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Liver fibrosis: latest advances in treatment

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Abstract: Liver fibrosis is a self-repair response of the liver, triggered by various chronic liver injuries, and can progress to cirrhosis and liver cancer. Globally, the prevalence of liver fibrosis is continuously increasing, posing a serious threat to public health. The pathophysiological process of liver fibrosis is very complex, involving interactions between multiple cells and cytokines, but the key lies in the excessive deposition of extracellular matrix (ECM) caused by the activation of hepatic stellate cells (HSCs). Currently, apart from liver transplantation, there are no targeted therapeutic methods. However, as understanding deepens continuously and the exploration of the pathophysiology of liver fibrosis has advanced, a series of anti-fibrotic therapies targeting different mechanisms have also made significant progress. Various treatment methods, including stem cells, nano-drug delivery systems (NDDS), natural products, traditional Chinese medicine formulas, and thyroid hormone receptor agonists, have shown significant anti-fibrotic effects by regulating key signaling pathways, inhibiting the stimulation of HSCs, promoting liver self-repair, and modulating immune responses. This review focuses on summarizing these anti-liver fibrosis methods, in-depth analysis of their mechanisms of action, and further discusses the challenges they face in clinical application.

1. Introduction

Liver fibrosis represents the common terminal pathological stage of various chronic liver injuries, characterized by significant architectural alterations in the liver and abnormal excessive accumulation of extracellular matrix (ECM). Without effective intervention, this condition may progress to cirrhosis and even hepatocellular carcinoma [1]. Viral hepatitis (particularly hepatitis B and C), metabolic dysfunction-associated steatohepatitis (MASH), autoimmune liver diseases (AILD), as well as inherited metabolic disorders (such as Wilson's disease and α1-antitrypsin deficiency) constitute the predominant etiological factors of liver fibrosis [2]. Currently, the prevalence of liver fibrosis remains alarmingly high worldwide, with marked geographical variations across different regions, presenting substantial new challenges for public health [3].

From a pathophysiological perspective, the core link of liver fibrosis is the abnormal activation of HSCs [4]. Under normal liver conditions, quiescent hepatic stellate cells (qHSCs) are tasked with metabolizing and storing substances similar to vitamin A. Upon the onset of fibrosis, these qHSCs become activated and convert into myofibroblasts. They lose their ability to store vitamin A and

start to express α-smooth muscle actin (α-SMA), while also producing pro-inflammatory soluble factors, collagen, and inhibitors of ECM degradation, thus contributing to inflammation and ECM accumulation in the liver [1]. This pathological process is regulated by various cells within the liver microenvironment, such as hepatocytes, liver sinusoidal endothelial cells, and Kupffer cells, which together form a complex network of cellular interactions [5]. When hepatocytes undergo pyroptosis, they release inflammasome particles into the extracellular environment. These particles are then engulfed by HSCs, leading to increased interleukin-1β (IL-1β) release and upregulation of α-SMA expression [6]. Activated KCs can facilitate the activation of HSCs by secreting pro-inflammatory cytokines like TNFα, TGFβ, IL-1β, and CCL2, thereby inducing the fibrosis process in MASH and alcoholic cirrhosis [7,8]. During hepatic fibrosis, liver sinusoidal endothelial cells (LSECs) undergo a process known as "capillarization," characterized by the loss of their distinctive fenestrated phenotype and specialized functions. These capillarized LSECs fail to maintain HSCs in a quiescent state, thereby promoting fibrotic progression [9,10]. At the molecular level, aberrant activation of multiple signaling pathways collectively drives the fibrotic progression, including the canonical TGF-β/Smad, PI3K/AKT, and Wnt/β-catenin pathways, as well as newly identified signaling axes such as Hippo and NLRP3 inflammasome-Caspase1 [11]. Due to the complex pathophysiology of liver fibrosis, currently, there are no targeted treatment methods available apart from liver transplantation. Nevertheless, over the past few years, as our comprehension and investigation of the pathophysiology of liver fibrosis have deepened progressively, a series of anti-fibrotic therapies targeting different mechanisms have also made significant progress. Various treatment methods, including stem cells, nano-drug delivery systems (NDDS), natural products, traditional Chinese medicine formulas, and thyroid hormone receptor agonists, have shown significant anti-fibrotic effects by regulating key signaling pathways, inhibiting the activation of HSCs, promoting liver self-repair, and modulating immune responses [12,13].

