Liver fibrosis is a pathological process of abnormal tissue proliferation in the liver caused by various pathogenic factors, which will further develop into cirrhosis or even hepatocellular carcinoma if liver injury is not intervened in time. As a diffuse progressive liver disease, its clinical manifestations are mostly excessive deposition of collagen-rich extracellular matrix resulting in scar formation due to liver injury. Hepatic fibrosis can be caused by hepatitis B and C, fatty liver, alcohol, and rare diseases such as hemochromatosis. As the metabolic center of the body, the liver regulates various vital activities. During the development of fibrosis, it is influenced by many other factors in addition to the central event of hepatic stellate cell activation. Currently, with the increasing understanding of TCM, the advantages of TCM with multiple components, pathways, and targets have been demonstrated. In this review, we will describe the factors influencing liver fibrosis, focusing on the effects of cells, intestinal flora, iron death, signaling pathways, autophagy and angiogenesis on liver fibrosis, and the therapeutic effects of herbal medicine on liver fibrosis.

1. Introduction
Liver fibrosis is a wound-healing response when the liver is injured, showing a dynamic process, which can be caused by nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), and cholestatic liver disease [1]. In addition, liver fibrosis is a determinant of mortality in NASH [2]. Advanced liver fibrosis creates the risk of cirrhosis and hepatocellular carcinoma, which kills approximately 1 million people worldwide each year as a complication of cirrhosis, while hepatocellular carcinoma ranks as the 16th most common cause of death, making the early diagnosis of liver fibrosis crucial [3]. Fibrosis is characterized by the production of myofibroblasts (MFB) that promote scar formation by activated Hepatic stellate cells (HSC), and the synthesis of extracellular matrix (ECM) by both MFB and HSC, and the balance of ECM is regulated by both matrix metalloproteinases (MMP) and tissue inhibitor of metalloproteinases (TIMP) that ultimately target HSC to form fibrosis, so it can be said that the dynamics of ECM regulation process is the process of liver fibrosis formation. In addition, nonparenchymal cells such as macrophages (MAC) and liver sinusoidal endothelial cells (LSEC) are also involved [4]. In addition, various signaling pathways, including transforming growth factor (TGF-β), platelet-derived growth factor (PDGF), and nuclear factor-κB (NF-κB), are also key pathways affecting liver fibrosis. Currently, there are still no specific and effective drugs to treat liver fibrosis, but there is increasing evidence that Chinese medicine and natural products provide effective help in the prevention and treatment of liver fibrosis [5, 6]. Therefore, in this paper, a large number of collections were carried out in the PUBMED database to fully understand the main events of liver fibrosis, which provided the possibility for targeted liver fibrosis therapy, as shown in Figure 1.

2. Cellular Factors
HSC, MAC, and LSEC all have a dual role in the formation of liver fibrosis. During liver injury, the activation and
proliferation of hepatic stellate cells, the increase of Ly6C<sup>hi</sup> in macrophages, the capillarization of hepatic sinusoidal endothelial cells, and the concomitant secretion of various inflammatory factors all contribute to the formation of fibrosis. The apoptosis of hepatic stellate cells, the increase of Ly6C<sup>lo</sup> in macrophages, and the normal differentiation of hepatic sinusoidal endothelial cells can make the activated hepatic stellate cells quiescent and even degrade the excess extracellular matrix, which can effectively prevent the development of liver fibrosis. This article will explain how cellular factors are actively activated to cause liver fibrosis.

2.1. Hepatic Stellate Cells. Hepatic stellate cells (HSC) are a class of nonparenchymal cells located in the endothelial cells of the hepatic sinusoids and the sinusoidal spaces surrounding the hepatocytes, also known as hepatic lipid storage cells. Under pathological conditions, HSC is converted to an activated state by stimulation of various environmental factors, which is a critical step in the development of liver fibrosis [7, 8]. Chronic liver injury leads to multiple damage-associated molecular patterns (DAMPs) producing a series of cytokines including insulin growth factor (IGF-1) and ET-1 that activate the secretion of HSC. At the same time, long-term stimulation that triggers an inflammatory response combined with LSEC [9] and KC [10] also releases damage factors like IL-6, TNF-α, and TGF-β to further promote the initiation of HSC activation [11]. Activated HSC themselves also secrete fibrogenic factors such as CTGF and leptin, which in turn enhance the ability to induce proliferation of HSC. In addition, α-SMA-containing myofibroblasts (MFb) contribute to the formation of fibrotic scar and synthesize I and III collagen-based ECM [12, 13], and excessive accumulation of ECM activates HSC, creating a positive feedback loop leading to fibrosis formation. In particular, PDGF and VEGF released from platelets are mitogenic mediators of HSC and bind to ECM to enable the already activated HSC to undergo the next step of proliferation [14]. Chemokine-chemokine receptors play a key role in liver fibrosis, especially the C-C motif chemokine receptor 2 (CCR2) activates HSC [15]. The process by which epithelial cells gradually lose their phenotypic characteristics while acquiring mesenchymal cell characteristics is called epithelial-mesenchymal transition (EMT), and the involvement of EMT also mediates the transdifferentiation and fibrosis of HSC [16]. When the Hh signaling pathway derepresses Smo and activates the Gli transcription factor, Gli contains a predicted paired frame 6 (PAX6) binding site in its transcriptional region, which promotes both HSC activation and proliferation [17].

2.2. Macrophages. Macrophages are derived from precursor cells in the bone marrow, which are immune cells [18]. Those active in the liver are called liver macrophages (Liver MAC) and mainly include kwashiorkor cells (KC) and monocyte-derived macrophages (MoMF) [19].

Under pathological conditions, there is a large amount of Ly6C<sup>lo</sup> from MoMF, which has a proinflammatory properties and can overexpress CCR1 and CCR2 [20], and Ly6C<sup>hi</sup>...
can not only release a large number of cellular, inflammatory, and chemokines such as TGF-β, PDGF, TNF-α, IL-1β, and CCL2 [21–24] but can also depend on chemokine aggregation to the site of liver injury. The precursor cells of Ly6C<sup>hi</sup> are Ly6C<sup>lo</sup> monocytes, but Ly6C<sup>hi</sup> has an opposite effect to Ly6C<sup>lo</sup>, where Ly6C<sup>hi</sup> can downregulate inflammatory factors and increase MMP, promoting the degradation of ECM. Through the study, when the CCR2 gene was knocked down in mice, Ly6C<sup>hi</sup> was reduced and Ly6C<sup>lo</sup> quantity was increased in the liver, corresponding to the reduction of HSC activation and some relief of liver fibrosis, indicating that Ly6C<sup>hi</sup> has proinflammatory and profibrotic properties, while Ly6C<sup>lo</sup> has anti-inflammatory and antifibrotic properties.

KCs are located in macrophages within the hepatic sinusoids, also known as resident cells [25]. When a liver injury occurs, KCs are activated by DAMPs and pathogen-associated molecular patterns (PAMPs) interacting with Toll-like receptors (TLRs). Activated KC generates various types of mediators of liver fibrosis progression (e.g., TGF-β, PDGF, IL-1β, MMPs, CCL2, cysteine-3, etc.) and also accelerates the progression of liver fibrosis by activating HSC to produce large amounts of collagen, allowing ECM to settle and aggregate [26].

2.3. Liver Sinusoidal Endothelial Cells. Liver sinusoidal endothelial cells (LSEC) are highly specialized endothelial cells with pores on the cell surface and open windows, whose vascular secretory signals regulate liver function and have an important role in maintaining the homeostasis of the hepatic endotrophic environment, which, in turn, is a key factor in the activation of HSC [27, 28]. Differentiated LSEC can maintain HSC in a quiescent form, which can accelerate the progression of liver fibrosis and stop its progression, but the opposite is true for capillary LSEC [29]. When LSEC forms an organized basement membrane and lacks open windows, it is capillary vascularization of LSEC, which then eventually leads to the activation of HSC through the synthesis of factors like TGF-β to form fibrosis, fibrosis aggravates LSEC, and LSEC promotes fibrosis, leading to a vicious cycle. The vascular endothelial factor VGEF pathway was found to protect LSEC from opening windows and prevent fibrosis [30]. Capillarization is induced in LSEC if the Gata4 gene is absent, inducing the expression of profibrotic vascular secretory factors, which in turn leads to the possibility of perisinusoidal capillarization or fibrosis and liver lesions [31]. It has been claimed that the addition of bone morphogenetic protein (BMP9) to LSEC in primary culture, as a regulator of the intrahepatic environment, not only prevents the loss of window pores but also integrates the Gata4 gene and restores LSEC differentiation [32]. Furthermore, autophagy affects liver fibrosis by affecting LSEC [33], when the liver is mildly injured, autophagy of LSEC enhances sinusoidal endothelial dysfunction (ED) and activates HSC, but, if the liver is too long or more severely injured, autophagy decreases, and ED fails to proceed. Autophagy of LSEC also enables chemokines, inflammatory factors such as C-C chemokine ligand 2 (CCL2), C-C chemokine ligand 2 (CCL5), and interleukin-6 (IL-6) are enhanced, promoting the hepatic inflammatory response and thus liver fibrosis [34].

