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# Hepatic Stellate Cell-Targeted Delivery of Ferroptosis Modulators for Liver Fibrosis: Emerging Nanocarriers, Pharmacological Targets and Translational Challenges

***Sakshi[1*], Payal[2], Kulpreet Kaur Sandhu[3], Sidhant Sharma[4], Dr. Avneet Gupta[5]***

[1*]Department of Pharmcology, L.R Institute of Pharmacy, Jabli Kyar, Solan H.P (173223) India,

[2]Department of Pharmaceutics, L.R Institute of Pharmacy, Jabli Kyar, Solan H.P (173223) India,

[3,4,5]Department of Pharmcology, L.R Institute of Pharmacy, Jabli Kyar, Solan H.P (173223) India

Email id - kaushalsakshi803@gmail.com

**ABSTRACT**

The frequent histological result of chronic hepatic damage is liver fibrosis, which is primarily caused by quiescent hepatic stellate cells (HSCs) being persistently activated into proliferative myofibroblasts that secrete extracellular matrix. Because selective induction of ferroptosis in activated HSCs reduces collagen deposition without necessarily harming hepatocytes, while hepatocyte or macrophage ferroptosis can worsen liver injury, ferroptosis—an iron-dependent form of regulated cell death characterised by unrestrained lipid peroxidation—has recently emerged as an appealing antifibrotic strategy. Because of this contradiction, the translation of ferroptosis-inducing pharmacology into safe antifibrotic therapy requires cell-selective administration.The system Xc−/glutathione/GPX4 axis, ACSL4-dependent lipid remodelling, iron-handling proteins, and the Nrf2-Keap1 and HIF-1α regulatory nodes are just a few examples of the molecular circuitry that connects ferroptosis to HSC biology. This review also examines the pharmacological agents—small molecules, natural products, and nucleic acid-based regulators—that take advantage of this circuitry. The growing toolkit of nanocarriers designed for HSC-selective delivery is then examined, including vitamin A/retinoid-decorated liposomes and lipid nanoparticles, polymeric and chitosan-based systems, peptide- and protein-guided platforms, inorganic and hybrid nanostructures, and exosome-based vehicles. It emphasises how ligand selection, particle architecture, and payload (small molecule, siRNA, or miRNA) determine antifibrotic efficacy and specificity.Lastly, the review critically examines translational barriers, such as the extracellular matrix and sinusoidal capillarization that prevent nanoparticle penetration, the possibility of unintentional hepatocellular ferroptosis, manufacturing and stability limitations, immunogenicity of carriers based on lipids and nucleic acids, and the lack of clinical trials and validated pharmacodynamic biomarkers. The key to moving HSC-targeted ferroptosis modulation from preclinical proof-of-concept to clinically feasible antifibrotic therapy is suggested to be bridging mechanistic pharmacology with logical nanocarrier engineering.

***Keywords:*** *Hepatic stellate cells; Ferroptosis; Liver fibrosis; Nanocarriers; Drug delivery; GPX4; SLC7A11; Vitamin A-targeted nanoparticles*

## 1. Introduction

Almost all types of chronic liver injury, such as viral hepatitis, alcohol-related liver disease, metabolic dysfunction-associated steatotic liver disease, and cholestatic disorders, share the pathological end-point of liver fibrosis. If left unchecked, it can lead to cirrhosis, liver failure, and hepatocellular carcinoma, which is responsible for well over a million deaths globally each year [1,2]. Since effective treatments have not been able to selectively target activated hepatic stellate cells (HSCs) while sparing other hepatic cell populations, no antifibrotic medication has been approved by regulators despite decades of research [3,4].A little more than ten years ago, ferroptosis was described as an iron-dependent, non-apoptotic method of controlled cell death caused by the buildup of lipid peroxides that exceeded the antioxidant defences of the cell [5,2]. HSCs exhibit a unique vulnerability to ferroptotic insult because, in contrast to quiescent hepatocytes, they heavily depend on the cystine/glutamate antiporter system Xc− and glutathione peroxidase 4 (GPX4) to survive their transdifferentiation into myofibroblasts. Additionally, an increasing amount of research indicates that selectively driving activated HSCs into ferroptosis can regress established fibrosis in rodent models [6,7,1].Ferroptosis in the liver, however, behaves as a true double-edged sword whose therapeutic value depends entirely on which cell type undergoes it because the same iron- and lipid-peroxidation-dependent machinery, when activated in hepatocytes or Kupffer cells, promotes rather than resolves liver injury [8,5]. The primary pharmacological justification for attaching ferroptosis-inducing drugs to carriers that can selectively bind to HSCs is this context-dependency.

