hepatic stellate cell activation and fibrosis development, offering a dual antioxidative and anti-inflammatory approach [65].

While nanomedicine presents a promising frontier in fibrosis treatment, challenges remain in translating these technologies from the laboratory to clinical settings. Issues such as the scalability of nanoparticle production, potential immunogenicity, and long-term safety need to be addressed. Additionally, the complexity of fibrotic diseases, which often involve multiple cell types and signaling pathways, requires a multifaceted therapeutic approach. Despite these challenges, the precision and targeted delivery capabilities of nanomedicine hold significant potential for improving the treatment of fibrosis and other complex diseases.

Nanomedicine Strategies for Liver Fibrosis

Nanomedicine strategies for liver fibrosis have emerged as promising approaches to address the limitations of traditional therapies, which often suffer from poor efficacy and significant side effects. Liver fibrosis, a reversible condition caused by chronic liver injury, can progress to severe complications like cirrhosis and liver failure if untreated. Nanomedicine offers targeted delivery of therapeutic agents, enhancing their efficacy and reducing systemic toxicity.

Targeted delivery systems

- Hepatic stellate cells targeting: Hepatic stellate cells play a crucial role in liver fibrosis progression. Nanomedicines targeting hepatic stellate cells, such as those using retinol or receptor-specific molecules, have shown promise in delivering antifibrotic agents directly to these cells, thereby suppressing their activation and resolving fibrosis [61, 66].

- Dual-targeted nanocarriers: Systems targeting both hepatic stellate cells and endothelial cells, such as those functionalized with α-SMA and VCAM-1 ligands, have demonstrated enhanced drug release and therapeutic efficacy by disrupting the inflammation-fibrogenesis feedback loop [53].

- CD44-targeting nanoparticles: Hyaluronic acid-bilirubin nanoparticles target CD44-overexpressing activated hepatic stellate cells, combining antioxidative and anti-inflammatory strategies to inhibit hepatic stellate cell activation and collagen production [67].

Theranostic applications

- Theranostic nanomedicine: Nanomedicine systems that combine therapy and diagnostics (theranostics) offer significant improvements in liver fibrosis management. These systems enhance imaging contrast, improve tissue penetration, and enable targeted drug delivery, providing a comprehensive approach to diagnosis and treatment [68, 69].

- Fluorescent probes: Silica cross-linked micelles modified with peptide CTCE9908 and loaded with fluorescent probes enable early diagnosis of liver fibrosis by targeting CXCR4-expressing hepatic stellate cells and monitoring reactive nitrogen species [69].

Innovative nanocarrier designs

- Flavonoid-based nanomedicines: Flavonoids, known for their anti-inflammatory and antioxidant properties, have been conjugated with nanoparticles to overcome limitations like poor solubility and rapid degradation. These nanomedicines, such as silymarin-loaded nanoparticles, have shown effectiveness against liver fibrosis [70].

- Aptamer-modified liposomes: Liposomal systems functionalized with aptamers, such as those targeting tenascin-C, enhance the selective delivery of antifibrotic agents like obeticholic acid to fibrotic tissues, improving therapeutic outcomes while minimizing systemic toxicity [69].

While nanomedicine strategies for liver fibrosis show great promise, challenges remain in translating these approaches from laboratory research to clinical application. Issues such as ensuring consistent drug delivery, overcoming biological barriers, and minimizing off-target effects need to be addressed. Additionally, the complexity of liver fibrosis pathogenesis requires multifaceted treatment strategies that can adapt to individual patient needs. Despite these challenges, the advancements in nanomedicine offer a hopeful outlook for more effective and targeted liver fibrosis therapies.

Nanomedicine Strategies for Pulmonary Fibrosis

Nanomedicine strategies for pulmonary fibrosis, particularly idiopathic pulmonary fibrosis, are emerging as promising therapeutic approaches due to their potential to enhance drug delivery, reduce systemic toxicity, and improve treatment efficacy. These strategies leverage the unique properties of nanoparticles to target specific pathways involved in the pathogenesis of pulmonary fibrosis, such as epithelial-mesenchymal transition, mitochondrial dysfunction, and oxidative stress. This section outlines key nanomedicine strategies for treating pulmonary fibrosis.

Epigenetic and epithelial-mesenchymal transition modulation

- Nanomedicine formulations, such as liposomes and polymeric nanoparticles, are being explored to modify epigenetic

regulators of epithelial-mesenchymal transition, a critical process in idiopathic pulmonary fibrosis pathogenesis. These formulations can enhance the delivery and efficacy of anti-idiopathic pulmonary fibrosis agents by providing controlled release and reducing systemic toxicity [71].

- Inhalable nanomedicines, such as those encapsulating PFD and modified with catalase, have been developed to penetrate mucus barriers and accumulate in fibrotic lesions, thereby enhancing therapeutic efficacy by reversing the immunosuppressive microenvironment [72].