3. Signaling Pathways

3.1. TGF-β1/Smads Signaling Pathway. Transforming growth factor β1 (TGF-β1) is the most prominent way to promote fibrosis formation [35], which is through the intracellular Smads signaling pathway [36]. The Smads pathway promotes HSC activation, and inactivated HSC and activated Smad2 and Smad3 induce type I and type III collagen production [37], promote MFB cell proliferation, and increase ECM deposition in the liver [38]. Smad4 inhibits the binding activity of Smad3 to collagen and the aggregation and degradation of ECM in vitro and in vivo. In acute liver injury, Smad7 can compete with receptor-activated Smad2 and Smad3 to bind TGF-β1 receptors and reduce ECM production, or Smad7 can interrupt TGF-β1 signaling by enhancing the degradation of TGF-β receptors. However, after HSC transdifferentiation to MFB, the ability of TGF-β1 to induce Smad7 expression decreases, Smad2 and Smad3 are phosphorylated, the TGF-β1/Smads signaling pathway is activated, and ECM is secreted in large amounts, accelerating liver fibrosis [39–41]. TGF-β1 can also promote liver fibrosis by activating non-Smads pathways, such as MAPK, NF-κB, and PI3K [42]. TGF-β1 can induce TIMP-1 expression after signaling to Smad3, while inhibiting MMP-1 expression, making the ratio of TIMP-1 to MMP-1 increase, and promoting liver fibrosis. Smad2 can induce MMP-2 expression, and by knocking down the Smad2 gene, we obtained that TGF-β1 through the Smad3 pathway upregulated the expression of TIMP-1 and inhibited the expression of MMP-2, which in turn inhibited the degradation of ECM [43].

3.2. WNT/β-Catenin Signaling Pathway. Wnt acts as a signaling cascade that transfers signals through cell surface receptors to protein components in the cell. There are two types of this signaling pathway, the nonclassical planar cell polarization pathway that regulates the cytoskeleton and thus cell shape, and Wnt/Ca<sup>2+</sup> that regulates intracellular Ca<sup>2+</sup> concentration, and the classical signaling pathway that regulates specific gene transcription, which is dependent on β-catenin for further action on downstream factors and ultimately translocates to the nucleus where it binds to the intranuclear transcription factor Tcf/Lef, thereby activating expression of the relevant target gene [44]. The main difference between the two pathways is that the nonclassical pathway operates independently of it, and the classical pathway involves the involvement of β-catenin. It is believed that the Wnt/β-catenin pathway is now considered to be the main influential pathway involved in the development of liver fibrosis, and β-catenin has an important role as a key signaling molecule in this pathway [45]. When Wnt is activated and β-catenin is phosphorylated, ECM accumulation leads to HSC activation [46]. The deletion of β-catenin leads to TGF-β upregulation and oxidative stress [47]. In addition
Phosphatidylinositol 3-kinase (PI3K) is a class of pathway.

3.4. Phosphatidylinositol 3-Kinase (PI3K)-Akt Signaling pathway, which affects the process of fibrosis [49]. This justifies the reliability of using the Wnt/β-catenin signaling pathway as an entry point for the treatment of fibrosis. Silencing or inhibition of β-catenin, in the Wnt/β-catenin signaling pathway, promotes improvement of liver fibrosis or cirrhosis by limiting the contractility of HSC and portal hypertension [50].

3.3. Inflammasome (NLRP3) Caspase-1 Signaling Pathway. Inflammasome (NLRP3) is a part of the natural immune system, and it has been shown that all components of NLRP3 are present in the HSC, that multiple functions of the HSC are regulated by NLRP3, and that NLRP3 recognizes the release of damage patterns such as DAMPs and PAMPs caused by liver injury, by recruiting and activating proinflammatory cysteine-containing aspartate proteolytic enzyme 1 caspase-1, so that activated caspase-1 activates the proinflammatory cytokines IL-1β and IL-18, leading to the activation of HSC and the occurrence of liver fibrosis [51–53]. IL-1β aggregates by recruiting neutrophils, and excess proinflammatory cytokines lead to the activation of reactive oxygen species (ROS), inflammatory cells, and growth factors, which not only further promote activation of inflammatory vesicles but also promote the activation of HSC, leading to liver fibrosis [54]. Signals induced by lipopolysaccharide (LPS) [55] can activate pro-IL-18 and pro-IL-1β to activated IL-18 and IL-1β via NF-κB, which can then activate liver fibrosis via proinflammatory cytokines, or they can act directly on NLRP3 inflammatory vesicles, which in turn activate its downstream signaling pathway caspase-1 via NLRP3 inflammasomes which in turn will promote proinflammatory processes in the maturation and secretion of the precursors pro-IL-1β and pro-IL-18 during the defense process, promoting liver fibrosis formation [42, 56–58]. At the same time, caspase-1 also induces the activation of intracellular NLRP3 inflammatory vesicles, which can lead to a vicious cycle of proinflammatory signaling [59].

3.4. Phosphatidylinositol 3-Kinase (PI3K)-Akt Signaling Pathway. Phosphatidylinositol 3-kinase (PI3K) is a class of inositol lipid substance kinases, the most widely studied class of which is I PI3K, with the regulatory subunit p58 and the catalytic subunit p110 as the main targets [60]. Protein kinase B (Akt) is a downstream target of the PI3K signaling pathway and regulates the cell-initiated kinase cascade reaction that allows AKT to be activated by being readily located on the plasma membrane [61] PI3K and Akt are involved in the regulation of various signaling pathways including liver fibrosis in the liver. Studies have found that the autophagy of BDL and CCL4-induced liver fibrosis can be activated to promote liver injury by activating the TGF-β1/Smads signaling pathway and inhibiting PI3K/Akt signaling pathway and regulating cross-talk between the two pathways [62]. The initiation of phosphorylation of PI3K, AKT, and even mTOR in the PI3K/AKT signaling pathway can trigger the activation and proliferation of HSC and affect the production of liver fibrosis [63]. It is noteworthy that mTOR, as a downstream signaling molecule of AKT, also plays an important role in this pathway [64]. The expression of mTOR acts on the PI3K/Akt signaling pathway, induces HSC proliferation, induces the expression of α-SMA and other fibrogenic factors, and induces ECM synthesis [65].

3.5. Nuclear Factor-κB Signaling Pathway. Nuclear factor-κB (NF-κB) is a transcriptional regulator of greater interest in liver fibrosis and consists of a heterodimer of RelA (p65) and p50 subunits. When a sustained liver injury occurs, it activates HSC and KC, which in turn releases proinflammatory, chemotactic, and cytokines, causing the recruitment of various factors to the damaged sites of liver inflammation and stimulating NF-κB, which in turn stimulates the production of each factor upon NF-κB activation, thus creating a positive feedback between NF-κB and inflammatory factors [66]. Studies have shown that the NF-κB pathway is a key factor in HSC activation and proliferation, and it inhibits apoptosis and promotes HSC activation. When the expression of NF-κB inhibitor protein α (1xBa) increased, the Bax/Bcl-2 ratio rises, the NF-κB signaling pathway is inhibited, and the process of liver fibrosis is slowed down. In contrast, when KC is activated, the expression of NF-κB-p65 is significantly increased, the activity of ATL and AST is also significantly increased, and the progression of fibrosis is significantly accelerated [67, 68]. Through experiments [69], the NF-κB signaling pathway can lead to liver fibrosis through miR-378, as miR-378 leads to the development of NASH and liver fibrosis by promoting the activation of the NFκB-TNFα axis.

3.6. CTGF Signaling. Connective tissue growth factor (CTGF) belongs to a signal in the Hippo signaling pathway and is closely associated with various pathways such as TGF-β, Ras, MEK, ERK, WNT, AKT, and MAPK [70–74]. Through research [75], activated HSC secretes CTGF, which in turn promotes HSC activation and migration and upregulates type I collagen and α-SMA and activated HSC differentiates into MFB, which also secretes a large number of collagen fibers, resulting in a large amount of ECM deposition, and the above process can be analyzed as positive feedback between CTGF and HSC. CTGF may be a downstream response element of the TGF-β1 pathway and mediates some of the active effects of the TGF-β1 pathway, which allows fibrosis to occur, while CTGF has a role in maintaining fibrosis by activating a series of transduction pathways that induce MFB proliferation and ECM synthesis and promote the formation of liver fibrosis [76, 77].

4. Intestinal Flora

4.1. PAMP. In addition to the intestinal flora, which can help the body to digest and absorb and regulate metabolism, its
components and functions and the alteration of the intestinal barrier can directly or indirectly affect the formation of liver disease, and in turn, the occurrence of various liver diseases can affect the stability of the intestinal flora [78, 79]. This is because the liver and the intestine are connected by the portal vein, bile passes through the liver to act on the intestine, nutrients from the intestine flow into the portal circulation to reach the liver, and the two interact to form a feeder loop called the enterohepatic axis [80, 81]. Amid this loop, if there is an imbalance in intestinal homeostasis or translocation between microbial components, etc., called PAMP, hepatocytes such as KC and HSC and immune receptors in the lamina propria of the intestine recognize this pattern, leading to an inflammatory response and thus inducing fibrosis [82]. Thus, it can be said that intestinal flora disorders induce liver fibrosis.

