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Immunomodulatory Effects of Stem Cell Therapy in Liver Fibrosis: A Systematic Review

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ABSTRACT

Liver fibrosis is known as a condition characterized by chronic inflammation and excessive extracellular matrix deposition that causes cirrhosis and liver failure. Stem cell therapy is a promising strategy for the management of liver fibrosis because it not only improves tissue regeneration but also modulates by immunomodulatory mechanisms.

This systematic review aimed to evaluate the immunoregulatory effects of stem cells in both experimental models and clinical studies of liver fibrosis. A total of 29 studies were included, comprising several stem cell sources, including bone marrow-derived mesenchymal stem cells (BM-MSCs), umbilical cord-derived MSCs (UC-MSCs), adipose tissue-derived MSCs (AT-MSCs), and stem cells from human exfoliated deciduous teeth (SHED), among others. Studies reported that stem cells could decrease proinflammatory cytokines (e.g., TNF-α, IFN-γ, IL-17) and fibrosis-related markers, while increasing levels of antiinflammatory cytokines (e.g., IL-10, IL-4) and regulatory immune cells such as Tregs (regulatory T cells). Stem cells could affect immune homeostasis via modulating in macrophage polarization, T cell subsets, and B cell activity, resulting in attenuated fibrotic progression and improved liver function.

Despite variability in cell types, routes of administration, and fibrosis models, the results support the potential of stem cell therapy to reform the hepatic immune microenvironment. However, more standardized protocols and clinical validations are required.

This study emphasizes the immunomodulatory potential of stem cells as a therapeutic method in liver fibrosis. It brings a clear view into their mechanisms of action and the foundation for future translational applications.

Keywords: Immunomodulation; Inflammation; Liver fibrosis; Mesenchymal stem cells; cell therapy

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INTRODUCTION

Liver fibrosis develops as a consequence of long-term inflammation and often results from different liver diseases, such as those caused by viruses, toxins, metabolic disorders, or autoimmune conditions.[1–4] It happens after many years of repeated liver injury and persistent immune system activity. This condition is characterized by the accumulation and architectural remodeling of the extracellular matrix (ECM), with increased amounts of collagen and other fibrous proteins such as elastin, especially in the space of Disse (the area between liver cells and blood vessels).[5] It is an abnormal condition that arises when the liver's healing response to injury becomes dysregulated.[6,7] Several causes can lead to liver fibrosis, such as viral infections, alcohol use, metabolic disorders, bile duct diseases, exposure to liver toxins, autoimmune conditions, and long-term use of certain drugs like methotrexate, methyldopa, chlorpromazine, and tolbutamide.[8–11]

Liver fibrosis and is complex processes controlled by various signaling molecules, including growth factors like TGF-β, cytokines such as IL-6, TLR4, and chemokines like CCL2 and CCL5.[12–15] These signals result from interactions between different liver cell types, mainly hepatic stellate cells (HSCs), hepatocytes, Kupffer cells (KCs) (the liver's resident macrophages), and infiltrating immune cells.[16,17] The main ECM producers are HSCs and cancer-associated fibroblasts. During ongoing liver damage, HSCs become activated, transform into myofibroblast-like cells, start producing α-smooth muscle actin (α-SMA), and release ECM components-especially collagen types I and III. This process promotes fibrosis and chronic inflammation.[17,18] Depending on the situation, these changes can either sustain fibrosis or aid in liver repair.[19–24]

Platelets play important roles in fibrosis. Under normal conditions, they help maintain liver stability, support blood vessel health, and regulate the immune response.[25,26] Higher platelet counts are linked to less fibrosis, likely due to the increased release of antifibrotic factors such as hepatocyte growth factor (HGF) and reduced levels of TGF-β, a key profibrotic molecule.[27] However, platelets can also worsen inflammation by attracting immune cells and releasing profibrotic factors such as TGF-β, platelet-derived growth factor (PDGF), and CXCL4.[25,26] Liver fibrosis involves the immune system by activating immune cells and promoting the release of cytokines, leading to chronic inflammation and progressive tissue damage. There is a need to consider new treatments for liver fibrosis.

Stem cell-based therapy has been shown to improve liver fibrosis in both laboratory and clinical research.[28] Stem cells are a group of cells that can renew themselves, multiply, and develop into different types of cells when exposed to specific conditions.[29] Recent phase I and II clinical trials have provided evidence that stem cells may help treat liver fibrosis and cirrhosis, increasing interest in their potential to reverse these conditions.[30] Mesenchymal stem cells (MSCs) have the ability to self-renew, differentiate into various cell types, and regulate the immune response.[31] Since abnormal immune activity plays a key role in liver fibrosis, MSCs are considered one of the most promising stem cell types for its treatment, as they can slow down or even reverse disease progression.[32,33]

The interaction between MSCs and immune cells is complex. MSCs can control immune cell activity through direct contact and by releasing signaling molecules. They express immunosuppressive surface proteins like PD-L1 and Fas-L, which bind to receptors on immune cells and reduce their function.[34,35] Studies show that MSCs can attach to activated immune cells, keeping them nearby and enhancing their immunosuppressive effects. In addition to direct contact, MSCs also release anti-inflammatory cytokines such as TGF-β, HGF, PGE2, and other molecules that help suppress immune responses.[36,37]

As mentioned earlier, part of the progression of liver fibrosis is related to immune cell involvement. The use of stem cells, especially MSCs, may have significant therapeutic effects in treating this disease. Although some narrative reviews have discussed the immunomodulatory effects of stem cells, no systematic review has yet examined the immunomodulatory effects of stem cell therapy in liver fibrosis. Thus, this study was conducted to investigate immunomodulatory effects of stem cell therapy in liver fibrosis.