This review provides an update on the current treatments for liver fibrosis, explores their main mechanisms of action, and further discusses the challenges they face in clinical application.

2. Stem Cell Therapy

Over the past few years, stem cell therapy has made significant progress in the treatment of liver fibrosis, offering a novel therapeutic approach to this clinical challenge. This therapy exerts its therapeutic effects through mechanisms such as promoting liver self-repair, modulating immune responses, and suppressing the abnormal activation of myofibroblasts [14]. Current research primarily focuses on investigating the role of mesenchymal stem cells (MSCs) and their exosomes (MSC-Exos) in liver tissue repair, studying the differentiation of induced pluripotent stem cells (iPSCs) into functional hepatocytes, and evaluating the clinical efficacy and safety of autologous stem cell transplantation therapies.

2.1 MSCs and MSC-Exos

MSCs are a type of adult stem cell with the potential for self-renewal and differentiation, widely distributed in various human tissues such as bone marrow, adipose tissue, placenta, and umbilical cord [15]. Among them, human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) have garnered significant attention due to their notable therapeutic potential. Research indicates that hUC-MSCs exert hepatoprotective effects by activating the Sirt3 protein to improve mitochondrial dysfunction in hepatocytes, regulating the Hippo/YAP signaling pathway to inhibit the abnormal activation of HSCs, and inducing the polarization of macrophages towards the M2 anti-inflammatory phenotype, thereby effectively reducing hepatic inflammatory responses [16,17]. Currently, two clinical trials targeting patients with decompensated cirrhosis (NCT05224960,

NCT05948982) are ongoing, aiming to evaluate the safety and efficacy of hUC-MSCs in the treatment of decompensated cirrhosis.

Although MSCs have demonstrated certain therapeutic effects, their standalone application is limited by several challenges, including low hepatic engraftment rates, limited survival capacity, and short duration of action, which restrict their therapeutic efficacy. However, combination therapy approaches and stem cell preconditioning techniques can effectively address these limitations of MSCs monotherapy. MSCs can produce synergistic effects when combined with traditional medicines. Placenta-derived mesenchymal stem cells (PD-MSCs) combined with WKYMm can achieve dual effects of vascular regeneration and anti-fibrosis by activating the FPR2 pathway. Human bone marrow-derived mesenchymal stem cells (hBM-MSCs) and adipose-derived mesenchymal stem cells (ADSCs) combined with the traditional Japanese medicine Juzentaihoto (JTT) have been shown to effectively alleviate carbon tetrachloride (CCl4)-induced liver injury and reverse the progression of liver fibrosis [18,19]. This combination therapy strategy has a synergistic effect, not only significantly enhancing therapeutic efficacy but also blocking the progression of liver fibrosis to end-stage liver disease [20]. It is worth noting that pharmacological preconditioning can also significantly enhance the therapeutic potential of mesenchymal stem cells [21]. hUC-MSCs pretreated with TC14012 can upregulate CXCR7 expression, reduce collagen deposition, inhibit the activation of hepatic stellate cells (HSCs), and alleviate inflammatory responses. IFN-α2 pretreatment, on the other hand, can promote the secretion of CSF-3, IL-8, and CCL20 by hUC-MSCs, recruit neutrophils, and thereby more effectively improve liver fibrosis [22,23].

Exosomes are nano-scale (30–150 nm in diameter) bilayer lipid vesicles that play multifaceted roles in the pathophysiology of liver fibrosis. These vesicles actively participate in disease progression by modulating hepatic stellate cell (HSC) activation and mediating intercellular crosstalk between HSCs and immune cells [24]. In recent years, the mechanisms underlying the anti-fibrotic effects of mesenchymal stem cell-derived exosomes (MSC-Exos) have become increasingly clear. These exosomes primarily exert their therapeutic effects by inhibiting the activation of HSCs and inflammatory cells, attenuating epithelial-mesenchymal transition (EMT), and protecting hepatocytes [25]. Different sources of MSC-Exos exhibit distinct regulatory mechanisms, bone marrow mesenchymal stem cell-derived exosomes (BMMSC-Exos) induce ferroptosis by modulating SLC7A11, thereby inhibiting HSC activation and improving liver fibrosis. In contrast, human adipose-derived mesenchymal stem cell exosomes (hADSC-Exos) exert therapeutic effects by inhibiting the PI3K/Akt/mTOR pathway and remodeling choline metabolism [26,27]. Moreover, MSC-Exos possess remarkable potential for drug delivery, serving as a natural biocompatible drug carrier that significantly enhances drug efficacy. For instance, exosomes loaded with luteolin (LUT) (LUT-Exos) can significantly improve the solubility and bioavailability of LUT, thereby enhancing its anti-fibrotic effects on liver fibrosis [28]. Table 1 summarizes additional MSCs and MSC-Exos with anti-fibrotic effects.

