CSPS | jpps Journal of Pharmacy and Pharmaceutical Sciences

TYPE Review
PUBLISHED 07 November 2023
DOI 10.3389/jpps.2023.11808

OPEN ACCESS

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RECEIVED 16 July 2023
ACCEPTED 17 October 2023
PUBLISHED 07 November 2023

CITATION
Mohammed OS, Attia HG, Mohamed BMSA, Elbaset MA and Fayed HM (2023), Current investigations for liver fibrosis treatment: between repurposing the FDA-approved drugs and the other emerging approaches. *J. Pharm. Pharm. Sci* 26:11808. doi: 10.3389/jpps.2023.11808

Current investigations for liver fibrosis treatment: between repurposing the FDA-approved drugs and the other emerging approaches

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Long-term liver injuries lead to hepatic fibrosis, often progressing into cirrhosis, liver failure, portal hypertension, and hepatocellular carcinoma. There is currently no effective therapy available for liver fibrosis. Thus, continuous investigations for anti-fibrotic therapy are ongoing. The main theme of anti-fibrotic investigation during recent years is the rationale-based selection of treatment molecules according to the current understanding of the pathology of the disease. The research efforts are mainly toward repurposing current FDA-approved drugs targeting etiological molecular factors involved in developing liver fibrosis. In parallel, investigations also focus on experimental small molecules with evidence to hinder or reverse the fibrosis. Natural compounds, immunological, and genetic approaches have shown significant encouraging effects. This review summarizes the efficacy and safety of current under-investigation antifibrosis medications targeting various molecular targets, as well as the properties of antifibrosis medications, mainly in phase II and III clinical trials.

KEYWORDS

liver fibrosis, anti-fibrotic agents, HSCs, therapeutic targets, pharmacotherapy

Introduction

Liver fibrosis results from a continuous scarring response caused by persistent tissue damage [1]. The main damaging etiologies are chronic hepatitis B (HBV) or hepatitis C virus (HCV) infection, alcohol misuse, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and other illnesses like Wilson's disease, autoimmune hepatitis, biliary cholangitis and hemochromatosis [2].

Deathly complications of cirrhosis include liver cancer, hepatic encephalopathy, ascites, systemic infection, and functional liver failure [3]. Currently, there are no

licensed treatments for advanced fibrosis. However, ongoing clinical research is promising and shows the possibility of reversal of liver fibrosis [4].

Hepatic disease complicated by fibrosis is a primary reason for liver transplantation [5]. Moreover, 2 million people yearly lose their lives due to liver disease, with cirrhosis being the eleventh largest cause of death globally [6].

The present article will review the mechanism of liver fibrosis and evidence-based pharmacological strategies attempting to treat this devastating liver pathology.

Biological mechanism of liver injury

Chronic exposure to external pathological factors can harm hepatocytes, stimulate the infiltration of lymphocytes, activate inflammatory cells like macrophages, and ultimately activate hepatic stellate cells (HSCs), transforming them into myofibroblasts, consequently producing too much extracellular matrix (ECM) which causes liver fibrosis and scarring [7]. In normal livers, HSCs reside in the perisinusoidal region and remain dormant quiescent HSCs (qHSCs). Myofibroblasts (activated HSCs, aHSCs) are known for synthesizing ECM components like fibrillar collagen types I and III, as opposed to the laminar types IV and VI, mostly common in healthy liver tissue. This trans-differentiation occurs as a result of a complex activation. This complex activation occurs as a reaction to several signals that promote fibrosis, such as signals emanating from hepatocytes that have been harmed, growth factors produced by Kupffer cells, and changes in the ECM. Liver fibrosis is believed to be associated with the activation of HSC. The quantity of aHSCs diminishes following the completion of injury treatment, potentially impeding or stopping the advancement of liver fibrosis. It is hypothesized that treating liver fibrosis may be associated with a reduced interaction between HSCs and other injured hepatic cells [4, 8].

Furthermore, activated HSCs exhibit enhanced contractility, have high levels of "alpha-smooth muscle actin (α-SMA), and release cytokines such as transforming growth factor-beta 1 (TGF-β1), platelet-derived growth factor (PDGF) and connective tissue growth factor (CTGF) [9]. aHSCs are continuously stimulated by their own autocrine. Moreover, chemotactically moving to the region of the injured liver, chemokines secreted by aHSCs build up in the body's inflammatory system, aggravating the injury caused by inflammation. Additionally, Damage-Associated Molecular Patterns (DAMPs) released by damaged hepatocytes activate "Kupffer cells" and a variety of immunological cells, which in turn activate HSCs and retain their existence by discharging pro-(inflammatory and fibrogenic) besides, the activation of the TGF-β1/Smad signal pathway, mitogen-activated protein kinase (MAPK) signal pathway and other signal pathways" [10].

In addition, CC chemokines (chemokine (C-C motif) ligand 2 (CCL2)-(CCL5)), which attract leukocytes to damaged sites, are secreted by Kupffer cells. Further, monocytes secrete mediators including Apoptosis-signal-regulating kinase 1 (ASK1), Pan-caspase, Galectin-3 (Gal-3), and other chemicals, which further harm hepatocytes, aggravate inflammation, encourage HSC activation and fibrosis [11, 12]. Moreover, TGF-β1 promotes monocytes to develop into macrophages. Macrophages, for example, secretes interleukin 1 (IL-1) and interleukin 6 (IL-6), which contribute to the exacerbation of the inflammatory reaction and the ongoing activation and survival of HSCs [13]. The initiation of HSCs is influenced by the paracrine crosstalk among macrophages and Kupffer cells.