Mitochondrial and cellular pathway targeting

- A 'double braking' strategy using nanomedicines targets mitochondrial permeability transition pore opening, a hallmark of injured alveolar epithelial cells in idiopathic pulmonary fibrosis. This approach involves nanoparticles co-assembled with cyclosporin A and siRNA to inhibit mitochondrial permeability transition pore opening, thereby reducing epithelial damage and fibrosis [73].

- Targeting the Rho kinase-MRTF-SRF pathway using myofibroblast-specific nanoparticles has shown potential in reducing myofibroblast activation and fibrosis in murine models, highlighting the importance of cell-specific targeting in nanomedicine strategies [62].

Ferroptosis and pyroptosis inhibition

- Ferroptosis inhibitors, such as deferoxamine, have been formulated into nanomedicines to improve solubility and targeting, offering a promising strategy for idiopathic pulmonary fibrosis treatment by reducing lipid peroxidation and iron chelation [74].

- Albumin-based nanoparticles delivering formononetin have been developed to block macrophage pyroptosis, a process contributing to lung injury and fibrosis, thereby improving lung function and survival in animal models [75]

Dual-drug and traditional medicine approaches

- Dual-drug nanoparticle formulations, combining PFD with other agents like galectin-3 inhibitors or traditional Chinese medicine components, have been designed to provide combination therapy for idiopathic pulmonary fibrosis. These formulations aim to target multiple pathways, such as collagen modulation and fibroblast autophagy regulation, to enhance treatment outcomes [76].

- Inhalable nanoparticles loaded with traditional Chinese medicine components, such as astragaloside IV and ligustrazine, have shown efficacy in reducing oxidative stress and inflammation, key drivers of idiopathic pulmonary fibrosis progression [77].

While nanomedicine strategies offer significant promise for treating pulmonary fibrosis, challenges remain in optimizing delivery systems, ensuring biosafety, and achieving precise targeting. The integration of traditional medicine with modern nanotechnology also presents a novel avenue for developing effective therapies. However, further research and clinical trials are necessary to fully realize the potential of these innovative approaches in the treatment of idiopathic pulmonary fibrosis and other forms of pulmonary fibrosis.

Natural Compounds and Herbal Nanomedicines for Anti-fibrotic Therapy

Natural compounds and herbal nanomedicines are emerging as promising alternatives for anti-fibrotic therapy, particularly in the treatment of liver fibrosis. These therapies leverage the bioactive properties of plant-derived compounds and the advanced delivery capabilities of nanotechnology to enhance therapeutic efficacy and reduce side effects. The integration of natural compounds with nanomedicine offers a novel approach to overcoming the limitations of conventional treatments, such as poor solubility and bioavailability. This section explores the potential of these innovative therapies, focusing on their mechanisms, efficacy, and challenges.

- Flavonoids-based nanomedicines: Flavonoids, such as silymarin and quercetin, have shown significant anti-fibrotic effects when formulated as nanomedicines. These compounds, when conjugated with nanoparticles, overcome limitations like poor solubility and rapid degradation, enhancing their bioavailability and target-specific action. Examples include silymarin-loaded gold nanoparticles and quercetin nanoliposomes, which have demonstrated effective anti-inflammatory and antioxidant activities, crucial for combating liver fibrosis [70].

- Plant-derived natural compounds: Edible plant-derived compounds, including phenolic acids and flavonoids, have been identified for their anti-fibrotic properties. Compounds like curcumin, resveratrol, and naringenin modulate key signaling pathways involved in fibrogenesis, such as TGF-β/Smad and nuclear factor kappa-light-chain-enhancer, to exert their effects. These compounds are noted for their minimal side effects, making them attractive candidates for long-term therapy [78].

- Herbal medicines and nutraceuticals: Traditional herbal medicines, including those from Chinese medicine, have shown promise in preclinical studies for their anti-inflammatory and regenerative properties. These include formulations that target cytokine production and hepatic stellate cell activation [79, 80]. A nutraceutical blend of olive oil, linseed oil, and ginger extract in nanoemulsion form has demonstrated superior efficacy in reducing liver fibrosis in animal models by modulating oxidative stress and fibrogenic markers [81].

- Nanoparticulate drug delivery systems: Nanoparticulate systems enhance the delivery and efficacy of plant-based therapeutics by improving their pharmacokinetics and bioavailability. These systems include solid lipid nanoparticles and polymeric nanoparticles, which facilitate targeted delivery and sustained release of active compounds. The integration of these systems with natural compounds holds significant promise for developing effective anti-fibrotic therapies [82]

While the potential of natural compounds and herbal nanomedicines in anti-fibrotic therapy is promising, several challenges remain. The translation of preclinical findings to clinical settings is hindered by issues related to safety, delivery, and efficacy. Moreover, the complex pathways involved in fibrogenesis require a multifaceted approach, often necessitating combination therapies for maximal therapeutic impact [83]. Ongoing research and clinical trials are essential to optimize these therapies and establish their role in the treatment of chronic liver diseases.