Table 1. Anti-liver fibrosis MSCs/MSC-Exos

MSCs / MSC-Exos	Animal Model	Mechanism	Reference
miR-4465-modified MSC-sEV (MSC-sEV$^{miR-4465}$)	CCl4-induced liver fibrosis in mice	Inhibit the expression of LOXL2 Inhibition of HSCs activation	[29]
Adipose-derived mesenchymal stem cells (ADSCs)	CCl4-induced liver fibrosis in mice	Activation of the Hippo signaling pathway Inhibit the activation of HSCs	[30]
Human umbilical cord-derived mesenchymal stemcells (hUC-MSCs)	CCl4-induced liver fibrosis in mice	Upregulated the expression of miR-148a-5p Inhibition of SLIT3 expression Inhibition of HSCs activation	[31]

Human adipose-derived mesenchymal stem cell exosomes (hADSC-Exos)	CCl4-induced liver fibrosis in mice	Inhibition of the p38 MAPK/NF-κB pathway	[32]
Human bone marrow mesenchymal stem cell-derived exosome (hBMMSC-Exos)	Thioacetamide (TAA)-induced liver fibrosis in mice	Inhibition of PI3K/AKT and NF-κB signaling pathways	[33]
Bone marrow mesenchymal stem cells (BMSCs)	CCl4-induced liver fibrosis in mice	The downregulation of the lnc-BIHAA1/rno-miR-667-5p signaling pathway	[34]
Human umbilical cord mesenchymal stem cell derived exosomes (hucMSC-Exos)	CCl4-induced liver fibrosis in mice	Promoting ferroptosis in HSCs	[35]
Human placental mesenchymal stem cells (hPMSCs)	CCl4-induced liver fibrosis in mice	Inhibition of the TGF-β/Smad signaling pathway Inhibition of HSCs activation Upregulating the expression of Cav1	[36]
Bioengineered MSC$^{GFPCxcr2\text{-}Mmp13}$	CCl4-induced liver fibrosis in mice	Decreases the hepatic oxidative stress	[37]
Phosphatase of regenerating liver-1 (PRL-1)-overexpressing placenta-derived mesenchymal stem cells (PD-MSCs$^{PRL\text{-}1}$)	BDL- induced liver fibrosis in mice	Relieve endoplasmic reticulum stress	[38]

2.2 Induced pluripotent stem cells (iPSCs)

Induced pluripotent stem cells originate from adult cells via reprogramming and have the ability to transform into functional liver cells that closely mimic normal hepatocytes [39]. This establishes the groundwork for its potential therapeutic applications in liver fibrosis. Functional hepatobiliary organs (HBOs) derived from the differentiation of iPSCs have proven to be significantly effective against cholestatic liver fibrosis in non-human primate models [40]. Additionally, macrophages derived from iPSCs, particularly the M2 subtype, have significantly reduced the expression of fibrosis-related genes and disease-associated histological markers of pathological changes in immunodeficient mouse models [41]. Human induced pluripotent stem cell-derived liver organoids (hiPSC-LOs) significantly improve chemically-induced liver fibrosis by promoting the polarization of M2 macrophages [42]. These research findings indicate that iPSCs can not only directly replace damaged hepatocytes but also exert their therapeutic effects by modulating the immune microenvironment.