Animal models to study liver fibrosis

An experimental study in rats is currently the gold standard experiment in liver fibrosis research to support a proposed disease-associated mechanism resembling clinical scenarios. Based on etiology, there are now multiple categories for *in vivo* models of liver fibrosis, including genetically modified, chemical, nutritional, surgical, and infection-based models.

Carbon tetrachloride (CCl_4), ethanol, thioacetamide (TAA), dimethylnitrosamine (DMN), and diethylnitrosamine (DENA) are substances that are frequently used to induce liver fibrosis and cause hepatic diseases. Further, the progression of NAFLD to hepatic fibrosis in experimental animals can be rendered using a variety of specialized diets, including the methionine- and choline-deficient or high-fat diet. Moreover, common bile duct ligation (BDL) can cause periportal biliary fibrosis and cholestatic damage.

Liver fibrosis treatment plans

The primary focus of current liver fibrosis treatment plans is the eradication of etiologies. Lifestyle modifications and bariatric surgery have been studied for hepatic metabolism problems [34], and antiviral medications for viral hepatitis [35, 36] have all produced clinical evidence for resolving hepatic fibrosis, indicating that scarring is reversible.

Indeed, it was demonstrated that repurposing FDA approved drugs or experimental molecules (Tables 1, 2) for targeting the hepatic cells interaction implicated in excessive collagen deposition can be accomplished through out the following strategies [37, 38].

Hepatic protection from hepatocyte death (apoptosis inhibition)

One of the main initiators of HSC activation and inflammatory reaction in all etiologies is hepatocyte cell death

through apoptosis [39]. Hence, in animal models of hepatic fibrosis, suppression of hepatocyte apoptosis hinders HSC activation [40].

Preclinical [41] and clinical research [42] have used emricasan, the pan-caspase apoptosis inhibitor. Emricasan slowed the progression of fibrosis and liver damage in a NASH mouse model [43]. The BDL model of biliary fibrosis similarly showed increased survival and decreased portal hypertension with emricasan therapy [44]. In patients with advanced stages of hepatic cirrhosis and portal hypertension, emricasan reduces the model for end-stage liver disease "MELD" scores [45]. The effectiveness of emricasan in treating NASH patients is currently being studied "NCT03205345 ENCORE-LF; NCT02960204 ENCORE-PH, NCT02686762 ENCORE-NF" [46].

ASK-1 (apoptosis signal-regulating kinase 1) is repressed via the drug selonsertib. When there is oxidative stress, ASK-1 induces apoptosis and enhances the production of inflammatory cytokines [47]. In a rodent NASH animal model, selonsertib reduced liver fibrosis [48]. According to a rodent NASH model, selonsertib improved inflammation, steatosis, fibrosis, and metabolic markers linked to NAFLD. In the DMN-induced fibrosis model, selonsertib decreased the accumulation of collagen, expression of type I collagen, fibronectin, and α-SMA [31]. Following promising results from clinical trials involving hepatic steatosis patients, the effectiveness of selonsertib as an anti-fibrotic medication has been evaluated in two phase III clinical trials [49].

TNF-α causes acute liver failure and hepatocyte death [50]. Hepatocyte death is accompanied by the formation of apoptotic bodies, which are absorbed through Kupffer cells. This increases the synthesis of death ligands TNF-α, Fas ligand (FasL), and Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), causing more hepatocyte deaths [51].

In a prior trial, individuals with chronic hepatitis C were treated with pirfenidone (PFD), a drug approved for treating lung fibrosis, for 24 months; PFD reduced liver fibrosis and inflammation [52]. Further, according to new research, PFD reduced liver fibrosis in mice fed a high-fat diet and lacking the melanocortin 4 receptor in a mice-model of NASH. The Melanocortin 4 receptor (MC4R) has been implicated in developing and progressing liver diseases, notably NASH and hepatocellular carcinoma (HCC). PFD also inhibited TNF-α provoked liver cell programmed cell death with decreased caspase 8 and 3 activation, indicating that PFD employs suppression of hepatocyte death and anti-fibrotic effects in non-alcoholic steatohepatitis [53]. Recent findings from a clinical trial "NCT04099407" on the impact of PFD medicine on fibrosis and its safety for 1 year in cases with persistent liver disorders show that 35% of those receiving PFD experienced a substantial reduction in fibrosis [54].

Oxidative stress reduction provides hepatic protection

Reactive oxygen species (ROS) and oxidative stress have significantly contributed to the onset of fibrogenesis by activating HSCs. Consequently, reducing these stressors and ROS reduces inflammation, which improves liver fibrogenesis. Antioxidants are emerging as possible anti-fibrotic treatments because they can reduce ROS production. As a result, several antioxidants are being examined in clinical studies with positive results, including "S-adenosyl-L-methionine (SAMe), silymarin, phosphatidylcholine, resveratrol, quercetin, N-acetylcysteine (NAC), s-allylcysteine (SAC), oroxylin A, methyl ferulic acid (MFA), vitamin E" and so on [55, 56]. In animal models and cell cultures, quercetin, daidzein, resveratrol, cyperus, curcumin, thymol, apigenin, rice bran oil, red yeast rice golden berry, and N-acetylcysteine (NAC) have effectively prevented liver injury and inhibited stellate cell activation [37, 57–66].