MATERIALS AND METHODS

Study Protocol Registration

The current study followed the PRISMA guidelines, which are used for conducting systematic reviews and meta-analyses.[38] PRISMA includes a checklist with 27 items that cover every part of the review, from the title

to the funding. It also includes a flowchart that shows how studies were selected. These tools help researchers organize their work more clearly and systematically.

Eligibility Criteria

The present study analyzed only articles investigating immunomodulatory effects of stem cell therapy in liver fibrosis. Studies with incomplete data, unpublished papers and review articles were not considered.

Information Sources and Searching Strategies

Searches were conducted using keywords such as "stem cell" OR "stem cells" OR "mesenchymal stem cell" OR "MSC" OR "hematopoietic stem cell" OR "HSC" OR "induced pluripotent stem cell" OR "iPSC" OR "bone marrow stem cell" OR "adipose-derived stem cell" OR "liver fibrosis" OR "hepatic fibrosis" OR "liver cirrhosis" OR "hepatic cirrhosis" OR "liver injury" OR "chronic liver disease" OR "immunomodulation" OR "immunoregulatory" OR "immune modulation" OR "immune response" OR "anti-inflammatory" OR "immunosuppressive" OR "immunomodulatory effect" OR "cytokines" OR "inflammatory response".

The data were collected from several scientific databases, such as Google Scholar, Elsevier, ScienceDirect, Wiley, SpringerLink, and Scopus. There were no limits on the year of publication or the journal. The search was done on March 10, 2025, and it identified 420 articles. After reviewing the articles, duplicate records were removed, and relevant studies were selected for further analysis.

Data Synthesis

The data were collected using specific inclusion criteria, including author and publication year, type of stem cells used, source of stem cells, method of administration, characteristics of liver fibrosis models, immune-related outcomes (such as cytokine levels and immune cell responses), and overall therapeutic effects. After applying these criteria, 29 studies were selected from the initial 420 articles. The PRISMA flow diagram (Figure 1) illustrates the process of identification, screening, and selection, along with the final number of studies included in the review.

RESULTS

Table 1 shows characteristics of studies included in systematic review. In this study, 29 studies were analyzed to evaluate the therapeutic and immunomodulatory effects of stem cells in models and clinical cases of liver fibrosis. The majority of the studies (21 out of 29) used MSCs that were derived from several sources, such as bone marrow, adipose tissue, umbilical cord, Wharton's jelly, tonsils, and amniotic membranes. HSCs were used in three studies, while human embryonic stem cell-derived MSCs and induced pluripotent stem cell-derived liver organoids were applied in a limited number of studies. Only a study utilized stem cells from human exfoliated deciduous teeth (SHED). In several of the MSC-based studies, researchers also used cell-free therapies such as MSC-conditioned medium or MSC-derived extracellular vesicles (EVs) to investigate the role of secreted factors in therapeutic effects.

With regards to the route of administration, intravenous injection was the most common method used for over two-thirds of the studies. Other methods were intrasplenic injection, hepatic artery infusion, and direct liver surface transplantation. In a few cases, stem cell therapies were delivered orally or used *in vitro* to assess immunological effects on immune cells such as peripheral blood mononuclear cells (PBMCs) or T cells.

Most studies used chemically induced models of liver fibrosis in rodents, with carbon tetrachloride (CCl_4), thioacetamide (TAA), dimethylnitrosamine (DMN), diethylnitrosamine (DEN), and bile duct ligation (BDL). In addition to animal models, three clinical studies were included that investigated stem cell therapy in patients with cirrhosis.

The key findings highlight the strong immunomodulatory capabilities of stem cells, particularly MSCs. These cells were capable to suppress pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-17 (IL-17), and interferon-gamma (IFN-γ). Simultaneously, these could increase the expression of anti-inflammatory and regulatory cytokines such as IL-10, IL-4, and transforming growth factor-beta (TGF-β). Several studies have reported an increase in regulatory T cells (Tregs) and a shift in T helper cell balance from pro-inflammatory Th1/Th17 profiles toward T_H2-dominant or tolerant states. MSCs could also promote the polarization of liver macrophages toward the M2 phenotype that is related with tissue repair. Some stem cells and their derivatives work by modulating key immunological signaling pathways, such as STAT3, JAK/STAT1, NF-κB, and indoleamine 2,3-

dioxygenase.[39] In one study, MSC-derived exosomes reduced B-cell activation and altered signaling by MAPK and NF-κB pathways, highlighting a wide immune-targeting effect.

