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Review

Progress of mesenchymal stem cells (MSCs) & MSC-Exosomes combined with drugs intervention in liver fibrosis

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ABSTRACT

Liver fibrosis is an intrahepatic chronic damage repair response caused by various reasons such as alcoholic liver, fatty liver, viral hepatitis, autoimmune diseases, etc., and is closely related to the progression of liver disease. Currently, the mechanisms of liver fibrosis and its treatment are hot research topics in the field of liver disease remedy. Mesenchymal stem cells (MSCs) are a class of adult stem cells with self-renewal and multidirectional differentiation potential, which can ameliorate fibrosis through hepatic-directed differentiation, paracrine effects, and immunomodulation. However, the low inner-liver colonization rate, low survival rate, and short duration of intervention after stem cell transplantation have limited their wide clinical application. With the intensive research on liver fibrosis worldwide, it has been found that MSCs and MSCs-derived exosomes combined with drugs have shown better intervention efficiency than utilization of MSCs alone in many animal models of liver fibrosis. In this paper, we review the interventional effects and mechanisms of mesenchymal stem cells and their exosomes combined with drugs to alleviate hepatic fibrosis *in vivo* in animal models in recent years, which will provide new ideas to improve the efficacy of mesenchymal stem cells and their exosomes in treating hepatic fibrosis in the clinic.

1. Introduction

The liver is mainly composed of hepatocytes, hepatic stellate cells (HSCs), and liver sinusoidal endothelial cells (LSECs) that perform a comprehensive range of hepatic functions, such as detoxification, bile acid synthesis, and participation in various metabolic processes. However, a variety of stimuli, such as alcohol, drugs, inflammation, or cholestasis, often cause damage to hepatocytes resulting in abnormal liver function and a series of pathophysiologic changes [1]. Liver fibrosis is a common intermediate pathological process of various chronic liver diseases, which is mainly manifested by diffuse excessive deposition of extracellular matrix, leading to abnormal changes in liver tissue structure and affecting the normal physiological functions of liver severely [2]. Clinically, if liver fibrosis is not effectively reversed or curbed, it will progress to irreversible cirrhosis, hepatocellular carcinoma, and other end-stage liver diseases, eventually, leading to the death of patients [3]. Therefore, finding effective therapeutic strategies to ameliorate liver fibrosis in patients is of great importance in preventing the development of end-stage liver diseases.

In the clinical setting, liver transplantation is mostly used for the treatment of end-stage liver diseases, but liver transplantation cannot be widely used due to the defects of extremely rare donors, high cost, rejection, etc [4]. Currently, mesenchymal stem cells for the treatment of liver disease have become a hot spot in the field of biomedicine. As the intermediate pathological process of end-stage liver disease, mesenchymal stem cells can effectively ameliorate hepatic fibrosis through hepatogenic differentiation, immunomodulation, paracrine effects, and other mechanisms [5]. However, it has been reported that MSCs transplanted in the body may have some disadvantages such as low inner-liver colonization and short duration of intervention, which affect their therapeutic efficacy [6]. Nowadays, an increasing number of researchers have demonstrated in animal models of liver fibrosis that the combination of MSCs with drugs can boost the therapeutic effect of MSCs in the treatment of liver fibrosis by promoting the homing of

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MSCs, differentiating them into functional hepatocyte-like cells, improving the microenvironment, inhibiting the activation of HSCs, and modulating the signaling pathway, and so on. In addition, MSCs-derived extracellular vesicles with the advantages of higher penetrability and lower carcinogenicity also effectively ameliorate liver fibrosis with ultimate safety. What's more, nanoscale intracellular vesicles can also be used as carriers of natural drugs for drug delivery. This provides new ideas to solve the poor efficiency of MSCs in the treatment of liver fibrosis in the clinic.

2. Molecular mechanisms of liver fibrogenesis

The onset and progression of liver fibrosis involves multiple cell types such as hepatocytes, HSCs, and LSECs (Fig. 1). Hepatocytes, as the most abundant cell type in the liver, their hepatocyte injury is thought to be the initiation of liver fibrogenesis [7]. Under the stimulation of various deleterious factors, damaged hepatocytes promote the activation of HSCs by releasing a range of cytokines, reactive oxygen species (ROS), and activating the Hedgehog (Hh) signaling pathway. In addition, damaged hepatocytes indirectly promote the activation of HSCs through the release of inflammatory elements to recruit macrophages and Kupffer cells to release platelet-derived growth factor (PDGF), Interleukin-1β (IL-1β), and IL-6 [8]. In return , activated HSCs release a series of pro-inflammatory factors, connective tissue growth factor (CTGF), and transforming growth factor beta (TGF-β) to enhance fibrosis, while simultaneously maintaining their continuous activation in an autocrine fashion [9]. Activated HSCs can also transdifferentiate into fibroblast-like cells [10], which are capable of synthesizing extracellular matrix proteins, such as collagen I (Col I), fibronectin (FN), and α-smooth muscle actin (α-SMA), leading to excessive deposition of extracellular matrix, which in turn promotes the development of liver fibrosis [11] [12]. Notably, epithelial-mesenchymal transition (EMT) is thought to be one of the mechanisms that generate myofibroblasts in liver fibrosis [13]. Studies have shown that quiescent HSCs, hepatocytes, biliary epithelial cells, and LSECs can promote hepatic fibrosis through EMT as sketched out in figure1 [14].

3. Conventional treatment of liver fibrosis

The complex pathological process of hepatic fibrosis involves multiple factors, and the treatment strategy should target the multi-point inhibition of the various processes of hepatic fibrosis formation and development, including removing the causative factors, eliminating hepatic inflammation, inhibiting hepatic stellate cell activation, or promoting the apoptosis of activated HSCs [15]. Currently, there are no definitive antifibrotic drugs available for clinical use, and the main approaches are to alleviate the liver injury and suppress hepatic inflammation by eliminating the underlying etiology in order to reverse and prevent liver fibrosis progression [1].

3.1. Treatment of etiologic factors

According to epidemiologic data, viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD) are the most common causes of chronic liver disease [16]. In viral hepatitis, antiviral therapy is mainly targeted, aiming at effective suppression and clearance of chronic hepatitis viruses. In China, alcoholic liver disease has become the second major factor causing liver damage and just ranked after viral hepatitis [17]. In patients with alcoholic liver disease are complicated by cholestasis, resulting in abnormal proliferation of connective tissue in the liver, while alcohol cessation and nutritional support can give rise to an effective improvement in symptoms [18]. Evidence suggests that hepatic insulin resistance and abnormal lipid metabolism are essential pathophysiologic features of NAFLD [19]. However, up to now, the pathophysiological mechanisms of NAFLD have not been fully elucidated, and there is still a lack of effective and specific therapeutic drugs in the clinic. Reducing body weight through exercise or obesity surgery can bring about an improvement in liver histology in NAFLD patients [20]. In summary, long-term effective suppression of hepatitis virus replication, alcohol cessation, exercise, and nutritional support can reduce sustained liver injury, which can promote hepatic fibrosis tissue self-repair.