Case Studies

Nanomedicine has emerged as a promising approach for the treatment of lung and liver fibrosis, offering targeted delivery and enhanced therapeutic efficacy. This approach leverages the unique properties of nanoparticles to overcome the limitations of traditional therapies, such as poor tissue penetration and systemic side effects. This section provides an overview of studies and advancements in

nanomedicine for lung and liver fibrosis, highlighting specific strategies and outcomes.

A study by Troncoso et al. [53] on α-SMA/VCAM-1 dual-targeted nanocarriers demonstrated several significant results regarding their design, drug release kinetics, and therapeutic efficacy in a liver fibrosis model. The nanocarriers were successfully prepared using a thin-film hydration and ultrasonic dispersion method. They were loaded with siRNA-heat shock protein 47, a therapeutic agent, and characterized using dynamic light scattering, transmission electron microscopy, and high-performance liquid chromatography to confirm their properties. Dual-targeted nanocarriers exhibited superior sustained release of their cargo *in vitro*. They achieved a cumulative release rate exceeding 80% over 72 h. This sustained release was significantly higher than that observed with single-target carriers, which only reached approximately 60% cumulative release within the same timeframe. The drug release profile from the dual-targeted nanocarriers closely fitted the Higuchi diffusion model, indicating a diffusion-controlled release mechanism. In a CCl4-induced mouse model of liver fibrosis (n = 48), *in vivo* fluorescence imaging revealed that the dual-targeted nanocarriers showed greater accumulation in the liver compared to other formulations. These nanocarriers also demonstrated a prolonged retention time within the liver, suggesting better localized therapeutic action. The *in vivo* elimination of the dual-targeted nanocarriers followed a first-order elimination model. Histological staining confirmed a significant reduction in collagen deposition in the livers of mice treated with the dual-targeted nanocarriers, indicating a decrease in fibrosis. Immunohistochemistry results showed lower expression levels of key fibrotic markers, specifically α-SMA and TGF-β1, in the dual-targeted treatment group. This suggests a reduction in activated hepatic stellate cells and overall fibrogenic signaling. Serum levels of ALT and AST, common indicators of liver damage, were significantly improved ($p < 0.05$) in the dual-targeted group, demonstrating better liver health. In summary, the dual-targeted nanocarriers effectively addressed liver fibrosis by simultaneously targeting activated hepatic stellate cells and VCAM-1–expressing endothelial cells. This approach led to enhanced drug release, improved hepatic accumulation and retention, and ultimately, superior therapeutic outcomes, including reduced fibrosis and improved liver function, by disrupting the inflammation–fibrogenesis feedback loop.

A study by Wang et al. [56] on precision-engineered nanocarriers for targeted treatment of liver fibrosis yielded several significant results, demonstrating the potential of vitamin A-modified micelles and biomimetic nanoclusters. The developed nanocarriers exhibited uniform sizes, with micelles measuring 125.4 ± 5.2 nm and nanoclusters measuring 84.7 ± 3.8 nm. Nanocarrier achieved high drug loading efficiency, exceeding 90%. The nanocarrier demonstrated sustained drug release properties, indicating their suitability for therapeutic applications. *In vitro* tests confirmed that the nanocarriers were effectively taken up by cells. They significantly affected hepatic stellate cells, which are relevant to liver fibrosis. In animal studies, nanoclusters consistently outperformed micelles. In a carbon tetrachloride-induced liver fibrosis model, nanoclusters achieved a substantial fibrosis reduction of 78.4%. Further analysis established clear links between drug concentration, cellular uptake, and the observed therapeutic results. Time-based tests revealed that the nanoclusters maintained a steady therapeutic effect of 85% ± 3% over a 72 h period. These results underscore the importance of well-designed nanocarriers in improving treatment outcomes for complex diseases, highlighting the great potential of vitamin A-modified micelles and biomimetic nanoclusters for targeted and long-lasting drug delivery.