The stem cell-based treatments could improve liver structure and function. Several studies have reported a significant decrease in fibrosis markers such as collagen type I and III, alpha-smooth muscle actin (α-SMA), and tissue inhibitors of metalloproteinases (TIMPs). Serum levels of liver enzymes, such as AST, ALT, and ALP, were also decreased. Histological analyses approved a decrease in collagen deposition, less inflammation, and an improve in liver architecture. Some studies have reported an increase in liver regeneration, as evidenced by increased hepatocyte proliferation markers (e.g., Ki-67) and upregulation of hepatocyte-specific genes and proteins. The MSCs and their secreted products could improve survival rates in fulminant liver failure models and showed clinical benefits in patients without major side effects or immune rejection. Stem cells could work by decreasing inflammation, increasing immune tolerance, and shifting the immune microenvironment toward regeneration, stem cells-especially MSCs-show significant antifibrotic and pro-regenerative potential. These properties make them promising candidates for future cell-based therapies targeting chronic liver diseases.

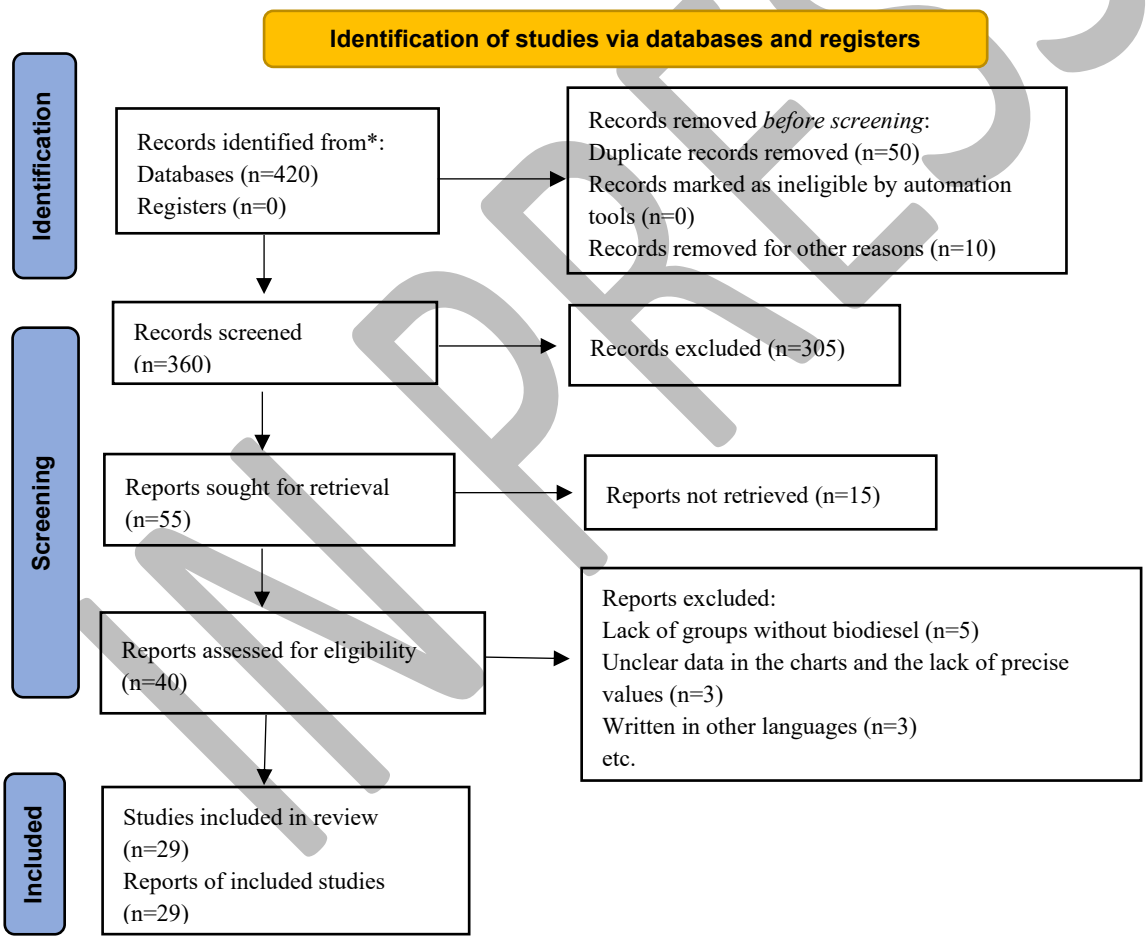

Figure 1. PRISMA flow diagram for included studies. The figure shows steps for selecting studies.