2.3 Autologous stem cell transplantation

As the pathological process of liver fibrosis progresses, the structure and function of the liver gradually deteriorate, severely affecting the patients' quality of life and prognosis, while traditional treatments encounter a therapeutic bottleneck [43]. In 2007, the technique of autologous peripheral blood mononuclear cell (PBMC) transplantation was first reported. The technique employs recombinant human G-CSF to mobilize PBMCs from the bone marrow to the peripheral blood in patients with decompensated cirrhosis, which are then separated, collected, and reinfused into the

patient's body through the hepatic artery. These mobilized PBMCs can transform into functional hepatocyte-like cells, thereby improving the patients' liver function, and offering a new therapeutic approach for patients with decompensated cirrhosis [44]. In a subsequent 10-year clinical study, it was further confirmed that PBSCs transplantation can significantly improve the long-term survival rates of cirrhosis patients without increasing the risk of hepatocellular carcinoma (HCC) [45].

In addition to PBMCs, the infusion of autologous adipose tissue-derived regenerative cells (ADRCs) via the hepatic artery has also been confirmed to be safe and effective for patients with liver cirrhosis. After the infusion of ADRCs, the serum albumin levels in cirrhosis patients remained stable or increased, and in some patients, liver regeneration-related factors significantly increased within a day [46]. In patients with cirrhosis caused by non-alcoholic steatohepatitis and fatty liver disease, the safety and efficacy of ADRCs therapy have been further established. Among the 7 patients who received ADRCs infusion, 6 showed improvements in serum albumin levels, 5 had an increase in prothrombin activity, and no treatment-related adverse events were observed throughout the treatment process [47]. Furthermore, for patients with end-stage liver disease, repeated infusions of autologous hematopoietic stem cells (AHSCT) through the portal and peripheral venous routes not only significantly improve liver function but also have minimal adverse reactions and more enduring therapeutic effects. The co-infusion of AHSCT with MSCs can enhance the therapeutic effect of AHSCT and prolong the duration of liver function improvement [48,49].

3. Nanoparticle drug delivery system

The complex pathological microenvironment of liver fibrosis significantly limits the therapeutic efficacy of conventional drugs. Nanoparticle drug delivery systems (NDDS), leveraging their unique size effects and functional programmability, can effectively overcome these limitations. Three major delivery technologies - targeted delivery strategies to breach pathological barriers, novel organelle-targeting therapeutic approaches, and pH-responsive intelligent delivery systems - provide new possibilities for precision treatment of liver fibrosis [50].

To overcome the pathological barriers caused by the capillarization of LSECs and the deposition of ECM, ensuring precise drug delivery to target cells, Wang et al. designed a versatile hyaluronic acid-based nanoparticle (HA@PRB/COL NPs), incorporating the autophagy inhibitor probucol (PRB) and modified with type I collagenase (COL). When confronted with barriers made of type I collagen, these nanoparticles act as nanodrills, breaking down the collagen and improving ECM penetration. They can also specifically bind to the CD44 receptor, enabling targeted delivery to HSCs and modulating their activation [51]. In a separate study, Sun and colleagues created a coordinated drug delivery system that employs neutrophil membrane hybrid liposomes encapsulating atorvastatin and amlodipine (NCM@AtAm) and vitamin A-loaded neutrophil membrane hybrid liposomes encapsulating albumin (VNCM@Bai) NPs that effectively bypass the capillary barrier of LSECs, enabling targeted delivery to HSCs and inhibiting their activation [52].

The Golgi apparatus, as a pivotal organelle within cells, plays an indispensable role in maintaining cellular homeostasis [53]. Numerous studies have demonstrated that targeting organelles can significantly enhance the precision of nanomedicine-based therapies while effectively reducing the incidence of adverse effects [54]. Li et al. developed a multifunctional nanoparticle named CREKA-CS-RA (CCR) by chemically conjugating retinoic acid to CREKA and chondroitin sulfate, followed by encapsulating vismodegib. This nanoparticle can precisely target the Golgi apparatus of activated HSCs and disrupt its structure and function. It significantly inhibits the activation of HSCs and has shown remarkable efficacy in alleviating CCL4-induced liver fibrosis symptoms in mice [55].