A study by Hou et al. [51] reported on idiopathic pulmonary fibrosis therapy. The M2-like FPM targeting nanoparticle, M2NP-BLZ@Mn-curcumin, successfully depleted approximately 80% of M2-like macrophages (FPM) in a bleomycin-induced fibrosis mouse model. This depletion was a key goal of the targeted delivery approach. Significant therapeutic benefits were achieved through the successful depletion of FPM. The study highlights a novel strategy with promising prospects for molecular-targeted fibrosis therapy. Beyond FPM depletion, the degradation of M2NP-BLZ@Mn-curcumin released Mn^{2+} and curcumin, which accumulated in the fibrotic lung tissue. These released components have anti-inflammatory and immune regulation effects, further enhancing the antifibrotic outcome and alleviating inflammation and oxidative stress reactions. The functionalized M2NP-BLZ@Mn-curcumin nanoparticles demonstrated preferential uptake by FPM, leading to their depletion from fibrotic lung tissues. This targeted delivery was facilitated by the M2-like FPM binding peptide (M2pep) functionalizing the nanocarrier surface. In summary, the study successfully demonstrated that M2pep-modified and BLZ945-loaded Mn-curcumin metal-organic framework nanoparticles (M2NP-BLZ@Mn-curcumin) can effectively target and deplete FPM (Figure 1), leading to significant therapeutic benefits in idiopathic pulmonary fibrosis, further augmented by the anti-inflammatory properties of the released components.

A study by Collins et al. [52] on biodegradable poly(lactic-co-glycolic acid) nanoparticles for liver fibrosis treatment yielded several significant results, demonstrating the potential of this drug delivery system. The poly(lactic-co-glycolic acid) nanoparticles were observed to be regular spheres, with particle sizes predominantly ranging between 100 and 150 nm. They also exhibited a polydispersity index below 0.2, indicating a narrow size distribution. The nanoparticles showed good stability and a high capacity for drug loading. Histological analysis revealed that the poly(lactic-co-glycolic acid)delivery group significantly reduced collagen deposition and inflammatory response in the liver. The liver tissue structure was also clearly restored. Serological tests indicated that levels of ALT and AST, which are markers of liver damage, returned close to normal in the poly(lactic-co-glycolic acid) delivery group. The content of hydroxyproline, a key indicator of fibrosis, decreased by approximately 55% compared to the model group. This therapeutic effect was superior to that observed with the free drug group. Pharmacokinetic analysis demonstrated that the area under the curve for the poly(lactic-co-glycolic acid) delivery group increased by about 1.8-fold compared to the free drug group. This increase in area under the curve suggests prolonged circulation of the drug and improved bioavailability when delivered via poly(lactic-co-glycolic acid)nanoparticles. In summary, the study confirmed that poly(lactic-co-glycolic acid) nanocarriers offer substantial advantages in antifibrotic therapy by improving drug stability and *in vivo* distribution, leading to significant therapeutic benefits observed in both histological and biochemical outcomes. These findings provide a promising direction for the clinical translation of antifibrotic drugs.

A study by Zhang et al. [84] demonstrated that a retinol-conjugated polyetherimine nanoparticle system was designed to selectively recruit retinol binding protein 4 into its protein corona components. This recruitment is a crucial step in directing the therapeutic agent to its target cells. Retinol binding protein 4, once bound to retinol on the retinol-conjugated polyetherimine carrier, played a pivotal role in directing the antisense oligonucleotide laden retinol-conjugated polyetherimine carrier specifically to hepatic stellate cells. These cells are recognized for their essential involvement in the progression of hepatic fibrosis. In 2 distinct mouse models of fibrosis—one induced