Table 1. Characteristics of studies included in systematic review

Authors	Type of stem cells	Method of administration	Characteristics of liver fibrosis models	Immune-related outcomes	Overall therapeutic effects
Fang et al.[40]	Human umbilical cord mesenchymal stem cells (hUCMSCs)	Intravenous injection	Patients with decompensated liver cirrhosis; 50 treated vs 53 matched controls	↓ IL-6, ↓ TNF-α, ↑ IL-10, ↑ TGF-β, ↑ T4 & Treg cells, ↓ T8 & B cells	↓ AST, improved albumin, bilirubin & PT; improved MELD & Child–Pugh scores; lower mortality
Liu et al.[41]	Mesenchymal stem cells (MSCs)	Intravenous injection via tail vein	Mouse model of acute liver injury (ALI) induced by CCl_4	↓ $Ly6C^{low}CD8^+$ TRM, ↓ NK cells, ↓ IgM^+IgD^+ B cells, ↓ MHC II & IgM, ↑ immunosuppressive monocyte-derived macrophages, dynamic modulation in injured vs. recovery phase	Improved liver histology, ↓ liver enzymes, ↑ survival rate
Götherström et al.[42]	Fetal mesenchymal stem cells (fMSCs) from first-trimester fetal liver	*In vitro* (co-culture with lymphocytes)	No *in vivo* liver fibrosis model used; *in vitro* immunological assays	↓Lymphocyte proliferation (mitogen-stimulated), no effect on MLC (alloreactivity)	High proliferative capacity of fMSCs; potential for ex vivo expansion and immunosuppressive application
Parekkadan et al.[43]	Bone marrow-derived mesenchymal stem cells (BM-MSCs)	*In vitro* indirect co-culture with hepatic stellate cells	Activated hepatic stellate cells (model of liver fibrosis), *in vitro*	↑ IL-10, ↑ TNF-α, ↑ HGF (from MSCs); ↓ collagen deposition and SC proliferation; ↑ SC apoptosis	Inhibition of fibrosis-related activity in SCs; suggests MSCs act via paracrine signals to reduce fibrosis
Guo et al.[44]	BM-MSCs	*In vitro* co-culture with patient-derived lymphocytes	Peripheral blood lymphocytes from patients with decompensated hepatitis B-associated cirrhosis	↓ Lymphocyte proliferation; ↑ $CD4^+CD25^+CD127^-$ Tregs; ↑ Treg/Th17 ratio; ↓ Th17 cell frequency vs. PHA group	Immunosuppressive effects of BMSCs; potential to restore immune balance in cirrhotic patients via soluble factors

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Table 1. Continued...

Authors	Type of stem cells	Method of administration	Characteristics of liver fibrosis models	Immune-related outcomes	Overall therapeutic effects
Zheng et al.[45]	Human umbilical cord-derived MSCs (hUC-MSCs), FSTL1-silenced via siRNA	Intravenous injection in mice (after 12 weeks of CCl_4-induced liver fibrosis)	Mouse model of chronic liver fibrosis (CCl_4-induced); 12-week fibrosis induction before MSC therapy	FSTL1 is critical for MSC-mediated suppression of inflammatory macrophages via JAK/STAT1/IDO signaling; ↓ immunosuppression with FSTL1 knockdown	FSTL1low MSCs failed to improve fibrosis, inflammation, or liver function → indicates FSTL1 is key to MSC anti-fibrotic effect
Milosavljevic et al.[46]	BM-MSCs and MSC-conditioned medium (MSC-CM)	Intravenous injection in mice (post-CCl_4 administration, weekly)	CCl_4-induced liver fibrosis in mice (1 month); inflammatory model	↓ IL-17, ↓ Th17 cells, ↑ IL-10, ↑ IDO, ↑ kynurenine, ↑ Tregs ($CD4^+FoxP3^+IL\text{-}10^+$); immune modulation blocked by IDO inhibition	MSCs and MSC-CM attenuated fibrosis via IDO-mediated suppression of Th17 response and enhancement of regulatory T cells
Tadokoro et al.[47]	Human induced pluripotent stem cell–derived liver organoids (hiPSC-LOs)	Transplantation onto liver surface in immunodeficient rodents	Chemically induced liver fibrosis; subacute/chronic models in rodents	↑ $CD163^+$ M2 macrophage polarization, ↑ macrophage-recruiting factors, ↓fibrosis-associated inflammation	hiPSC-LOs improved liver function, reduced fibrosis, increased survival; better than liver buds (hiPSC-LBs)
El-Akabawy & El-Mehi[48]	Endogenous hematopoietic stem cells mobilized by StemEnhance ($CD34^+$ cells)	Oral administration of StemEnhance	Thioacetamide (TAA)-induced liver fibrosis in mice	↑ VEGF expression, ↓ TNF-α expression	↑ $CD34^+$ stem cells in circulation, ↓ hepatic fibrosis, improved histology, ↑ liver regeneration
Pinheiro et al.[49]	Adipose tissue-derived mesenchymal stem cells (conditioned medium)	Intravenous injection of MSC-CM on days 5 & 6 post-BDL	Bile duct ligation (BDL)-induced cholestatic liver fibrosis in C57Bl/6 mice	↓ IL-17A (pro-fibrotic), ↑ IL-6 & IL-4 (regenerative cytokines)	↓ liver enzymes (transaminases, ALP), ↓ collagen deposition, cytokine shift toward regeneration

Table 1. Continued...