4.2. Lipopolysaccharide. When intestinal permeability is disrupted or the microbial composition of the gut is altered, a series of metabolic toxins are produced, such as LPS, an endotoxin that further affects liver function, mainly by triggering an inflammatory response, via the enterohepatic axis. In binding to Toll4, a Toll-like receptor, or mediated through kupffer cells, inflammatory factors are produced into the portal circulation [83]. Naihua Hu et al. [84] demonstrated that different concentrations of LPS had an inducing effect in a model of inflammation and fibrosis in LX2 cells, resulting in enhanced expression of inflammatory factors such as IL-6, IL-1β, and TNF-α. In addition, LPS was able to regulate the expression of the NF-κB signaling pathway and MAPK proteins, including the JNK and p38 pathways associated with the activation of inflammatory mediators, with the consequent production of inflammatory factors that induce liver fibrosis formation [85].

4.3. FXR. Nuclear transcription factor receptor (FXR) and bile acids (BA) also interfere with fibrogenesis in terms of intestinal flora; BA is synthesized by the liver and acts in the intestine to produce secondary bile acids that inhibit FXR, which together with BA regulate the homeostasis of intestinal flora. When elevated concentrations of BA induce physiological activation and proliferation of HSC leading to pathological lesions of liver fibrosis, FXR can reverse this phenomenon by maintaining low concentrations of bile in hepatocytes. In addition, it prevents liver injury, which triggers liver fibrosis when FXR is inhibited [86, 87]. In addition, FXR can regulate the inflammatory response activated by BA in concert with LPS, mainly because FXR interconnects with NLRP3 or caspase-1 to produce non-positive regulation of NLRP3 action [88].

5. Autophagy

When HSC is normal, its cytoplasm contains a large number of lipid droplets [89]. When the liver is damaged and the HSC is activated, the lipid droplet content in the cytoplasm decreases, and as the HSC is converted to MFB, the autophagic flux increases, and when inhibited by the autophagy inhibitor bafilomycin A1, the lipid droplet content normalizes and the HSC returns to normal; i.e., the increased autophagic content is associated with HSC activation [90, 91]. Because autophagy lysosomes degrade abnormal proteins, etc., eliminating intracellular metabolic wastes and improving HSC survival and the substances recovered by autophagy provide energy and nutrients to HSC [92]. Studies have shown that autophagy is dependent on ROS, mTOR, and IL-7, and another factor in the process of liver fibrosis [93, 94]. When damage occurs in hepatocytes, it stimulates the production of large amounts of ROS in the liver, and the accumulation of excessive ROS can exceed the normal range of the antioxidant system in the body, allowing the occurrence of oxidative stress that causes abnormal fibrosis in the liver, while the activation of mTOR accelerates liver fibrosis when the organism is in a state of nutritional deficiency [95]. Autophagy can also protect the liver by degrading abnormal metabolites to prevent cellular damage or generate excessive autophagy leading to cellular scorching and the inability of HSC to survive [96, 97].

6. Iron Death

Iron death can occur through the Fenton reaction that generates a large amount of ROS that accumulate in the body and cannot be metabolized in time, leading to excessive oxidative stress, promoting lipid peroxidation and oxidative damage to the cell membrane, which in turn leads to cell death [98–100]. When the body lacks glutathione (GSH) also causes excessive accumulation of ROS and iron death, and when glutathione peroxidase 4 (GPX4) activity decreases, polyunsaturated fatty acids are produced in the body to undergo lipid peroxidation and cannot be metabolized by GPX4, resulting in cell death by intracellular hoarding [101, 102].

In the liver, HSC contains iron ions, and the development of liver fibrosis is closely related to iron ions and lipid peroxidation in HSC, and the progression of liver fibrosis can be regulated by iron death. When hepatic iron concentration (HIC) exceeds the normal level, HSC function is abnormal, and in more severe cases, it progresses to cirrhosis. Iron death in HSC leads to an increase in α-SMA and type I collagen, allowing ECM deposition, or increased production of proinflammatory factors through TGF-β and NF-κB signaling pathways, resulting in liver fibrosis. Liver fibrosis due to iron death also occurs mostly in hepatocytes and macrophages, which can likewise lead to an inflammatory response through the overproduction of HIC and inflammatory cells, activating HSC and producing liver fibrosis [103]. Through studies [104], the therapeutic effect of MgIG on liver fibrosis is produced by promoting the accumulation of iron and lipid peroxides, and the complete disappearance of the antifibrosis effect of MgIG when the inhibitor Fer-1 inhibits iron death in liver fibrosis also confirms the strong association between iron death and liver fibrosis.

7. Angiogenesis

Angiogenesis is an important factor contributing to liver fibrosis and is essential for the repair of liver injury [105].
LSEC and HSC express a range of proangiogenic cytokines, including vascular endothelial growth factor (VEGF), endothelin-1 (ET-1), and platelet-derived growth factor (PDGF), with downregulation of VEGF expression and upregulation of ET-1 expression indicating that LSEC undergoes capillarization [33].

7.1. VEGF. HSC can promote the expression of VEGF and even the receptor of VEGF, resulting in angiogenesis-induced fibrosis, and VEGF has a better ability to regulate angiogenesis than other cytokines, and, in terms of intestinal inflammation and monocyte infiltration, VEGF also produces effects leading to fibrosis [105]. It was shown that, after histochemical scoring, VEGF can be used as a predictor for the study of fibrosis progression [106]. In addition, VEGF is known to have the ability to alleviate liver fibrosis in bone marrow mesenchymal stem cells (BMSC), and it has been reported that VEGF can increase the permeability of sinusoidal endothelial cells and can affect changes in tissue collagen, a pathway in which BMSC can be better expressed [107].

7.2. ET-1. ET-1 is caused by the massive accumulation of extracellular matrix ECM activated by HSC and also stimulates proliferation and collage synthesis by inducing contracture of activated HSC, which can act on LSEC in addition to HSC [108], and ET-1 can reduce the size and number of window pores in LSEC [30], which in turn can affect liver microcirculation. In CCL4-induced liver fibrosis, ET-1 expression was increased, suggesting that ET-1 could be a promising marker [109]. Not only that, ET-1 acts as a mitogen of smooth muscle vessels with its receptors ET₄R and ET₃R to regulate vasoconstriction and diastole. When ET-1 is upregulated in the expression of HSC, ETR is also elevated, leading to increased hepatic sinusoidal resistance and producing portal hypertension, which suggests an exacerbation of fibrosis [110].

7.3. PDGF. PDGFs have five isoforms and two receptors, PDGFR-α and PDGFR-β. PDGFR-α has more affinity than PDGFR-β and binds more easily to other signaling molecules, such as Ras, MEK, and the extracellular signal-regulated kinase ERK, which are involved in the regulation of fibrogenesis [111, 112]. PDGFR-β expression shows an upregulation trend with HSC activation and PDGFR-β acts as the most promising proliferation mediator for HSC, inducing further HSC proliferation [113]. Liver sinusoidal endothelial cell vascularization increases liver permeability due to loss of PDGFR-β activity [30], and most liver samples from patients with liver fibrosis show increased levels of PDGFR-β expression, while PDGFR-β is a key pathway to induce HSC activation and proliferation [114].

8. TCM Therapeutic Perspectives

So far, the treatment effect of liver fibrosis in Western medicine has progressed slowly, except for surgical treatments such as liver resection; there is no specific curative medicine that can have a good treatment effect on liver fibrosis without complications and adverse reactions. Although the term “liver fibrosis” does not exist in traditional Chinese medicine, it has a long history and profound sources, and the concept of “ruffian, lumps, and accumulation” has been used for a long time, and the modern concept of liver fibrosis belongs to this concept [115]. Moreover, many TCM have the advantages of multicomponent, multipathway, and multitarget, with antioxidant, anti-inflammatory, anticancer, and hepatoprotective effects, and this feature can be fully reflected in liver fibrosis.

Through studies [116–119], tetramethylpyrazine can increase the MMP/TIMP-1 ratio and accelerate the degradation of ECM with antifibrotic effects, block the pathway of TGF-β1 and Nrf2/β-linked protein, inhibit the activation and migration of HSC, increase the storage of lipid droplets within HSC, or exert antifibrotic effects through cellular autophagy, with anti-inflammatory and antioxidant effects, etc., or inhibit hepatic fibrosis by reducing oxidative stress. *Chrysanthemum* [120, 121] can reverse liver fibrosis, mainly by inhibiting the TGF-β1 signaling pathway and thus reducing the value-added activation of HSC. Evodiamine [122] was able to reduce IL-6, TNF-α, and types I and III collagen expression, inhibit the TGF-β1/Smads signaling pathway, and attenuate liver fibrosis. Breviscapin [123] reduces inflammatory factors by killing TLR4/NF-κB signaling pathway, which can reduce liver fibrosis by decreasing apoptotic response, blocking oxidative stress, and inhibiting inflammation. Curcumin, a major component of turmeric, activates PPAR-α signaling, inhibits PI3K/Akt signaling, enhances cellular autophagy, and thus inhibits ECM production [89, 124] and also reduces lipid peroxidation to prevent liver fibrosis. α-SMA, a marker of HSC activation, was significantly reduced in expression after treatment with the flavonoid baicalin and reversed the effect of PDGF-BB on promoting the ability of HSC-T6 cells to promote activation [125, 126]. In contrast, *Scutellaria baicalensis* decoction has a preventive effect on liver injury, which may be related to the involvement in the metabolism of some tryptophan to reduce oxidative stress and inhibit collagen regeneration [127]. Emodin extracted from various anthraquinones further affects the fibrotic process by inhibiting epithelial-mesenchymal transition (EMT), reducing Ly6C<sup>hi</sup> macrophage infiltration Ly6C<sup>hi</sup> [128], mediating the p53 signaling pathway to induce HSC apoptosis and the TLR4 pathway to slow down inflammation production and lipid deposition in NAFLD models [129, 130]. Moreover, all three can mediate the NF-κB pathway, inhibit the TGF-β and the levels of inflammatory factors such as TNF-α, and antagonize the profibrotic effects of the inflammatory response [129–135]. Studies have shown that ursolic acid (UA) can regulate EMT or MFB via Rho [136, 137], improve the integrity of the intestinal barrier, reduce intestinal flora disorders [138, 139], and modulate the NOX4/NLRP3 inflammatory vesicle signaling pathway to attenuate liver fibrosis [140].

