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Current Treatment on Liver Fibrosis: An Update

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ABSTRACT
The abnormal buildup of extracellular matrix proteins in the liver is the primary symptom of liver fibrosis, a disorder that worsens with time and may be fatal. Liver fibrosis can develop into cirrhosis, liver failure, and hepatocellular cancer if it is not treated. The current standard of therapy for managing liver fibrosis involves dietary changes, weight loss, and the treatment of underlying liver disorders. Clinical trials have shown varied degrees of antifibrotic drug efficacy, including pentoxifylline, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors. Targeting specific biochemical pathways linked to fibrosis, such as the transforming growth factor-beta signaling pathway, is a new strategy. Additionally, research is being done to create antifibrotic treatments that can hasten the breakdown of already fibrotic tissue and improve liver regeneration. Despite the advances, there are still a number of problems with treating liver fibrosis. Among the most significant obstacles to be addressed are the lack of effective treatment choices, the potential side effects of pharmaceutical therapies, and the need for better non-invasive diagnostic techniques. The review focuses on deeper understanding of fibrosis pathogenesis, novel therapies, targeted approaches of drug delivery and latest research in treatment of liver Fibrosis
Keywords: *Liver fibrosis, Gene therapy, Liver transplantation, pathogenesis, Stem cell therapy, targeted drug therapy.*

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INTRODUCTION

Liver Fibrosis is a chronic wound-healing reaction to a variety of symptoms. A defining feature of the condition is excessive extracellular matrix {ECM} protein deposition, which comprises three major protein families ie- glycoproteins, collagens and proteoglycans. [1]
Increased collagen deposition, particularly fibrillar collagens, is the most prevalent fibrosis symptom. Despite the fact that the number of collagens revealed in the liver continues to grow, Types III and I collagens seem to be the most closely related and have developed the most [2].
Excess ECM protein deposition disrupts the liver's natural design by causing it to function improperly and eventually resulting in pathological damage [3].
In fibrogenesis the hepatic stellate cells {HSCs} perform a key role. Mesenchymal cells are found in the subendothelial space and account for about 15% of the total cells in a healthy human liver [4]. During chronic inflammatory damage they have the ability to differentiate from dormant vitamin Astoring cells into myofibroblasts [5].
Mesenchymal stem cells {MSC's} are multipotent cells that may be easily extracted and cultured in vitro from adult's bone marrow or human umbilical tissue, allowing them to develop into a variety of cell types, including hepatocytes [6,7].
MSCs are known to have immunomodulatory properties and have been found to diminish inflammation, damage, and hepatocyte death in a variety of liver injury (acute liver injury)(ALI) models[8,9,10].
A few experimental liver disease animal models Endorse the concept that the hepatic stellate cell {HSC}is the main cell that produces excessively collagen during fibrogenesis [11].
Collagen protein localisation and elevated mRNA levels have been demonstrated in HSCs derived from experimental models of hepatic fibrosis [12,13,14]. HSCs are typically found in close contact with collagen fibres and enhanced cell populations within the Centrilobular scar [15]. Finally, HSCs isolated from liver fibrosis animal models synthesise more collagen than control animals [16,17].

Elimination of related damage factors suppression of hepatic stellate cell (HSC) stimulation - encouragement of Extracellular matrix degradation and tolerance to inflammatory responses are the main goals of current liver fibrosis treatment strategies [18,19].
Severe HCV infection, drinking, and non-alcoholic steatohepatitis are the leading causes for liver fibrosis in rich countries (NASH). The formation of nodules of regenerated hepatocytes distinguishes the hepatic structure when an accumulation of ECM proteins distorts the hepatic structure by producing a fibrous scar. Cirrhosis causes hepatic insufficiency and portal hypertension due to liver degeneration and increased intrahepatic resistance to blood flow[20].
Fibrosis and scarring are caused by activated fibroblasts laying down connective tissue that comprises collagen & glycosaminoglycan. Immune cells, such as macrophages, start the process by producing soluble substances that activate fibroblasts. TGF beta, the most well-studied pro-fibrotic mediator, is produced in the interstitium, the gap between surfaces, by macrophages as well as any damaged tissue. CTGF, platelet-derived growth factor (PDGF), and interleukin 10 are soluble fibrosis mediators (IL-10). These stimulate signalling pathways such as AKT or mTOR[21], causing fibroblasts to grow and stimulate, depositing extracellular matrix into the connective tissue surrounding them. Healing process is a challenging procedure that requires close attention to the formation and destruction of extracellular matrix (ECM) [22].
Repeated Infectious (mostly hepatitis B and C viruses), toxic or drug induced, metabolic, and autoimmune factors, as well as the relative chronic stimulation of the wound-healing process, all contribute to the development of fibrillar extracellular matrix (ECM) in the liver. Cirrhosis of the liver and hepatic failure are possible side effects of the procedure. Cirrhosis is a lethal form of fibrosis. Significant angioarchitectural changes, as well as the creation of liver parenchyma regenerating nodules separated by and encased with fibrotic Septa [23].