A useful path to this selectivity is provided by nanomedicine. For more than ten years, ligands derived from these pathways have been used to deliver nucleic acid and small-molecule payloads to HSCs with a reasonable degree of precision because HSCs are the primary hepatic reservoir of retinoids (vitamin A) and re-express receptors for retinol-binding protein and platelet-derived growth factor receptor-β upon activation [9,10]. A unique and quickly expanding subfield of HSC-targeted, ferroptosis-modulating nanomedicine has emerged as a result of this targeting logic being explicitly applied to ferroptosis-inducing payloads in more recent times.The mechanistic underpinnings of HSC ferroptosis, the pharmacological agents currently used to induce it, the nanocarrier architectures designed for its cell-selective delivery, and the translational challenges that need to be addressed before these approaches can proceed to the clinic are all summarised in this review.

## 2. Hepatic Stellate Cells and the Pathophysiology of Liver Fibrosis

In the quiescent state, HSCs store the majority of the body's vitamin A in cytoplasmic lipid droplets and play a primarily homeostatic role in the hepatic milieu in the perisinusoidal area of Disse [11,12]. Chronic hepatocellular injury causes HSCs to lose their vitamin A stores and transdifferentiate into proliferative, contractile, matrix-secreting myofibroblasts with de novo expression of α-smooth muscle actin (α-SMA) due to paracrine signals from injured hepatocytes, Kupffer cells, and infiltrating immune cells, particularly transforming growth factor-β (TGF-β) and platelet-derived growth factor [13,14,15].These myofibroblastic HSCs (MF-HSCs) become the primary source of type I and III collagen, fibronectin, and other extracellular matrix (ECM) components. Progressive fibrogenesis, capillarization of the sinusoids, and ultimately cirrhotic transformation of the liver are driven by their sustained accumulation rather than their brief, physiological activation during wound healing [1,14].

Therapeutic approaches have increasingly concentrated on removing this pre-existing myofibroblast population rather than only blocking upstream activating cytokines because MF-HSC persistence rather than their initial activation appears to be rate-limiting for fibrosis progression [1].

Apoptosis, autophagy-dependent death, and, more recently, ferroptosis have all been investigated as mechanisms for eliminating MF-HSCs. Ferroptosis has drawn special attention due to its unique biochemical dependence on iron and polyunsaturated lipid metabolism, both of which are pharmacologically tractable [6,16,17].

## 3. Ferroptosis: Mechanistic Basis and Its Dual Role in Liver Disease

### *3.1 Iron metabolism and the Fenton reaction*

A labile, redox-active intracellular iron pool is necessary for ferroptosis because it catalyses Fenton chemistry, producing hydroxyl radicals that start lipid peroxidation chain reactions [13, 14]. The size of this labile pool is regulated by cellular iron handling proteins, such as ferritin, transferrin receptor (TFRC), and ferritinophagy receptor NCOA4. When these proteins are dysregulated, either by increased iron intake or ferritin autophagy, cells become more vulnerable to ferroptotic death [2].

### *3.2 Lipid peroxidation: ACSL4 and LPCAT3*

Polyunsaturated fatty acid-containing phospholipids are the lipid substrates for peroxidation, and their production is dependent on lysophosphatidylcholine acyltransferase 3 (LPCAT3), which incorporates these into membrane phospholipids, and acyl-CoA synthetase long-chain family member 4 (ACSL4), which esterifies arachidonic and adrenic acid into a CoA-thioester form. Ferroptosis sensitivity is thus determined by ACSL4 expression, and its upregulation—or the introduction of ACSL4-inducing cargoes—has been suggested as a pharmacological lever to make target cells more sensitive to ferroptotic drugs [18].