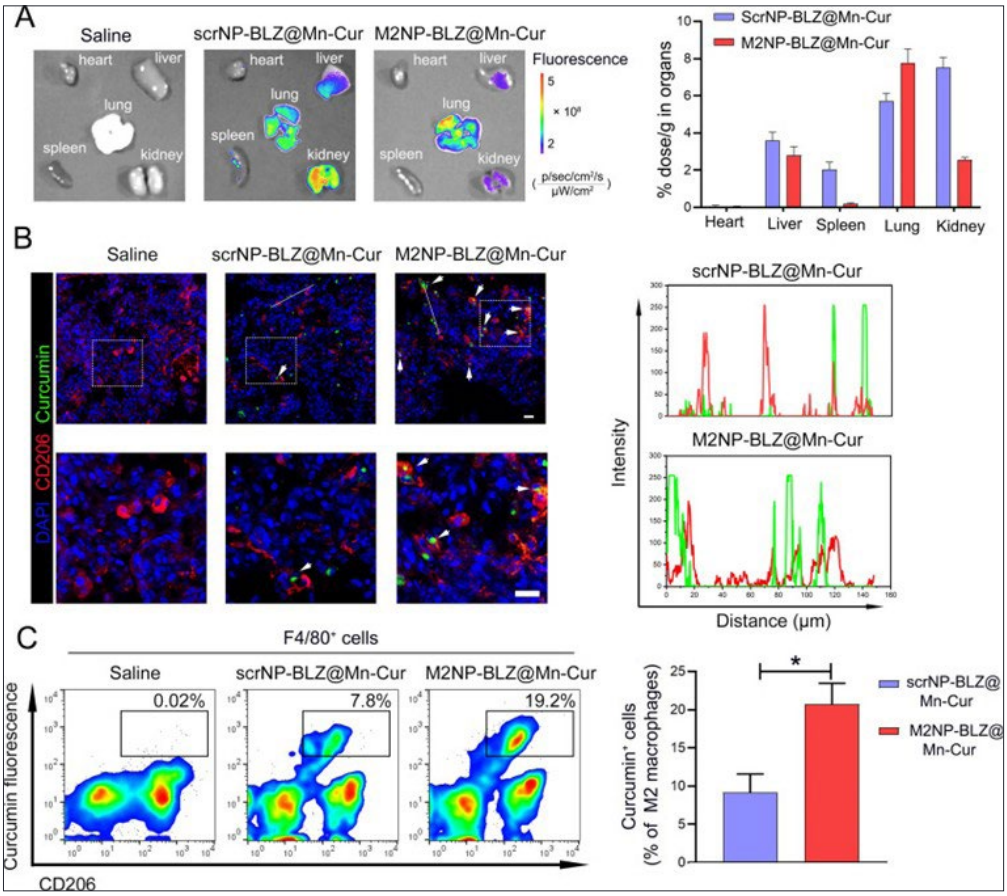

Figure 1: (A) Biodistribution of nanoparticles. *Ex vivo* fluorescence images and quantification of scrambled (scr)NP-BLZ@Mn-curcumin or M2NP-BLZ@Mn-curcumin in major organs of BLM-treated mice. **(B)** Targeting M2 macrophages. Immunofluorescence staining shows the localization of scrNP-BLZ@Mn-curcumin and M2NP-BLZ@Mn-curcumin (white triangles) with CD206+ M2 macrophages. **(C)** Flow cytometry analysis of nanoparticle uptake. Left: Representative plots of the curcumin+CD206+ population within F4/80+ lung macrophages [51].

by carbon tetrachloride and the other by bile duct ligation—the antisense oligonucleotide laden retinol-conjugated polyetherimine particles proved effective. These particles successfully suppressed the expression of type I collagen (collagen I), which is a key marker and contributor to fibrosis. Consequently, the treatment significantly ameliorated hepatic fibrosis in both models, indicating the therapeutic potential of this delivery system. The findings suggest that this delivery system, which is specifically designed to leverage the power of corona proteins for targeting, represents a promising new tool. It offers a novel strategy for the targeted delivery of therapeutic agents, particularly for the treatment of hepatic fibrosis, by overcoming limitations associated with traditional ligand-modified nanoparticles. In summary, the paper successfully demonstrated a novel strategy for targeted drug delivery by exploiting the protein corona. The retinol-conjugated polyetherimine nanoparticle system, by selectively recruiting retinol binding protein 4, effectively delivered antisense oligonucleotide to hepatic stellate cells, leading to the suppression of collagen I expression and amelioration of hepatic fibrosis in mouse models.

A study by Sun et al. [85] outlines a novel drug delivery strategy designed to overcome significant barriers in treating liver fibrosis, focusing on precise activation and enhanced drug penetration (Figure 2). This approach combines a nanosized iron-locked drug generator with an orally absorbed iron chelator to achieve therapeutic effects. Conventional liver-targeting nanoplatforms face considerable hurdles in delivering antifibrotic drugs to pathological sites due to complex physical barriers and the liver's clearance mechanisms in fibrotic livers. A new drug delivery strategy was developed to bypass these penetration barriers. This strategy involves the coadministration of two components: (i) Pro-hyaluronidase (a nanosized iron-locked drug generator) and (ii) deferasirox (an orally absorbed iron chelator). The intravenously injected Pro-HAase rapidly accumulates in the microcapillaries of the fibrotic liver. Subsequently, deferasirox, after oral absorption and targeting the liver, disrupts the polyphenol-iron coordination within Pro-hyaluronidase. This disruption liberates antifibrotic components, including procyanidine and hyaluronidase. A key advantage is deferasirox's preferential disassembly of Pro-hyaluronidase accumulated in the liver sinusoid, rather than in systemic circulation or other organs. This is due to deferasirox's absorption requiring sequential processes of traversing the intestinal mucosa and targeting the liver, thereby preventing off-target activation and depletion of normal iron pools. The *in-situ* disassembly process significantly decreases the sequestration of Pro-hyaluronidase by mononuclear phagocyte system cells. This promotes gradient-driven permeation of the therapeutic components (procyanidine and hyaluronidase) into surrounding liver tissues within 2 h. The inactive iron-deferasirox complex formed during disassembly is subsequently excreted via biliary pathways, contributing to the strategy's self-detoxification ability. The cooperation between Pro-hyaluronidase and deferasirox, in conjunction with oral nattokinase mediated antifibrosis therapy, leads to the complete reversal of liver fibrosis. This strategy also effectively suppresses the chronic hepatotoxicity associated with residual liver iron, which can accumulate after multiple doses