PH-responsive nano-drug delivery systems have emerged as a research hotspot due to their

precise drug-controlled release properties [56]. Samaneh et al. have developed a novel pH-sensitive VA-targeting PLGA-ES100 nanoparticles. The coating design of ES100 ensures the stability of imatinib in the gastric acid environment and promotes its effective release at the appropriate pH values in the intestine, thereby enhancing the targeting and therapeutic efficacy of imatinib [57]. In a separate study, researchers developed a novel class of Zeolitic Imidazolate Framework-8 (ZIF-8) lipid nanoparticles (VA-PFD@ZIF-8@DMPC NPs) that are loaded with Pirfenidone (PFD) and modified with Vitamin A (VA). These nanoparticles take advantage of the pH sensitivity of ZIF-8, maintaining stability under normal physiological conditions and releasing the drug in acidic environments, which helps to minimize drug leakage. Additionally, the modification with Vitamin A (VA) allows these nanoparticles to target the retinol-binding protein receptors (RBPRs) on the surface of HSCs, thereby enhancing the drug concentration in the liver fibrosis treatment area [58]. Table 2 summarizes more nanoparticles and their main anti-fibrosis mechanisms.

Table 2. Anti-liver fibrosis nanoparticles

Nanoparticles (NPs)	Core components	Animal Model	Mechanisms	Reference
Cholinized-polymer functionalized lipid-based nanoparticles (CP-LNPs)	Cholinized-Polymer (CP) Curcumin	CCl4-induced liver fibrosis in mice	Alleviating oxidative stress in hepatocytes Inhibiting the proliferation and migration of aHSCs	[59]
PM nanoparticles (PM)	Polydopamine (PDA) Macrophage membrane (MM)	CCl4-induced liver fibrosis in mice	Alleviating inflammation and reducing oxidative stress	[60]
HyaluronicAcid-Bilirubin Nanoparticles (HABN)	Bilirubin Hyaluronic acid (HA)	CD-HFD-induced MASH fibrosis in mice	Antioxidant Inhibit the activation of HSCs	[61]
HCQ@retinol-liposome nanoparticles (HCQ@ROL-LNPs)	Hydroxychloroquine (HCQ) Retinol	Thioacetamide (TAA)-induced liver fibrosis in mice	Inhibition of autophagy in aHSCs Enhancing the stability and targeting of the drug	[62]
Betulinic acid-loaded GC Nanoparticles (BA-GC-NPs)	Galactose Chitosan Betulinic acid (BA)	CCl4-induced liver fibrosis in mice	Targeting hepatic stellate cells and inhibiting their activation Enhancing the liver-targeting efficacy of the drug	[63]
Engineer edlipid nanoparticles (LNPs)	siGTSE1	CCl4-induced liver fibrosis in mice	Targeted RNA delivery to the liver Suppressing GTSE1 expression Inhibits the activation of HSCs	[64]
B. aegyptiaca/chitosan nanoparticles (BCN)	Balanites aegyptiaca Chitosan	CCl4-induced liver fibrosis in mice	Enhancing antioxidant stress Regulate the expression of genes related to liver fibrosis	[65]

PolyMet-pRLX-LNPs (PRLNP)	Polymeric metformin Relaxin plasmid (pRLX)	CCl4-induced liver fibrosis in mice	Targeting and inhibiting activated HSCs Enhancing drug delivery efficiency	[66]
Silibinin albumin nanocrystals (SLB-HSA NCs)	Silibinin (SLB) Human serum albumin (HSA)	CCl4-induced liver fibrosis in mice	Increasing cellular uptake of aHSCs through SPARC-mediated endocytosis	[67]
Biomimetic all-trans retinoic acid (ATRA) loaded PLGA nanoparticles (TM-ATRA/NPs)	All-Trans Retinoic Acid (ATRA) Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)	CCl4-induced liver fibrosis in mice Choline deficient l-amino acid diet induced liver fibrosis in mice	Inducing apoptosis of HSCs Inducing quiescence of activated fibroblasts	[68]
Lipid-encapsulated TGFβRI-siRNA Drug (LNP-siTGFβRI)	siRNA against type I TGF-β receptor (TGFβRI) mRNA	Schistosomiasis-induced liver fibrosis in mice	Suppressing the expression of TGFβRI Inhibits the activation of HSCs	[69]
Folic acid modified D-α-tocopheryl polyethylene glycol 1000 succinate nanoparticles (FT@XBP1)	Folic acid (FA) D-α-tocopheryl polyethylene glycol 1000 Succinate (TPGS) *Xbp1* siRNA	Fat-, fructose- and cholesterol-rich diet-induced MASH in mice	Inhibiting Xbp1 expression Promoting the polarization of macrophages towards the M2 phenotype Promoting the release of exosomes that inhibit the activation of HSCs	[70]
Activating hepatic stellate cell membrane (HSCM)-coated PLGA@Melatonin nanoparticles (HSCM@PLGA@Melatonin)	Melatonin Activated hepatic stellate cell membrane (HSCM)	CCl4-induced liver fibrosis in mice	Regulating oxidative stress and endoplasmic reticulum stress	[71]
Small interfering RNA-loaded lipid nanoparticles (siRNA-loaded LNPs)	siRNA CL15A6 CL15H6	Thioacetamide (TAA)-induced liver fibrosis in mice	Reprogramming aHSCs Inhibition of hedgehog (Hh) and TGFβ1 signaling pathways	[72]