### *3.3 The system Xc−/glutathione/GPX4 axis*

The principal cellular defence against ferroptosis is the system Xc− cystine/glutamate antiporter, encoded by SLC7A11, which imports cystine for glutathione (GSH) biosynthesis; GSH in turn serves as the essential cofactor for GPX4, the selenoenzyme that reduces lipid hydroperoxides to non-toxic lipid alcohols [19]. Pharmacological or genetic inhibition of SLC7A11 (for example by erastin or sulfasalazine) or of GPX4 directly (for example by RSL3 or FIN56) depletes this defence and precipitates ferroptotic death, and this axis constitutes the principal druggable node exploited by essentially all ferroptosis-inducing agents discussed in this review .

### *3.4 FSP1-CoQ10 and parallel antioxidant defences*

Ferroptosis suppressor protein 1 (FSP1) and its regeneration of reduced coenzyme Q10 constitute a GPX4-independent defence system that offers an alternative pathway to resistance to ferroptosis and is a potential target for combination strategies aimed at overcoming resistance to system Xc−/GPX4-directed agents .

### *3.5 Ferroptosis in HSCs versus hepatocytes and macrophages: a double-edged sword*

The overall impact of ferroptosis on liver fibrosis is largely dependent on the type of cell that is impacted, according to a recurrent theme in the literature. Ferroptosis inhibitors like ferrostatin-1 have been demonstrated to lessen iron- or carbon tetrachloride-induced liver injury in certain models [5]. Ferroptotic death of hepatocytes, which is frequently caused by iron overload or oxidative insults, releases damage-associated molecular patterns that activate Kupffer cells and, indirectly, HSCs, thereby promoting rather than resolving fibrosis. On the other hand, it has been consistently demonstrated that selectively inducing ferroptosis in already-activated, myofibroblastic HSCs regresses fibrosis in preclinical models by depleting the very cell population responsible for excess ECM deposition [6,1,5].

The single most significant pharmacological constraint influencing the rational design of HSC-targeted ferroptosis-inducing nanomedicines is this cell-type-dependent duality. This is because untargeted or poorly targeted delivery runs the risk of inducing hepatocyte or macrophage ferroptosis, which would exacerbate rather than alleviate liver injury.

## 4. Pharmacological Ferroptosis Modulators Targeting Hepatic Stellate Cells

### *4.1 Small-molecule system Xc− and GPX4 inhibitors*

Inhibiting SLC7A11-mediated cystine import, erastin and its analogues, coupled with the anti-inflammatory sulfonamide sulfasalazine, have shown antifibrotic action by inducing HSC ferroptosis in experimental models. Although their limited therapeutic window currently restricts standalone clinical application, RSL3 and comparable direct GPX4 inhibitors work farther downstream and are commonly employed as reference ferroptosis

inducers in mechanistic studies of HSC biology [20].

### *4.2 Repurposed kinase inhibitors: sorafenib*

The oral multikinase inhibitor sorafenib, which was previously approved for the treatment of hepatocellular cancer, has been modified to trigger ferroptosis in HSCs. By suppressing the HIF-1α/SLC7A11 signalling axis, sorafenib decreased SLC7A11 and GPX4 protein levels and selectively induced iron accumulation, reactive oxygen species generation, and lipid peroxidation in HSCs in carbon-tetrachloride-induced fibrotic liver. Its antifibrotic effect was eliminated by ferroptosis inhibitors ferrostatin-1 and deferoxamine [21]. Sorafenib has emerged as one of the most commonly used payloads in HSC-targeted nanocarrier design due to its approval and well-defined toxicity profile [22, 23].

### *4.3 Natural products and other repurposed agents*

Curcumol, which encourages autophagy-dependent ferroptosis, and artemisinin derivatives like artemether, which prevent ubiquitination of iron-regulatory protein 2 to increase the labile iron pool and cause ferroptotic HSC death, are two examples of natural compounds that cause HSC ferroptosis through overlapping mechanisms [8]. Despite not being traditional ferroptosis inducers, flavonoids like galangin and butein have been added to HSC-targeted nanocarrier formulations for their antifibrotic effects, and their ferroptosis-related mechanisms of action are rapidly being reevaluated [24,12].