PATHOGENESIS

The formation of liver fibrosis is linked to a variety of factors, including viral infection, alcohol misuse , metabolic problems, obesity, toxins, steatosis & cholestasis with alcohol abuse being the most common cause. Acetaldehyde and reactive oxygen species are created during alcohol metabolism. Acetaldehyde, in particular, can cause liver fibrosis by increasing the synthesis of transforming growth factor-B (TGF) thereby up-regulating the production of type I collagen in HSCs [24,25]. TGF-1 is thought to be a key factor in the development of alcoholic liver disease, while ROS generated at the same time can harm the liver by promoting hepatocyte destruction or apoptosis [26].The wound healing reaction causes collagen and ECM protein accumulation in fibroblasts which is the major cause of liver fibrosis [27].
The ECM of a healthy liver is a dynamic structural component. It comprises polymers that serve as both hepatic scaffolding and extracellular signal transducers. The ECM in normal liver tissue is made up of tenascin , collagen, Lamenin, glycoproteins, fibronectin, von willebrand factor, and proteoglycans [29]. It's found in Glisson's capsule, portal tracts, central veins & Disse's subendothelial space [30].
Hepatic fibrosis is influenced by a variety of cells and cytokines & HSC activation is regarded to be the fundamental link in liver fibrosis [31,32].
Liver fibrosis (LSECs) is caused by changes in four primary liver cells: hepatocytes, HSC, macrophages, and liver sinusoidal endothelial cells. HSCs reside in the sinus area and come into direct contact with hepatic epithelial cells and endothelial cells, accounting for around 13% of total liver cells [34-35]. Kupffer cells as well as HSCs, are certainly responsible for both fibrogenesis and fibrolysis of the liver among the several innate immune liver cells. When a liver injury occurs, macrophages generate a fibrotic response by recruiting additional immune cells and stimulated Kupffer cells induce hepatocyte damage, resulting in HSC activity [36-37]. The fibrolytic nature of macrophages and HSC is regarded to be the primary cause of fibrosis reversal and can be utilized as a therapeutic tool [38-39]. Immunotherapy targeting profibrogenic macrophages and HSC in the treatment of liver fibrosis could be advantageous [40-41].
Viral infection and nonalcoholic steatohepatitis are two further factors that contribute to the progression of liver fibrosis (NASH). As seen by increased production of the latent cytokine TGF1 as well as elevated serum alanine and aspartate aminotransferase levels NASH is regarded to be the most major etiological cause in the development of liver fibrosis (ALT & AST respectively). Collagen deposition will also occur, increasing the risk of hepatocyte destruction [42]. Increased levels of free fatty acids {FFAs} result in activation of the peroxisome proliferator activated receptor alpha (PPAR)which produces reactive oxygen species (ROS) and causes cell-damage [43].