Authors	Type of stem cells	Method of administration	Characteristics of liver fibrosis models	Immune-related outcomes	Overall therapeutic effects
Huang et al.[50]	Bone marrow-derived MSCs and MSC-conditioned medium (MSC-CM)	Intravenous infusion	Acute: Fulminant hepatic failure (FHF) model in mice - Chronic: Liver fibrosis model	- ↓ Macrophage ($F4/80^+$) infiltration in liver and spleen - MSC-CM ↑ Th2, ↑ Treg, ↓ Th17; no effect on Th1 - MSCs had limited effect on T cell subsets - *In vitro*: ↑ apoptosis in macrophages and HSCs	- FHF: MSC > MSC-CM in survival and histology improvement -Fibrosis: MSC-CM>MSC in suppressing fibrosis, HSC activation, and improving regeneration (↑Ki67,↓ TUNEL, ↑ PAS staining)
Chai et al.[51]	Human umbilical cord MSCs (UC-MSCs)	Intravenous injection	Rat model of liver fibrosis induced by DMN	Increased IL-4 and IL-10; promoted Kupffer cell mobilization; anti-inflammatory environment	Reduced liver fibrosis; alleviated fibrosis via IL-4 mediated macrophage mobilization; improved liver microenvironment
Kim et al.[52]	Bone marrow-derived MSCs genetically engineered to overexpress hepatocyte growth factor (HGF)	Direct injection into the spleen	Rat liver fibrosis induced by dimethylnitrosamine (DMN)	Decreased fibrogenic cytokines PDGF-bb and TGF-β1; increased expression of MMP-9, MMP-13, MMP-14, and urokinase-type plasminogen activator; decreased TIMP-1	More significant reduction of liver fibrosis and improved hepatocyte function compared to unmodified MSCs
Zhao et al.[53]	Bone marrow-derived MSCs from third-party donors	Intravenous infusion weekly (median 4 doses)	Refractory acute graft-versus-host disease (aGVHD) after allogeneic hematopoietic stem cell transplantation	Increased CD3+CD4+/CD3+CD8+ T cell ratio; increased CD4+CD25+Foxp3+ regulatory T cells (Tregs); increased thymic function marker (sjTRECs); no increased infection or tumor relapse risk	75% overall response rate in MSC group vs 42.1% control; reduced incidence and severity of chronic GVHD; improved immune regulation

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Table 1. Continued...

Authors	Type of stem cells	Method of administration	Characteristics of liver fibrosis models	Immune-related outcomes	Overall therapeutic effects
Kantarcıoğlu et al.[54]	Autologous bone marrow-derived MSCs	Intravenous infusion (1 × 10^6 cells/kg)	Liver cirrhosis (biopsy-proven)	Possible immunomodulation via secreted factors ("endocrine" effect); no significant change in liver histology	Safe and well tolerated; improved MELD scores in 8/12 patients; increased serum albumin; HCV RNA clearance in nonresponders; no significant fibrosis regression on biopsy
Pulavendran et al.[55]	Bone marrow-derived MSCs vs HSCs	Transplantation into female mice with liver inflammation	Acute liver inflammation and fibrosis	↓ TNF-α, ↓ IL-6, ↓ α-SMA, ↓ collagen type I in MSC group; ↑ antioxidant enzymes; normalization of aminotransferases	MSCs prevented inflammation and fibrosis; HSCs did not. MSCs protected liver via anti-inflammatory and antifibrotic mechanisms
Mansour et al.[56]	Human umbilical cord blood-derived MSCs (HUCB-MSCs), $CD34^-$ cells, HMNCs	Injection into CCl4-induced fibrotic rats	CCl4-induced liver fibrosis	HUCB-MSCs: ↓ immune response, ↑ host tolerance; ↑ liver regenerative markers	$CD34^-$ cells & HUCB-MSCs showed most liver functional and histological improvement; HUCB-MSCs had lowest immunogenicity
Sharma et al.[57]	Autologous MSCs and HSCs	Hepatic artery infusion (under fluoroscopic guidance)	Decompensated liver cirrhosis (clinical trial, Phase I)	MSCs secreted IL-6 and IL-8; HSCs secreted IL-8; coculture did not alter cytokine profile or cell viability	Infusion was safe and well tolerated with no complications; efficacy needs assessment in larger trials
Yoo et al.[58]	MSCs from BM, AT, CB, WJ	In vitro co-culture with activated T cells	Immune modulation model (in vitro)	All MSC types suppressed T-cell proliferation; reduced IFN-γ and TNF-α; increased IDO expression in response to inflammatory cytokines	AT-, CB-, and WJ-MSCs were as immunosuppressive as BM-MSCs, suggesting their suitability for allogeneic therapy

Table 1. Continued...