Yinchenhao decoction [115], whose main components are *Artemisia capillaris* Thunb., *Gardenia jasminoides*, and rhubarb, is one of the classical herbal formulas that can be applied to treat liver fibrosis.
effectively repair liver tissues and cure hepatic fibrosis. Studies have shown [141, 142] that the protective effect of Yinchenhao decoction on liver fibrosis is closely related to PI3K-Akt, TNF, and MAPK signaling pathways and the components of the decoction such as aloe vera emodin, rheinic acid, kaempferol, and quercetin are important components for liver protection, and they not only have therapeutic effects on liver injury caused by CCL4 but also improve fatty liver and inhibit cirrhosis, as well as improving liver fibrosis by inhibiting HSC proliferation and activation. In addition, gardenia glycosides [143], the main component of Yinchenhao decoction, can inhibit TGF-β1-induced EMT and also inhibit type I collagen-induced by the TGF-β1 pathway to protect the liver and inhibit the development of liver fibrosis. Fuzheng Huayu capsule (FZHYC), as a Chinese medicine preparation approved by the State Food and Drug Administration (SPDA) of China and the Food and Drug Administration (FDA) of the United States [144], is effective in improving fibrosis or cirrhosis including hepatitis B with liver and kidney deficiency and blood stasis blockade [145]. The expression of HBV liver fibrosis was adjusted by inhibiting HSC activation by altering the number or function of CD4T cells in T lymphocytes [146]. Another study noted that α-SMA was significantly inhibited in HSC regulated by the FZHYC action [144]. In addition to this, inhibition of NF-kB signaling pathway, lipid peroxidation, and reduction of HA and collagen content in fibrotic patients help to reach the efficacy of FZHYC in activating blood and removing blood stasis and supporting the deficiency [147–149].

9. Summary

In this paper, we mainly elaborate on liver fibrosis from cytokines and various related signaling pathways and then discuss the relationship with liver fibrosis from important aspects such as intestinal flora, autophagy, iron death, and angiogenesis and elaborate the role and mechanism in the process of liver fibrosis. We found that the influence on the onset and regression of liver fibrosis through various pathways cannot be unilateral; it must be multifactorial, multifaceted, and multiple pathways interacting and cooperating to make changes in liver fibrosis. Finally, the research on the treatment of liver fibrosis from the aspect of Chinese herbal medicine is mainly discussed, and it is found that, in experiments, various types of Chinese herbal medicine and compounding play a good therapeutic effect on the suppression of liver fibrosis with fewer side effects, but still need to be used carefully according to the changes of the disease to avoid aggravating liver fibrosis [150]. Moreover, microRNA, Hedgehog (Hh) signaling pathway, PPAR nuclear receptor signaling pathway, and hepatic lymphocytes also have a certain influence on the formation of liver fibrosis. So far, there are no specific drugs for clinical treatment in either Western or Chinese medicine, and compared to the singularity of research on the development of Western drugs, the treatment of liver fibrosis by Chinese medicine and compound prescriptions is based on a holistic approach, regulating all aspects of the body, providing ideas for the treatment of fibrosis and suggesting the great potential of Chinese medicine [151].

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] M. M. Akcali and K. C. Aççahlı, “Liver fibrosis,” Turkish Journal of Gastroenterology, vol. 29, no. 1, pp. 14–21, 2018.
[2] V. G. Eduardo, C. B. Luis, W. S. Wong et al., “Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease,” Gastroenterology, vol. 155, no. 2, pp. 443–457, 2018.
[3] S. K. Asrani, H. Devarbhavi, J. Eaton, and P. S. Kamath, “Burden of liver diseases in the world,” Journal of Hepatology, vol. 70, no. 1, pp. 151–171, 2019.
[4] D. Dhar, J. Bagleri, T. Kisseleva, and D. A. Brenner, “Mechanisms of liver fibrosis and its role in liver cancer,” Experimental Biology and Medicine, vol. 245, no. 2, pp. 96–108, 2020.
[5] P. Manka, A. Zeller, and W.-K. Syn, “Fibrosis in chronic liver disease: an update on diagnostic and treatment modalities,” Drugs, vol. 79, no. 9, pp. 903–927, 2019.
[6] F.-F. Cai, Y.-Q. Bian, R. Wu et al., “Yinchenhao decoction suppresses rat liver fibrosis involved in an apoptosis regulation mechanism based on network pharmacology and transcriptomic analysis,” Biomedicine & Pharmacotherapy, vol. 114, Article ID 108863, 2019.
[7] Z. Zhang, M. Guo, Y. Li et al., “RNA-binding protein ZFP36/TTP protects against ferroptosis by regulating autophagy signaling pathway in hepatic stellate cells,” Autophagy, vol. 16, no. 8, pp. 1482–1505, 2020.
[8] Y. Tao, T. Qiu, X. Yao et al., “Autophagic-CTSB-inflamasome axis modulates hepatic stellate cells activation in arsenic-induced liver fibrosis,” Chemosphere, vol. 242, Article ID 124959, 2019.
[9] X. Yang, Z. Wang, J. Kai et al., “Curcumin attenuates liver sinusoidal endothelial cell angiogenesis via regulating Glis-PROX1-HIF-1α in liver fibrosis,” Cell Proliferation, vol. 53, no. 3, Article ID e12762, 2020.
[10] L. Chen, X. Yao, H. Yao, Q. Ji, G. Ding, and X. Liu, “Exosomal miR-103-3p from LPS-activated THP-1 macrophage contributes to the activation of hepatic stellate cells,” The FASEB Journal, vol. 34, no. 4, pp. 5178–5192, 2020.
[11] H. Liu, F. Dong, G. Li et al., “Liuweiwuling tablets attenuate BDL-induced hepatic fibrosis via modulation of TGF-β/Smad and NF-xb signaling pathways,” Journal of Ethnopharmacology, vol. 210, pp. 232–241, 2018.
[12] Y. Nakano, A. Kamiya, H. Sumiyoshi, K. Tsuruya, T. Kagawa, and Y. Inagaki, “A deactivation factor of fibrogenic hepatic stellate cells induces regression of liver fibrosis in mice,” Hepatology, vol. 71, no. 4, pp. 1437–1452, 2020.
[13] B. Khambu, S. Yang, N. Huda, G. Liu, and X.-M. Yin, “Autophagy in non-alcoholic fatty liver disease and alcoholic liver disease,” Liver Research, vol. 2, no. 3, pp. 112–119, 2018.
[14] T. Medeiros, G. N. Saraiva, L. A. Moraes et al., “Liver fibrosis improvement in chronic hepatitis C after direct acting-antivirals is accompanied by reduced profibrogenic biomarkers—a role for MMP-9/TIMP-1,” Digestive and Liver Disease, vol. 52, no. 10, pp. 1170–1177, 2020.
Evidence-Based Complementary and Alternative Medicine

[15] T. Kisseleva and D. Brenner, “Molecular and cellular mechanisms of liver fibrosis and its regression,” *Nature Reviews Gastroenterology & Hepatology*, vol. 18, no. 3, pp. 151–166, 2021.

[16] B. Liu, X. Deng, Q. Jiang et al., “Scoparone alleviates inflammation, apoptosis and fibrosis of non-alcoholic steatohepatitis by suppressing the TLR4/NF-κB signaling pathway in mice,” *International Immunopharmacology*, vol. 75, Article ID 105797, 2019.

[17] Y. Zeng, Z. Zhang, W. Wang et al., “Underlying mechanisms of apoptosis in HepG2 cells induced by polyphenyll I through Forks death and mitochondrial pathways,” *Toxicology Mechanisms and Methods*, vol. 30, no. 6, pp. 397–406, 2020.

[18] A. Remmerie, L. Martens, T. Castoldi et al., “Osteoponin expression identifies a subset of recruited macrophages distinct from kupffer cells in the fatty liver,” *Immunity*, vol. 53, no. 3, pp. 641–657, 2020.

[19] D. Cheng, J. Chai, H. Wang, L. Fu, S. Peng, and X. Ni, “Hepatocyte mitochondria and liver fibrogenesis,” *Nature*, vol. 11, no. 4, pp. 1139–1161, 2021.

[20] D. Cheng, J. Chai, H. Wang, L. Fu, S. Peng, and X. Ni, “Hepatocyte mitochondria and liver fibrogenesis,” *Nature*, vol. 11, no. 4, pp. 1139–1161, 2021.