4. Natural Products and Traditional Chinese medicine formulas

Natural products have unique advantages in developing drugs for liver fibrosis treatment due to their structural diversity, low toxicity, and wide range of sources [73]. Numerous studies have thoroughly elucidated the mechanisms of action of several representative natural products. The flavonoid luteolin-7-diglucuronide (L7DG), extracted from Perilla frutescens and Verbena officinalis, can inhibit the activity of protein tyrosine phosphatase 1B (PTP1B), thereby activating the AMPK pathway and suppressing the activation of HSCs [74,75]. The polyphenolic natural

compound curcumin exhibits hepatoprotective effects by modulating multiple signaling pathways to inhibit HSCs activation, attenuate hepatocyte EMT, and reduce extracellular matrix synthesis. Notably, it has also shown significant anti-inflammatory and antioxidant effects in animal models [76]. Andrographolide (AP), a diterpenoid lactone compound, exerts inhibitory effects on angiogenesis and HSCs activation through the Nrf2 and TGF-β1/Smad pathways. However, it should be noted that high-dose AP administration may induce toxic side effects, warranting further investigation to determine its optimal clinical dosage [77].

In the field of liver fibrosis treatment, a series of Traditional Chinese medicine formulas have been widely explored and applied due to their significant efficacy. These prescriptions combine multiple herbal components, leveraging their synergistic effects through various mechanisms to collectively inhibit the progression of liver fibrosis [78]. Qijia Rougan Formula (QRF) is an optimized formulation derived from the "Sanjia San" prescription documented in Wu Youke's "Treatise on Pestilence" during the Ming Dynasty. This herbal formulation contains 8 antifibrotic active components that exert therapeutic effects through suppressing macrophage M2 polarization by modulating the JAK1/STAT6-microRNA-23a negative feedback loop, and reducing hepatocyte apoptosis via inhibition of the Akt/mTOR signaling pathway, thereby demonstrating comprehensive antifibrotic activity [79-81]. Xiaochaihu Decoction (XCHT) contains 164 bioactive constituents that target 95 liver fibrosis-associated molecules. Notably, key components including quercetin and β-sitosterol exert therapeutic effects by modulating critical signaling pathways such as IL-17 and TNF [82]. It ameliorates liver sinusoidal capillarization through the MK/integrin signaling pathway while concurrently inhibiting liver fibrosis progression by modulating gut microbiota composition and preserving intestinal barrier integrity [83,84].

Both natural products and Traditional Chinese medicine formulas have exhibited significant therapeutic effects in the treatment of liver fibrosis through multi-target and multi-pathway mechanisms. Natural products are characterized by their well-defined active components and specific targets, while Traditional Chinese medicine formulas exert comprehensive regulatory effects through the synergistic actions of multiple components. Future research should further elucidate their molecular mechanisms, optimize dosing regimens, and accelerate clinical translation and application.

5. Thyroid Hormone Receptor agonists

Thyroid hormones are key regulators of metabolic balance in the liver and throughout the body. As a primary target organ for thyroid hormone action, the physiological function of the liver is closely related to thyroid hormone levels [85]. Thyroid hormone (TH) exerts its biological activity by specifically binding to thyroid hormone receptors (TR) with the assistance of transmembrane transport proteins [86]. Numerous studies have confirmed that the TH/TR signaling axis plays a crucial regulatory role in improving metabolic-related diseases such as fatty liver, hepatitis, liver fibrosis, and liver injury [87]. Among the thyroid hormone receptor family, the β-subtype receptor (THR-β) is an extremely important subtype [88]. Resmetirom, as a liver-targeted selective THR-β agonist, has demonstrated significant therapeutic effects in animal models of metabolic dysfunction-associated steatohepatitis (MASH). It not only markedly reduces hepatic fat deposition and lowers cholesterol levels in both the liver and circulatory system but also significantly improves the activity score of non-alcoholic fatty liver disease (NAFLD). More importantly, this drug effectively downregulates the expression of fibrosis markers such as α-smooth muscle actin and inhibits the transcriptional activity of pro-fibrotic genes [89]. A phase II clinical trial completed in 2019 first validated the clinical efficacy of Resmetirom in MASH patients [90]. Subsequently, a phase III randomized controlled study further confirmed that both the 80 mg and 100 mg daily dose groups of