### *4.4 Nucleic-acid-based and epigenetic regulators*

In addition to tiny chemicals, a number of nucleic acid and epigenetic mechanisms have been demonstrated to control HSC ferroptosis and are desirable payloads for delivery via nanocarriers. The m6A-methylation-regulated IGF2BP3/Notch/Jag1 axis regulates GPX4 expression and HSC ferroptotic sensitivity [25], TRIM26 mediates ubiquitin-dependent degradation of SLC7A11 [13], and N6-methyladenosine modification more broadly connects autophagy signalling to ferroptosis in HSCs [17]. Through the xCT/GPX4 axis, cell-derived vesicles containing pro-ferroptotic cargo, such as human umbilical cord mesenchymal stem cell-derived exosomes releasing BECN1, promote HSC ferroptosis and show a physiological pathway to the same pharmacological end point [26].

## 5. Emerging Nanocarrier Platforms for HSC-Targeted Ferroptosis Delivery

A number of anatomical obstacles specific to the fibrotic liver must be overcome for effective HSC targeting, such as sinusoidal capillarization, loss of fenestration, and thick pericellular collagen deposition that prevents nanoparticle penetration into the Disse space [14,23]. As a result, ligand-directed nanocarriers have been designed around a number of HSC-specific recognition techniques, which are outlined below.

### *5.1 Vitamin A/retinoid-conjugated liposomes and lipid nanoparticles*

The retinol-binding protein (RBP) receptor, which is retained on activated HSCs, is exploited by the most widely verified HSC-targeting technique. The proof of concept for this strategy was established when vitamin A-coupled liposomes containing siRNA against gp46 (the rat HSP47 homologue) nearly completely resolved dimethylnitrosamine-induced cirrhosis in rats [27,10]. COL1A1 siRNA has now been delivered via vitamin-A-scaffolded lipid nanoparticles and lipid-like materials [28], while vitamin-A-coupled liposomes containing MMP-2 siRNA have been demonstrated to suppress fibrogenic signalling in vitro [15].

In order to achieve combination chemotherapeutic and gene-silencing antifibrotic effects while improving HSC-selective absorption via the RBP receptor, most recent formulations incorporate vitamin A-functionalized fluorinated peptide-lipid hybrid nanoparticles to co-deliver sorafenib and siRNA against HSP47 [22,23]. Similarly, dual siRNAs that concurrently inhibit collagen formation and encourage its breakdown have been co-delivered using hyperbranched cationic lipoids and cholesterol-polyethylene glycol-vitamin A helper lipids [3]. This platform has been expanded into theranostic applications by vitamin-A-modified melanin nanoparticles, which combine photothermal antifibrotic therapy with photoacoustic imaging [29].

### *5.2 Retinoic-acid- and retinol-modified polymeric nanoparticles*

In addition to lipid-based systems, vitamin A-functionalized nanoparticles have been used to deliver the proteasome inhibitor bortezomib, which modulates the TGF-β1/Smad3 fibrogenic pathway [28], and retinoic acid-modified polymeric nanoparticles constructed from acrylic resins have been used to deliver the flavonoid galangin selectively to HSCs via the RBP receptor [12]. Through increased hepatic and HSC-directed accumulation, vitamin-A-coupled solid lipid nanoparticles containing butein have also shown antifibrotic activity in vivo [12].

### *5.3 Collagen- and receptor-binding polymeric and peptide-based systems*

An alternate approach takes advantage of chitosan's natural affinity for collagen: anti-TGF-β siRNA has been delivered using chitosan nanoparticles modified with platelet-derived growth factor receptor-β-binding peptides, combining ECM-anchoring with active HSC uptake [14]. In order to overcome the extra endosomal escape barrier that restricts the effectiveness of nucleic acid payloads, a similar retinol-binding-protein-hijacking nanopolyplex has been particularly designed to encourage cytoplasmic siRNA release once within HSCs [4]. Another version that takes use of HSC-associated receptor recognition for chemotherapeutic antifibrotic administration is chondroitin sulfate-based nanoparticles containing the tyrosine kinase inhibitor imatinib [30].