Reactive oxygen species (ROS) are frequently produced by NADPH oxidase (NOX) [67], and NOX1, 2, and 4 are crucial for HSC activation [68]. Setanaxib, previously named GKT137831, an inhibitor of NOX1, NOX4 inhibitor, and NADPH oxidase, decreases reactive oxygen species, nitric oxide, and fibrotic gene expression in CCL_4 liver fibrosis in mice [69]. A recent phase II clinical trial introduced Setanaxib as an anti-cholestatic and anti-fibrotic agent for primary biliary cholangitis "NCT03226067" [70].

Hepatic protection via gut microbiome restoration

Bacteria, protozoa, fungi, and viruses make up the gut microbiota in the human digestive tract. The gut microbiota is responsible for keeping the immune system in balance, preventing autoimmune, and preventing and eradicating pathogen invasion [71]. The pathophysiology of obesity and NAFLD/NASH is influenced mainly by the gut microbiota, particularly Firmicutes, and Bacteroidetes, with a relative decline in Firmicutes and an increase in Bacteroidetes [72]. Probiotics (*Lactobacillus reuteri*) and metronidazole medication, either alone or combined with metformin, may be an effective therapeutic strategy for treating NASH rat models by altering the gut microbiome [73]. Given the pathophysiological importance of gut dysbiosis to fibrogenesis, several studies have looked at the use of microorganisms (Probiotics), functional ingredients (Prebiotics), and fecal microbiota transplantation as anti-fibrotic therapies [72]. Prebiotics are indigestible food components, and probiotics are living microorganisms claimed to help or rebuild the intestinal microflora. Microorganisms functional ingredients have demonstrated protective benefits on NASH and liver toxicity in animal models of persistent hepatic damage, confirming the pathogenic importance of gut

dysbiosis in chronic liver disorders [72]. A meta-analysis of VSL#3, the most extensively studied probiotic supplement in NASH/NAFLD patients, revealed possible anti-inflammatory and insulin-sensitizing benefits consistent with the preclinical evidence [74].

Lipid-lowering agents for hepatic protection

Statins are inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which controls the rate-limiting step in hepatocyte cholesterol biosynthesis [75]. Statins have been demonstrated to have anti-inflammatory and anti-fibrotic activities in various animal models representing chronic liver disease [76]. According to two recent studies using retrospective cohorts, statins may help reduce fibrosis and steatosis and aid in avoiding disease progression in persons with NAFLD [77, 78]. But to verify their effectiveness, prospective trials are necessary. Steatosis and the NAFLD activity scores were decreased in participants who took atorvastatin [79]. According to emerging scientific and clinical data, statins may prevent fibrosis and delay the course of chronic liver disease "NCT03780673; NCT02968810; NCT04072601" [12].

Prevention of HSC activation

When hepatic fibrosis develops and progresses, one of the most crucial stages is the activation of HSCs. Liver damage stimulates dormant HSCs to become active. Kupffer cells and other cells constantly activate HSCs via PDGF, TGF-β1, CTGF, and other mediators that stimulate HSC proliferation and extend HSC longevity through associated signaling pathways. In addition, HSCs' autocrine function initiates its own activation [11]. The stimulation of HSCs is also influenced by several proteases, including dipeptidyl peptidase 4 (DPP4) and HMG-CoA reductase. Therefore, stopping HSC activation and proliferation is essential for lowering or reversing hepatic fibrosis. A recent animal study showed that linagliptin, a DPP4 family member, could decrease acute hepatic injury via modulation of C/EBP-β and CX3CL1/Fractalkine [80].

TGF-β1/Smad signal pathway

Stimulating the TGF-β1/Smad signal pathway is a critical step in advancing liver fibrosis. The type I receptor is attracted following serine residue phosphorylation and activated by TGF-β1 in HSCs after liver injury. Smad2/3 is a receptor-regulated protein that is re-phosphorylated by an active type I receptor and then dissociates from the receptor to combine with Smad4. This complex undergoes nuclear translocation and inhibits TGF-β1 via negative feedback by repressing the expression of Smad7, which controls the expression of genes associated with fibrosis, activation of HSC, stimulation of the overproduction and deposition of extracellular matrix, and aggravates fibrosis [81]. As a result, reducing liver fibrosis and stopping HSC activation and proliferation requires blocking the TGF-β1/Smad signal pathway.

Fluorofenidone [1-(3-fluorophenyl)-5-methyl-2-([1H])-pyridone] is a recent pyridone anti-fibrosis molecule that has shown a notable therapeutic effect on fibrosis. Such an effect was prominently demonstrated in the kidney, liver, and lungs [82]. Fluorofenidone reduced the TGF-β1-induced initiation of HSCs caused by and inhibited the TGFβ1-1/Smad and MAPK signaling, reducing hepatic damage or fibrosis triggered by pig serum in rodents [83]. Moreover, praziquantel, a schistosomicide with reasonable safety, markedly reduced collagen formation, up-regulated Smad7 expression in HSCs, inhibited the TGF-β1/Smad signal pathway, and hindered the stimulation of HSCs in mice with liver fibrosis caused by CCl_4 [84].