[21] Y. Zeng, Z. Zhang, W. Wang et al., “Underlying mechanisms of apoptosis in HepG2 cells induced by polyphenyll I through Forks death and mitochondrial pathways,” *Toxicology Mechanisms and Methods*, vol. 30, no. 6, pp. 397–406, 2020.

[22] J. Leslie, M. G. Macia, S. Luli et al., “c-Rel orchestrates energy-dependent epithelial and macrophage reprogramming in fibrosis,” *Nature Metabolism*, vol. 2, no. 11, pp. 1350–1367, 2020.

[23] B. Cai, P. Dongiovanni, K. E. Corey et al., “Macrophage MerTK promotes liver fibrosis in nonalcoholic steatohepatitis,” *Cell Metabolism*, vol. 31, no. 2, pp. 406–421, 2020.

[24] Q. Yao, S. Li, X. Li, F. Wang, and C. Tu, “Myricetin modulates macrophage polarization and mitigates liver inflammation and fibrosis in a murine model of nonalcoholic steatohepatitis,” *Frontiers of Medicine*, vol. 7, p. 71, 2020.

[25] J. Xue, T. Xiao, S. Wei et al., “miR-21-regulated M2 polarization of macrophage is involved in arsenicosis-induced hepatic fibrosis through the activation of hepatic stellate cells,” *Journal of Cellular Physiology*, vol. 236, no. 8, pp. 6025–6041, 2021.

[26] P. An, L.-L. Wei, S. Zhao et al., “Hepatocyte mitochondria-derived danger signals directly activate hepatic stellate cells and drive progression of liver fibrosis,” *Nature Communications*, vol. 11, no. 1, p. 2362, 2020.

[27] T. Su, Y. Yang, S. Lai et al., “Single-cell transcriptomics reveals zone-specific alterations of liver sinusoidal endothelial cells in cirrhosis,” *Cellular and Molecular Gastroenterology and Hepatology*, vol. 11, no. 4, pp. 1139–1161, 2021.

[28] S. Petrillo, M. Manco, F. Alturda, S. Fagoonee, and E. Tolosano, “Liver sinusoidal endothelial cells at the crossroad of iron overload and liver fibrosis,” *Antioxidants & Redox Signaling*, vol. 35, no. 6, pp. 474–486, 2021.

[29] J. Poisson, S. Lemoine, C. Boulanger et al., “Liver sinusoidal endothelial cells: physiology and role in liver diseases,” *Journal of Hepatology*, vol. 66, no. 1, pp. 212–227, 2017.

[30] L. Chen, T. Gu, B. Li et al., “Delta-like ligand 4/DLL4 regulates the capillarization of liver sinusoidal endothelial cell and liver fibrogenesis,” *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, vol. 1866, no. 10, pp. 1663–1675, 2019.

[31] M. Winkler, T. Staniczek, S. W. Kürschner et al., “Endothelial GATA4 controls liver fibrosis and regeneration by preventing a pathogenic switch in angioocrine signaling,” *Journal of Hepatology*, vol. 74, no. 2, pp. 380–393, 2021.

[32] A. Desroches-Castan, E. Tillet, N. Ricard et al., “Bone morphogenetic protein 9 is a paracrine factor controlling liver sinusoidal endothelial cell fenestration and protecting against hepatic fibrosis,” *Hepatology*, vol. 70, no. 4, pp. 1392–1408, 2019.

[33] M. Ruart, L. Chavarria, G. Camparcios et al., “Impaired endothelial autophagy promotes liver fibrosis by aggravating the oxidative stress response during acute liver injury,” *Journal of Hepatology*, vol. 70, no. 3, pp. 458–469, 2019.

[34] A. Hammoutene, L. Biquard, J. Lasselin et al., “A defect in endothelial autophagy occurs in patients with non-alcoholic steatohepatitis and promotes inflammation and fibrosis,” *Journal of Hepatology*, vol. 72, no. 3, pp. 528–538, 2020.

[35] D. Xiang, J. Zou, X. Zhu et al., “Physalin D attenuates hepatic stellate cell activation and liver fibrosis by blocking TGF-β1/Smad and YAP signaling,” *Phytomedicine*, vol. 78, Article ID 153294, 2020.

[36] Q. Cheng, C. Li, C.-F. Yang et al., “Methylferulic acid attenuates liver fibrosis and hepatic stellate cell activation through the TGF-β1/Smad and NOX4/ROS pathways,” *Chemico-Biological Interactions*, vol. 299, pp. 131–139, 2019.

[37] Q. Zhang, X. Chang, H. Wang et al., “TGF-β1 mediated inflammation and fibrosis in a murine model of nonalcoholic steatohepatitis,” *Cell Death & Disease*, vol. 11, no. 10, pp. 2279–2294, 2021.

[38] N. Liu, J. Feng, X. Lu et al., “Isorhamnetin inhibits liver fibrosis by reducing autophagy and inhibiting extracellular matrix formation via the TGF-beta1/smad3 and TGF-beta1/p38 MAPK pathways,” *Mediators of Inflammation*, vol. 2019, Article ID 6175091, 14 pages, 2019.

[39] K. Tzavlaki and A. Moustakas, “TGF-β signaling,” *Biomolecules*, vol. 10, no. 3, p. 487, 2020.

[40] M. Mu, S. Zuo, R.-M. Wu et al., “Ferulic acid attenuates liver fibrosis and hepatic stellate cell activation via inhibition of TGF-β1/Smad and NOX4/ROS signaling,” *Drug Design, Development and Therapy*, vol. 12, pp. 4107–4115, 2018.

[41] X. Zhong, M. Huang, H.-G. Kim et al., “SIRT6 protects against liver fibrosis by deacetylation and suppression of SMAD3 in hepatic stellate cells,” *Cellular and Molecular Gastroenterology and Hepatology*, vol. 10, no. 2, pp. 341–364, 2020.

[42] J. Zhao, M. Han, L. Zhou et al., “TAF and TDF attenuate liver fibrosis through N5SATP9, TGFβ1/Smad3, and NF-xB/NLRP3 inflammasome signaling pathways,” *Hepatology International*, vol. 14, no. 1, pp. 145–160, 2020.

[43] H. Xie, D. Su, J. Zhang et al., “Raw and vinegar processed Curcuma wenyujin regulates hepatic fibrosis via blocking TGF-β1/Smad signaling pathways and up-regulation of MMP-2/TIMP-1 ratio,” *Journal of Ethnopharmacology*, vol. 246, Article ID 111768, 2020.

[44] N. Krishnamurthy and R. Kurzrock, “Targeting the Wnt/beta-catenin pathway in cancer: update on effectors and inhibitors,” *Cancer Treatment Reviews*, vol. 62, pp. 50–60, 2018.

[45] Y. S. Jung, S. A. Stratton, S. H. Lee et al., “TMEM9-v-ATPase activates Wnt/β-catenin signaling via APC lysosomal degradation for liver regeneration and tumorigenesis,” *Hepatology*, vol. 73, no. 2, pp. 776–794, 2021.
Evidence-Based Complementary and Alternative Medicine

[46] C. Zhang, X.-Q. Liu, H.-N. Sun et al., “Octreotide attenuates hepatic fibrosis and hepatic stellate cells proliferation and activation by inhibiting Wnt/β-catenin signaling pathway, c-Myc and cyclin D1,” International Immunopharmacology, vol. 63, pp. 183–190, 2018.

[47] N. E. El-Asmahawy, G. M. Al-Asmahawy, H. E. Fakher, and N. F. Khedr, “The role of WNT/β-catenin signaling pathway and glutamine metabolism in the pathogenesis of CCl4-induced liver fibrosis: repositioning of niclosamide and concerns about lithium,” Cytokine, vol. 136, p. 155250, 2020.

[48] I. H. Lee, E. Im, H. J. Lee et al., “Apoptotic and anti-hepatofibrotic effect of honokiol via activation of GSK3β and suppression of Wnt/β-catenin pathway in hepatic stellate cells,” Phytotherapy Research, vol. 35, no. 1, pp. 452–462, 2021.

[49] Y. Feng, S. Gao, R. Wei et al., “Effects of probiotics on intestinal flora, inflammation and degree of liver cirrhosis in rats with liver cirrhosis by regulating Wnt/β-catenin signaling pathway,” Journal of Biological Regulators and Homeostatic Agents, vol. 35, no. 1, pp. 25–33, 2021.

[50] F. Zhang, F. Wang, J. He et al., “Regulation of hepatic stellate cell contraction and cirrhotic portal hypertension by Wnt/β-catenin signalling via interaction with Gli1,” British Journal of Pharmacology, vol. 178, no. 11, pp. 2246–2265, 2021.

[51] S. Gaul, A. Leszcynska, F. Alegre et al., “Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis,” Journal of Hepatology, vol. 74, no. 1, pp. 156–167, 2021.

[52] C. Y. Han, H. S. Rho, A. Kim et al., “FXR inhibits endoplasmic reticulum stress-induced NLRP3 inflammasome in hepatocytes and ameliorates liver injury,” Cell Reports, vol. 24, no. 11, pp. 2985–2999, 2018.

[53] A. R. Mridha, A. Wree, A. A. B. Robertson et al., “NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice,” Journal of Hepatology, vol. 66, no. 5, pp. 1037–1046, 2017.