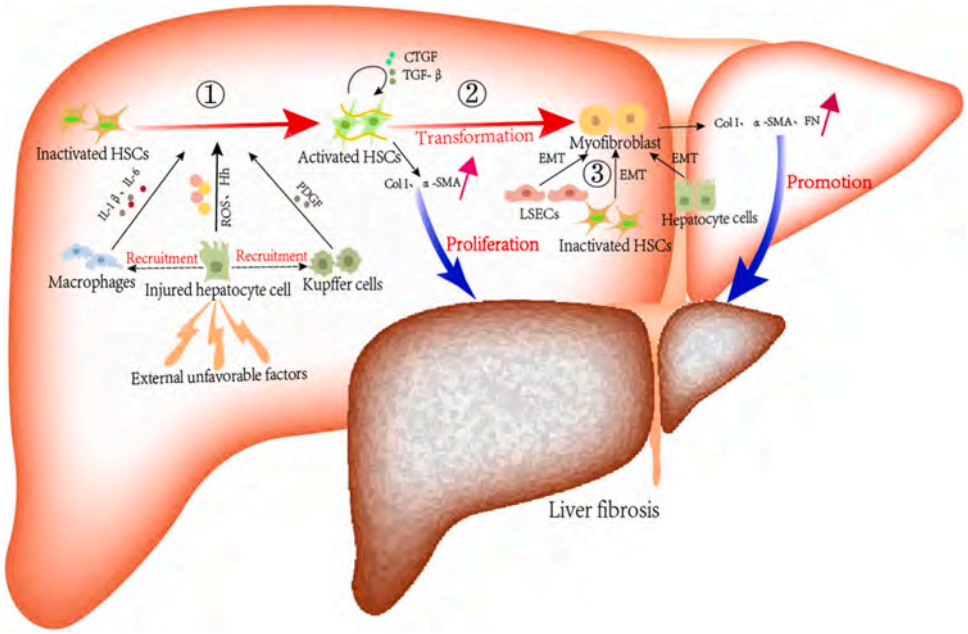

Fig. 1. Mechanism of liver fibrosis. ① External unfavorable factors cause hepatocyte injury, damaged hepatocytes release ROS, and Hh, and can also recruit macrophages to release IL-1β and IL-6 and Kupffer cells to release PDGF to promote the activation of HSCs; ② Activated HSCs secrete extracellular matrix proteins, and also release CTGF and TGF-β cytokines to maintain their activation; ③ Activated HSCs can be directly transformed into myofibroblasts, and LSECs, Inactivated HSCs, and Hepatocyte cells can be transformed into myofibroblasts by EMT to promote fibrosis.

3.2. Antifibrotic therapy

Chronic inflammatory response is a prerequisite for the formation of liver fibrosis, inhibition of inflammation and promotion of hepatic injury tissue self-repair is an important anti-hepatic fibrosis measure, and inhibition of the imbalance of hepatic extracellular matrix production and degradation is a key countermeasure for anti-fibrosis treatment [1]. Compared with the basic treatment of antiviral, anti-inflammatory, and immunosuppression of Western drugs, traditional Chinese medicine (TCM) is widely used in the treatment of liver diseases owing to its advantages of less toxic side-effects, higher safety, and targeted regulation of fibrosis-related signaling pathways [21]. Chen et al. [22] found that Chaihu saponin inhibited the proliferation and migration activity of HSC-T6 by inhibiting the TGF-β1/mitogen-activated protein kinase (MAPK) signaling pathway, which in turn improved hepatic fibrosis. In addition, the Fuzheng Huayu capsule achieves anti-hepatic fibrosis by regulating the nuclear factor kappa-B (NF-κB) signaling pathway, inhibiting the activation of HSCs, and alleviating oxidative stress and anti-inflammation in a variety of manners [23]. Quercetin, as a compound extracted, isolated, and purified from various plant species, can improve hepatic insulin resistance through inhibition of reactive oxygen species-associated inflammation as well as effective modulation of the signal transducer and activator of transcription 3/cellular signaling inhibitory factor 3/insulin receptor substrate 1 (STAT3/SOCS3/IRS1) Signaling Pathway, which in turn ameliorates hepatic fibrosis [24]. We summarized the commonly used antifibrotic drugs and therapeutic mechanisms in clinical practice (Table 1).

Table 1
Clinical antifibrotic drugs and therapeutic mechanisms.

Researcher	Year	Drug	Mechanism
Chen et al. [22]	2013	Chaihu saponin	Inhibition of the TGF-β1/MAPK signaling pathway inhibits the proliferative and migratory activities of HSC-T6
Wang et al. [23]	2015	Fuzheng Huayu Capsules	Modulation of the NF-κB signaling pathway, inhibition of HSCs activation, ECM deposition, attenuation of oxidative stress and anti-inflammation
Khodarahmi et al. [24]	2019	Quercetin	Inhibition of reactive oxygen species-associated inflammation and amelioration of hepatic insulin resistance through effective modulation of the STAT3/SOCS3/IRS1 Signaling Pathway
Wang et al. [25]	2019	Anluo Fibroblast Pills	Inhibition of TGF-β1/Smads signaling pathway, which in turn enhances Matrix Metallopeptidase 13 (MMP-13) expression and inhibits MMP-2 and Tissue Inhibitor of Metalloprotease-1 (TIMP-1)/2 expression
Vargas-Pozada et al. [26]	2022	Caffeine	Blockade of a significant increase in phosphorylated ERK, JNK, p38, and p SMAD3L protein levels attenuates liver fibrosis by blocking MAPK and TGF-β/SMAD3 signaling pathways
Xiu et al. [27]	2021	Doxazosin	Inhibition of HSCs activation and up-regulation of p-mTOR expression in the PI3K/Akt/mTOR signaling pathway to inhibit autophagy to attenuate liver fibrosis
Cai et al. [28]	2021	Parsley phenol	Reduced the expression of α-SMA, p-ERK1/2, p-JNK1/2, and p-p38 in hepatic fibrosis, and exerted anti-hepatic fibrosis effects by blocking the MAPK pathway

4. Mechanisms of improvement of liver fibrosis by mesenchymal stem cells

MSCs are a class of pluripotent stem cells with self-renewal, multi-directional differentiation, and immunomodulatory properties [29]. Studies have shown that MSCs can migrate to the site of liver injury to inhibit the activation of HSCs, directional differentiation into hepatocytes, and participation in immune regulation, which can directly or indirectly eliminate extracellular matrix deposition, and thus effectively ameliorate hepatic fibrosis [5]. With these impressive advantages, MSCs have been the most promising seed cells for the treatment of liver fibrosis in basic experiments and clinical studies.