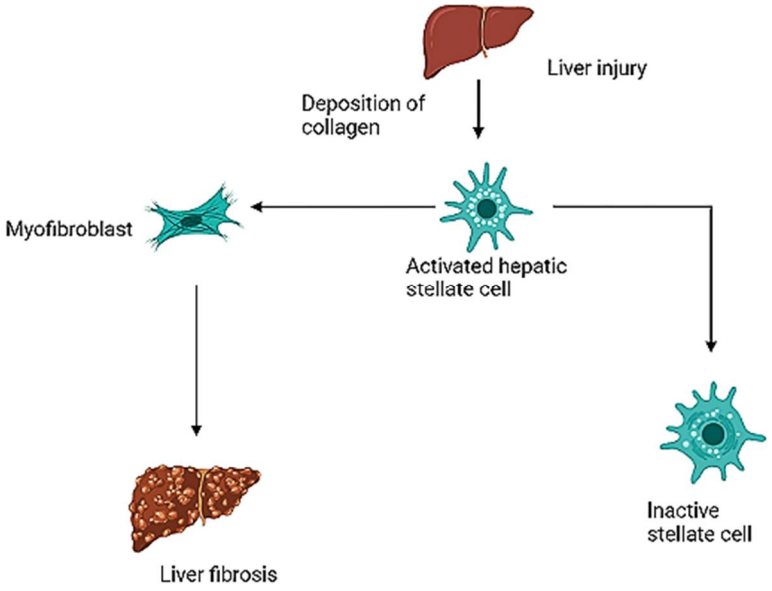

Fig-1 Pathogenesis of fibrosis

DIAGNOSIS OF LIVER-FIBROSIS

Currently, three parameters are used to study and diagnosis of liver fibrosis - imaging, serology, & histology. Because fibrosis is usually asymptomatic, Diagnosis of liver fibrosis in the middle and late stages is difficult to detect. TGF-, hy- and other serological markers have been associated to liver fibrosis in studies [44].Once blood tests reveal liver fibrosis, the diagnosis is usually confirmed with a liver biopsy, which is an invasive procedure. A needle is being used to collect a small sample of fresh liver tissue Samples to make pathological sections, which are then used to assess the severity of liver fibrosis using haematoxylin-eosin staining and -SMA immunohistochemistry. To specific staining procedures such as biochemical staining, Sirius red staining, Masson staining, and others [45, 46]. Imaging is used to detect the amount of liver damage and the hemodynamics of hepatic portal hypertension. A diagnosis can be made using a variety of techniques, including ultrasonography and magnetic resonance imaging. Ultrasound is a low-cost and high-resolution diagnostic technique that has been widely utilised to diagnose and treat liver fibrosis [47,48].

CURRENT TREATMENT

Nanodrug therapy:

Liposomes, polymers & particular moieties are frequently used in the creation of Nanomedicines for liver problems. Liposomes with a large number of polymers can be utilised to deliver pharmaceutical compounds, small interfering nucleic acids, antibodies, and moieties for targeting and imaging. Nanoparticle systems incorporating stimuli responsive polymers and liposomes have received a lot of attention as a potential treatment for liver fibrosis and other diseases, including cancer [49,50]

Nanoparticles are classified based on their size, shape, condition, and chemical composition [51]. Nanoparticles are a type of nanotechnology material that consists of components in the form of (10–100) nm particles [52]. Drug delivery & chemical and biological detection also gas sensing, CO2 collection & other health related applications can all be done with NPs in the biomedical system [53, 54].

Each of the NP systems now being used to treat liver fibrogenesis has its own set of features. Because inorganic NPs have unique architectures that allow them to transport drugs for treatment, they are a good therapeutic alternative. These NPs have a metal oxide or metal core that is covered by an organic coating. These metal cores have unique optical, electrical& magnetic characteristics due to their size& shape. They also provide several benefits in terms of drug integration. These NPs are currently in the preclinical stage of research due to their lack of biocompatibility [55,56].

We are going to study 3 kind of nanodrugs,

i-Inorganic Nanoparticles
ii-liposomes
iii-Nano micelles

i-Inorganic Nanoparticles:

Inorganic NPs are extensively used in the treatment of liver fibrosis. Cerium oxide NPs, silver NPs and gold NPs are examples of inorganic NPs [57].

In terms of structure, size, and functionalization, gold nanoparticles {AuNPs} are straightforward to manufacture and change [58]. These NPs bind to the (NH2) and (SH) groups with a high affinity [59] And they're used in drug development. Both delivery and diagnosis are possibilities. They are characterised by a cheerful demeanour. Biocompatibility and stability are critical in the treatment of liver fibrosis. They are regarded to be the safest form of inorganic medication delivery. And [60,61] Kabir et al. Claim that intragastric injection of Silymarin-coated AuNPs were employed for 14 days in rats exposed to carbon monoxide. HSCs were inactivated, Kupffer cells were attenuated, and the number of Kupffer cells was reduced as a result of hepatic injury caused by carbon tetrachloride (CCl4). Several fibrosis markers levels [62]. In Caco-2 cells, Domsa et al. Discovered that AuNPs have antioxidant, anti-inflammatory, and anti-apoptotic activities. It was made with Cornus mas extract [63].as well as some other plants. Their ability to protect gold nanoparticles control the cell's function. Process (64) and chlorogenic acid have anti-inflammatory and antioxidant effects. Characteristics of inflammation [65]. which were examined by Hwang et al. Found that delivering acid AuNPs to mice with chlorogenic acid resulted in a decrease in pro-inflammatory cytokines. Inflammation-causing cytokines [66]. AuNPs on the other hand, have the potential to be beneficial. The activation of liver macrophages causes hepatotoxicity. In an experimental environment, Bartneck et al. Discovered Hepatitis with an immune response in mice [67].