Resmetirom were significantly superior to the placebo group in terms of MASH resolution and improvement in liver fibrosis by at least one stage [91]. Based on these breakthrough results, the U.S. FDA officially approved Resmetirom in March 2024 for use in combination with lifestyle interventions to treat adult patients with non-cirrhotic MASH and moderate to severe liver fibrosis (stages F2-F3) [92]. The latest systematic review and meta-analysis data also indicate that Resmetirom can improve liver fat content, liver enzymes, and fibrosis biomarkers in patients with MASLD, with no significant impact on thyroid function and demonstrating good safety and tolerability [93]. Currently, two extended clinical studies (NCT05500222, NCT04951219) are underway to evaluate the long-term efficacy and safety of Resmetirom in a broader population, providing more comprehensive evidence-based medical support for its clinical application.

6. Conclusion and Future Perspectives

Liver fibrosis is the common pathological end stage of various chronic liver injuries, with the core pathological mechanism being the excessive deposition of ECM due to the abnormal activation of HSCs. Although liver transplantation is currently the only effective treatment, its application is limited by donor shortages and high costs. In recent years, with the deepening understanding of the complex pathophysiology of this disease, treatment methods are continuously making new progress, and innovative therapies are emerging. Stem cell therapy exerts anti-fibrotic effects through mechanisms such as promoting liver self-repair, modulating immune responses, and inhibiting HSCs activation. NDDS overcome the limitations of traditional drugs by targeting drug delivery to HSCs and other fibrogenic cells. Various novel nanoparticles have achieved precise treatment by targeting specific organelles or responding to pH changes, significantly improving drug efficacy and reducing side effects. Natural products, such as flavonoids and polyphenols, exert anti-fibrotic effects by modulating key signaling pathways, inhibiting inflammation, and promoting ECM degradation. Traditional Chinese medicine formulas, through the synergistic action of multiple herbs, comprehensively regulate the body's immune response and metabolic processes, showing significant anti-fibrotic effects. Thyroid hormone receptor β (THR-β) agonists, such as Resmetirom, have demonstrated significant anti-fibrotic effects in models of MASH and have been approved by the FDA for the treatment of non-cirrhotic MASH and moderate to severe liver fibrosis. Despite significant progress in basic research and clinical trials, these treatment methods still face many challenges in clinical application, such as low survival and engraftment rates of stem cells in vivo, high production costs of MSC-Exos, technical barriers and ethical issues with iPSCs, and concerns regarding the targeting, biocompatibility, and long-term efficacy and safety of nanoparticles. Therefore, the treatment of liver fibrosis requires a multidisciplinary and multifaceted approach.

In the future, it is crucial to delve deeper into the molecular mechanisms of liver fibrosis to identify new therapeutic targets. Further optimization of stem cell therapy strategies is needed to enhance the survival rate, engraftment ability, and paracrine effects of MSCs and iPSCs, while establishing standardized preparation protocols for MSC-Exos. The precision of nanotherapy should be advanced by optimizing the targeting specificity, biocompatibility, and controlled-release performance of NDDS to increase drug accumulation in fibrotic livers and reduce off-target effects. The advantages of natural products and traditional Chinese medicine formulations should be integrated, with high-throughput screening used to identify effective anti-fibrotic components and standardized extraction and quality control systems established. More large-scale, multicenter randomized controlled trials should be conducted to validate the long-term efficacy and safety of the aforementioned therapeutic approaches, providing stronger evidence for clinical application. Finally, the ethical review and regulatory frameworks for iPSCs and gene-editing technologies should be improved, and the production costs of stem cells, exosomes, and nanoparticles should be

reduced to enhance the accessibility of treatment.

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