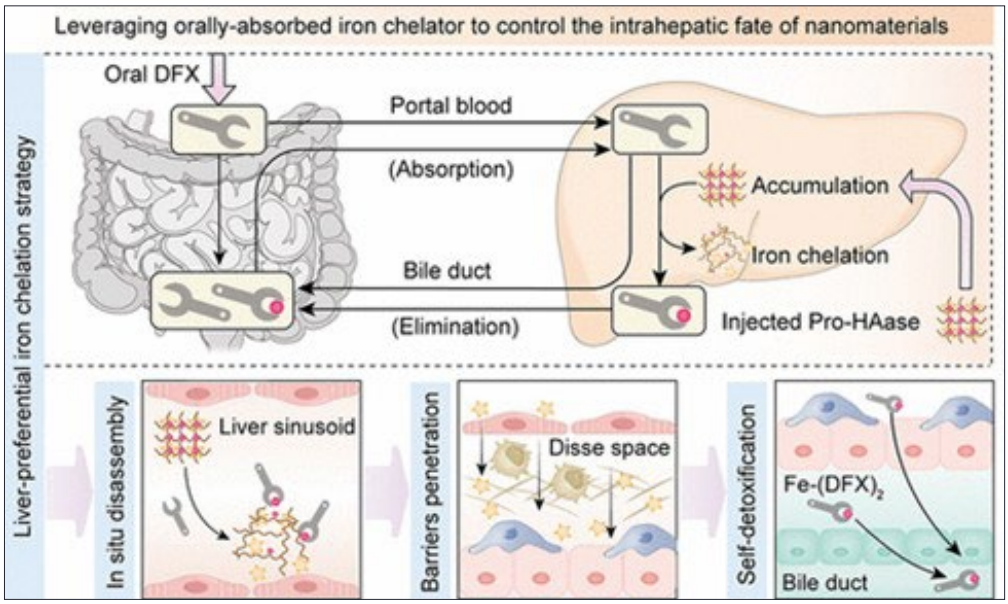

Figure 2: Novel drug delivery strategy was designed to overcome drug penetration barriers in a fibrotic liver and cooperated with oral nattokinase-mediated antifibrosis therapy [85].

of Pro-hyaluronidase. The high spatiotemporal precision, unique barrier-penetration mechanism, and self-detoxification capability of this strategy provide a foundation for designing similar iron-locked nanosystems to improve treatments for liver fibrosis and other liver diseases. In summary, the paper demonstrates a highly effective and precisely controlled drug delivery system for liver fibrosis. By leveraging an iron-locked drug generator activated by an orally absorbed chelator, the strategy ensures targeted drug release, enhanced tissue penetration, reduced systemic toxicity, and ultimately, the complete reversal of liver fibrosis, while also mitigating iron-related hepatotoxicity.

A study by Cheng et al. [86] on hepatic stellate cell membrane-camouflaged Poly(lactic-co-glycolic acid) nanoparticles core loaded with an antifibrotic agent, named HSC-PLGA-BAY, yielded several significant results regarding their efficacy in treating liver fibrosis. The developed HSC-PLGA-BAY nanosystem demonstrated selective targeting towards activated hepatic stellate cells. This specificity is crucial for effective treatment, as activated hepatic stellate cells are the primary drivers of liver fibrosis progression. The internalization of these nanoparticles by activated hepatic stellate cells was mediated by homologous cell adhesion molecules present on the hepatic stellate cell membrane. Specifically, integrins and N-cadherin were identified as key molecules facilitating this targeted delivery. Treatment with HSC-PLGA-BAY significantly increased the apoptosis (programmed cell death) of activated hepatic stellate cells. This is a critical mechanism for reducing the population of fibrosis-promoting cells. The study observed an amelioration of liver fibrosis progression in a bile duct ligation-induced fibrotic mice model. This animal model is commonly used to mimic human liver fibrosis, suggesting the potential translational relevance of these findings. Collectively, these findings indicate that the hepatic stellate cell targeted therapeutic platform holds promising potential as an effective strategy for liver fibrosis treatment. The ability to precisely deliver antifibrotic agents to the cells responsible for fibrosis, coupled with demonstrated efficacy in an *in-vivo* model, highlights its therapeutic promise. In summary, the study successfully developed a novel nanoparticle system that leverages hepatic stellate cell membrane camouflage for targeted delivery of an antifibrotic agent. This system effectively targets activated hepatic stellate cells, promotes their apoptosis, and significantly reduces liver fibrosis progression in a preclinical model, positioning it as a promising candidate for future liver fibrosis therapies.