Peroxisome proliferator-activated receptors (PPARs)

The superfamily of ligand-activated transcription factors known as PPARs tightly regulate energy homeostasis and metabolic activity. Peroxisome proliferator-activated receptor gamma (PPARγ) is predominantly regarded as a prospective target of liver fibrosis treatment among the three isoforms of PPARs (PPARα, PPARγ, and PPARα/δ)). The PPARγ expression reduces HSC activation, even though it is abundantly expressed in qHSCs [85].

Better steatosis and lobular inflammation were observed in a randomized clinical study of the insulin sensitizer PPAR receptor activator pioglitazone in individuals with non-cirrhotic NASH. Still, no meaningful effect on fibrosis was observed [86]. Treatment with pioglitazone for up to 2 years was related to fibrosis enhancement at any phase and remission of NASH, according to a following meta-analysis of 8 clinical trials for PPAR receptor activator treatment [87].

Elafibranor (GFT505) is a dual PPARα/δ agonist produced by Genfit in France [88]. Elafibranor improves the lipid profile, increases insulin sensitivity, and has anti-inflammatory and anti-fibrotic properties, among other things, which all work together to reduce the symptoms of NASH [89]. It has been shown in animal experiments that elafibranor administration helps to lower hepatic steatosis, inflammation, fibrosis, and the level of biomarkers for liver dysfunction, as well as in preventing the production of pro-inflammatory and pro-fibrosis genes [90]. Preventative and curative effects of elafibranor treatment for CCl_4-induced hepatic fibrosis in rats [91]. Subgroup analysis from the phase III clinical study suggests that elafibranor may effectively treat those with severe NASH [92].

The farnesoid X receptor (FXR)

A nuclear receptor family member is crucial for controlling the metabolism of bile acids, lipids, and glucose. It was a desirable target because it regulates bile acid balance in treating cholestatic diseases [93]. The liver, small intestine, and HSCs express FXR at significant levels. Fascinatingly, overexpression of FXR prevented HSCs from producing collagen [94]. According to recent studies, FXR agonists may effectively treat liver illnesses other than cholestatic ones. In mouse NASH models, the FXR agonist WAY-362450, for instance, decreased liver fibrosis and inflammation [95]. FXR agonist also reduced hepatic fibrosis in several different hepatic fibrosis models (BDL, CCL_4, and porcine models) by inducing small heterodimer partner (SHP) gene expression [96].

Obeticholic acid (OCA), a bile acid derivative, is a potent FXR activator that lowers liver fat and fibrosis in animal models of fatty liver disease [97]. In a phase 2 experiment, cases with diabetes mellitus type 2 and NAFLD received OCA at 25 or 50 mg once daily for 42 days. This therapy reduced liver fibrosis and inflammation markers while increasing insulin sensitivity "NCT00501592" [98].

Wnt/β-catenin signaling

According to studies, the initiation of HSCs and hepatic scarring are linked by the Wnt/β-catenin signal pathway. Wnt protein, along with frizzled receptor and lipoprotein receptor-related protein (LRP)-5/6, forms a complex that prevents the breakdown of β-catenin. In the presence of coactivators such as cyclic AMP response element-binding protein (CREB), β-catenin is activated, accumulates, and is then easily located in the nucleus, which triggers the transcription of associated target genes [99]. By increasing epithelial-mesenchymal transition (EMT) and collagen deposition, the Wnt/β-catenin signal pathway, which is abnormally active in activated HSCs following liver damage, helps reduce liver fibrosis [100].

The CRBP and β-catenin connection is broken down by the small molecular inhibitor ICG001. In a mouse model of liver fibrosis induced by CCl_4, ICG001 significantly reduced HSC activation and ECM buildup. It also stopped macrophages from migrating and drastically cut CCL12 production [101]. The CRBP/β-catenin inhibitor PRI-724 attenuated HCV-induced liver fibrosis in mice by inhibiting HSC activation [102]. Octreotide is a somatostatin analog. It inhibited LX2 activation and proliferation, reduced Wnt1 and β-catenin expression *in vitro* and *in vivo*, and lowered CCl_4-induced liver fibrosis in rats [22].

Inhibition of type I collagen synthesis

Up to 50% of the dry weight of the liver in people with liver cirrhosis is made up of collagen [103]. The most prevalent collagen in fibrotic livers is collagen type I. Additionally, the enzyme known as lysyl oxidase-like-2 (LOXL2) alters the cross-linking of type I collagen, leading to an elevation in its levels [104]. Lysyl oxidase (LOX) is a crucial player in collagen stability in chronic liver disease models in animals [105], and chronic human liver disorders have been linked to the overexpression of LOX enzymes [106]. These data gave justification for examining the function of an anti-LOX2 in the management of liver fibrosis. Simtuzumab (SIM) is a humanized antibody that can inhibit collagen cross-linking by targeting LOX2. Unfortunately, data from (phase II) clinical trials on NASH patients with liver F3 (NCT01672866) fibrosis and F4 cirrhosis (NCT01672879) revealed that SIM treatment was not able to reduce hepatic collagen or hepatic venous pressure [107].