[54] A. Wree, M. D. McGeough, M. E. Inzaugarat et al., “NLRP3 inflammasome driven liver injury and fibrosis: roles of IL-17 and TNF in mice,” Hepatology, vol. 67, no. 2, pp. 736–749, 2018.

[55] L. Catrysses, M. Farhang Ghaheemani, L. Vereecke et al., “A20 prevents chronic liver inflammation and cancer by protecting hepatocytes from death,” Cell Death & Disease, vol. 7, no. 6, p. e2250, 2016.

[56] H. Hwangbo, M. Y. Kim, S. Y. Ji et al., “Auranofin attenuates non-alcoholic fatty liver disease by suppressing lipid accumulation and NLRP3 inflammasome-mediated hepatic inflammation in vivo and in vitro,” Antioxidants, vol. 9, no. 11, p. 1040, 2020.

[57] C. Jimenez Calvente, H. Del Pilar, M. Tameda, C. D. Johnson, and A. E. Feldstein, “MicroRNA 223 3p negatively regulates the NLRP3 inflammasome in acute and chronic liver injury,” Molecular Therapy, vol. 28, no. 2, pp. 653–663, 2020.

[58] Y.-S. Shi, X.-X. Li, H.-T. Li, and Y. Zhang, “Pelargonidin ameliorates CCl4-induced liver fibrosis by suppressing the ROS-NLRP3-IL-1β axis via activating the Nrf2 pathway,” Food & Function, vol. 11, no. 6, pp. 5156–5165, 2020.

[59] G. Yang, J. H. Jang, S. W. Kim et al., “Sweroside prevents non-alcoholic steatohepatitis by suppressing activation of the NLRP3 inflammasome,” International Journal of Molecular Sciences, vol. 21, no. 8, p. 2790, 2020.

[60] M. L. Tomasi and K. Ramani, “SUMOylation and phosphorylation cross-talk in hepatocellular carcinoma,” Translational Gastroenterology and Hepatology, vol. 3, p. 20, 2018.

[61] M. Morales-Ruiz, A. Santel, J. Ribera, and W. Jimenez, “The role of Akt in chronic liver disease and liver regeneration,” Seminars in Liver Disease, vol. 38, no. 01, pp. 011–016, 2017.

[62] L. Wu, Q. Zhang, W. Mo et al., “Quercetin prevents hepatic fibrosis by inhibiting hepatic stellate cell activation and reducing autophagy via the TGF-β1/Smads and PI3K/Akt pathways,” Scientific Reports, vol. 7, no. 1, pp. 9289–9317, 2017.

[63] Z. Yu, Y. Jv, L. Cai et al., “Gambogenic acid attenuates liver fibrosis by inhibiting the PI3K/AKT and MAPK signaling pathways via inhibiting HSP90,” Toxicology and Applied Pharmacology, vol. 371, pp. 63–73, 2019.

[64] A.-Y. Xiu, Q. Ding, Z. Li, and C.-Q. Zhang, “Doxazosin attenuates liver fibrosis by inhibiting autophagy in hepatic stellate cells via activation of the PI3K/Akt/mTOR signaling pathway,” Drug Design, Development and Therapy, vol. 15, pp. 3643–3659, 2021.

[65] R. Wang, F. Song, S. Li, B. Wu, Y. Gu, and Y. Yuan, “Salvianolic acid A attenuates CCl4-induced liver fibrosis by regulating the PI3K/AKT/mTOR, Bcl-2/Bax and caspase-3/cleaved caspase-3 signaling pathways,” Drug Design, Development and Therapy, vol. 13, pp. 1899–1900, 2019.

[66] J. Feng, K. Chen, X. Xia et al., “Salidroside ameliorates autophagy and activation of hepatic stellate cells in mice via NF-κappa B and TGF-β pathways,” Drug Design, Development and Therapy, vol. 12, pp. 1837–1853, 2018.

[67] Q. Yu, P. Cheng, J. Wu, and C. Guo, “PPARγ/NF-κB and TGF-β1/Smad pathway are involved in the anti-fibrotic effects of levo-tetradrophalmitone on liver fibrosis,” Journal of Cellular and Molecular Medicine, vol. 25, no. 3, pp. 1645–1660, 2021.

[68] C. Wan, F. Jin, Y. Du et al., “Genistein improves schistosomiasis liver granuloma and fibrosis via dampening NF-κB signaling in mice,” Parasitology Research, vol. 116, no. 4, pp. 1165–1174, 2017.

[69] T. Zhang, J. Hu, X. Wang et al., “MicroRNA-378 promotes hepatic inflammation and fibrosis via modulation of the NF-κB-TNFR pathway,” Journal of Hepatology, vol. 70, no. 1, pp. 87–96, 2019.

[70] A. Mohammadipour, M. Hashemnia, F. Goudarzi, and A. P. Ravan, “Increasing the effectiveness of tyrosine kinase inhibitor (TKI) in combination with a statin in reducing liver fibrosis,” Clinical and Experimental Pharmacology and Physiology, vol. 46, no. 12, pp. 1183–1193, 2019.

[71] J. He, J. Gong, Q. Ding et al., “Suppressive effect of SATB1 on hepatic stellate cell activation and liver fibrosis in rats,” FEBS Letters, vol. 589, no. 12, pp. 1359–1368, 2015.

[72] Q. Wang, X. Chou, F. Guan et al., “Enhanced Wnt signalling in hepatocytes is associated with schistosoma japonicum infection and contributes to liver fibrosis,” Scientific Reports, vol. 7, no. 1, p. 230, 2017.

[73] P.-J. Chen, L.-M. Kuo, Y.-H. Wu, Y.-C. Chang, K.-H. Lai, and T.-L. Hwang, “BAY 41-2272 attenuates CTGF expression via sGC/cGMP-Independent pathway in TGFβ1-activated hepatic stellate cells,” Biomedicines, vol. 8, no. 9, p. 330, 2020.

[74] B. Yu, G.-N. Jin, M. Ma et al., “Taurocholate induces connective tissue growth factor expression in hepatocytes through ERK-YAP signaling,” Cellular Physiology and Biochemistry, vol. 50, no. 5, pp. 1711–1725, 2018.
10 Evidence-Based Complementary and Alternative Medicine

[75] F. A. Mendes, J. M. Coelho Aguar, S. A. Kahn et al., "Connective-tissue growth factor (CTGF/CCN2) induces astrogensis and fibronectin expression of embryonic neural cells in vitro," *PLoS One*, vol. 10, no. 8, Article ID e0136869, 2015.

[76] Y.-W. Sun, Y.-Y. Zhang, X.-J. Ke, X.-j. Wu, Z.-F. Chen, and P. Chi, "Pirfenidone prevents radiation-induced intestinal fibrosis in rats by inhibiting fibroblast proliferation and differentiation and suppressing the TGF-β1/Smad/CTGF signaling pathway," *European Journal of Pharmacology*, vol. 822, pp. 199–206, 2018.

[77] Y. Cai, G. Huang, L. Ma et al., "Smurf2, an E3 ubiquitin ligase, interacts with PDE4B and attenuates liver fibrosis through miR-132 mediated CTGF inhibition," *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, vol. 1865, no. 2, pp. 297–308, 2018.

[78] J. S. Bajaj and A. Khoruts, "Microbiota changes and intestinal microbiota transplantation in liver disease and cirrhosis," *Journal of Hepatology*, vol. 72, no. 5, pp. 1003–1027, 2020.

[79] R. Wang, R. Tang, B. Li, X. Ma, B. Schnabl, and H. Tilg, "Gut microbiome, liver immunology, and liver diseases," *Cellular & Molecular Immunology*, vol. 18, no. 4, pp. 1–17, 2021.

[80] J. P. Arab, R. M. Martin-Mateos, and V. H. Shah, "Gut-liver axis, cirrhosis and portal hypertension: the chicken and the egg," *Hepatology international*, vol. 12, no. 1, pp. 24–33, 2018.

[81] E. Scorletti, P. R. Afolabi, E. A. Miles et al., "Design and rationale of the INSYTE study: a randomised, placebo controlled study to test the efficacy of a symbiotic on liver fat, disease biomarkers and intestinal microbiota in non-alcoholic fatty liver disease," *Contemporary Clinical Trials*, vol. 71, no. 8, pp. 113–123, 2018.

[82] A. Tripathi, J. Debelius, D. A. Brenner et al., "The gut-liver axis and the intersection with the microbiome," *Nature Reviews Gastroenterology & Hepatology*, vol. 15, no. 7, pp. 397–411, 2018.

[83] K. M. Schneider, C. Elfers, A. Ghallab et al., "Intestinal dysbiosis amplifies acetaminophen-induced acute liver injury," *Cellular and Molecular Gastroenterology and Hepatology*, vol. 11, no. 4, pp. 909–933, 2021.

[84] N. Hu, C. Wang, X. Dai et al., "Phyllgenin inhibits LPS-induced activation and inflammation of LX2 cells by TLRA/MyD88/NF-κB signaling pathway," *Journal of Ethnopharmacology*, vol. 248, Article ID 112361, 2020.