A study by Sun et al. [87] investigated the efficacy of rosiglitazone (RGZ)-loaded lipid nanoparticles (LNPs) functionalized with RGD peptides (RGZ/PFP@LNP-RGD) combined with ultrasound for treating liver fibrosis. The results demonstrated significant improvements both *in-vitro* and *in-vivo*. Treatment with RGZ/PFP@LNP-RGD led to a decrease in the expression of crucial fibrosis markers. These included collagen Iα1, α-SMA, and TGF-β1 at both the protein and mRNA levels. The application of ultrasound further augmented the release of RGZ from the nanocarriers. This enhanced release subsequently improved the inhibition of hepatic stellate cell activation, which is central to fibrosis progression. When RGZ/PFP@LNP-RGD was combined with ultrasound treatment, there was a marked reduction in liver fibrosis. This effect was more pronounced compared to treatment with free RGZ alone. The combined therapy also resulted in improved liver function. Histological and biochemical assessments corroborated these findings, confirming reduced expression of fibrosis markers and decreased liver damage. The findings suggest that RGZ/PFP@LNP-RGD, particularly when used in conjunction with ultrasound, presents a promising noninvasive therapeutic approach for liver fibrosis. This strategy offers enhanced targeting to activate hepatic stellate cells, controlled drug release, and reduced systemic toxicity.

A study by Zou et al. [72] describes the development and demonstrated efficacy of an inhalable microenvironment-responsive hybrid nanomedicine, PFD@FPNs-catalase, designed to treat idiopathic pulmonary fibrosis. The PFD@FPNs-catalase nanomedicine is engineered to overcome the dense airway mucus barrier. Its small particle size, electronegativity, and PEGylated surface enable it to penetrate mucus by overcoming supramolecular interactions. This enhanced penetration leads to improved accumulation of the nanomedicine in the lung lesions. Despite its complex design, the nanomedicine demonstrates high stability and excellent

biocompatibility. This is attributed to the relatively low quantity of silica doping used in its formulation. The nanomedicine is modified with catalase on its surface. This surface-anchored catalase is demonstrated to relieve hypoxia within the lung microenvironment. By alleviating hypoxia, the PFD@FPNs-catalase nanomedicine effectively reverses the immunosuppressive microenvironment often associated with idiopathic pulmonary fibrosis. The combined effects of improved drug delivery, hypoxia relief, and immunosuppressive microenvironment reversal lead to enhanced therapeutic efficacy against idiopathic pulmonary fibrosis. Nanomedicine remarkably inhibits the progression of idiopathic pulmonary fibrosis, showcasing bright prospects for future idiopathic pulmonary fibrosis therapy. In summary, the research successfully developed an inhalable, mucus-penetrating nanomedicine (PFD@FPNs-catalase) that addresses critical limitations in idiopathic pulmonary fibrosis treatment. Its ability to navigate biological barriers, relieve hypoxia, and reverse immunosuppression significantly enhances its therapeutic potential, marking a promising advancement for idiopathic pulmonary fibrosis therapy.

A study by Ouyang et al. [75] focused on developing an albumin-based nanomedicine to treat lung injury and fibrosis by targeting macrophage pyroptosis. An albumin-based nanoformulation, named formononetin@albumin nanoparticles, was successfully developed to deliver formononetin for the treatment of lung injury and fibrosis. The formononetin@albumin nanoparticles demonstrated efficient accumulation at the impaired lung lesions. This targeted delivery is attributed to the leaky vasculature present in injured tissue and the affinity between albumin and the overexpressed secreted protein acidic and rich in cysteine protein. formononetin@albumin nanoparticles were found to remarkably improve lung function and prolong animal survival in a bleomycin-induced lung injury and fibrosis model. This therapeutic effect was achieved by blocking the NLRP3 inflammasome-involved pyroptosis process in macrophages. Through multi-omics analysis, formononetin was identified and proven to be a pyroptosis inhibitor. The study also elucidated the corresponding lipid metabolism-related mechanisms underlying this inhibition. The treatment with formononetin@albumin nanoparticles showed no noticeable side effects, indicating a favorable safety profile. This research represents the first instance of employing an albumin-based nanoparticle for the active delivery of a pyroptosis inhibitor to impaired lung tissue. The findings provide a promising strategy for the treatment of lung injury and fibrosis, addressing challenges such as the lack of specific inhibitors and the dense stroma in affected lungs. In summary, the study successfully developed and validated formononetin@albumin nanoparticles as an effective and safe nanomedicine for lung injury and fibrosis. It demonstrated that these nanoparticles actively deliver formononetin to lung lesions, where formononetin inhibits macrophage pyroptosis via NLRP3 inflammasome blockade, leading to improved lung function and survival without significant side effects. This innovative approach offers a new therapeutic avenue for these debilitating conditions.