Collagen production may be inhibited by knocking down Hsp47, a Col1 chaperone, with small interfering RNA. In three *in-vivo* models of liver fibrosis, Sato et al. found significant anti-fibrotic effects using vitamin A-coupled liposomes carrying Hsp47 siRNA, mostly taken up by HSCs [108]. BMS 986263, a lipid-based nanoparticle designed to deliver Hsp47 siRNA, underwent human trials and demonstrated its safety [109].

Immune modulation

Fibrosis is caused by inflammatory cells invading the liver, notably macrophages. Kupffer cells, resident macrophages in the liver, can become more activated in response to pathogen-associated molecular patterns (PAMPs) and DAMPs, which can cause inflammatory and immune reactions in the liver. Activated Kupffer cells cause liver inflammation and fibrosis by producing chemokines like CCL2 and CCL5, which bind to their corresponding receptors, C-C chemokine receptors 2 and 5 (CCR2 and CCR5). These chemokines promote HSC activation [110]. Damage to the liver triggers the production of CCL2 from Kupffer cells, which recruits monocytes and promotes their maturation into inflammatory LY6C(high) macrophages [111]. Since macrophages initiate the pro-inflammatory response to liver damage, they are particularly interesting [112]. Therapeutic strategies to reduce fibrosis may 1 day focus on influencing patients' first innate immune response. In general, anti-inflammatory therapies can be categorized into three main groups. The first group focuses on inhibiting the arrival of inflammatory cells, while the second group aims to reduce macrophage activity. The third group is dedicated to regulating macrophage function and polarization. These approaches are typically given priority when developing treatments for inflammation. It's important to note that targeting these different aspects of the inflammatory process can provide a multifaceted strategy for managing inflammation-related conditions [10].

Preventing recruitment of inflammatory cells

Cenicriviroc (CVC), a dual CCR2/CCR5 inhibitor, decreased liver fibrosis in animal models by reducing the recruitment of pro-inflammatory macrophages [113]. Patients suffering from

NASH who took part in the CENTAUR trial "NCT02217475" or the AURORA study of phase III clinical trial that concluded the excellent safety profile of CVC in treating patients suffering from liver fibrosis caused by NASH "NCT03028740" [114]. Furthermore, research is being done on a medication that combines CVC with tropifexor (an FXR agonist), which has been shown to reduce inflammation in NASH animal models. Patients with NASH and liver fibrosis (F2 or F3) participate in a phase 2 study [115].

Reducing macrophage activity

The pathogenesis of liver fibrosis involves galectin-3, mainly released by activated macrophages [116]. Belapectin (or GRMD-02), an inhibitor of galectin-3, has been shown to have anti-fibrotic solid effects in mice and rat models of liver fibrosis [117]. Cirrhosis caused by non-alcoholic fatty liver disease is the focus of a current phase 2b/3 clinical investigation "NCT04365868". In addition, a phase 1 trial looks at the safety and acceptability of GB1211, another galectin-3 receptor inhibitor "NCT03809052" [38].

Promotion of macrophage polarization

Promoting a shift from a pathogenic to a restorative phenotype can speed up the recession of fibrosis and encourage liver regeneration [118]. This can be accomplished using pharmacological agents that stimulate macrophage polarization. Macrophage reprogramming in liver illnesses has been studied with many agents, including prostaglandin E2 (PGE2), colony-stimulating factor 1 receptor (CSF-1R), steroids (e.g., dexamethasone), Interleukin 4 (IL-4) and interleukin 10 (IL-10) and secretory leukocyte protease inhibitor (SLPI) agonists [119]. Furthermore, nanotechnology [120] uniquely transforms macrophages into repair cells [119].

Target receptor-ligand interactions and intracellular signaling

Identifying membrane and nuclear receptors expressed by HSCs has opened up new avenues for anti-fibrotic treatments. Here's some information about the significance of these receptors and their potential as therapeutic targets: Nuclear Receptors (NRs) are a family of ligand-activated transcription factors that play a role in various biological processes, including the function and development of cells within the hematopoietic and immune systems [121]. They are classified into six subfamilies and comprise a DNA-binding domain (DBD) and a ligand-binding domain (LBD). In the context of liver fibrosis, NRs have been implicated in regulating HSC activation and fibrogenesis [122, 123]. In addition to NRs, membrane Receptors expressed by HSCs have also been identified as potential targets for anti-fibrotic therapies. These receptors, such as G protein-coupled receptors (GPCRs), can activate intracellular signaling pathways and modulate HSC activation and fibrogenesis.

Targeting these receptors with specific agonists or antagonists may help regulate HSC activation and fibrogenesis, leading to the development of novel anti-fibrotic treatments. For example, activation of the farnesoid X receptor (FXR), a nuclear receptor, has been shown to inhibit HSC activation and reduce liver fibrosis in preclinical models. While identifying these receptors has provided valuable insights into the pathogenesis of liver fibrosis, there are still challenges to overcome in developing effective and safe anti-fibrotic therapies. Further research is needed to understand the mechanisms of action of these receptors fully and to explore their potential as therapeutic targets in liver diseases [123].