4.1. Inhibition of HSCs activation

Hepatic stellate cell activation synthesizes and secretes extracellular matrix, which plays a critical role in liver fibrosis [7] [30]. Chen et al. [31] found that when bone marrow mesenchymal stem cells (BMSCs) were directly co-cultured with HSCs *in vitro*, BMSCs significantly inhibited the proliferation of HSCs through a cell-cell contact pattern partially mediated by activation of the Notch signaling pathway activation. Consistent with *in vitro* results, Zhang et al. [10] demonstrated that BMSCs attenuated the ubiquitination of p27 in HSCs by down-regulating the expression of the E3 ubiquitin ligase SKP2, which targeted the expression of p27 and thus exerted an anti-fibrotic effect in mice. In addition, α-SMA is a dramatic cytokine involved in HSCs activation during the process of liver fibrogenesis. It has been shown that exosomes secreted by BMSCs can promote hepatocyte regeneration, inhibit α-SMA expression, and mainly inhibit HSCs activation through the Wnt/β-catenin pathway, thus attenuating liver fibrosis [32].

4.2. Directional differentiation into hepatocyte-like cells

Hepatocytes are the first cells to be involved during liver injury among multiple causes. Studies have shown that MSCs can differentiate into hepatoid cells to replace damaged hepatocytes, and these derivative hepatoid cells could express hepatocyte markers and exert hepatocyte functions such as glycogen synthesis, low-density lipoprotein uptake, urea production, and indocyanine green uptake [33]. Many investigators transplanted MSCs *in vivo* with preconditioned hepatic direction-induced differentiation *in vitro*, which significantly improved liver function and attenuated the degree of fibrosis in hepatic fibrosis animals [34–36]. SUZY et al. [37] also demonstrated that transplantation of MSCs-derived hepatoid cells could effectively ameliorate liver fibrosis in rats. However, the clinical application of hepatoid cells derived from hepatic-induced differentiation MSCs lineage in the treatment of liver fibrosis is limited by the poor efficiency and reproducibility of hepatic directional differentiation. Therefore, improving the efficiency and success rate of hepatic differentiation from MSCs would be beneficial to the *in vivo* implantation of MSCs and enhance the therapeutic effect of liver fibrosis.

4.3. Immunomodulation

It has been found that the liver secretes a large number of immune cells, and the development of liver diseases is closely linked to aspects of the immune response [38] [39], therefore, hepatic fibrosis can be treated by immunomodulation. It is reported that MSCs inhibit the proliferation of immune cells and their translocation to the liver through the secretion of regulatory cytokines (e.g., hepatocyte growth factor, epidermal growth factor, and nerve growth factor), which promotes hepatic repair and inhibits the development of hepatic fibrosis [40]. In addition, MSCs regulate liver fibrosis by inhibiting the synthesis of pro-inflammatory cytokines such as tumor necrosis factor tumor necrosis factor-α (TNF-α), interferon interferon-γ (IFN-γ), and IL-17, and promoting the production of anti-inflammatory cytokines IL-4 and IL-10

in various types of immune cells, including T cells, natural killer cells, neutrophils, and Kupffer cells [41]. *In vitro* experiments have confirmed that MSCs associate with functional antigen-presenting cells, block B cells differentiation, and inhibit the immune response of T cells and NK cells in both contact and non-contact co-cultures [40]. Similarly, it has been demonstrated *in vivo* that MSCs inhibit M1 macrophage activation, significantly reduce hepatic inflammation and collagen deposition through immunomodulation, and ameliorate acute rat liver injury [42]. In addition, dendritic cells play an important role in antigen presentation to naive T cells, while MSCs inhibited the secretion of TNF-α, IFN-γ, and IL-12 by dendritic cells, and also promoted the secretion of IL-10 by them, synthetically, reducing their pro-inflammatory potential [41].

5. Mesenchymal stem cells combined with drugs to improve liver fibrosis

MSCs have shown promising applications in anti-inflammatory and antifibrotic therapies due to their strong differentiation potential [42], paracrine effects [43], and immunomodulatory abilities [44]. However, after implantation, MSCs are confronted with low liver colonization and limited survival rates [6]. What's more, colonized surviving MSCs face harsh microenvironments and inflammatory responses [45]. In recent years, with the advantages of low toxicity, few adverse reactions, promotion of intrahepatic homing of stem cells, improvement of the intrahepatic microenvironment, and targeted regulation of fibrosis-related signaling pathways such as TGF-β/Smad, Rho, and NF-κB and so on, traditional Chinese medicines have been widely used in liver diseases. An increasing number of researchers have demonstrated that MSCs combined with drugs can improve the effectiveness in the treatment of liver fibrosis in animal models (Fig. 2). This gives new ideas to address the poor efficacy of utilization of MSCs alone in the treatment of liver fibrosis.

5.1. Promoting MSCs homing and proliferation

The homing of MSCs to damaged tissue sites is a prerequisite for their application in the treatment of systemic diseases. Exogenous MSCs transplanted into the body are preferentially captured by the vascular system of target tissues and then migrate to target tissues via vascular endothelial cells, and the homing mechanism is similar to that of lymphocyte chemotaxis to sites of inflammatory damage [46]. It has been reported that the homing rate of primary MSCs can reach 55 %-65 %, but the homing rate after 24 hours of culture is only 10 % [47]. Due to the small number of primary MSCs, they need to be cultured and expanded *in vitro* to increase the number of cells, but this will reduce their homing ability and prevent them from homing in target tissues [48], which becoming the obvious deficiency for the long-term healing of patients. Therefore, only through in-depth investigation of the mechanism of promoting MSCs homing can we obtain a large number of MSCs and at the same time improve their homing efficiency, and then improve the therapeutic efficacy of MSCs in liver fibrosis.