Calcium phosphate nanoparticles (CaPNPs) are employed in bone regeneration and as medication or gene carriers [68]. In a study on Mice with CCl4-induced liver fibrosis, Wang et al. Used them as agents for the delivery of TNF-Stimulated gene 6 (TSG-6) into the fibrotic liver. CaPNPs (made by biomineralization using bovine serum albumin) functionalized with TSG-6 accumulated in the liver and reduced fibrotic mechanisms (activation of HSCs and release of fibrogenic cytokines), according to their findings [69].

The liver is the primary target of zinc oxide NPs (ZnONPs) [70]. Bashandy et al. Demonstrated that therapy with ZnONPs can reduce hepatic lipid peroxidation, boost antioxidant protection, and lower the level of inflammatory markers in rats with Thioacetamide-induced liver fibrosis, reducing tissue degradation [71]. Several studies have found that silver nanoparticles have unfavourable effects on liver cells, resulting in severe oxidative stress [72].

Cerium oxide NPs were shown to concentrate in the liver after being given intravenously for a long time (8 weeks) to rats with CCl4induced hepatic damage, where they destroyed (ROS) [73]. decreased inflammation, apoptosis portal hypertension [74].

The structures of these inorganic NPs allow them to be customised with specific drugs for liver fibrosis treatment, such as doxorubicin , cisplatin, and capecitabine. In addition, the majority of inorganic NPs have been found to be safe [75].

Because, of the advancement and application of nanodrug delivery technology in recent years there are numerous nanodrug delivery systems used to treat liver fibrosis, which are generally classified into inorganic nanoparticles and organic nanoparticles based on the natural characteristics of nanoparticles. Metal ion nanoparticles and inorganic oxides (SiO2, Fe2O3) are examples of inorganic nanoparticles (Ag, Au). Their size and shape provide unique electrical, optical & magnetic capabilities, all of which are required for a successful nanomedicine delivery system. These materials have a diverse set of properties. In terms of pharmaceutical administration for the treatment of liver fibrosis, these materials provide a variety of advantages. By taking advantage of the advantages of being able to functionalize the surface of gold nanoparticles and accurately control the particle size, gold nanoparticles can be formed into nanocages, nanorods & nanosatellites, for example. SiO2 is also capable of sustaining a large number of bioactive chemicals due to its enormous void volume, specific surface area & chemical and thermal stability. Additionally, active groups can be produced by coating the inner core and surface of inorganic nanoparticles with organic compounds, which can be utilised to link proteins, polypeptides & other medications while also assuring their stability. Recent research has demonstrated that {SiO2} causes the production of inflammatory agents and transaminases in serum, as well as liver injury, in a dose dependent manner. Kupffer cells, which promote the release of bioactive chemicals that mediate liver injury may be involved in the underlying process of injury [76-77].

ii-Liposome:

Liposomes are one of the most effective carriers for delivering pharmaceuticals to various sick locations, and the most successful treatment for liver fibrosis is regarded to be drug administration via liposome based drug nanocarriers. [78].Cationic liposomes, which are used for miRNA distribution, are lipid-based NP systems that can inhibit inflammation, cell proliferation, and oxidative stress, all of which are involved

in liver fibrosis. On the other hand, the chemical properties of these cationic NPs limit their use in the therapy of hepatic fibrosis [79].