Neurochemical receptors

In HCV patients, regular cannabis usage is a risk factor for increased liver fibrosis [124]. In liver fibrosis, cannabinoid receptors CB1 and CB2 are overexpressed. Compared to CB2 knockout mice (KO) mice, CB1 KO mice show less liver fibrosis [125]. Hepatic stellate cells are turned into myofibroblasts by CB1 agonists. Experimental liver fibrosis is inhibited and reversed by CB1 receptor agonists like Rimonabant [126]. Without causing depression, a peripherally acting CB1 antagonist could treat liver fibrosis.

The renin–angiotensin system (RAS)

An important component of fibrogenesis is angiotensin II (Ang II). HSCs release Ang II, which binds to the AT1 receptor that is also expressed by HSCs [127]. Human HSCs are induced to contract and proliferate, and collagen I gene expression is elevated *in vitro* due to Ang II [128]. Inflammation, fibrosis, and lipid peroxidation products after bile duct legation were all reduced in AT1a receptor mutant animals [129]. In light of this, inhibiting the RAS with ACE inhibitors or AT1 receptor blockers may be a successful method for treating liver fibrosis. Losartan treatment for a prolonged period of time reduces nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, inflammation, and fibrogenesis in chronic HCV patients [130].

Endothelin 1

The stimulation of HSCs contractility by endothelin may contribute to HSCs activation. An experimental hepatic fibrosis model showed anti-fibrotic action and decreased the level of stellate cell activation by blocking the endothelin receptor with the drug bosentan [131]. Despite initial enthusiasm, bosentan's development for this application was hindered by signs of hepatotoxicity.

Tyrosine kinase receptors

Numerous growth-promoting cytokines interact with cells through tyrosine kinase receptors, including PDGF, fibroblast

growth factor (FGF), and transforming growth factor alpha (TGF-α). These receptors are a group of surface molecules that add phosphate groups to specific tyrosine residues upon binding with their respective ligands. HSC proliferation is decreased via the antagonism of pathways that mediate PDGF or vascular endothelial growth factor (VEGF) signals [132]. For instance, multiple receptor tyrosine kinase inhibitors such as sorafenib target the PDGF receptor and have anti-fibrotic effects in animal models [133].

Gene therapy

SiRNA of 21–23 nucleotides is used in the RNA intervention (RNAi) as a method for precisely silencing individual genes [134]. The direct deletion of TGF-β1 using siRNA has been shown to markedly diminish the expression of α-SMA and collagen type I in HSC-T6 cells and to have anti-fibrotic effects in mice and rats with CCl4-induced hepatic fibrosis [135]. Histone deacetylase 2 (HDAC2) is an up-regulated protein in fibrotic liver tissues caused by CCl4 or HSCs treated with TGF-β1. In HSC-T6 cells treated with TGF-β1, siRNA against HDAC2 expression reduced the expression of collagen type I alpha 1 (COL1a1) and α-SMA [136]. By slowing down the Wnt/β-catenin signal pathway, inhibiting the proliferation of HSC-T6 cells, and inducing apoptosis, β-catenin siRNA slowed the advancement of hepatic fibrosis [99]. That implies that β-catenin siRNA offers a novel method for managing liver fibrosis [137].

In addition to siRNA-based therapy, microRNA (miRNA) may be used to treat liver fibrosis. One form of endogenous non-coding short RNA called miRNA controls the expression of RNA after transcription. In a clinical trial "NCT01200420" of hepatitis C infection, miravirsen (SPC3649), nucleotides, and DNA mixture successfully stopped miR-122 from doing its job and decreased hepatic fibrosis [138]. Mice with hepatic fibrosis caused by CCl4 had markedly better liver function after being treated with the small non-coding RNA MiR-101, which controls the MAPK response. By suppressing the levels of α-SMA and COL1a1, lowering the accumulation of ECM components, and blocking the phosphatidylinositol-3-kinase (PI3K)/Akt/the mammalian target of rapamycin (mTOR) signal pathway, MiR-101 inhibited liver fibrosis and protected liver parenchyma from injury [139].

Monoclonal antibodies

Monoclonal antibodies are relatively new and developing, becoming crucial to modern pharmacology [140]. Using monoclonal antibodies has fewer adverse side effects and, by itself or in conjunction with other medications, can produce significant results. Many monoclonal antibody treatments with clinical approval are available for a variety of diseases, and they can be used alone or in combination with other therapy (e.g., cetuximab [141], herceptin with docetaxel or paclitaxel [140]. While monoclonal antibodies are a relatively recent strategy for treating liver fibrosis, the field is still in the early stages. Nevertheless, several formulations reached clinical assessment.

Phytomedicines with multidimensional liver fibrosis effects

Without briefly addressing herbal substances, some of which have shown promise in numerous studies, a review of hepatic anti-fibrotic therapy would not be complete. Several investigations examined Phytodrugs and herbal formulations for treating liver fibrosis. The Phytodrugs with the most significant research into their potential anti-fibrotic effect are resveratrol, silymarin, and curcumin [142, 143].