It was found that the combination of drugs enhanced the homing of BMSCs pretreated with Melatonin and effectively maintained the balance between extracellular matrix production and degradation for better therapeutic effects in a mouse model of liver fibrosis [49]. In addition, the combination of MSCs with traditional Chinese medicine to improve liver fibrosis has also been reported in several papers. BMSCs combined with Zhanggan Zhuyu can effectively promote the homing of BMSCs to the liver and repair the damaged liver tissues [50]. Human umbilical cord mesenchymal stem cells (hUCMSCs) combined with Icariin could promote the migration of hUCMSCs to the damaged liver tissues and acceleratethe recovery of liver function in mice [51]. Rougan Huaxian particles mobilize BMSCs to home to fibrotic liver tissue and can repair tissue damage, the mechanism of which may be related to the stromal cell-derived factor-1 (SDF-1)/CXCR4 axis [52]. The SDF-1 is produced at the site of organic injury, and its concentration is higher than that at the

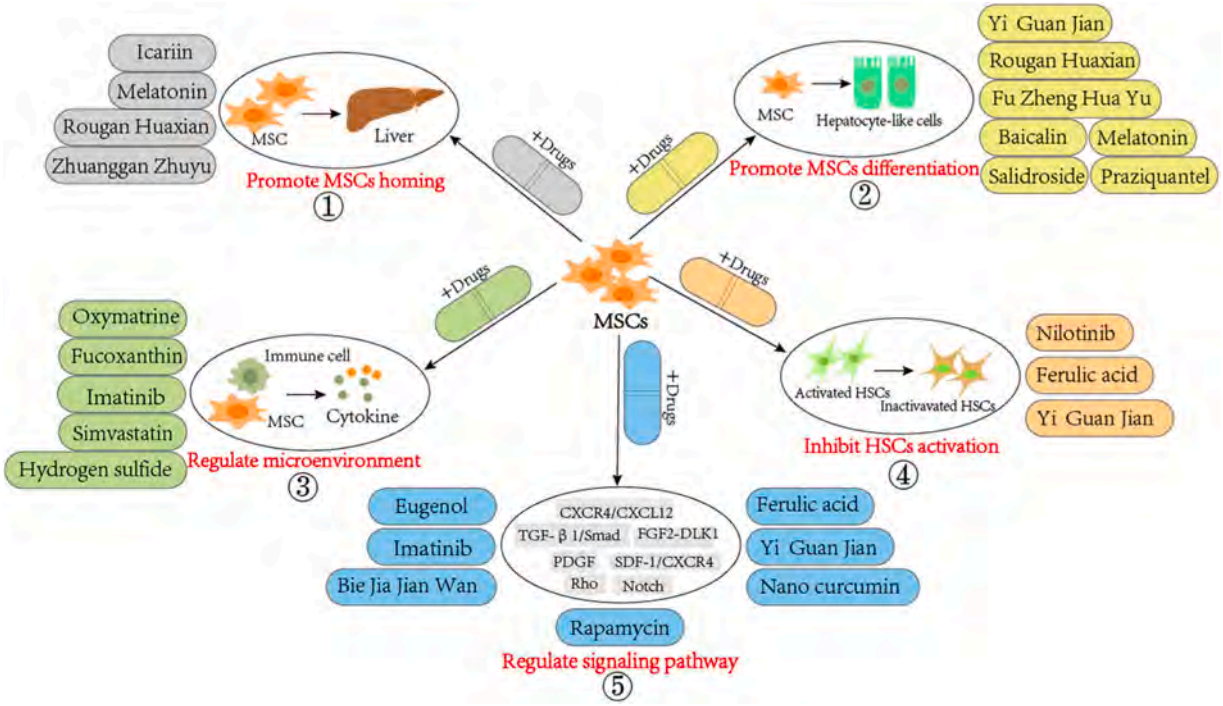

Fig. 2. MSCs combined with drugs to treat liver fibrosis mechanism. ① MSCs combined with Icariin, Melatonin, Rougan Huaxian, Zhuanggan Zhuyu promote homing of MSCs to the liver; ② MSCs combined with Yi Guan Jian, Rougan Huaxian, Fu Zheng Hua Yu, Baicalin, Melatonin, Salidroside, and Praziquantel promote the differentiation of MSCs into hepatoid cells; ③ MSCs combined with Oxymatrine, Fucoxanthin, Imatinib, Simvastin, and Hydrogen sulfide inhibit the secretion of immune cells by secreting anti-inflammatory factors and suppressing the secretion of inflammatory factors to regulate the microenvironment; ④ MSCs combined with Nilotinib, Ferulic acid, and Yi Guan Jian promote the activation of HSCs; ⑤ MSCs combined with Eugenol, Imatinib, Bie Jia jian Wan, Ferulic acid, Yi Guan Jian, Nano curumin, and Rapamycin modulate the signaling pathways related to liver fibrosis.

bone marrow, while CXCR4 expression is enhanced, promoting the migration of MSCs from the bone marrow to the targeted injury site [53]. The above study confirms that MSCs combined with drugs improve the efficiency of treating liver fibrosis by promoting their colonization in the damaged liver, which in turn improves the efficiency of treating liver fibrosis.

5.2. Promoting differentiation of MSCs into functional hepatocyte-like cells

It has been demonstrated that MSCs can differentiate into hepatoid cells both *in vivo* and *ex vivo* and have the synthetic and secretory functions of hepatocytes. When hepatocyte injury occurs, transplanted MSCs undergo hepatogenic differentiation in the periportal region of the damaged liver to replace dying hepatocytes [54]. However, it is absolutely challenging to expanding such cells in large numbers *in vivo* while maintaining their favourable differentiation potential and maximizing the differentiation efficiency of MSCs. Many investigators have found that MSCs combined with drugs can promote their differentiation into hepatocyte-like cells, which is more effective than MSCs treating liver fibrosis separately [55] [56].

It has been reported that MSCs transplantation can inhibit liver inflammation and promote the recovery of impaired liver function, but it has little effect on reducing the area of fibrosis, while MSCs combined with baicalin transplantation can promote the differentiation of MSCs into hepatocyte-like cells and improve the therapeutic effect [57]. Studies have shown that Yi Guan Jian, a traditional Chinese formula, can reverse liver cirrhosis [58]. Yan et al. [59] demonstrated that Yi Guan Jian induced BMSCs to differentiate into hepatocyte-like cells via a mechanism that may be mediated by up-regulating the SDF-1/CXCR4 axis to activate the MAPK/ERK1/2 signaling pathway. Fu et al. [60] have also found that consistent decoction through SDF-1 also induces hepatic differentiation of bone marrow MSCs. *In vivo* in *Schistosoma mansoni* induced hepatic fibrosis in mice, MSCs combined with Praziquantel (PZQ) treatment resulted in a significant reduction in the expression of α-SMA, Col I, and interleukin 13 in the liver, and the efficacy of the treatment was superior to the individual treatment of MSCs, the mechanism of which is that PZQ enhances the ability of MSCs to differentiate into functional hepatoid cells. In addition, in the animal model of CCl_4-induced hepatic fibrosis, researchers compared the therapeutic efficacy of pre-treatment of MSCs with traditional Chinese medicines, such as Rhodiola rosea glycosides [61], Rougan Huaxian Granules [55], and Fuzheng Huayu [56], with semplice transplantation of MSCs separately to treat hepatic fibrosis, finding that these medicines uncontrovertibly strengthened the effectiveness in ameliorating hepatic fibrosis by promoting the differentiation of MSCs into functional hepatocyte-like cells. Table 2 summarized the mechanism of different drugs to promote the differentiation of MSCs into functional hepatic cells.