Luk et al. [80] created a Liposome infused with M6P modified liposomes carrying 18-glycyrrhetinic acid and injected it into a Wistar rat model of CCl4induced liver injury. When compared to a single injection of 18-glycyrrhetinic acid, rats treated with M6P-HSA loaded with 18-glycyrrhetinic acid have substantially lower blood indexes of glutamicpyruvic transaminase {ALT}, glutamicoxalacetic transaminase {AST}, and liver fibre. Additionally, Sirius red staining showed a significant improvement in collagen deposition in the liver tissues, revealing that the former can significantly lower the degree of liver fibrosis in the model rats. According to research, the Hedgehog signalling pathway can be activated after liver injury, boosting the trans differentiation of HSCs into active myofibroblasts, whereas smoothened inhibitors can successfully protect the liver.[81]

Another study looked at how cyclic peptides could be used to alter liposomes and deliver drugs to fibrotic liver cells. HSC proliferation was assumed to be aided by platelet-derived growth factor {PDGF}. As a result, for the treatment of liver fibrosis, sterically stabilised liposomes and cyclic peptides loaded with interferon (INF) can be employed to target the PDGF receptor. The antifibrotic efficacy of INF in the NP form was demonstrated in a thioacetamide (TAA)induced fibrosis animal model. [82].

iii-Nanomicelles:

Nanomicelles are exceedingly stable, tiny in size, and have a hydrophilic covering that prevents interactions with plasma, thus extending circulation time [83].

Hyaluronic acid (HA) micelles can also be used to target HSC and LSEC by targeting the HA receptor. HA micelles containing losartan are a successful NP system for the treatment of advanced liver fibrosis in a C3H or HeN mouse model. It has been established that the over expression of CD44 receptors during liver injury is beneficial for medication delivery to HSC via HA receptors. In vitro & in vivo, losartan, an angiotensin receptor type 1 receptor blocker, lowered SMA levels [84].

Lin et al. Looked at poly (lacticcoglycolic acid) NPs that were loaded with sorafenib. In vivo and in vitro research is accessible. According to their findings, this delivery approach provides antifibrotic effects that are superior to free sorafenib (tyrosine kinase inhibitor) [85].

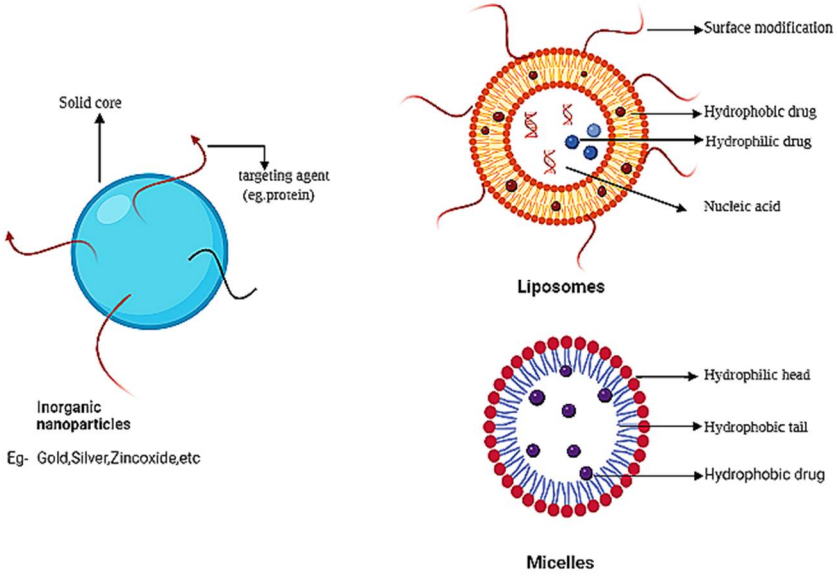

FIG.2 Nanodrugs (inorganic, liposome , Nanomicelle)

TARGETED DRUG THERAPY

Targeted drug therapy utilizes drugs that specifically target the molecular mechanisms and pathways that underlie the onset and progression of liver fibrosis. These treatments are intended to slow down or even stop the fibrotic process, preventing further liver damage and encouraging tissue healing. With a better understanding of the aetiology of liver fibrosis, various new anti-fibrosis drugs have emerged and are being tested in clinical trials.