Authors	Type of stem cells	Method of administration	Characteristics of liver fibrosis models	Immune-related outcomes	Overall therapeutic effects
Mardpour et al.[59]	Human embryonic stem cell-derived MSCs (ES-MSCs) and their extracellular vesicles (EVs)	Administered *in vivo* in TAA-induced liver injury model	Chronic liver injury (TAA-induced in rats)	↑ TGF-β1, IL-10, MMP9, MMP13, BCL-2; ↓ IFN-γ, TNF-α, IL-2, Col1α, αSMA, TIMP1, BAX	ES-MSCs and EVs reduced fibrosis, necrosis, inflammation, and liver damage, showing strong immunomodulatory and anti-fibrotic effects
Kim et al.[60]	Tonsil-derived MSCs (T-MSCs), used as conditioned medium (T-MSC CM)	Injection of T-MSC CM or recombinant IL-1Ra	CCl_4-induced liver injury in mice	↓ Inflammatory markers; ↓ fibrogenic genes (Col1a1, TGF-β, TIMP1); IL-1Ra identified as key anti-inflammatory/anti-fibrotic mediator produced by T-MSCs	Significant reduction in liver inflammation and fibrosis; IL-1Ra replicated effects of T-MSC CM, confirming mechanism of action
Feng et al.[61]	Mesenchymal Stem Cells (MSCs)	Intravenous	Liver fibrosis (LF), various mouse models incl. μMT and anti-CD20 treatment	↓ Infiltration, activation, and cytokine production by intrahepatic B cells; MSC-derived exosomes modulate MAPK & NF-κB signaling; scRNA-seq identified B cell subtype (B-II) enriched in LF; adoptive transfer + MSC validated B cell role in LF progression	Significant reduction in fibrosis, collagen deposition, and inflammation via targeting B cell–driven pathology
Li et al.[62]	hUC-MSC-derived exosomes	Transplantation	CCl4-induced liver fibrosis (in vivo and in vitro models)	↓ Collagen I/III, TGF-β1, p-Smad2; ↑ E-cadherin, ↓ N-cadherin, vimentin; reversal of TGF-β1-induced EMT in hepatocytes; protection of hepatocyte architecture; ↓ inflammation and collagen deposition	Alleviated liver fibrosis by inhibiting EMT and reducing hepatic inflammation and fibrogenesis

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Table 1. Continued...

Authors	Type of stem cells	Method of administration	Characteristics of liver fibrosis models	Immune-related outcomes	Overall therapeutic effects
Wu et al.[63]	Adipose-derived MSC exosomes	Tail vein injection (3x/2 weeks)	DEN + CCl_4-induced liver fibrosis (mice)	↓ HSC activation; ↓ profibrogenic markers; ↑ Glul and OAT; ↓ GLS2; RNA-seq: glutamine/ammonia metabolism modulation; Glul inhibition reversed effects	Significantly alleviated liver fibrosis via suppression of HSC activation and modulation of glutamine metabolism
Hammam et al.[64]	Wharton's Jelly MSCs (WJMSCs)	IV transplantation±oral PZQ	Schistosoma mansoni-induced liver fibrosis	↓ α-SMA, collagen-I, IL-13; ↑ human hepatocyte marker expression; gelatin zymography and morphometry indicated fibrosis regression; PZQ enhanced WJMSC effects	Significant regression of fibrosis, improved by PZQ co-treatment; WJMSCs differentiated into hepatocyte-like cells
Yamza et al.[65]	SHED (Stem cells from Human Exfoliated Deciduous Teeth)	Intrasplenic transplantation	CCl4-induced liver fibrosis in mice	SHED homed to liver and expressed HLA-ABC, HepPar1, and human albumin. No cell fusion observed. Expressed human hepatocyte-specific genes (albumin, CYP1A1, FAH, TAT, UGT, transferrin, TTR), and secreted human albumin, urea, BUN. No immune rejection reported.	Improved liver function, reduced fibrosis and inflammation. Functional integration and hepatic differentiation confirmed after both primary and secondary transplantation.
Tian et al.[66]	MSC-derived Exosomes (MSC-EXOs)	Intravenous injection	CCl4-induced liver fibrosis in mice	MSC-EXOs modulated macrophage polarization via miR-148a targeting KLF6 and inhibiting STAT3 signaling. Promoted anti-inflammatory phenotype and reduced pro-inflammatory cytokines.	Reduced fibrosis, improved liver histology and inflammation. Exosomes and miR-148a agomir both showed potent anti-fibrotic effects.
Wolbank et al.[39]	Human amniotic mesenchymal SCs, amniotic epithelial SCs, and adipose-derived SCs	In vitro co-culture with PBMCs	[Not applicable]	Dose-dependent, contact-dependent suppression of PBMC proliferation (up to 93% inhibition). Cryopreservation reduced efficacy; subcultivation did not. Mild alloreactivity.	Demonstrated strong immunosuppressive potential; viable alternative to BMSCs for allogeneic therapies.

Table 1. Continued...