5.3. Improvement of the microenvironment

The changes with the properties and functions of MSCs could be induced by the microenvironment [65]. Therefore, maintaining the homeostasis of the hepatic microenvironment is vital to sustaining normal cell proliferation, differentiation, metabolism, and functional activities. It has been found that many drugs in combination with MSCs can effectively ameliorate liver fibrosis via modulating the microenvironment *in vivo*.

The effectiveness of Fucoidan has been reported in liver diseases due to its anti-inflammatory and antifibrotic effects. Slautin et al. [66] demonstrated that embryonic stem cells in combination with Fucoidan significantly reduced the severity of hepatic fibrosis, reduced the levels of pro-inflammatory cytokines and fibrosis-associated proteins, such as the levels of TGF-β, α-SMA, TIMP-1, meanwhile increased the levels of HGF, MMP-13 and MMP-9 which were conducive to ameliorating liver fibrosis. The combination of BMSCs synergistically with Oxidized picloram was significantly better than oxidized picloram or BMSCs separately treating for hepatic fibrosis in rats, eventhough it did not increase the colonization of BMSCs in the liver. Notably, the serum levels of IL-4 and IL-10 were significantly higher than those of BMSCs alone, suggesting that oxidized picloram may improve liver fibrosis by promoting the secretion of IL-4 and IL-10 from MSCs [48]. It has also been shown that MSCs combined with Hydrogen sulfide attenuated choledochotomy-induced hepatic fibrosis through mechanisms such as anti-inflammatory, antioxidant, anti-apoptotic, and regenerative properties [67]. MSCs combined with Imatinib significantly ameliorated the fibrotic process in rats *in vivo* by polarizing macrophages to an anti-inflammatory profile and by increasing the frequency of these cells in the liver tissues [68] [69]. MSCs combined with the Juzentaihoto (JTT) induced anti-inflammatory macrophage production by increasing the CD4+/CD8+ ratio, which in turn enhanced the therapeutic effect of MSCs [70]. The anti-fibrotic effect of MSCs combined with Simvastatin (SIMV) can be attributed to their influence on the MMP/TIMP balance, which is crucial in fibrosis [71]. In conclusion, the combination of MSCs modulates the microenvironment through mechanisms such as down-regulation of inflammatory mediators, and up-regulation of antioxidant factors and inflammatory factors, and effectively ameliorates hepatic fibrosis.

Table 2
Mechanisms of different drugs to promote the differentiation of MSCs into functional hepatocyte-like cells.

Researcher	Year	Drug	Mechanism
Ouyang et al. [61]	2010	Rhodioloside	Inhibition of TGF-β1 expression and increased expression of alpha-fetoprotein (AFP) and albumin (ALB)
Qiao et al. [57]	2011	Baicalin	Not mentioned
Wang et al. [55]	2014	Rougan Huaxian Granules	Not mentioned
Cho et al. [62]	2015	Melatonin	Regulation of BMP, p38, ERK, and NF-κB pathways
Chen et al. [56]	2016	Fu Zheng Hua Yu	Activation of the classical Wnt and ERK pathways and inhibition of the Notch pathway promoted hepatocyte differentiation, maturation, and proliferation
Hammam et al. [63]	2016	Praziquantel	Reduced expression of alpha-smooth muscle actin, Col I, and interleukin 13
Yan et al. [59]	2017	Yi Guan Jian	Upregulation of the SDF-1/CXCR4 axis to activate the mitogen-activated protein kinase/ERK1/2 signaling pathway
Fatima et al. [64]	2021	Glycyrrhizic acid	Not mentioned

5.4. Inhibition of HSCs activation

Studies have confirmed that MSCs inhibit HSCs activation by inhibiting cell proliferation or stimulating apoptosis, thus exerting an anti-fibrotic effect [72]. Chen et al. [31] confirmed that BMSCs inhibited the proliferation of HSCs when they were co-cultured directly with HSCs *in vitro*. Consistent with the *in vitro* results, MSCs transplantation attenuated the level of liver fibrosis in rats by inhibiting the proliferation of HSCs and promoting apoptosis of HSCs [72]. To improve the efficiency of MSCs to inhibit HSCs activation, many researchers have found that MSCs in combination with drugs more significantly inhibit HSCs activation and thus alleviate liver fibrosis better.

Ferulic acid has been reported to be very effective in the treatment of hepatic fibrosis, and when Zhang et al. [73] combined BMSCs with ferulic acid in the treatment of fibrosis in rats, they demonstrated that it alleviated hepatic fibrosis by inhibiting cytoskeletal rearrangement and delivering miR-19b-3p to the activated HSCs, in return, which

inactivated the RhoA/ROCK signaling and then attenuated the activation of HSCs. This innovate research indicated that the combined administration was superior to the efficacy of ferulic acid or BMSCs treatment separately. In addition, BMSCs combined with decoction consistently inhibited the activation of HSCs by modulating the RhoA/ROCK1 pathway and thus exerted an antifibrotic effect, and the combined treatment of the two was superior to the effect of each individually [74]. Researchers combined NO exogenous donor nitroprusside and MSCs to treat liver fibrosis in mice and showed that MSCs combined with nitroprusside increased apoptosis of HSCs, which further contributed to the antifibrotic effect of MSCs [75]. Nabil et al. [76] demonstrated that the combination of nilotinib and hepatic MSCs conditioned medium had a more effective antifibrotic and anti-inflammatory effect on activated HSCs than MSCs alone.

5.5. Regulation of signaling pathways

The TGF-β/Smad pathway is one of the important signaling pathways associated with liver fibrosis, and its activation accelerates the progression of liver inflammation and fibrosis [77]. Studies have shown that eugenol can enhance the antifibrotic activity of adipose derived mesenchymal stem cells (ADMSCs) by modulating the TGF-β/Smad signaling pathway in rats. Compared with ADMSCs treatment in isolation, ADMSCs combined with eugenol significantly improved plasma fibrinogen concentration, IL-10 levels and proliferating cell nuclear antigen expression, and reduced hepatic expression of fibrosis marker genes (Col I and α-SMA) and proteins (α-SMA, TGF-β1, and phosphorylated Smad3) [78]. In addition, MSCs combined with simvastatin can ameliorate liver injury and exert a potent antifibrotic effect by inhibiting the TGF-β/Smad signaling pathway [79].