### *5.4 Inorganic and hybrid nanoparticles*

In addition to biological targeting ligands, inorganic nanostructures provide additional ferroptosis induction methods. In addition to providing a source of redox-active iron by nature, iron oxide nanoparticles have been co-loaded with microRNA-214-3p to accomplish dual suppression of GPX4 and lipocalin-2, boosting ferroptosis in liver cancer cells. This approach is conceptually transferable to HSC-targeted antifibrotic design. By quickly depleting intracellular glutathione, manganese silicate nanoparticles co-delivered with sorafenib induce ferroptosis [31]. Iron-delivering nanovesicles can be combined with system Xc⁻-inhibiting medications, as demonstrated by cell-membrane-derived transferrin nanovesicles laden with $Fe^{3+}$ and sorafenib, which take advantage of transferrin receptor overexpression to synergistically augment ferroptosis in hepatic malignant cells [32].

Additionally, microRNA-29b and microRNA-122 have been delivered to HSCs via superparamagnetic iron oxide-decorated, vitamin-A-conjugated

cationic micelles in a magnetic resonance imaging-trackable manner, combining therapeutic gene silencing with non-invasive nanocarrier biodistribution monitoring [33].

### *5.5 Exosomes and cell-derived vesicles*

Exosomes produced from mesenchymal stem cells are a physiologically derived nanocarrier substitute that naturally promotes HSC absorption. By controlling the xCT/GPX4 axis and decreasing collagen deposition in vivo, human umbilical cord mesenchymal stem cell exosomes modified to deliver BECN1 induce HSC ferroptosis and show that endogenous extracellular vesicles can be repurposed as pro-ferroptotic delivery vehicles with an intrinsically favourable safety and biocompatibility profile compared to synthetic nanocarriers [26,34].

## 6. Pharmacological and Molecular Targets for Rational Nanocarrier Design

Explicit alignment between the intracellular pharmacological target (which identifies the ferroptotic mechanism involved) and the delivery ligand (which affects cell selectivity) is advantageous for rational nanocarrier design. Below is a summary of the main druggable nodes related to HSC-targeted ferroptosis modulation.

### *6.1 SLC7A11/xCT*

The most commonly targeted node is still SLC7A11, which can be drugged by nucleic acid techniques that facilitate its degradation, like TRIM26-mediated ubiquitination, as well as small drugs like erastin, sulfasalazine, and sorafenib [13,1].

### *6.2 GPX4*

RSL3-class inhibitors and nanocarrier-delivered microRNAs intended to reduce its expression directly target GPX4 activity and its transcriptional or post-transcriptional regulation via pathways including IGF2BP3/Notch/Jag1 [25].

### *6.3 ACSL4 and lipid remodelling enzymes*

Strategies that upregulate ACSL4 within HSC-targeted nanocarriers could potentially increase the effectiveness of co-delivered system Xc−/GPX4 inhibitors because ACSL4 controls the availability of peroxidation-prone phospholipid substrates and its expression level modulates the ferroptotic sensitivity of both hepatocellular carcinoma and HSCs [18].

### *6.4 Iron-handling proteins: TFRC and ferritinophagy*

While ferritinophagy mediated by NCOA4 offers an additional pathway to increase the labile iron pool and sensitise HSCs to ferroptotic drugs, transferrin receptor overexpression has been used both therapeutically and diagnostically, as in transferrin-Fe3+ nanovesicles [2,32].

### *6.5 Nrf2/Keap1 and HIF-1α regulatory nodes*

By maintaining glutathione synthesis and upregulating cytoprotective genes, the Nrf2-Keap1 antioxidant pathway prevents ferroptosis. Its suppression has been suggested as an additional tactic to make resistant cells more sensitive to system Xc−/GPX4-targeted drugs [34,44]. On the other hand, sorafenib's pro-ferroptotic activity in HSCs is based on the reduction of HIF-1α, which positively regulates SLC7A11 expression. This makes HIF-1α an additional upstream target for combination treatments administered by nanocarriers [21].