In animal studies, resveratrol treatment ameliorated steatosis and persistent hepatic disease [144]. Significant protective benefits on indices of liver inflammation and the degree of hepatic steatosis, but not on fibrosis, were seen in NAFLD patients in a randomized, double-blind clinical study comparing oral resveratrol supplementation to a placebo for 12 weeks [145].

A natural herbal flavonoid compound called silymarin (Silybum marianum) is derived from cardoon milk. In a study using cultured human liver HSCs, silybin was discovered to inhibit the pro-fibrogenic actions of HSCs, such as cell proliferation, cell motility, and the production of extracellular matrix components [146]. In non-cirrhotic individuals with NASH, the NAFLD Activity Score showed no statistically marked improvement while being safe, according to a recently finished phase 2 trial titled (SyNCH; NCT00680407) [147].

Curcumin, the main component of *Curcuma longa*, has been studied in many medical conditions and has been found to have anti-inflammatory effects in chronic liver disease antiviral and tumor-preventive properties [148]. Thus, in NASH *in-vivo* models, curcumin treatment suppressed hepatic inflammation, steatosis, formation, and progression of fibrosis [149]. In a rat model of CCl4-induced hepatic fibrosis, curcumin was found to stop HSCs via inducing apoptosis and to prevent liver fibrosis [150]. A complete list of herbal remedies for liver fibrosis is more thoroughly reviewed by Latief and Ahmad (Table 1) [142].

Combination therapies

Due to the complexity of the etiology, combination therapy that affects two or more targets is likely necessary. The following theories for combination medications have been demonstrated to increase efficacy, and decrease associated adverse effects of single therapies (1): drugs that target several pathways (2); medicines

TABLE 1 Examples of ongoing research regarding repurposing FDA-approved drugs and using experimental drugs in the treatment of liver fibrosis.

FDA-approved drug repurposing	Proposed target	References	Investigational stage
Aspirin	TLR4/NFκB- TGFβ	[14]	Preclinical
Liraglutide	GLP-1	[15]	Phase III
Losartan	Angiotensin II	[16]	Phase IV
Pentoxifylline	TNFα	[17]	
Pirfenidone	TGFβ	[18]	Phase II
Praziquantel	SMAD7	[19]	
Sorafenib	PDGFR (platelet-derived growth factor receptor)/HIF-1α	[20]	Phase III
Pioglitazone	CTGF(connective tissue growth factor)	[21]	Preclinical
Octreotide	Wnt/β-catenin	[22]	Preclinical
Statins	HMG CoA Reductase	[23]	Phase II
Sitagliptin	Dipeptidyl Peptidase-4	[24]	
Rosiglitazone	PPAR gamma	[25]	Phase II
Erythropiotein	ROS/cytokines	[26, 27]	Preclinical

TABLE 2 Examples of current studies investigating the utilization of FDA-unapproved medications and experimental drugs for managing liver fibrosis.

FDA-unapproved medications and experimental drugs	Proposed targets	References	Investigational stage
Cenicriviroc	CCR2/5	[28]	Phase III +ve
Resmetirom	THRβ	[29]	Phase III +ve
Emricasan	Pan-caspase	[30]	Phase II
Selonsertib	ASK1	[31]	Phase II
Hydronidone	FGFR1	[32]	Phase II +ve
Cilofexor	FXR	[33]	Phase II +ve

that target diverse characterizations of the disease (3); drugs that combine small-molecule and macromolecular drugs; and (4) drugs that target metabolism and liver fibrosis [151].

Mechanistically complementary, as in the case of participants with NAFLD receiving both an acetyl-CoA carboxylase (ACC1/2) inhibitor (PF-05221304) and diacylglycerol acyltransferase-2 (DGAT2) inhibitor (PF-06865571) [152]. Co-administration of PF-05221304 and PF-06865571 may be a practical strategy. Also, targeting several aspects of a disease, such as FXR (which targets fibrosis and inflammation) and ACC (which decreases fat formation): Patients with NASH showed improvements in hepatic steatosis, biochemistry, and stiffness when receiving a combination of the ACC inhibitor GS-0976 (firsocostat) and the nonsteroidal FXR agonist GS-9674 (cilofexor) (NCT02781584) [153].

Besides, the combination of the small-molecule medications cenicriviroc (CVC) and tropifexor (LJN452) for patients with NASH and liver fibrosis (NCT03517540) offers additional benefits compared to monotherapy [154]. Similarly, small-molecule drug medications combined with macromolecular drugs: In patients with NASH, the FXR agonist cilofexor (GS-9674), ACC inhibitor GS-0976 (firsocostat), and the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide has shown quiet promising results in countering the progression of the disease evaluated (NCT03987074) [155].

Discussion

This review delved into the diverse hepatic cell types implicated in liver fibrosis and explored numerous promising treatment avenues. Its overarching goal is to guide further research in this field. Initially, early research focused on the activation of HSCs and collagen deposition as primary points of interest in understanding fibrosis mechanisms. However, recent investigations have broadened their focus to encompass metabolic processes, HSC proliferation, apoptosis, and epigenetic modifications. These studies have significantly expanded our comprehension of fibrosis pathogenesis, opening up exciting new avenues for research into anti-fibrotic therapies.