[85] C. Xie, X. Li, J. Zhu, J. Wu, S. Geng, and C. Zhong, "Magnesium isoglycyrrhizinate suppresses LPS-induced inflammation and oxidative stress through inhibiting NF-κB and MAPK pathways in RAW264.7 cells," *Bioorganic & Medicinal Chemistry*, vol. 27, no. 3, pp. 516–524, 2019.

[86] M. Camilleri, S. L. Nord, D. Burton et al., "Randomised clinical trial: significant biochemical and colonic transit effects of the farnesoid X receptor agonist tropifexor in patients with primary bile acid diarrhoea," *Alimentary Pharmacology & Therapeutics*, vol. 52, no. 5, pp. 808–820, 2020.

[87] J. Zhou, N. Huang, Y. Guo et al., "Combined obeticholic acid and apoptosis inhibitor treatment alleviates liver fibrosis," *Acta Pharmaceutica Sinica B*, vol. 9, no. 3, pp. 526–536, 2019.

[88] H. Hao, L. Cao, C. Jiang et al., "Farnesoid X receptor regulation of the NLRP3 inflammasome underlies cholestasis-associated sepsis," *Cell Metabolism*, vol. 25, no. 4, pp. 856–867, 2017.

[89] D. Kong, Z. Zhang, L. Chen et al., "Curcumin blunts epithelial-mesenchymal transition of hepatocytes to alleviate hepatic fibrosis through regulating oxidative stress and autophagy," *Redox Biology*, vol. 36, Article ID 101600, 2020.

[90] J. Gao, B. Wei, T. M. de Assuncao et al., "Hepatocellular carcinoma cell autophagy inhibits extracellular vesicle release to attenuate liver fibrosis," *Journal of Hepatology*, vol. 73, no. 5, pp. 1144–1154, 2020.

[91] X.-W. Zhang, J.-C. Zhou, D. Peng et al., "Disrupting the TRIB3-SQSTM1 interaction reduces liver fibrosis by restoring autophagy and suppressing exosome-mediated HSC activation," *Autoophagy*, vol. 16, no. 5, pp. 782–796, 2020.

[92] D. Meng, Z. Li, G. Wang, L. Ling, Y. Wu, and C. Zhang, "Carvedilol alleviates liver fibrosis by suppressing autophagy and promoting apoptosis in hepatic stellate cells," *Biomedicine & Pharmacotherapy*, vol. 108, pp. 1617–1627, 2018.

[93] M. Bernard, B. Yang, F. Migneault et al., "Autophagy drives fibroblast senescence through MTORC2 regulation," *Autoophagy*, vol. 16, no. 11, pp. 2004–2016, 2020.

[94] J. Zhu, W. Zhang, L. Zhang et al., "IL-7 suppresses macrophage autophagy and promotes liver pathology in Schistosoma japonicum -infected mice," *Journal of Cellular and Molecular Medicine*, vol. 22, no. 7, pp. 3353–3363, 2018.

[95] M. Shen, M. Guo, Z. Wang et al., "ROS-dependent inhibition of the PI3K/Akt/mTOR signaling is required for Oroxylin A to exert anti-inflammatory activity in liver fibrosis," *International Immunopharmacology*, vol. 85, Article ID 106637, 2020.

[96] Q. He, L. Wang, R. Zhao et al., "Mesenchymal stem cell-derived exosomes exert ameliorative effects in type 2 diabetes by improving hepatic glucose and lipid metabolism via enhancing autophagy," *Stem Cell Research & Therapy*, vol. 11, no. 1, p. 223, 2020.

[97] W. Chen, Z. Zhang, Z. Yao et al., "Activation of autophagy is required for Oroxylin A to alleviate carbon tetrachloride-induced liver fibrosis and hepatic stellate cell activation," *International Immunopharmacology*, vol. 56, pp. 148–155, 2018.

[98] L. Wang, Z. Zhang, M. Li et al., "P33-dependent induction of ferroptosis is required for arteremeter to alleviate carbon tetrachloride-induced liver fibrosis and hepatic stellate cell activation," *IUBMB Life*, vol. 71, no. 1, pp. 45–56, 2019.

[99] C. Li, Y. Liu, Z. Dong et al., "TCDD promotes liver fibrosis through disordering systemic and hepatic iron homeostasis," *Journal of Hazardous Materials*, vol. 395, Article ID 122588, 2020.

[100] Y. Li, C. Jin, M. Shen et al., "Iron regulatory protein 2 is required for arteremeter -mediated anti-hepatic fibrosis through ferroptosis pathway," *Free Radical Biology and Medicine*, vol. 160, pp. 845–859, 2020.

[101] Z. Kong, R. Liu, and Y. Cheng, "Artesunate alleviates liver fibrosis by regulating ferroptosis signaling pathway," *Biomedicine & Pharmacotherapy*, vol. 109, pp. 1035–1043, 2019.

[102] Z. Zhang, M. Guo, M. Shen et al., "The BRD7-P53-SLC25A28 axis regulates ferroptosis in hepatic stellate cells," *Redox Biology*, vol. 36, Article ID 101619, 2020.

[103] K. J. Mehta, S. J. Farnaud, and P. A. Sharp, "Iron and liver fibrosis: mechanistic and clinical aspects," *World Journal of Gastroenterology*, vol. 25, no. 5, pp. 521–538, 2019.

[104] M. Sui, X. Jiang, J. Chen, H. Yang, and Y. Zhu, "Magnesium isoglycyrrhizinate suppresses LPS-induced inflammation and oxidative stress through inhibiting NF-κB and MAPK pathways in RAW264.7 cells," *Bioorganic & Medicinal Chemistry*, vol. 23, no. 3, pp. 516–524, 2019.
Evidence-Based Complementary and Alternative Medicine

[105] Z. Wang, J. a. Li, W. a. Xiao, J. Long, and H. Zhang, “The STAT3 inhibitor S3I-201 suppresses fibrogenesis and angiogenesis in liver fibrosis,” Laboratory Investigation, vol. 98, no. 12, pp. 1600–1613, 2018.

[106] S. Elzamly, H. A. Agina, A. E.-L. Elbalshy, M. Abushashim, E. Saad, and Z. Y. Abd Elmageed, “Integration of VEGF and α-SMA expression improves the prediction accuracy of fibrosis in chronic hepatitis C liver biopsy,” Applied Immunohistochemistry & Molecular Morphology, vol. 25, no. 4, pp. 261–270, 2017.

[107] K. Yuan, C. Lai, L. Wei et al., “The effect of vascular endothelial growth factor on bone marrow mesenchymal stem cell engraftment in rat fibrotic liver upon transplantation,” Stem Cells International, vol. 2019, Article ID 5310202, 13 pages, 2019.

[108] D. Ezhilarasan, “Endothelin-1 in portal hypertension: the intricate role of hepatic stellate cells,” Experimental Biology and Medicine, vol. 245, no. 16, pp. 1504–1512, 2020.

[109] G. Li, Y. Peng, T. Zhao et al., “Plumbagin alleviates capillarization of hepatic sinusoids in vitro by downregulating ET-1, VEGF, LN, and type IV collagen,” BioMed Research International, vol. 2017, Article ID 5603216, 12 pages, 2017.

[110] H. Kong, J. He, S. Guo et al., “Endothelin receptors promote schistosomiasis-induced hepatic fibrosis via splenic B cells,” PLoS Pathogens, vol. 16, no. 10, Article ID e1008947, 2020.

[111] H.-Z. Ying, Q. Chen, W.-Y. Zhang et al., “PGDF signaling pathway in hepatic fibrosis pathogenesis and therapeutics,” Molecular Medicine Reports, vol. 16, no. 6, pp. 7879–7889, 2017.

[112] N. Roehlen, E. Crouchet, and T. F. Baumert, “Liver fibrosis: mechanistic concepts and therapeutic perspectives,” Cells, vol. 9, no. 4, p. 875, 2020.

[113] C. Chen, X. Li, and L. Wang, “Thymosinβ4 alleviates cholestatic liver fibrosis in mice through downregulating PDGF/ PDGFR and TGFβ/Smad pathways,” Digestive and Liver Disease, vol. 52, no. 3, pp. 324–330, 2020.

[114] X. Wang, Y. Gao, Y. Li et al., “Rosoxetin B alleviates cholestatic liver fibrosis through inhibiting PDGF-B/ PDGFR-β pathway in hepatic stellate cells,” Cell Death & Disease, vol. 11, no. 6, p. 458, 2020.

[115] H. Li, “Advances in anti hepatic fibrotic therapy with Traditional Chinese Medicine herbal formula,” Journal of Ethnopharmacology, vol. 251, Article ID 112442, 2020.

[116] C. Lu, W. Xu, F. Zhang, J. Shao, and S. Zheng, “Nrf2 knockdown attenuates the ameliorative effects of ligustrazine on hepatic fibrosis by targeting hepatic stellate cell transdifferentiation,” Toxicology, vol. 365, pp. 35–47, 2016.

[117] Z. Hu, H. Su, Y. Zeng et al., “Tetramethylypyrazine ameliorates hepatic fibrosis through autophagy-mediated inflammation,” Biochemistry and Cell Biology, vol. 98, no. 3, pp. 327–337, 2020.

[118] X. Ma, Q. Ruan, X. Ji, J. Yang, and H. Peng, “Ligustrazine alleviates cyclophosphamide-induced hepatotoxicity via the inhibition of Txnip/Tfrx/NF-kB pathway,” Life Sciences, vol. 274, Article ID 119331, 2021.