Table 1- Effective fibrotic drugs. [86]

Drug	Mechanism	Clinical phase
-GKT137831	Antioxidant	2
-Selonsertib-(GS-4997)	ASK1 blocker	3
-PRI(724)	CBP or beta catenin inh	I or IIa
-Elafibranor	PPAR agonistic	3
-Cenicriviroc	CCR2 or CCR5 antagonist	2/3
-Solithromycin	Macrolide antibiotics	2
-BMS(986263)	Anti-(HSP47)	Ib or 2
-NGM(282)	FGF (19 analogue)	II-b
Vitamin-(E)	Antioxidant	2 or IIK
-Statins	Lipid lowering agent	2/3/4
-IMMI24 (e)	LPS - immune	2
-Emricasan	Cascapeblocker	2
-Obeticholic acid	FXR-agonistic	3
-Pioglitazone	PPAR-agonistic	4
-Saroglitazar	PPAR agonistic	2
-GR-MD-02	Galectin-3 inhibitor	II-b

THE GENE-THERAPY

Although liver transplantation seems to be the only treatment option for end-stage liver fibrosis, it coincides with a slew of disadvantages, including immunological rejection difficulty finding a liver donor and a poor prognosis to mention a few. In recent years, gene therapy has been presented as a remedy to these problems, including RNA- intervention oligonucleotide chains & decoy oligonucleotides. RNA intervention {RNAi} is a strategy for knocking off specific genes using siRNA (small interfering RNA) of 21–23 nucleotides (Buchman, 2005) [87].

Direct elimination of TGF-1 using siRNA reduced the formation of SMA and type I collagen in HSC-T6 cells in mice and rats with CCl4-induced hepatic fibrosis and had an anti-fibrotic effect (Cheng et al., 2009) [88].

HDAC2 (Histone Deacetylase 2) is a protein that is increased in TGF-1-treated HSCs and CCl4induced fibrotic liver tissues. The expression of SMA and COL1a1 was reduced in HSC-T6 cells treated with TGF-1 when siRNA inhibiting the expression of HDAC2 was used. [89].

(B-Catenin siRNA) inhibited collagen synthesis and catenin expression in HSCs in a time dependent manner, down-regulated the beta-catenin signal pathway, reduced proliferation, and caused death in HSC-T6 cells, slowing fibrosis progression [90].

It suggests that (B-catenin siRNA) could be employed in a unique method to treat liver fibrosis. In vitro, lentivirus delivered CB1 siRNA (CB1-RNAi-LV) significantly reduced CB1 expression as well as HSC activation and proliferation. (CB1-RNAi-LV) benefitted rats with DMN-induced liver fibrosis by decreasing TGF. The Smad signal pathway reduced SMA expression and improved EMT [91-92].

In addition to (siRNA)based treatment the microRNA (miRNA) is another treatment option for liver fibrosis. MiRNA is a noncoding short RNA found in the human body that regulates the expression of RNA after it has been transcribed. Miravirsen (SPC3649), a nucleic acid & DNA mixture, successfully inhibited the activity of miR-122 and prevent liver fibrosis in a phase 2a research (NCT01200420) of HCV infection [93-94].

MiR-101 - a short non-coding RNA that controls the (MAPK) response, improved the liver function of mice with hepatic fibrosis caused by CCl4. MiR-101 dramatically reduced liver parenchyma damage and delayed hepatic fibrosis by lowering the levels of SMA & (COL1a1) decreases the accumulation of ECM components, and modulating the PI3K-AKT-mTOR signal -pathway [95].

(MiR 29b), a short noncoding RNA significantly suppressed in fibrotic liver tissues and primary activated HSCs, considerably lowered Smad3 expression in the HSC line LX1 and decreased -SMA and type I collagen production in mice with CCl4-induced hepatic fibrosis. Moreover, MiR-29b has a significant impact. By inhibiting HSC activity and preventing apoptosis, researchers were able to slow the progression of hepatic fibrosis. HSCs are stimulated by the Protein kinase pathway [96].

MESENCHYMAL STEM CELL THERAPY

Described in the 1980s, and defined as cells in bone marrow, attaching to surfaces and featuring a spindle shaped morphology [97]. At present, it is well-known that the MSC has therapeutic potential for liver disease due to its nonimmunogenicity, homing to injured sites, differentiation capacity, release of molecules & immunomodulatory properties [98–100]. However, argument exists in antifibrotic effects of