Despite these advancements, most anti-fibrosis medications, whether designed for liver fibrosis induced by chronic liver disease or other factors, remain in the preclinical development stage. However, there is a glimmer of hope as certain drugs,

boasting proven anti-fibrosis efficacy, excellent safety profiles, and patient tolerance, have progressed to the clinical development phase.

Yet, tackling the complexity of fibrosis emergence and progression presents a formidable challenge. Fibrosis is a multifactorial, multistep process, which makes achieving therapeutic progress through targeting a single element, pathway, or link quite challenging. Therefore, the most promising approach lies in developing combination therapies that address multiple pathways simultaneously. This comprehensive strategy should encompass both direct and indirect anti-fibrotic treatments, complemented by therapeutic measures aimed at managing or alleviating the underlying primary disease. In essence, a multifaceted treatment approach offers the best chance of combatting the intricate web of fibrosis.

Author contributions

HF, BM, and ME: Conceptualization, data curation, writing-review, editing, visualization, and revision. HA: Supervision, fund acquisition, writing-review and editing. OM: Conceptualization, administration, visualization. All authors contributed to the article and approved the submitted version.

Funding

This work was partly funded by the Deanship of Scientific Research at Najran University, Saudi Arabia, under the general research funding program with a grant code (NU/NRP/MRC/12/3).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

The authors thank the Deanship of Scientific Research at Najran University for funding this work under the general research funding program with a grant code (NU/NRP/MRC/12/3). The authors would like to thank Science Shake Inc. for conducting proofreading and English language editing (https://www.science-shake.com/).

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Glossary

ACE-I	Angiotensin-converting enzyme inhibitors
ACC1/2	Acetyl-CoA carboxylase 1/2
aHSCs	Activated HSCs
ALP	Alkaline phosphatase
ALT	Alanine transaminase
Ang II	Angiotensin II
ASK1	Apoptosis-signal-regulating kinase 1
AST	Aspartate transaminase
BDL	Bile duct ligation
CB1	Cannabinoid receptors CB1
CB2	Cannabinoid receptors CB2
CCL2	Chemokine (C-C motif) ligand 2
CCl4	Carbon tetrachloride
CCL5	Chemokine (C-C motif) ligand 5
COL1a1	Collagen type I alpha 1
COX	Cycloxygenase 2
CREB	Cyclic AMP response element-binding protein
CSF-1R	Colony-stimulating factor 1 receptor
CTGF	Connective tissue growth factor
CVC	Cenicriviroc
DAMPs	Damage-linked molecular patterns
DGAT2	Diacylglycerol acyltransferase-2
DMN	Dimethylnitrosamine
DPP4	Dipeptidyl peptidase 4
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
FAK	Focal adhesion kinase
FasL	Fas ligand
FGF	Fibroblast growth factor
FN	Fibronectin
TIMPs	Tissue inhibitors of metalloproteinases
TNF-α	Tumor necrosis factor-alpha
FXR	Farnesoid X Receptor
Gal-3	Galectin-3
GFT505	Elafibranor
GLP-1	glucagon-like peptide-1
GPx	Glutathione peroxidase
GRMD-02	Belapectin
GSH	Glutathione
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDAC2	Histone deacetylase 2
HMG-CoA	Hydroxymethylglutaryl-coenzyme A
HSCs	Hepatic stellate cells
ICAM-1	Intercellular adhesion molecule 1
IL-1	Interleukin 1
IL-10	Interleukin 10
IL-1β	Interleukin-1 beta
IL-4	Interleukin 4
IL-6	Interleukin 6
iNOS	Inducible nitric oxide synthase
KO	Knockout mice
LOX	Lysyl oxidase
LOXL2	Lysyl oxidase-like-2
LRP	Lipoprotein receptor-related protein −5/6
MAPK	Mitogen-activated protein kinase
MAT 1A	Methionine adenosyltransferase 1 alpha
MDA	Malondialdehyde
MELD	Model for End-Stage Liver Disease
MFA	Methyl ferulic acid
miRNA	MicroRNA
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
VEGF	Vascular endothelial growth factor
MMP-1	Matrix metalloproteinase 1
MMPs	Matrix metalloproteinases
NAC	N-acetylcysteine
NADPH	Nicotinamide adenine dinucleotide phosphate
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NFκB	Nuclear factor kappa
NOX	NADPH oxidase
OCA	Obeticholic acid
PAI-1	Plasminogen activator inhibitor 1
PAMPs	Pathogen-associated molecular patterns
PDGF	Platelet-derived growth factor
PFD	Pirfenidone
PGE2	Prostaglandin E2
PINP	Type 1 procollagen peptide
PPARs	Peroxisome proliferator-activated receptors
PPARγ	Peroxisome proliferator-activated receptor gamma
qHSCs	Quiescent HSCs
RAS	Renin-angiotensin system
RBO	Rice bran oil
ROS	Reactive oxygen species
SAC	S-allyl cysteine
SAMe	S-adenosyl-L-methionine
SHP	Small heterodimer partner
SLPI	Secretory leukocyte protease inhibitor
SOD	Superoxide dismutase
TAA	Thioacetamide
TAZ	Transcriptional coactivator with PDZ-binding motif
TGF-α	Transforming growth factor alpha
TGF-β1	Transforming growth factor beta 1
YAP	Yes-associated protein
α-SMA	α-smooth muscle actin