## 7. Translational Challenges

### *7.1 Achieving cell-type selectivity and avoiding off-target ferroptosis*

Given the conflicting effects of ferroptosis in hepatocytes and Kupffer cells, the primary translational risk in this sector is that any leakage of a ferroptosis-inducing payload into both cell types could worsen rather than alleviate liver injury [8,5]. Vitamin A/retinoid, PDGFR-β peptides, and collagen-binding chitosan are examples of ligand-based targeting strategies that significantly increase selectivity but rarely achieve absolute HSC specificity in vivo. Thorough, cell-type-resolved pharmacodynamic assessment is still necessary to advance any candidate formulation [9,14,23].

### *7.2 The extracellular matrix and sinusoidal capillarisation as physical barriers*

Nanoparticle extravasation and penetration to the space of Disse are physically impeded by progressive collagen deposition and loss of sinusoidal fenestration in fibrotic liver; consequently, nanocarrier efficacy frequently decreases precisely as fibrosis—and consequently, therapeutic need—increases [22, 26]. Although they are partial solutions, collagen-affinity techniques like chitosan-based nanoparticles and enzyme-assisted matrix-penetrating designs increase formulation complexity and may have off-target proteolytic effects [22].

### *7.3 Manufacturing, scale-up, and physicochemical stability*

Many of the platforms reviewed here-multi-component lipid-peptide hybrids, dual-ligand conjugates, and co-loaded small-molecule/nucleic-acid systems-are structurally complex, raising concerns regarding batch-to-batch reproducibility, colloidal and chemical stability during storage, and the feasibility of good manufacturing practice-compliant scale-up, all of which remain comparatively under-addressed in the current literature [22,33].

### *7.4 Immunogenicity and toxicological considerations*

Although several vitamin-A-coupled formulations have explicitly reported no innate immune induction, systematic long-term toxicological evaluation is still lacking, especially with regard to chronic iron loading from inorganic ferroptosis-potentiating nanoparticles [27]. Cationic lipid and polymeric nanocarriers used for nucleic acid delivery can cause innate immune activation or complement-mediated reactions.

### *7.5 Absence of validated biomarkers and clinical trial infrastructure*

In contrast to the serial liver biopsy-dependent endpoints typically used in antifibrotic drug development, the field currently lacks non-invasive, validated pharmacodynamic biomarkers capable of confirming HSC-selective ferroptosis induction in patients [1,3]. No HSC-targeted ferroptosis-modulating nanomedicine has yet entered human clinical trials for liver fibrosis. To narrow this gap and enable early-phase human proof-of-mechanism studies, standardised non-invasive fibrosis biomarkers must be closely integrated with imaging-trackable nanocarrier designs, such as magnetic-resonance-visible micelles [33].

## 8. Conclusion and Future Perspectives

As long as it can be limited to activated hepatic stellate cells, ferroptosis has developed from a mechanistically fascinating type of controlled cell death into a truly effective antifibrotic tactic. Strong preclinical evidence of antifibrotic efficacy has been produced by the convergence of well-characterized molecular targets, such as system Xc−/GPX4, ACSL4-dependent lipid remodelling, iron-handling proteins, and the Nrf2/HIF-1α regulatory network, with an increasingly complex nanocarrier toolbox, including vitamin A-directed lipid nanoparticles, collagen-anchoring polymeric systems, iron-delivering inorganic nanostructures, and exosome-based vehicles.

The main obstacles to clinical translation are now more logistical and safety-related than mechanistic: producing multi-component nanocarriers in a repeatable and scalable manner; definitively ruling out off-target hepatocellular or macrophage ferroptosis; penetrating the collagen-rich extracellular matrix that characterises the very fibrotic tissue being treated; and developing biomarkers and trial designs appropriate for a truly novel therapeutic mechanism. To advance HSC-targeted ferroptosis regulation from an active field of preclinical innovation to a clinically significant antifibrotic treatment, further research that combines logical, target-informed nanocarrier design with exacting, cell-resolved safety pharmacology will be crucial.

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