Authors	Type of stem cells	Method of administration	Characteristics of liver fibrosis models	Immune-related outcomes	Overall therapeutic effects
Motawi et al.[67]	Bone marrow-derived MSCs (BM-MSCs)	Intravenous infusion (tail vein) in rats	CCl4-induced liver fibrosis in rats	Decreased procollagen I & III, TIMP-1, endoglin, TGF-β1; increased MMP-1; confirmed homing by *SRY* gene PCR	MSCs and simvastatin (SIMV) improved liver fibrosis markers and histology; MSCs more effective than SIMV; antifibrotic effect linked to MMP/TIMP balance

aGVHD: acute graft-versus-host disease; ALI: acute liver injury; ALP: alkaline phosphatase; α-SMA: alpha-smooth muscle actin; AST: aspartate aminotransferase; AT: adipose tissue; BAX: BCL2 Associated X; BCL-2: B-cell lymphoma 2; BDL: bile duct ligation; BM: bone marrow; BM-MSCs: bone marrow-derived mesenchymal stem cells; BUN: blood urea nitrogen; CB: cord blood; CCl_4: carbon tetrachloride; Col1a1: collagen type I alpha 1; Col1&alpha: collagen type I alpha; CYP1A1: cytochrome P450 family 1 subfamily A member 1; DEN: diethylnitrosamine; DMN: dimethylnitrosamine; EMT: epithelial-mesenchymal transition; ES-MSCs: human embryonic stem cell-derived MSCs; EVs: extracellular vesicles; FAH: fumarylacetoacetate hydrolase; FHF: fulminant hepatic failure; fMSCs: fetal mesenchymal stem cells; GLS2: glutaminase 2; Glul: glutamate-ammonia ligase; GVHD: graft-versus-host disease; HCV: hepatitis C virus; HGF: hepatocyte growth factor; hiPSC-LBs: human induced pluripotent stem cell-derived liver buds; hiPSC-LOs: human induced pluripotent stem cell–derived liver organoids; HLA-ABC: human leukocyte antigen class I, A, B, C; HMNCs: human mononuclear cells; HSCs: hepatic stellate cells; hUC-MSCs: human umbilical cord-derived mesenchymal stem cells; HUCB-MSCs: human umbilical cord blood-derived MSCs; IDO: indoleamine 2,3-dioxygenase; IFN-γ, interferon-gamma; IL: interleukin; IL-1Ra: interleukin-1 receptor antagonist; IV: intravenous; JAK: Janus kinase; KLF6: Krüppel-like factor 6; LF: liver fibrosis; MAPK: mitogen-activated protein kinase; MELD: Model for End-Stage Liver Disease; MHC: major histocompatibility complex; miR-148a: microRNA-148a; MLC: mixed lymphocyte culture; MMP: matrix metalloproteinase; mo: month; MSC-CM: mesenchymal stem cell-conditioned medium; MSC-EXOs: mesenchymal stem cell-derived exosomes; MSCs: mesenchymal stem cells; μMT: mu-heavy chain membrane exon knockout; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NK: natural killer; OAT: ornithine aminotransferase; PAS: periodic acid-Schiff; PBMCs: peripheral blood mononuclear cells; PDGF-bb: platelet-derived growth factor BB; PHA: phytohemagglutinin; p-Smad2: phosphorylated Smad2; PT: prothrombin time; PZQ: praziquantel; RNA-seq: RNA sequencing; SC: stellate cell; scRNA-seq: single-cell RNA sequencing; SHED: stem cells from human exfoliated deciduous teeth; SIMV: simvastatin; siRNA: small interfering RNA; sjTRECs: signal-joint T-cell receptor excision circles; SRY: sex-determining region Y; STAT: signal transducer and activator of transcription; TAA: thioacetamide; TAT: tyrosine aminotransferase; TGF-&beta: transforming growth factor-beta; Th: T helper; TIMP-1: tissue inhibitor of metalloproteinases 1; T-MSC CM: tonsil-derived MSC conditioned medium; T-MSCs: tonsil-derived mesenchymal stem cells; TNF-&alpha: tumor necrosis factor-alpha; Treg: regulatory T cell; TRM: tissue-resident memory; TTR: transthyretin; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; UC-MSCs: umbilical cord mesenchymal stem cells; UGT: UDP-glucuronosyltransferase; VEGF: vascular endothelial growth factor; WJ: Wharton's jelly; WJMSCs: Wharton’s Jelly mesenchymal stem cells; wk: week.

DISCUSSION

The immunomodulatory effects of stem cells, especially MSCs, have known as a major mechanism for the treatment of liver fibrosis. Across the 29 reviewed studies, immunomodulation significantly showed a central property of stem cell therapy. It not only affects the inflammatory environment but also decreases the progression of fibrosis and liver regeneration. The findings indicate that stem cell-based therapies do not rely solely on direct differentiation into hepatocytes but also by reprogramming the immune microenvironment that is involved in fibrogenesis.

One of the most important results was the suppression of pro-inflammatory cytokines. Several studies have reported significant downregulation of TNF-α, IL-6, IL-17A, and IFN-γ following stem cell therapy, such as El-Akabawy & El-Mehi,[48] Pulavendran et al,[55] and Mardpour et al.[59] These cytokines play essential roles in activating HSCs that work as the primary drivers of fibrosis in liver injury. MSCs significantly disrupt the positive feedback loop that sustains chronic inflammation and fibrogenesis by damaging the signals. Additionally, studies[60,66] utilizing MSC-conditioned media or exosomes confirmed that soluble factors secreted by MSCs are sufficient to modulate immune responses without the requirement for direct cell replacement.