While nanomedicine offers significant advancements in the treatment of lung and liver fibrosis, challenges remain in translating these strategies from laboratory to clinical settings. Issues such as nanoparticle stability, potential toxicity, and regulatory hurdles need to be addressed to ensure safe and effective clinical applications. Additionally, the complexity of fibrotic diseases necessitates a comprehensive understanding of the underlying mechanisms to develop more targeted and personalized therapies. Despite these challenges, the potential of nanomedicine to revolutionize fibrosis treatment is substantial, offering hope for improved patient outcomes.

Clinical Translation, Challenges, and Future Directions of Anti-fibrotic Nanomedicine

The clinical translation of anti-fibrotic nanomedicine presents a promising yet challenging frontier in medical science. Nanomedicine offers the potential for precise and efficient delivery of therapeutic agents directly to fibrotic sites, which is crucial for conditions like liver fibrosis. Despite the potential, the path from laboratory research to clinical application is fraught with challenges, including issues related to manufacturing, regulatory compliance, and clinical trial design. This section explores the current state of anti-fibrotic nanomedicine, the challenges faced in its clinical translation, and future directions for overcoming these hurdles.

Current state of anti-fibrotic nanomedicine

- Liver fibrosis treatment: Nanomedicine has shown potential in treating liver fibrosis by enabling targeted delivery of antifibrotic agents, thereby improving therapeutic efficacy and reducing systemic side effects. This approach is particularly beneficial given the limitations of traditional therapies, which often have limited efficacy and significant side effects [18, 68].

- Extracellular vesicles: Extracellular vesicles, a type of naturally derived nanovesicle, have demonstrated effectiveness in alleviating organ fibrosis through mechanisms such as anti-inflammation and extra cellular matrix degradation. These vesicles can be engineered to enhance their therapeutic potency, offering a promising avenue for anti-fibrotic therapy [88].

Challenges in clinical translation

- Manufacturing and scale-up: Reproducible manufacturing and scale-up of nanomedicines are significant challenges. Ensuring consistent quality and efficacy during large-scale production is critical for clinical translation [89].

- Regulatory and safety issues: Regulatory barriers and safety concerns, such as instability *in-vivo* and potential toxicity, pose significant hurdles. A thorough understanding of the physicochemical properties and interactions of nanomedicines is essential to address these issues [89, 90].

- Clinical trial design: Designing effective clinical trials for nanomedicines is complex. It requires careful consideration of trial phases, patient selection, and endpoints to ensure reliable and robust data. The success rate of therapeutics entering phase I trials is low, highlighting the need for strategic planning in trial design [90, 91].

Future directions

- Collaborative efforts: Successful clinical translation of nanomedicines necessitates collaboration among academia, industry, and regulatory bodies. This collaboration can facilitate the development of safe and effective nanomedicine products by addressing challenges related to quality control, pharmacokinetics, and cost-effectiveness [89, 92].

- Innovative technologies: Employing technologies such as quality-by-design and microfluidics can accelerate the translation process. These approaches can improve the understanding of nanomedicine behavior and enhance the design of scalable and clinically relevant solutions [89].

• Regulatory pathways: Exploring alternative regulatory pathways, such as the United States Food and Drug Administration's 505(b)(2) pathway, can expedite the approval process for nanomedicines based on already approved drugs and platforms [91].

While the potential of anti-fibrotic nanomedicine is significant, the path to clinical application is complex and requires overcoming numerous challenges. The integration of innovative technologies and collaborative efforts among stakeholders is crucial for advancing the field. Additionally, understanding the disease heterogeneity and patient preselection strategies can further enhance the clinical translation of nanomedicines. As the field evolves, these strategies will be vital in realizing the full potential of nanomedicine in treating fibrotic diseases.

Conclusion

This review underscores the transformative potential of nanomedicine in developing sophisticated anti-fibrotic strategies for liver and lung diseases. The advent of targeted nanocarriers, such as dual-functionalized systems, macrophage-targeting metal-organic frameworks, and herbal compound-loaded nanoparticles, enables the precise disruption of key fibrotic pathways—including TGF-β/Smad, Rho kinase, and macrophage-driven inflammation. These platforms overcome the limitations of conventional therapies by ensuring sustained, site-specific drug release, reducing off-target effects, and facilitating synergistic multi-agent approaches. Despite the promising preclinical data, the clinical translation of these technologies necessitates overcoming hurdles in scalable manufacturing, long-term biosafety, and regulatory approval. Future progress hinges on interdisciplinary collaboration and continued innovation to refine targeting specificity and therapeutic efficacy. Ultimately, nanomedicine provides a powerful and versatile toolkit, heralding a new era of targeted, effective, and potentially reversible treatments for fibrosis.

Acknowledgments

None.

Conflict of Interest

None.

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