[119] F. Zhang, C. Ni, D. Kong et al., “Ligustrazine attenuates oxidative stress-induced activation of hepatic stellate cells by interrupting platelet-derived growth factor-β receptor-mediated ERK and p38 pathways,” Toxicology and Applied Pharmacology, vol. 265, no. 1, pp. 51–60, 2012.

[120] C. Balta, H. Herman, O. M. Boldura et al., “Chrysin attenuates liver fibrosis and hepatic stellate cell activation through TGFβ/Smad signaling pathway,” Chemico-Biological Interactions, vol. 240, pp. 94–101, 2015.

[121] Z. Y. Cui, G. Wang, J. Zhang et al., “Parthenolide, bioactive compound of Chrysanthemum parthenium L., ameliorates fibrogenesis and inflammation in hepatic fibrosis via regulating the crosstalk of TLR4 and STAT3 signaling pathway,” Phytotherapy Research, vol. 35, pp. 1–14, 2021.

[122] D. Yang, L. Li, S. Qian, and L. Liu, “Evodiamine ameliorates liver fibrosis in rats via TGF-β1/Smad signaling pathway,” Journal of Natural Medicines, vol. 72, no. 1, pp. 145–154, 2018.

[123] Y. Liu, P. H. Wen, X. X. Zhang, Y. Dai, and Q. He, “Breviscapine ameliorates CCH-induced liver injury in mice through inhibiting inflammatory apoptotic response and ROS generation,” International Journal of Molecular Medicine, vol. 42, no. 2, pp. 755–768, 2018.

[124] M. Farzaei, M. Zobeiri, F. Parvizi et al., “Curcumin in liver diseases: a systematic review of the cellular mechanisms of oxidative stress and clinical perspective,” Nutrients, vol. 10, no. 7, p. 855, 2018.

[125] X. Wu, F. Zhi, W. Lun, Q. Deng, and W. Zhang, “Baicalin inhibits PDGF-BB-induced hepatic stellate cell proliferation, apoptosis, invasion, migration and activation via the mR-395/ASLA axis,” International Journal of Molecular Medicine, vol. 41, no. 4, pp. 1992–2002, 2018.

[126] X. Zhong and H. Liu, “Baicalin attenuates diet induced nonalcoholic steatohepatitis by inhibiting inflammation and oxidative stress via suppressing JNK signaling pathways,” Biomedicine & Pharmacotherapy, vol. 98, pp. 117–117, 2018.

[127] H. Chang, H. Meng, Y. Wang, Z. Teng, and S.-M. Liu, “Inhibitory effect of Scutellariae Radix on hepatic fibrosis based on urinary metabolomic,” China Journal of Chinese Materi Medica, vol. 43, no. 10, pp. 2140–2146, 2018.

[128] X.-A. Zhao, G. Chen, Y. Wu et al., “Emodin alleviates liver fibrosis of mice by reducing infiltration of Gr1hi monocytes,” Evidence-based Complementary and Alternative Medicine, vol. 2018, no. 3, 11 pages, Article ID 5738101, 2018.

[129] B. Liang, L. Gao, F. Wang et al., “The mechanism research on the anti-liver fibrosis of emodin based on network pharmacology,” IJUMB Life, vol. 73, no. 9, pp. 1166–1179, 2021.

[130] X. Xue, Y. Quan, L. Gong, X. Gong, and Y. Li, “A review of the processed Polygonum multiflorum (,ı_hunb.) for hepatic fibrosis in chronic hepatitis C liver biopsy,” Artificial Cells, vol. 98, pp. 1–14, 2018.

[131] S. Saadati, B. Hatami, Z. Yari et al., “The effects of curcumin supplementation on liver enzymes, lipid profile, glucose homeostasis, and hepatic steatosis and fibrosis in patients with non-alcoholic fatty liver disease,” European Journal of Clinical Nutrition, vol. 73, no. 3, pp. 441–449, 2019.

[132] S. Saadati, A. Sadeghia, A. Mansour et al., “Curcumin and inflammation in non-alcoholic fatty liver disease: a randomized, placebo controlled clinical trial,” BMC Gastroenterology, vol. 19, no. 1, pp. 133–136, 2019.

[133] E. Nozari, A. Moradi, and M. Samadi, “Effect of Atorvastatin, Curcumin, and Quercetin on miR-21 and miR-122 and their correlation with TGFβ1 expression in experimental liver fibrosis,” Life Sciences, vol. 259, Article ID 118293, 2020.

[134] J. Yang, D. Xiang, D. Xiang et al., “Baicalin protects against 17α-ethynylestradiol-induced cholestasis via the sirtuin 1/ hepatic nuclear receptor-1a/farnesoid X receptor pathway,” Frontiers in Pharmacology, vol. 10, p. 1685, 2020.

[135] R. Xie, M. Liu, and S. Li, “Emodin weakens liver inflammatory injury triggered by lipopolysaccharide through elevating microRNA-145 in vitro and in vivo,” Artificial Cells,
Nanomedicine, and Biotechnology, vol. 47, no. 1, pp. 1877–1887, 2019.

[136] C. Huang, D. Gan, F. Luo et al., "Interaction mechanisms between the NOX4/ROS and RhoA/ROCK1 signaling pathways as new anti- fibrosis targets of ursolic acid in hepatic stellate cells," Frontiers in Pharmacology, vol. 10, p. 431, 2019.

[137] E. Nomikou, M. Livitsanou, C. Stournaras, and D. Kardassis, "Transcriptional and post-transcriptional regulation of the genes encoding the small GTPases RhoA, RhoB, and RhoC: implications for the pathogenesis of human diseases," Cellular and Molecular Life Sciences, vol. 75, no. 12, pp. 2111–2124, 2018.

[138] S.-Z. Wan, C. Liu, C.-K. Huang, F.-Y. Luo, and X. Zhu, "Ursolic acid improves intestinal damage and bacterial dysbiosis in liver fibrosis mice," Frontiers in Pharmacology, vol. 10, p. 1321, 2019.

[139] W. Zhang, D. Gan, J. Jian et al., "Protective effect of ursolic acid on the intestinal mucosal barrier in a rat model of liver fibrosis," Frontiers in Physiology, vol. 10, p. 956, 2019.

[140] Q. Liu, Y. Nie, W. Zhang, Y. Wan, C. Huang, and X. Zhu, "Ursolic acid reverses liver fibrosis by inhibiting NOX4/NLRP3 inflammasome pathways and bacterial dysbiosis," Gut Microbes, vol. 13, no. 1, Article ID 1972746, 2021.

[141] F.-F. Cai, R. Wu, Y.-N. Song et al., "Yinchenhao decoction alleviates liver fibrosis by regulating bile acid metabolism and TGF-β/smad/ERK signalling pathway," Scientific Reports, vol. 8, no. 1, Article ID 15367, 2018.

[142] J. Zhang, X. Liu, J. Wu et al., "A bioinformatics investigation into the pharmacological mechanisms of the effect of the Yinchenhao decoction on hepatitis C based on network pharmacology," BMC Complementary Medicine and Therapies, vol. 20, no. 1, p. 50, 2020.

[143] J.-H. Park, J. Yoon, K. Y. Lee, and B. Park, "Effects of geniposide on hepatocytes undergoing epithelial-mesenchymal transition in hepatic fibrosis by targeting TGFβ/Smad and ERK-MAPK signaling pathways," Biochimie, vol. 113, pp. 26–34, 2015.

[144] W. Wu, H. Piao, F. Wu et al., "Yu Jin Pulvis inhibits carbon tetrachloride-induced liver fibrosis by blocking the MAPK and PI3K/Akt signaling pathways," American Journal of Tourism Research, vol. 11, no. 9, pp. 5998–6006, 2019.

[145] X. J. Ge, C. Q. Zhao, and L. M. Xu, "Effect of Fuzheng Huayu capsules on survival rate of patients with liver cirrhosis," Chinese Journal of Hepatology, vol. 25, no. 11, pp. 834–840, 2017.

[146] M. Wu, Y. Zhou, S.-L. Qin et al., "Fuzheng huayu capsule attenuates hepatic fibrosis by inhibiting activation of hepatic stellate cells," Evidence-based Complementary And Alternative Medicine, vol. 2020, Article ID 3468791, 14 pages, 2020.

[147] T. Wang, X. Zhou, H. Liu et al., "Fuzheng Huayu capsule as an adjuvant treatment for HBV-related cirrhosis: a systematic review and meta-analysis," Phytotherapy Research, vol. 32, no. 5, pp. 757–768, 2018.

[148] W. Liu, Z. Li, Z. Sun et al., "The components data of fuzheng huayu extracts, cordyceps sinensis mycelia polysaccharide, gypenosides and amygdalin," Data in Brief, vol. 25, Article ID 104087, 2019.

[149] H. Tian, L. Liu, Z. Li et al., "Chinese medicine CGA formula ameliorates liver fibrosis induced by carbon tetrachloride involving inhibition of hepatic apoptosis in rats," Journal of Ethnopharmacology, vol. 232, pp. 227–235, 2019.

[150] L.-M. Xu and P. Liu, "Guidelines for diagnosis and treatment of hepatic fibrosis with integrated traditional Chinese and