Stem cells also promoted anti-inflammatory and regulatory immune pathways. Several studies, including Chai et al,[51] Huang et al,[50] and Zhao et al,[53] reported an increase in regulatory T cells (Tregs) and anti-inflammatory cytokines such as IL-10 and IL-4. For instance, Chai et al[51] showed that human umbilical cord MSCs could decrease fibrosis via mobilizing Kupffer cells and increasing IL-4-mediated responses. Similarly, Huang et al[50] reported that MSC-conditioned media increased T_H2 and Treg populations while lowering pro-inflammatory Th17 cells, resulting in shifted the immune landscape toward a pro-regenerative state. These findings show that MSCs not only cause silence harmful immune activation but also significantly encourage tolerance and healing.

Additionally, macrophage polarization worked as a key immunological mechanism. MSCs and their derivatives could induce a shift from M1 (pro-inflammatory) to M2 (anti-inflammatory) macrophages in some models. The shift was related with a decrease in secretion of fibrogenic mediators and an increase in production of matrix metalloproteinases (MMPs), enzymes involved in extracellular matrix remodeling and fibrosis resolution. For example, Tian et al,[66] reported that exosomes derived from MSCs could promote M2 polarization by miR-148a targeting KLF6, ultimately decreasing liver inflammation and fibrosis. This modulation of innate immune cells highlighted the multifaceted role of MSCs in rebalancing the immune response.

The suppression of T-cell proliferation and modification of T-cell subsets were also well reported. Yoo et al[58] reported that MSCs from different sources—such as bone marrow, adipose tissue, cord blood, and Wharton's jelly—were all capable of suppressing activated T-cell proliferation and cytokine production. The effects were partly mediated by the upregulation of indoleamine 2,3-dioxygenase (IDO), an enzyme that plays a central role in immune suppression.[39] The results support that stem cells exert broad effects on both innate and adaptive immunity.

Moreover, B-cell modulation has recently gained attention as a novel immunological target in liver fibrosis. Feng et al,[61] reported that MSC-derived exosomes decreased intrahepatic B-cell activation and cytokine production, identifying a unique B-cell subset involved in liver fibrosis progression. These findings highlight new routes for understanding how MSCs may affect less-studied components of the immune system and further expand their therapeutic potential.

The route of administration and type of stem cell product also impacted immunomodulatory outcomes. Intravenous infusion was the most common method and allowed systemic distribution and liver homing of stem cells, as reported by Motawi et al.[67] However, localized delivery methods, such as intrasplenic or hepatic artery infusion, may increase targeting in some cases. Thus, live cells have traditionally been applied and increased evidences that support the efficacy of cell-free therapies such as exosomes and conditioned media. These evidences decrease concerns related to immune rejection or tumorigenesis.

This collection of studies brings a comprehensive overview of the immunomodulatory effects of several types of stem cells in liver fibrosis, emphasizing the significant potential of stem cell therapies for regulating immune responses and promoting liver regeneration. One of the key strengths of this body of work is the diversity of stem cell sources, including bone marrow, umbilical cord, adipose tissue, and embryonic stem

cells, which allows a broad understanding of their therapeutic potential. In addition, the inclusion of both in vitro and in vivo models strengthens the evidence by demonstrating consistent immunomodulatory effects across different experimental settings.

This study has limitations. Several studies employed animal models or in vitro systems that may not fully replicate human liver fibrosis complexity or immune interactions, limiting direct clinical translation. The variability in stem cell types, dosages, administration routes, and fibrosis models also makes it difficult to compare results directly or establish standardized treatment protocols. Thus, the long-term safety and potential immunogenicity of stem cell therapies needs more investigations.

Future studies should focus on well-designed clinical trials to show these promising preclinical findings and optimize stem cell sources, delivery methods, and dosing regimens. Additionally, deeper mechanistic studies exploring stem cell-immune system interactions at the molecular level can help clear understanding of therapeutic strategies. Addressing these gaps is essential to advance stem cell therapies for liver fibrosis.

CONCLUSIONS

In conclusion, these studies show the central role of immune modulation in the therapeutic effects of stem cells for liver fibrosis. These not only work by engraftment and differentiation, but also by suppressing pro-fibrotic immune pathways and promoting regulatory responses. This multifactorial immune intervention not only blocks fibrogenesis but also starts tissue repair and regeneration. Understanding and harnessing these immunomodulatory mechanisms may show the way for more targeted and effective stem cell therapies for the treatment of chronic liver diseases.

Future researches are required to elucidate the signaling pathways involved in immune modulation via stem cells and defining the optimal cell source, delivering route, and dosing regimen to increase therapeutic efficacy. Personalized cell products aligned with a patient's immune profile can present a promising direction. The immunological properties of stem cells stand as a cornerstone of their antifibrotic potential, offering hope for more effective therapy strategies in liver fibrosis.

STATEMENT OF ETHICS

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

readers can access the data supporting our findings. Upon reasonable request (rahimi.8844@yahoo.com)

AI ASSISTANCE DISCLOSURE

Not applicable.

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