MSCs. Some papers indicated that bone marrow derived MSCs not only fail to improve liver fibrosis [101, 102], but also have potential to become myofibroblasts and HSCs which can boost development of liver fibrosis [103, 104]. Oppositely, Zhao et al. Reported that MSCs would show better antifibrotic effects on liver under injection at earlier times during liver injury [105].
(BMMSCs) were used in clinical studies to cure a range of ailments & notably liver fibrosis, as a result of its initial separation and determination [106].
Collagen reduction, HSC death, proinflammatory cytokine decrease, and liver enzyme recovery all seem to be benefits of BMMSC therapy. Recent times, researchers have found that BMMSCs overexpressed with hepatocyte nuclear factor 4 alpha (HNF-4) did best in a CCL4-induced animal model than untreated BMMSCs, intimating that HNF-4-BMMSC transplantation improved liver function parameters and HNF-4 used to have a beneficial impact on MSC anti-inflammation [107,108].
(BMMSCs) were shown to help accelerate liver regeneration in a rat model of BDL-induced liver fibrosis by upregulating HGF and MMP-2 expression while downregulating cytokeratin-19 (CK-19) expression [109]. Furthermore, other research has shown that BMMSCs aid in the management of fibrosis and are required for the development of liver fibrosis [110].
While -ADSCs can be obtained through liposuction and proliferated ex vivo, they have the potential to be used in regenerative medicine therapy [111].
Hao et al. Investigated (ADSCs) and (BMMSCs) in the treatment of liver fibrosis, discovering that ADSCs were significantly more capable of inhibiting HSC activation, proliferation & activation, as well as the level of AST or ALT, laying the groundwork for ADSCs to be a viable therapy option for hepatic fibrosis [112]. Many studies [113–118] have demonstrated the efficacy of ADSCs in the treatment of liver fibrosis in animal models, and Zhang et al. Discovered that cultivating ADSCs in a 3D environment resulted in higher expression of IGF-1, HGF & interleukin-6 (IL-6) than in a 2D environment, resulting in better liver function after transplanting spheroids to a liver fibrosis mouse- model [119].
Despite the fact that (ADSCs) are considered an assisted tool in liver regeneration therapy and have significant potential in the treatment of liver damage, there is still debate about the timing of transplantation, the implications of short and long-term use, and the route of administration. As a result, more research is needed to uncover more specific and accurate mechanisms of liver regeneration. Some clinical trials involving ADSC transplantation are currently being conducted (NCT04088058, NCT03254758, NCT02705742, NCT03254758).

LIVER TRANSPLANTATION

A Liver fibrosis is from its mature stages, is exceedingly hazardous to human life, posing a significant risk of (mortality &morbidity). Liver transplantation is now the only widely accepted lifesaving therapy option for people with advanced liver fibrosis. The very first successful liver transplantation was recorded & short and long-term evaluations of post-transplanted patients have steadily improved [120] due to technological advances in immunosuppressive therapy management, improved post-surgery complications management& superior donor to recipient matching.
The Liver transplants are functional (3D models) of the liver that are operated in vitro and retain important biological features [121].
The Hepatic progenitor cells or stem cells are frequently developed and extracted to make liver organoids. Implanting liver organoids into mice with liver failure improved liver function to some extent, demonstrating that the wounded liver can engraft & relocate [121].
In a similar study, liver organoids were transplanted into mice with liver damage and produced similar quantities of alpha 1 antitrypsin & human albumin as adult hepatocyte transplantation [122]. In 3D liver tissue, endothelial & mesenchymal cells were co-cultured with (iPSCs) to develop hepatocytes. These liver buds can create serum proteins and conduct detox after budding & forming capillaries [123].
By developing ultrasound liver equipment & biocompatible scaffolds which work well in vivo & in vitro, liver tissue engineering may help reduce the number of patients on the waiting list [124]. A 3D - physiological microenvironment is critical for developing tissue models in vitro [125], but it's important to find efficient biocompatible structures with ideal materials. Presently, major approaches are based on biomaterials, including such polymer-based 3D, (decellularised ECM) & (bio printing 3D) constructs, bioreactors & liver on chip [126].

CONCLUSION

In conclusion, it is extremely challenging to choose the optimal therapy alternatives for people with hepatic fibrosis due to the multiplicity of pathways that contribute to the condition. The undeniable fact is that liver transplantation remains the most direct and effective option for treating liver fibrosis until we discover the secret code to unlock it. Fortunately, though, there is expanding consensus that it is essential to specifically

adapt treatment for patients with liver fibrosis depending on a range of factors. In light of this, it is easy to predict that combination therapy for liver fibrosis involving several drugs, even drug and cell therapy, will become a significant leading edge. Future research should concentrate on creating non-invasive diagnostic tools, increasing precision medicine techniques, and discovering more efficient and safe medicines that can be tailored for specific individuals.

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CONFLICTS OF INTERESTS:
The authors declare that there is no conflict of interest regarding the publication of this paper

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