Combining drugs with MSCs to ameliorate liver fibrosis by modulating other signaling pathways has also been reported. In an animal model of hepatic fibrosis, Li et al. [74] demonstrated that BMSCs combined with consistent decoction inhibited the expression of RhoA and ROCK1, key molecules of the Rho pathway and thus inhibited HSCs activation. The combined intervention of the two resulted in a significant reduction of α-SMA, Col I positive area, and a more pronounced reduction of hepatic inflammation and fibrosis than BMSCs individually. In addition, the PDGF signaling pathway plays an important role in the accumulation of extracellular matrix, and the use of imatinib, a selective tyrosine kinase inhibitor targeting the PDGF receptor, effectively blocks PDGF receptor signaling [80]. Table 3 summarized the mechanisms relate to MSCs combined with drugs further ameliorate liver fibrosis by modulating signaling pathways.

6. The mechanisms of mesenchymal stem cells derived exosomes combined with drugs to ameliorate hepatic fibrosis

Although MSCs combined with drugs show great advantages in the treatment of liver fibrosis, combination therapy does not circumvent the potential risks of MSCs themselves. Russo et al. [85] showed that BMSCs implanted *in vivo* were able to promote the activation of HSCs and fibroblasts, which raised the risk of fibrotic lesions in the liver. What's more, MSCs have been reported to have the ability to produce a broad spectrum of cytokines, chemokines, and growth factors, and are considered to be dubious cells that may promote tumor growth [86].

In recent years, MSCs-derived exosomes (Mesenchymal Stem Cells derived exosomes, MSC-Exos) , nano-sized extracellular vesicles, have shown great potential in the treatment of liver fibrosis with the advantages of smaller size, lower immunogenicity, and noncarcinogenicity, etc. Rong et al. [32] found that the therapeutic effect of BMSC-Exos on liver fibrosis was significantly greater than that of BMSCs, and mechanistically, BMSC-Exos exerted anti-fibrotic effects by inhibiting the Wnt/β-catenin signaling pathway to inhibit hepatic stellate cell activation and reduce the expression of α-SMA to exert antifibrotic effects. Tan et al. [87] found that glutathione peroxidase 4 (GPX4) is a key regulator

Table 3
Mechanisms of MSCs combined with drugs to ameliorate hepatic fibrosis through modulation of signaling pathway.

Researcher	Year	Strategy	Signaling pathway	Mechanism
Sogol et al. [80]	2008	MSCs combine with Imatinib	PDGF signaling pathway	Improving the accumulation of extracellular matrix in the liver by blocking the PDGF signaling pathway.
Wen et al. [81]	2017	BMSCs combine with Bie Jia jian Wan	Notch signaling pathway	Promoting differentiation of BMSCs into hepatocyte-like cells by inhibiting Notch signaling.
Yan et al. [59]	2017	BMSCs combine with Yi Guan Jian	SDF-1/CXCR4 signaling pathway	Promoting differentiation of BMSCs into hepatocyte-like cells by upregulation of the SDF-1/CXCR4 axis for activation of the MAPK/ERK1/2 signaling pathway
Qiao [82]	2017	BMSCs combine with Yi Guan Jian	FGF2-DLK1 signaling pathway	Promoting the transfer of BMSCs to liver tissues, and increasing the expression of FGF2 protein through FGF2-DLK1 signaling pathway, thus reducing the expression of DLK1 genes.
Jang et al. [79]	2018	MSCs combine with Simvastatin (Sim)	TGF-β/Smad3 signaling pathway	Inhibiting TGF-β/Smad signaling and blocking upregulation of Col I, α-SMA, TGF-β1 and phosphorylated Smad3
Zheng et al. [83]	2019	hUCMSCs combine with Rapamycin	CXCR4/CXCL12 signaling pathway	Increasing cells migration in mice through the CXCR4/CXCL12 axis and improving liver function, inflammatory cytokine levels.
Fathy et al. [78]	2020	ADMSCs combine with Eugenol (EUG)	TGF-β1/Smad signaling pathway	Inhibiting the TGF-β1/Smad signaling pathway, reduced hepatic expression of fibrosis marker genes (Col I and α-SMA) and proteins (α-SMA, TGF-β1, and phosphorylated Smad3)
Mazhari et al. [80]	2020	MSCs combine with Imatinib	PDGF signaling pathway	Reducing serum ALT and AST levels and down-regulated the expression of α-SMA, Col I and Col III by blocking the PDGF signaling pathway.
El-Monem et al. [84]	2021	BMSCs combine with Nano Curcumin (Nano-Cur)	TGF-β1/Smad signaling pathway	Inhibiting the TGF-β1/Smad signaling pathway, decreased TGF-β1 levels and attenuated the expression of Smad 2,3 and Col I and Col III genes

(*continued on next page*)

Table 3 (*continued*)

Researcher	Year	Strategy	Signaling pathway	Mechanism
Zhang et al. [73]	2022	BMSCs combine with Ferulic acid	RhoA/ROCK signaling pathway	Inhibition of cytoskeletal rearrangement and delivery of miR-19b-3p to activated HSCs, inactivation of RhoA/ROCK signaling attenuates HSCs activation and liver fibrosis
Li et al. [74]	2022	BMSCs combine with Yi Guan Jian	Rho signaling pathway	Inhibiting the expression of RhoA and ROCK1, key molecules of the Rho pathway, and thus inhibiting HSCs activation

of iron death, and intravenous injection of hUCMSC-Exos enhanced iron elimination in HSCs through the BECN1/xCT/GPX4 pathway, attenuated collagen deposition in the liver, and then improved liver fibrosis.

Some researchers have found that MSC-Exos, in combination with certain drugs, can further improve the level of fibrosis by improving the ability to target activated hepatic stellate cell (aHSC), modulating signaling pathways, and acting as a drug delivery vehicle.

6.1. Improvement of targeted aHSC capacity

In injured livers, transplanted MSC-Exos could not be efficiently enriched in the periphery of aHSC, due to the low percentage of HSCs. Some researchers found that MSC-Exos combined with drugs could improve the ability of MSC-Exos to target HSCs activation after implantation *in vivo* [88]. You et al. [89] demonstrated that the combination of adipose MSC-Exos with vitamin A derivatives could lead to the enrichment of exosomes in the periphery of aHSC, which could in turn improve the efficiency of treatment of liver fibrosis. The researchers also demonstrated that even with a 10-fold lower dose of vitamin A derivative-containing exosomes compared to a normal dose of pure exosomes, the former still had a more significant antifibrotic effect than the latter. In addition, hydroxychloroquine (HCQ) synergistically inhibits autophagy and reduces extracellular matrix deposition with BMSC-Exos, which in turn ameliorates hepatic fibrosis, with superior efficacy to HCQ or BMSC-Exos alone [90]. The therapeutic pathway relies on a liposome and exosomes two-membrane hybrid nanomimetic drug delivery system, HCQ@VA-Lip-Exo, with the ability to specifically target aHSC.

6.2. Regulation of signaling pathways

Lupatadine (RUP), an antihistamine, has been reported to have good therapeutic effects on silica-induced pulmonary fibrosis and diethylnitrosamine-induced hepatic fibrosis [91] [92]. DIDAMOONY et al. [93] demonstrated that BMSC-Exos combined with RUP improved hepatic fibrosis by inhibiting the PAF/RIPK3 and TGF-β1/hedgehog signaling pathway, anti-inflammatory and antioxidant, which in turn ameliorated hepatic fibrosis, with better efficacy than BMSC-Exos individual treatment. In addition, as mentioned above in this review, MSCs combined with PZQ promote the differentiation of MSCs into functional hepatocyte-like cells and effectively ameliorate *schistosomiasis*-induced hepatic fibrosis. There is evidence that NF-κB activation is associated with schistosome-induced fibrosis [94]. After liver injury, activation of NF-κB will lead to the production of various inflammatory factors, including IL-6 and TNF-α, causing massive hepatocyte death, inflammation, and activation of HSCs, which leads to fibrosis [95]. Ellakany et al. [96] demonstrated in a mouse model study of *Schistosoma mansoni* infection that the expression of NF-κB was significantly reduced after the combination of BMSC-Exos and PZQ. Upon immunohistochemical examination, it was found that the number and diameter of granulomas were reduced, inflammation was alleviated, and hepatic fibrosis subsided more significantly, of which the mechanism may be related to the inhibition of the NF-κB signaling pathway.

6.3. Anti-inflammatory and antioxidant

Oxidative stress is regarded as an imbalanced action between the production of reactive oxygen species (ROS) and their elimination through protective mechanisms, which may lead to chronic inflammation. Various inflammatory stimulus are generated during oxidative metabolism have been reported to lead to the synthesis and secretion of pro-inflammatory cytokines, which are the critical causes of many chronic diseases [97]. Wei et al. [98] showed that binding of MSC-Exos to glycyrrhizic acid significantly enhanced the expression of proteins with anti-inflammatory activity and restored the expression of dysregulated proteins associated with inflammation and oxidative stress, thus further enhancing the therapeutic potential of MSC-Exos in liver injury *in vivo* and *in vitro*. Similarly, MSC-Exos combined with nilotinib, a second-generation tyrosine kinase inhibitor, significantly ameliorated hepatic fibrosis in rats *in vivo* by inhibiting oxidative stress, inflammation, and apoptosis [99]. Besides, the combination of MSC-Exos with RUP provided additional improvement in inhibiting DEN-induced hepatic fibrosis in rats compared to treatment with MSC-Exos alone. The mechanism is mediated through the antioxidant, anti-inflammatory, anti-necrotic and anti-fibrotic effects of RUP, which creates a more favorable environment for the homing and action of MSC-Exos. This in turn enhances miR-200a expression more effectively, thereby reducing oxidative stress, inflammation, necrotic apoptosis and subsequent fibrosis [93].

With the continuous development of research, the use of MSC-Exos has gradually become a research hotspot as a natural biocompatible drug delivery carrier for the treatment of fibrosis (Table 4). Azizsoltani et al. [100] used hUCMSC-Exos as a drug carrier via transfering

Table 4
Mechanism of improvement of hepatic fibrosis by combining MSC-Exos with drugs.

Researcher	Year	Strategy	Mechanism
Sidhom et al. [99]	2020	MSC-Exos+nilotinib	Inhibition of oxidative stress, inflammation and apoptosis
Fang et al. [102]	2021	ADMSCs-Exos +quercetin	Improved hepatocyte targeting, anti-inflammatory and anti-oxidant
You et al. [89]	2021	MSC-Exos+Vitamin A	Improved ability to target aHSC and enrich exosomes around aHSC
Wei et al. [98]	2021	MSC-Exos+ glycyrrhizic acid	Enhanced expression of proteins with anti-inflammatory activity
Ashour et al. [101]	2022	MSC-Exos+LUT	Enhancement of LUT drug activity and promotion of LUT penetration into hepatocytes
Zhang et al. [90]	2023	BMSC-Exos+HCQ	Specific targeting of aHSC functions to synergistically inhibit autophagy and reduce extracellular matrix deposition
DIDAMOONY et al. [93]	2023	BMSC-Exos+RUP	Inhibition of PAF/RIPK3 and TGF-β1/hedgehog signaling pathways, anti-inflammatory and antioxidant
Ellakany et al. [96]	2023	BMSC-Exos+PZQ	Inhibition of NF-κB signaling pathway
Azizsoltani et al. [100]	2023	hUCMSC-Exos+OCA	Activation of FXR signaling pathway enhances extracellular matrix degradation by up-regulating MMP-13 and down-regulating TIMP-1

orbicularicularis acid (OCA) into exosomes by water bath ultrasound to activating the FXR signaling pathway, and through the up-regulation of MMP-13, the down-regulation of TIMP-1, enhancing the degradation of extracellular matrix and thus ameliorating hepatic fibrosis. Lignan (LUT), a plant flavonoid, has excellent therapeutic potential in many liver diseases, especially liver fibrosis. However, its poor water solubility and susceptibility to metabolism have hindered its clinical application. Ashour et al. [101] demonstrated that the efficacy of MSC-Exos as drug carriers synergized with LUTs for the treatment of liver fibrosis was superior to that of MSC-Exos alone. In addition, Fang et al. [102] found that quercetin and vitamin A-loaded exosomes derived from ADMSCs for the treatment of acute liver injury in mice, quercetin enhanced the therapeutic efficacy of the exosomes, while vitamin A enhanced the targeting of exosomes to the liver, and found that quercetin- and vitamin A-loaded exosomes derived from MSCs reduced the rapid senescence-like response induced by acute liver injury.

Despite the unique advantages of MSC-Exos for the treatment of liver fibers, the different extraction methods of exosomes result in significant differences in exosomes purity and yield [103]. In addition, the impact of issues such as how to improve the targeting aHSC ability, drug-carrying capacity, and delivery efficiency of MSC-Exos for the treatment of liver fibrosis is crucial but problematic [104] [105]. It is worth noting that the studies of MSC-Exos for the treatment of hepatic fibrosis have been conducted mainly in animal models, while clinical trials on the safety and efficacy aspects need to be further improved and mapped out.

7. Progress of clinical research on mesenchymal stem cells and their exosomes combined with drugs for the treatment of liver diseases

Several clinical trials have shown that infusing autologous BMSCs can significantly improve liver function in cirrhotic patients [106]. Furthermore, MSCs have also been proven to be safe and effective in the treatment of liver failure [107]. In addition to autologous MSCs, LIANG and other researchers [108] found that in 26 patients with cirrhosis due to autoimmune diseases and treated with allogeneic MSCs transplantation, the patients' serum alanine aminotransferase and total bilirubin levels were significantly decreased, serum albumin improved, and no serious adverse events were observed in any of the cases during 24 hours after MSCs infusion. The latest research results of domestic academician Wang Fusheng showed that umbilical cord MSCs significantly improved liver function and long term survival in patients with decompensated cirrhosis, and this study provided new evidence for the safety and efficacy of MSCs in the treatment of cirrhosis [109]. In addition, MSCs in combination with drugs for the treatment of liver disease have also been reported [110], and in a study of patients with compensated cirrhosis evaluated by intraportal infusion of autologous MSCs in combination with pioglitazone, the patient's clinical status remained stable without signs of deterioration or any major adverse effects, and a transient improvement in Model for End-Stage Liver Disease (MELD) scores was observed at month 3 post-infusion, which eventually returned to baseline levels at month 12. It is suggested that MSCs in combination with pioglitazone are safe and feasible. However, due to the safety and adverse effects of the drugs themselves, the combination of MSCs has mostly been evaluated for its effectiveness in animal models of liver fibrosis, while its clinical application in liver diseases is less. Therefore, an in-depth exploration of the mechanism of MSCs combination drugs to improve liver fibrosis is expected to be an effective and safe therapeutic strategy for liver disease in clinical practice.

MSC-Exos, as a newly discovered transport vehicle mediating cell-to-cell interactions, plays an important role in many different diseases such as respiratory distress syndrome, renal disease, graft-versus-host disease, osteoarthritis, stroke, etc., with the advantages of its wide range of sources, good plasticity and low immunogenicity [111]. However, MSC-Exos combination drug therapy for hepatic fibrosis has only been performed in animal models, and there is a lack of uniform standards for the therapeutic dosage, route of administration, and source of parent mesenchymal stem cells of MSC-Exos, besides the above-mentioned factors of the drug itself, before its formal clinical application in the treatment of liver disease. In addition, the stability and efficacy of MSC-Exos in the liver still need to be further evaluated.

8. Discussion and outlook

Liver fibrosis, as an intermediate pathological process from chronic liver disease to cirrhosis and hepatocellular carcinoma, has become a research hotspot for the treatment of liver diseases due to its reversible properties. However, there is no very effective means to treat liver fibrosis in clinical practice. MSCs, as a kind of pluripotent stem cells, have no ethical issues and wide sources compared with liver transplantation and hepatocyte transplantation, which have attracted much attention in animal experiments and clinical studies of cell transplantation for the treatment of liver fibrosis. Unfortunately, MSCs confront with the challenges such as *in vivo* microenvironment inadaptation and attenuation of inflammatory response ability after isolation and culture *in vitro* [45], which ultimately leads to a low colonization rate and short duration of intervention after transplantation of MSCs into the liver [6]. Therefore, it has not been widely used in clinical practice.

With the deepening of relevant studies worldwide, MSCs combination drugs have shown better therapeutic effects than MSCs alone in many animal models of hepatic fibrosis. MSCs combination drugs are more effective in ameliorating hepatic fibrosis by promoting the homing and proliferation of MSCs, regulating the microenvironment, differentiating into hepatocyte-like cells, inhibiting hepatic stellate cell activation, and regulating signaling pathways, among other mechanisms. However, clinically, few studies have been reported on the combination of MSCs with drugs for the treatment of hepatic fibrosis, owing to the problems of few subject patients, large individual differences, and insufficient evaluation of the efficacy and potential side effects of the drugs alone. Not only that, MSCs combined with drugs to treat liver fibrosis do not circumvent the potential risk of MSCs themselves, such as Di et al. [6] indicated that BMSCs could present fibroblast-like morphology after transplantation into immune co-deficient mice. In addition, it was reported that MSCs promoted the activation of HSCs after implantation in hepatic fibrotic mice, which accelerated the process of hepatic fibrotic lesions [112]. More importantly, it has been reported that MSCs are considered as dubious cells that may promote tumor growth. Therefore, in order to better exploit the potential of MSCs combined with drugs for the treatment of liver fibrosis, the delivery route and therapeutic dose of MSCs should be standardized to prolong the bioactivity duration of transplanted MSCs. In addition, the drug concentration, route of administration, and safety of the drug itself need to be further explored in depth.

MSC-Exos carry a variety of nucleic acids, proteins, and lipids derived from MSCs, conferring therapeutic efficacy to MSC-Exos in liver diseases consistent with parental MSCs. In addition, with the advantages of smaller size, low immunogenicity, and nontumorigenicity, MSC-Exos may be clinically useful as the best biological tool in the treatment of various liver diseases. Some researchers have demonstrated in animal models of liver fibrosis that MSC-Exos combined with drugs can improve the effect of MSC-Exos in the treatment of liver fibrosis. It is noteworthy that the purity and yield of exosomes from different sources of MSCs and different extraction methods result in great differences, and there is a lack of effective and uniform standardized isolation methods by nowadays. In addition, challenges such as quality control, long-term storage, and safety of isolated MSC-Exos have not been addressed; low yields and high costs prevent the large-scale use of MSC-Exos as a drug delivery vehicle. Therefore, how to efficiently extract or prepare MSC-Exos on a large scale, drastically reduce the cost, and greatly improve its drug-

carrying capacity, delivery efficiency, and targeting ability still need to be further investigated.

In summary, mesenchymal stem cells and their exosomes combined with drugs can effectively improve liver function, reverse hepatic fibrosis, and promote the healing of liver tissue in many animal models of liver fibrosis. However, the specific mechanisms by which combination therapy intervenes in liver fibrosis are unclear, which makes widespread clinical application difficult. Therefore, before stipulating it as a clinical approach, it is necessary to conduct more preclinical studies on the stability and safety of the combination of MSCs and their exosomes in liver disease, to fully assess the effects and risks of different drug treatments, and to ensure the safety of the combination therapy. The combined strategy is expected to be a new direction in the treatment of liver disease, providing an efficient and safe treatment option for patients with liver fibrosis and improving the status of liver health worldwide.

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CRediT authorship contribution statement

Junsong Ye: Supervision, Funding acquisition. **Yu Jin:** Methodology. **Lin Zhou:** Supervision. **Xuesong Wang:** Writing – review & editing. **Yan Xu:** Writing – review & editing, Writing – original draft, Investigation. **Xiaolei Zhou:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict interests.

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